Journal of Gastrointestinal Cancer (2023) 54:1240–1251
https://doi.org/10.1007/s12029-023-00915-6

ORIGINAL RESEARCH

Effect of Time to Minimally Invasive Esophagectomy After Neoadjuvant Chemotherapy for Esophageal Squamous Cell Carcinoma

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Accepted: 25 January 2023 / Published online: 1 February 2023

Abstract

Background Neoadjuvant chemotherapy (NAC) with docetaxel, cisplatin, and 5-fluorouracil/capecitabine (DCF/DCX) followed by esophagectomy has been the recommended treatment for esophageal squamous cell carcinoma (ESCC). However, the optimal interval from NAC to surgery has not yet been established. This study evaluated the impact of time to surgery (TTS) in the treatment of ESCC.

Methods Between August 2018 and September 2021, 97 patients who underwent radical esophagectomy following 3–6 cycles of NAC with DCF/DCX for ESCC at a single hospital were analyzed. TTS was categorized into three groups: 16–41 days (group 1; 33 patients), 42–55 days (group 2; 29 patients), and 56–135 days (group 3; 35 patients). Survival outcomes included overall survival (OS) and progression-free survival (PFS).

Results Mean age was 59.6 ± 6.8 years, and 95 patients were male. One patient had grade-III anemia, 12 had grade-II anemia, and four had grade-II neutropenia; all other NAC-related toxicities were as grade I. Regarding pathologic tumor response, 18.6% achieved complete response, 71.1% achieved partial response, and 10.3% had stable disease. Forty-eight patients (49.5%) had a postoperative complication, but only six (6.2%) with grade IIIa and two (2.1%) with grade IVa according to the Clavien-Dindo classification. Median follow-up time was 24 months. Groups 1 and 3 had worse OS (HR [95% CI]: 3.36 [1.16–11.7] and 1.83 [0.55–6.10]) and worse PFS (HR [95% CI]: 3.27 [1.25–8.53] and 1.61 [0.58–4.45]) compared to group 2.

Conclusion We suggest the optimal TTS after NAC is 6–8 weeks. However, this finding must be confirmed by prospective trials.

Keywords Esophageal cancer · Time to surgery · Neoadjuvant chemotherapy · Esophagectomy

Introduction

Esophageal cancer is the ninth most common cancer and the sixth leading cause of cancer death worldwide [1]. In Asia, esophageal squamous cell carcinoma (ESCC) accounts for most esophageal cancers [2]. Treatment of esophageal cancer, in general, is complicated, and there are still many controversies. Most Asian countries apply the guidelines of the Japan Esophageal Society for esophageal cancer [3], including neoadjuvant treatment for locally advanced ESCC. Since the findings of JCOG9907 study in 2012, neoadjuvant chemotherapy (NAC) has been widely recommended. There is also controversy about whether chemotherapy or chemoradiotherapy should be used as neoadjuvant therapy to improve the effectiveness of the treatment. The results from JCOG1109 study suggest using docetaxel-cisplatin-capecitabine (DCX) or docetaxel-cisplatin-5-fluorouracil (DCF) NAC to achieve optimal effectiveness [4, 5].

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Since 2018, we have applied DCX/DCF NAC in the treatment of ESCC at our hospital. Minimally invasive esophagectomy (MIE) has been performed 2–8 weeks after NAC completion. However, many patients returned to the hospital for surgery late after NAC for personal reasons as well as COVID-19 outbreaks. In two studies, JCOG9907 and JCOG1109 [6, 7], esophagectomy was performed within 5 weeks after NAC. Although there are some studies evaluating the effect of time to surgery (TTS) after NAC on the effectiveness of multimodal therapies [8–10], no study assesses the impact of TTS after NAC for ESCC. After NAC, patients need time to recover, but delaying surgery too long can result in cancer recurrence and reduce the treatment effectiveness. We therefore conducted this study to evaluate the effect of TTS after NAC in the treatment of ESCC.

Methods

Patient Recruitment

This was a retrospective assessment from a prospective study. We recruited patients who had received radical MIE following a DCX/DCF NAC for ESCC at the Department of Digestive Surgery of a referral hospital between August 2018 and September 2021. The study was approved by the Ethics Committee of University of Medicine and Pharmacy at Ho Chi Minh City. All procedures were in accordance with the Helsinki Declaration revised in 2008.

Patients were diagnosed using contrast esophagogastrography, esophagogastroduodenoscopy, and computed tomography (CT) of the neck, thorax, and abdomen. An esophageal endoscopic ultrasound was performed if the tumor was suspected as cT1. Magnetic resonance imaging and/or positron emission tomography were performed to examine undecided metastases.

Inclusion criteria were (1) ESCC staged $cT_{2\text{-}3}N_0M_0$ or $cT_{1\text{-}3}N_{1\text{-}3}M_0$ (according to the 8th edition of American Joint Committee on Cancer [AJCC] staging) [11], (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 [12], and (3) undergoing a radical MIE after NAC. Exclusion criteria included (1) white cell count of < 4000/ml, (2) hemoglobin of < 90 g/l, (3) platelet count of < 100,000/ml, (4) reduced respiratory function (forced expiratory volume in 1 s [FEV1] of < 1.2L, FEV1% of < 50%, or diffusing capacity for carbon monoxide [DLCO] of < 50%), (5) abnormal cardiac function (abnormal electrocardiogram and/or left ventricular ejection fraction of < 50%), (6) renal impairment (serum creatinine of > 1.5 mg/dL), (7) abnormal liver function (total bilirubin of > 1.2 mg/dL, aspartate aminotransaminase [AST] or alanine aminotransaminase [ALT] of > 1.5 × upper level of normal), (8) pregnancy or breast-feeding, (9) concomitant malignancy, and (10) tumors that were intraoperatively evaluated as unresectable.

