BMC Gastroenterology

RESEARCH

Open Access

Prolonged time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery is related to unimproved pathological response and poor survival prognosis for esophageal squamous cell carcinoma

Guanzhi Ye[1†], Gaojian Pan[1†], Xiaolei Zhu[1†], Hongming Liu[1], Ning Li[1], Guojun Geng[1*] and Jie Jiang[1*]

Abstract

Background The optimal time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery for esophageal squamous cell carcinoma remains unknown. This research aims to assess the impact of time interval on pathological response and survival prognosis.

Methods Esophageal squamous cell carcinoma patients receiving neoadjuvant immunotherapy combined with chemotherapy followed by esophagectomy between January 2021 and March 2024 were included. The pathological response, survival outcomes, surgical outcomes, and postoperative complications were compared between the timely surgery group (time interval ≤ 6 weeks) and the delayed surgery group (time interval > 6 weeks).

Results A total of 133 cases were included in this research. The pathological complete response (pCR) rates in timely surgery group and delayed surgery group were 23.4% and 12.8% ($P=0.167$). There were no statistically significant differences between the two groups in terms of anastomotic fistula ($P=0.321$), pulmonary infection ($P=0.427$), chylothorax ($P=0.502$), multiple organ dysfunction syndrome ($P=0.206$), operation time ($P=0.359$), blood loss ($P=0.093$), number of resected lymph nodes ($P=0.091$), hospital stay ($P=0.167$), and R0 resection rate ($P=0.523$). The 3-year overall survival (OS) rates were 77.5% in timely surgery group, and 63.5% in delayed surgery group ($P=0.046$). The 3-year disease-free survival (DFS) rates were 59.1% and 38.4% in the two groups, respectively (P = 0.037). Additionally, multivariate Cox regression analyses indicated that the time interval from immunochemotherapy to surgery was independent prognostic factor for both OS ($P=0.049$) and DFS ($P=0.025$).

Conclusions Prolonged time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery did not improve pCR rate and was associated with worse OS and DFS in esophageal squamous cell carcinoma.

†Guanzhi Ye, Gaojian Pan and Xiaolei Zhu contributed equally to this work.

*Correspondence:
Guojun Geng
ggj622@126.com
Jie Jiang
jiangjie06@126.com

Keywords Neoadjuvant therapy, Immunotherapy, Chemotherapy, Esophageal squamous cell carcinoma, Time interval

Introduction

Esophageal carcinoma is a malignant tumor with high morbidity and mortality worldwide, causing a huge burden on human health [1]. Esophageal squamous cell carcinoma is the predominant pathological type of esophageal carcinoma, and is more common