Neoadjuvant Chemotherapy

Patients underwent 3–6 chemotherapy cycles of DCX or DCF regimen. The DCX regimen contained docetaxel (60–70 mg/m^2, day 1), cisplatin (60–70 mg/m^2, day 1), and capecitabine (2000 mg/m^2, days 1–14) every 3 to 4 weeks. Those who had severe dysphagia received DCF regimen in which capecitabine was replaced by 5-FU (400 mg/m^2, days 1–5). After completing three cycles, CT scan was performed to evaluate whether the tumor was resectable. Radical MIE could be performed if the largest diameter of the tumor was < 5 cm and there was a boundary between the tumor and surrounding tissues. If the tumor was evaluated as unresectable, more cycles of NAC were required.

Surgical Techniques

MIE was performed at least 2 weeks after NAC completion. The esophagus was resected by the three-hole approach (McKeown's esophagectomy). Two- (thoracic and abdominal) or three-field (cervical, thoracic, and abdominal) lymphadenectomy was considered intraoperatively. The thoracic esophagus was mobilized, and mediastinal lymphadenectomy was performed by the right thoracoscopic approach, with or without robotic assistance. Total mediastinal lymph node dissection was performed if possible [13]. When the superior mediastinum could not be approached, extended or standard mediastinal lymphadenectomy was the alternative option [13]. Gastric mobilization and abdominal lymphadenectomy were performed by laparoscopic approach. The gastric conduit was anastomosed with the cervical esophageal stump through a posterior mediastinal or substernal route.

Outcome's Assessment

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 of the National Cancer Institute. Complete response (CR) after neoadjuvant was determined as the disappearance of tumor on postoperative pathology (pCR). Partial response (PR) was defined as a ≥ 30% reduction in the longest diameter of the primary tumor on CT [14]. Progressive disease (PD) was defined as a ≥ 20% increase in this diameter [14]. When the tumor did not meet the criteria for PR and PD, stable disease (SD) was defined [14]. Postoperative complications were graded following the extended Clavien-Dindo classification [15]. Overall survival (OS) was the time from the initiation of NAC to the date of death or the last follow-up for survivals. Progression-free survival (PFS) was the time from the

initiation of NAC to the date of the first detectable recurrence or metastasis, the date of death if no recurrence or metastasis was detected, or the last follow-up for survivals without any recurrence or metastasis.

The TTS was calculated from the end of the last cycle of the NAC to the date of esophagectomy. This variable was divided into three groups: ≤ 41 days (< 6 weeks), 42–55 days (6–8 weeks), and ≥ 56 days (≥ 8 weeks). The categorization was based on several considerations: (i) with the availability of the data, we chose to have as large groups as possible to maintain an adequate sample size for each group and to have enough statistical power, (ii) the medial group was chosen from 6 to 8 weeks which is corresponding with the real clinical practice, and (iii) the cutoffs were in accordance with the analysis taking into account the non-linear effect of time to surgery on the risk of mortality or disease progression.

Statistical Analysis

Summary statistics were mean ± standard deviation and range for continuous variables and the number of patients and percentage for categorical variables. Kruskal–Wallis test and Fisher's exact test were used to compare continuous and categorical variables in different groups of TTS. OS and PFS were summarized using the Kaplan–Meier method and were visualized by the Kaplan–Meier curves by the three groups of TTS. Cox proportional hazard model was used to evaluate factors associated with the survival outcomes. First, we assessed the relationship of TTS as a continuous variable with OS and PFS; the non-linear effect was evaluated using restricted cubic splines with five knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. Then, uni- and multivariable Cox models were used to evaluate factors associated with OS and PFS. In this analysis, TTS was categorized into three groups as described above. All variables with significant association ($p < 0.05$) in univariable models were included in the multivariable models. Results from the models were reported by hazard ratio (HR) and the corresponding 95% confidence interval (CI) and p value. All analyses were performed using the R statistical software version 4.1.3.

Results

From August 2018 to September 2021, 120 patients with clinically resectable ESCC received 3–6 cycles of NAC with DCX or DCF regimen. Ten patients (8.3%) had operatively unresectable tumors, 11 (9.2%) received a palliative esophagectomy because of an invasive and/or metastatic malignancy, and two (1.7%) had severe adhesion in the right pleural cavity and undertook transhiatal esophagectomy. Finally, 97 patients who underwent the radical MIE after NAC were included in this study. Min, first quartile, median, third quartile, and max TTS were 16, 38, 49, 62, and 135 days, respectively. There were 33 patients (34%) in group 1 (16–41 days), 29 patients (29.9%) in group 2 (42–55 days), and 35 patients (36.1%) in group 3 (56–135 days).

Patients' Characteristics

Mean age was 59.6 years. Men were predominant (95 patients, 97.9%). The majority of the tumors were located in the middle (47.4%) or lower esophagus (48.5%). The three groups were similar in terms of age, sex, body mass index (BMI), ECOG PS score, comorbidities, and tumor features. Most of the patients received three (61.9%) or six (32%) cycles of NAC. The number of NAC cycles was different between groups: the more cycles of NAC received, the longer TTS (Table 1).

Toxicity and Response

Most NAC-related toxicities were observed in grade I, including leukopenia (12.4%), neutropenia (8.2%), anemia (50.5%), thrombocytopenia (28.9%), increased AST (9.3%), increased ALT (8.2%), and renal toxicity (3.1%). Grade-II toxicities were found in 16 cases, including neutropenia (4 patients, 4.1%) and anemia (12 patients, 12.4%). Only one patient experienced grade-III toxicity of anemia. No grade-IV toxicity was observed (Table 2). In general, longer TTS groups had higher rate of more severe toxicity of leukopenia, neutropenia, and anemia, which might be due to the more cycles of NAC received. However, group 2 (TTS of 42–55 days) had a higher rate of grade-I thrombocytopenia, increased AST, and increased ALT than the other groups. Regarding pathologic tumor response, 18.6% of all patients achieved pCR, 71.1% achieved PR, and 10.3% were evaluated as SD; no one had PD. Group 2 (TTS of 42–55 days) had the highest rate of pCR, whereas group 1 (TTS of 16–41 days) had the highest rate of SD; however, the difference was not significant.

Surgical Outcomes

Mean operating time seemed to be lower in the longer TTS groups, possibly due to the lower percentage of robot-assisted surgery (Table 3). Most patients (80.4%) received three-field lymphadenectomy, and most (86.6%) received total mediastinal lymphadenectomy. The level of lymph node dissection was similar between the three groups. The retrosternal route was applied in most patients (73.2%) and was similar in the three groups. Around half of all patients were categorized as stage I after NAC.

Table 1 Patient's characteristics

	All patients (*N* = 97)	16–41 d (*N* = 33)	42–55 d (*N* = 29)	56–135 d (*N* = 35)	*p* value
Age (years)	59.6 ± 6.8 (42–77)	60.3 ± 7.4 (47–77)	59.1 ± 7.2 (45–71)	59.4 ± 6.0 (42–73)	0.744
Sex, male	95 (97.9)	33 (100.0)	29 (100.0)	33 (94.3)	0.328
BMI (kg/m^2)	21.5 ± 2.7 (16–29)	21.5 ± 2.6 (16– 27)	21.5 ± 2.3 (17–26)	21.6 ± 3.2 (17–29)	0.972
Nutritional status					0.643
Underweight (BMI < 18.5)	16 (16.5)	6 (18.2)	3 (10.3)	7 (20.0)	
Normal weight (BMI: 18.5–24.9)	69 (71.1)	24 (72.7)	23 (79.3)	22 (62.9)	
Overweight (BMI ≥ 25)	12 (12.4)	3 (9.1)	3 (10.3)	6 (17.1)	
ECOG PS score					0.248
0	69 (71.1)	21 (63.6)	24 (82.8)	24 (68.6)	
1	28 (28.9)	12 (36.4)	5 (17.2)	11 (31.4)	
Hypertension	14 (14.4)	4 (12.1)	5 (17.2)	5 (14.3)	0.935
Type II diabetes	8 (8.2)	3 (9.1)	1 (3.4)	4 (11.4)	0.584
Chronic lung disease	3 (3.1)	2 (6.1)	1 (3.4)	0 (0.0)	0.397
Chronic renal disease	1 (1.0)	0 (0.0)	0 (0.0)	1 (2.9)	> 0.999
Former/current smoker	67 (69.1)	25 (75.8)	19 (65.5)	23 (65.7)	0.603
Respiratory function					0.466
No limitation	70 (72.2)	26 (78.8)	22 (75.9)	22 (62.9)	
Mild limitation	25 (25.8)	7 (21.2)	6 (20.7)	12 (34.3)	
Moderate limitation	2 (2.1)	0 (0.0)	1 (3.4)	1 (2.9)	
Tumor location					0.639
Upper esophagus	4 (4.1)	2 (6.1)	1 (3.4)	1 (2.9)	
Middle esophagus	46 (47.4)	12 (36.4)	15 (51.7)	19 (54.3)	
Lower esophagus	47 (48.5)	19 (57.6)	13 (44.8)	15 (42.9)	
Differentiation status					0.942
Well-differentiated	7 (7.2)	3 (9.1)	2 (6.9)	2 (5.7)	
Moderately differentiated	82 (84.5)	27 (81.8)	24 (82.8)	31 (88.6)	
Poorly differentiated	8 (8.2)	3 (9.1)	3 (10.3)	2 (5.7)	
Cycle of NAC					0.010
3	60 (61.9)	27 (81.8)	18 (62.1)	15 (42.9)	
4	2 (2.1)	1 (3.0)	0 (0.0)	1 (2.9)	
5	4 (4.1)	0 (0.0)	2 (6.9)	2 (5.7)	
6	31 (32.0)	5 (15.2)	9 (31.0)	17 (48.6)	
Length of follow-up (months)	24 (8–51)	20 (8–49)	29 (9–51)	26 (11–46)	0.005

Summary statistics are mean ± standard deviation (range), *n* (%), and median (range)

BMI body mass index, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *NAC* neoadjuvant chemotherapy

There were 48 patients (49.5%) with any postoperative complication; most were classified as grade I (24.7%) or grade II (16.5%). Group 3 (TTS of 56–135 days) had the highest rate of any complication (57.1%) as well as ≥ -grade-IIIa complications (14.3%). Group 2 (TTS of 42–55 days) had no ≥ -grade-IIIa complications. However, there was no significant difference between the three groups regarding the rate and classification of postoperative complications (Table 3).

Survival Outcomes

Median follow-up time was 24 months (range: 8–51 months). Median follow-up time was highest in group 2 (TTS of 42–55 days) (29 months) and lowest in group 1 (TTS of 16–41 days) (20 months), possibly due to the difference in survival probability of the three groups. Group 2 had the best survivals and group 1 had the worst in terms of both OS (Fig. 1A) and PFS (Fig. 1B). In the analyses taking into

Table 2 Toxicity and response to neoadjuvant chemotherapy

	All patients (*N* = 97)	16–41 d (*N* = 33)	42–55 d (*N* = 29)	56–135 d (*N* = 35)	*p* value
Leukopenia					0.100
None	85 (87.6)	32 (97.0)	25 (86.2)	28 (80.0)	
Grade I	12 (12.4)	1 (3.0)	4 (13.8)	7 (20.0)	
Neutropenia					0.105
None	85 (87.6)	31 (93.9)	25 (86.2)	29 (82.9)	
Grade I	8 (8.2)	2 (6.1)	4 (13.8)	2 (5.7)	
Grade II	4 (4.1)	0 (0.0)	0 (0.0)	4 (11.4)	
Anemia					0.499
None	35 (36.1)	10 (30.3)	9 (31.0)	16 (45.7)	
Grade I	49 (50.5)	19 (57.6)	17 (58.6)	13 (37.1)	
Grade II	12 (12.4)	4 (12.1)	3 (10.3)	5 (14.3)	
Grade III	1 (1.0)	0 (0.0)	0 (0.0)	1 (2.9)	
Thrombocytopenia					0.041
None	69 (71.1)	22 (66.7)	17 (58.6)	30 (85.7)	
Grade I	28 (28.9)	11 (33.3)	12 (41.4)	5 (14.3)	
Increased AST					0.251
None	88 (90.7)	31 (93.9)	24 (82.8)	33 (94.3)	
Grade I	9 (9.3)	2 (6.1)	5 (17.2)	2 (5.7)	
Increased ALT					0.473
None	89 (91.8)	31 (93.9)	25 (86.2)	33 (94.3)	
Grade I	8 (8.2)	2 (6.1)	4 (13.8)	2 (5.7)	
Renal toxicity					0.773
None	94 (96.9)	32 (97.0)	29 (100.0)	33 (94.3)	
Grade I	3 (3.1)	1 (3.0)	0 (0.0)	2 (5.7)	
Pathologic tumor response					0.555
CR	18 (18.6)	5 (15.2)	8 (27.6)	5 (14.3)	
PR	69 (71.1)	23 (69.7)	19 (65.5)	27 (77.1)	
SD	10 (10.3)	5 (15.2)	2 (6.9)	3 (8.6)	
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Summary statistics are *n* (%)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

account the potential non-linear effect of TTS as a continuous variable (Fig. 2), the risk of death or disease progression was highest at 28–35 days, then decreased and was lowest at around 49–56 days, then gradually increased and was stable from days 70 to 77 onwards.

The Cox models confirmed the differences in survival outcomes between the three groups (Table 4). In the univariable analysis, group 1 (TTS of 16–41 days) significantly increased the risk of death and/or disease progression (HR [95% CI]: 3.36 [1.16–11.7] for OS and 3.27 [1.25–8.53] for PFS) compared to group 2 (TTS of 42–55 days). Group 3 (TTS of 56–135 days) also had higher risk of death and/or disease progression than group 2 but the magnitude of the effect was lower (HR [95% CI]: 1.83 [0.55–6.10] and 1.61 [0.58–4.45] respectively). We also found other factors significantly associated with the survival outcomes in the univariable analyses, including type II diabetes (worse outcomes), tumor stage after NAC (the more advanced stage, the worse outcomes), and pathologic tumor response (the worse response, the worse outcomes). In the multivariable analyses including four factors, all the associations remained but with weaker magnitude based on the HRs.

Discussion

This study evaluated the effect of the time gap between NAC completion and radical surgery on the survival outcomes of patients with ESCC. We found that this time gap should not be too short (< 42 days) or too long (> 56 days). A period of around 42–55 days after NAC completion might be optimal for performing a radical esophagectomy.

Table 3 Operative characteristics and complications

	All patients (*N* = 97)	16–41 d (*N* = 33)	42–55 d (*N* = 29)	56–135 d (*N* = 35)	*p* value
Operating time (mins)	427.4 ± 64.9 (260–600)	434.5 ± 60.2 (260–570)	432.9 ± 73.0 (350–600)	416.0 ± 62.2 (280–550)	0.433
Approach for thoracic phase					0.029
Thoracoscopic surgery	84 (86.6)	25 (75.8)	25 (86.2)	34 (97.1)	
Robot-assisted surgery	13 (13.4)	8 (24.2)	4 (13.8)	1 (2.9)	
Approach for abdominal phase					0.678
Laparoscopic surgery	92 (94.8)	31 (93.9)	27 (93.1)	34 (97.1)	
Open surgery	4 (4.1)	2 (6.1)	1 (3.4)	1 (2.9)	
Robot-assisted surgery	1 (1.0)	0 (0.0)	1 (3.4)	0 (0.0)	
Level of lymphadenectomy					0.692
Two-field	19 (19.6)	5 (15.2)	7 (24.1)	7 (20.0)	
Three-field	78 (80.4)	28 (84.8)	22 (75.9)	28 (80.0)	
Level of mediastinal lymphadenectomy					0.123
Standard	1 (1.0)	0 (0.0)	0 (0.0)	1 (2.9)	
Extended	12 (12.4)	7 (21.2)	1 (3.4)	4 (11.4)	
Total	84 (86.6)	26 (78.8)	28 (96.6)	30 (85.7)	
Route of reconstruction					0.919
Posterior mediastinal route	26 (26.8)	8 (24.2)	8 (27.6)	10 (28.6)	
Retrosternal route	71 (73.2)	25 (75.8)	21 (72.4)	25 (71.4)	
Tumor stage after NAC (ypTNM)					0.917
I	49 (50.5)	14 (42.4)	17 (58.6)	18 (51.4)	
II	9 (9.3)	2 (6.1)	3 (10.3)	4 (11.4)	
IIIA	17 (17.5)	7 (21.2)	4 (13.8)	6 (17.1)	
IIIB	15 (15.5)	7 (21.2)	3 (10.3)	5 (14.3)	
IVA	7 (7.2)	3 (9.1)	2 (6.9)	2 (5.7)	
Any complication	48 (49.5)	15 (45.5)	13 (44.8)	20 (57.1)	0.547
Clavien-Dindo classification					0.410
None	49 (50.5)	18 (54.5)	16 (55.2)	15 (42.9)	
Grade I	24 (24.7)	5 (15.2)	8 (27.6)	11 (31.4)	
Grade II	16 (16.5)	7 (21.2)	5 (17.2)	4 (11.4)	
Grade IIIa	6 (6.2)	2 (6.1)	0 (0.0)	4 (11.4)	
Grade IIIb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Grade IVa	2 (2.1)	1 (3.0)	0 (0.0)	1 (2.9)	
Grade IVb	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Grade V	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Summary statistics are mean ± standard deviation (range) and n (%)

Neoadjuvant therapy followed by esophagectomy is the standard treatment for locally advanced ESCC [3, 16, 17]. It enables downstaging of the tumor and eliminates micrometastases, thereby increasing the possibility of radical esophagectomy and the survival rate. Among neoadjuvant therapy approaches, chemoradiotherapy is preferred to chemotherapy because of higher response rates compared to chemotherapy [18]. Many studies have been conducted to evaluate the safety, efficacy, and optimal use of neoadjuvant chemoradiotherapy in the treatment of ESCC. However, the findings of JCOG1109 study suggested a considerable advantage of NAC with DCF followed by esophagectomy [5]. In NAC studies, esophagectomy was performed 4–8 weeks after chemotherapy [6, 7, 19]. Many studies have been conducted to assess the impact of extending the time between neoadjuvant chemoradiotherapy and esophagectomy [8–10]. However, to our knowledge, no similar study for NAC has been undertaken. Delaying surgery after NAC allows patients to recover from the side effects of the drugs and improve their nutrition. However, prolonging the time between chemotherapy and surgery raises concerns about tumor progression, which has a negative impact on

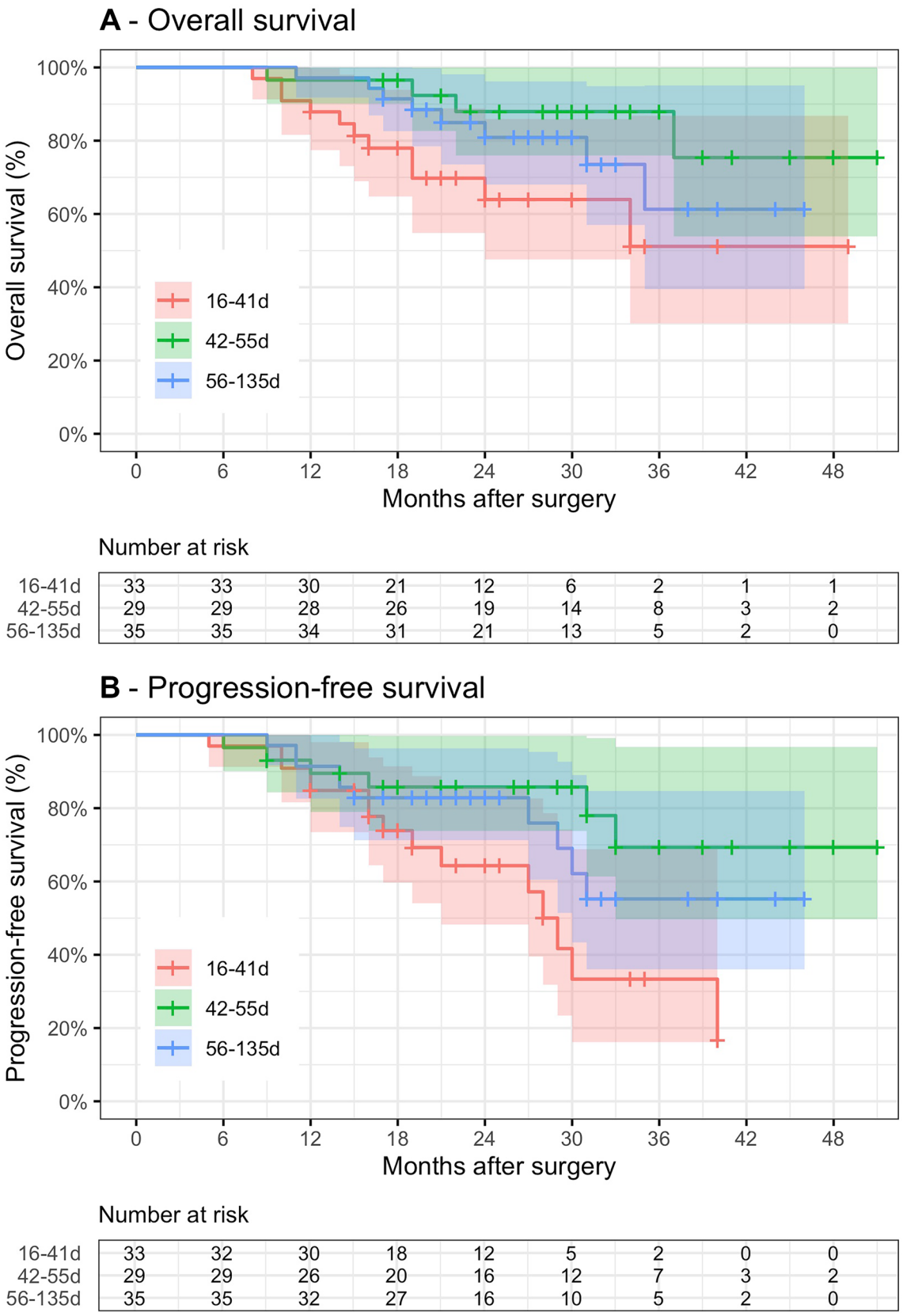
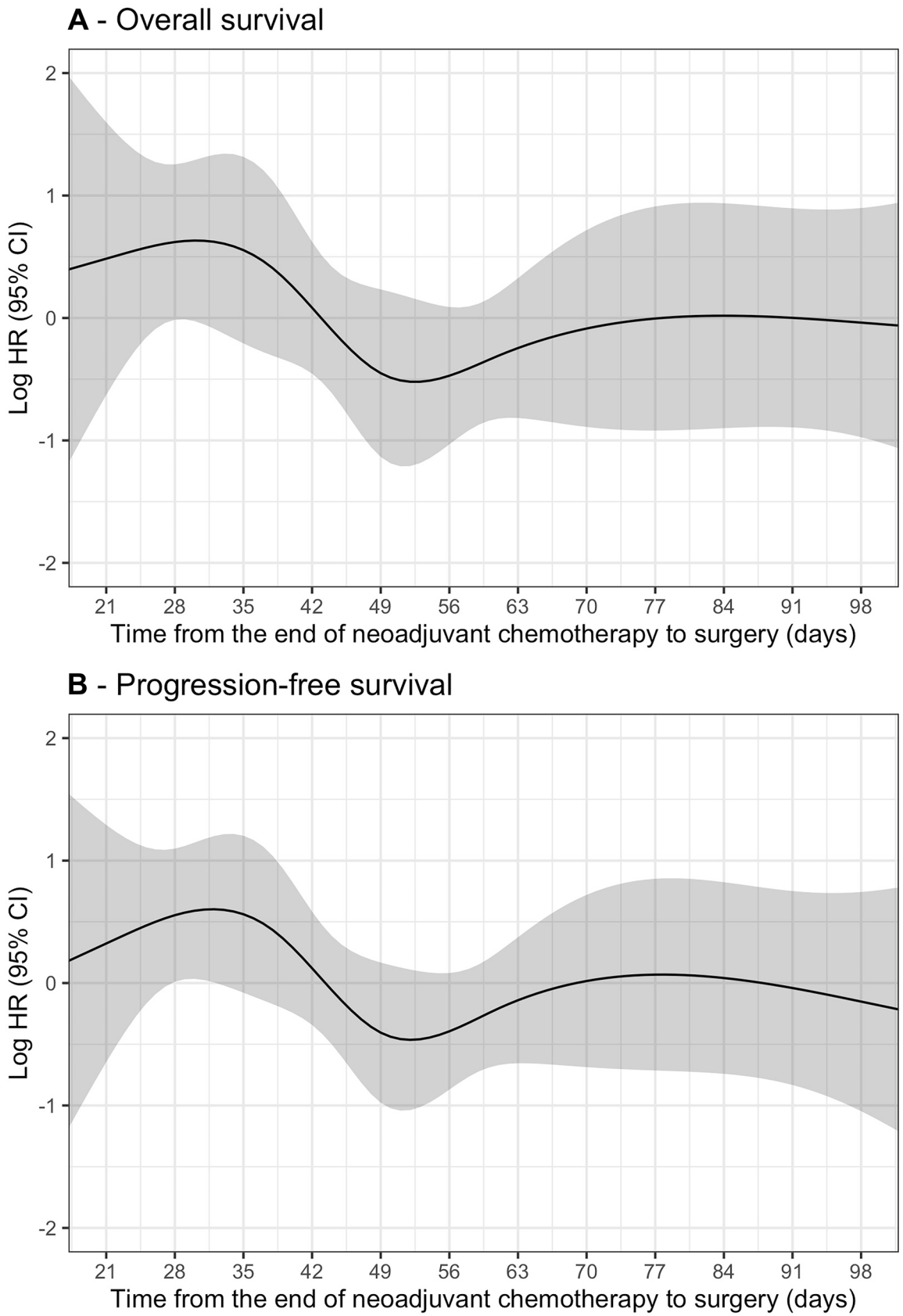


Fig. 1 Survivals by groups of time from the end of neoadjuvant therapy to surgery**.** Colored lines are the Kaplan–Meier estimate and colored regions are the 95% confidence interval for overall survival (**A**) and progression-free survival (**B**)


A - Overall survival
Log HR (95% CI)
2
1
0
-1
-2
21
28
35
42
49
56
63
70
77
84
91
98
Time from the end of neoadjuvant chemotherapy to surgery (days)
B - Progression-free survival
Log HR (95% CI)
2
1
0
-1
-2
21
28
35
42
49
56
63
70
77
84
91
98
Time from the end of neoadjuvant chemotherapy to surgery (days)

◂**Fig. 2** Association between survivals and time from the end of neoadjuvant chemotherapy to surgery using restricted cubic splines. Black lines are the log HR and grey regions are the 95% CI estimated from univariable Cox proportional hazard models for OS (**A**) and PFS (**B**) where the non-linear effect of TTS was investigated using restricted cubic splines with five knots. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTS, time to surgery

the treatment. Early surgery on patients after chemotherapy, on the other hand, is preferred because chemotherapy does not cause as much fibrosis and inflammation as chemoradiotherapy.

According to our study, diabetes mellitus was a strong risk factor for decreased OS and DFS. This finding contradicted the study results of Liu et al. [20], who suggested

Table 4 Univariable and multivariable analyses for overall survival and progression-free survival using a Cox proportional hazards model

	OS (univariable analysis)		OS (multivariable analysis)		PFS (univariable analysis)		PFS (multivariable analysis)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	1.00 (0.94–1.07)	0.983			0.98 (0.93–1.04)	0.538		
Nutritional status								
Underweight	0.40 (0.09–1.72)	0.217			0.56 (0.20–1.63)	0.289		
Normal weight	1				1			
Overweight	0.95 (0.28–3.24)	0.940			0.60 (0.18–2.02)	0.413		
ECOG PS score								
0	1				1			
1	0.50 (0.15–1.72)	0.274			0.93 (0.37–2.34)	0.883		
Hypertension	1.71 (0.64–4.63)	0.287			1.68 (0.69–4.10)	0.254		
Type II diabetes	**5.25 (1.87–14.7)**	**0.002**	**4.63 (1.53–14.0)**	**0.007**	**3.57 (1.45–8.81)**	**0.006**	**3.78 (1.40–10.2)**	**0.009**
Former/current smoker	0.86 (0.37–1.98)	0.716			0.98 (0.47–2.04)	0.951		
Mild/moderate limitation of respiratory function	0.80 (0.29–2.17)	0.659			1.02 (0.44–2.40)	0.955		
Tumor location								
Upper esophagus	1.17 (0.15–9.06)	0.883			1.26 (0.29–5.50)	0.757		
Middle esophagus	1				1			
Lower esophagus	1.11 (0.48–2.57)	0.808			0.85 (0.41–1.78)	0.672		
Differentiation status								
Well-differentiated	0.52 (0.07–3.91)	0.529			0.30 (0.04–2.17)	0.231		
Moderately-differentiated	1				1			
Poorly-differentiated	0.37 (0.05–2.80)	0.338			0.27 (0.04–2.01)	0.202		
Cycle of NAC								
3–4	1				1			
5–6	0.85 (0.36–2.00)	0.703			0.69 (0.32–1.50)	0.344		
Approach for thoracic phase								
Thoracoscopic surgery	1				1			
Robot-assisted surgery	1.89 (0.69–5.17)	0.213			1.61 (0.66–3.94)	0.298		
Level of lymphadenectomy								
Two-field	1				1			
Three-field	1.17 (0.39–3.49)	0.778			1.81 (0.63–5.18)	0.272		
Level of mediastinal lymphadenectomy								
Standard	1				1			
Extended/total	0.95 (0.28–3.20)	0.930			0.65 (0.20–2.14)	0.479		
Route of reconstruction								
Posterior mediastinal route	1				1			
Retrosternal route	0.85 (0.34–2.14)	0.726			1.29 (0.57–2.90)	0.536		
Tumor stage after NAC (ypTNM)								
I	**1**		**1**		**1**		**1**	
II	**3.57 (1.04–12.3)**	**0.044**	**1.68 (0.43–6.55)**	**0.453**	**2.98 (1.03–8.65)**	**0.044**	**2.37 (0.69–8.19)**	**0.173**

Table 4 (continued)

	OS (univariable analysis)		OS (multivariable analysis)		PFS (univariable analysis)		PFS (multivariable analysis)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
IIIA	**2.05 (0.60–7.05)**	**0.252**	**1.14 (0.31–4.22)**	**0.840**	**2.04 (0.75–5.55)**	**0.163**	**1.38 (0.44–4.35)**	**0.586**
IIIB	**3.88 (1.30–11.6)**	**0.015**	**1.17 (0.30–4.60)**	**0.824**	**2.77 (1.07–7.17)**	**0.036**	**1.76 (0.53–5.83)**	**0.358**
IVA	**3.37 (0.68–16.6)**	**0.135**	**1.79 (0.30–10.5)**	**0.522**	**2.14 (0.47–9.86)**	**0.327**	**1.84 (0.35–9.74)**	**0.474**
Pathologic tumor response								
CR	**1**		**1**		**1**		**1**	
PR	**3.66 (0.48–27.9)**	**0.211**	**2.36 (0.28–20.3)**	**0.433**	**1.07 (0.36–3.15)**	**0.908**	**0.54 (0.15–1.94)**	**0.346**
SD	**33.6 (4.14–273)**	**0.001**	**18.6 (1.70–203)**	**0.017**	**5.19 (1.55–17.4)**	**0.008**	**2.05 (0.43–9.85)**	**0.370**
Time from the end of NAC to surgery								
16–41 d	**3.36 (1.16–11.7)**	**0.027**	**2.29 (0.69–7.59)**	**0.177**	**3.27 (1.25–8.53)**	**0.016**	**2.65 (0.95–7.39)**	**0.063**
42–55 d	**1**				**1**		**1**	
56–135 d	**1.83 (0.55–6.10)**	**0.325**	**1.18 (0.33–4.21)**	**0.799**	**1.61 (0.58–4.45)**	**0.357**	**1.66 (0.57–4.84)**	**0.350**

Factors in bold face are those with significant association with OS and DFS in the univariable analysis. They are included in the multivariable analysis using Cox proportional hazard model

BMI body mass index, *CI* confidence interval, *CR* complete response, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *HR* hazard ratio, *NAC* neoadjuvant chemotherapy, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *SD* stable disease, *PD* progressive disease

that diabetes mellitus was a protective factor for esophageal cancer. Moreover, in a study by Okamura et al. [21], diabetic patients with inadequate glycemic control were identified as a risk factor that poorly impacted the prognosis of patients with esophageal cancer after curative esophagectomy. The authors also provided evidence to explain the favorable metabolism of cancer cells in diabetic patients. Meanwhile, a meta-analysis by Zheng et al. [22] found no association between diabetes mellitus and the prognosis of patients with esophageal cancer. Our study showed that SD after NAC had a poorer effect on OS and DFS than pCR. This finding was consistent with the results of some previous studies. Tiesi et al. [23] found that non-responders had lower long-term survival rates in patients receiving NAC. Meanwhile, Al-Kaabi et al. [24] reported that incomplete responders had a poorer 5-year survival rate than complete responders.

The study found that patients with TTS from 6 to 8 weeks seemed to have a lower rate of severe postoperative complications (Clavien-Dindo classification ≥ grade IIIa) than those with TTS > 8 weeks or < 6 weeks. A meta-analysis on the effect of TTS after neoadjuvant chemoradiotherapy for esophageal cancer showed that a > 7–8 weeks delay in surgery significantly increased perioperative mortality [8]. Theoretically, radiation therapy causes more local edema, inflammation, and fibrosis than chemotherapy. Late toxicity of radiation also has a more severe impact on patients. Chemotherapy also causes systemic adverse effects, edema, and fibrosis to a certain extent. Wang et al. [25] found that early surgery (within 21 days) increased the incidence of lymphatic leakage in patients receiving NAC for gastric cancer. Therefore, although the results were inconclusive, we believed that surgery should be considered neither too soon nor too late after NAC.

In our study, patients in the group with TTS of 6–8 weeks had the highest OS and PFS. In a meta-analysis, Qin et al. [8] suggested that a > 7–8 weeks delay in surgery after neoadjuvant chemoradiotherapy for esophageal cancer significantly reduced OS. When studying the effect of TTS after NAC on gastric cancer patients, Wang et al. [25] found that delayed surgery after chemotherapy was an independent risk factor for decreased OS and PFS. Therefore, avoiding performing esophagectomy too soon or late after NAC is reasonable.

The study has severe limitations. First, this is an observational study which leads to some imbalances of the three groups. Although we tried to minimize these imbalances by multivariable analyses, potential bias could not be ruled out completely. Only a randomized controlled design could eliminate this limitation, but it might not be feasible in practice. Second, the sample size was relatively small, and the separation of TTS into three groups was arbitrary and based on the availability of the data. However, to our knowledge, this is the first study on the effect of TTS on the survival outcomes, and it might provide information for further studies. Third, patients who dropped out during or after NAC were not included which could bias the results.

In conclusion, time from NAC completion to radical esophagectomy should be considered in the treatment of patients with ESCC. We suggest the optimal TTS after NAC is 6–8 weeks. The surgery should not be performed too early, before 6 weeks after NAC. More studies with larger sample size are required to confirm our findings.

Author Contribution All authors contributed to the study conception and design. Material preparation and data collection were performed by Nguyen Vo Vinh Loc and Lam Viet Trung. Data analysis was performed by Nguyen Vo Vinh Loc and Nguyen Lam Vuong. The first draft of the manuscript was written by Nguyen Vo Vinh Loc, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability The data that support the findings of this study are available from the corresponding author, NLV, upon reasonable request.

Declarations

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.

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

Conflict of Interest The authors declare no competing interests.

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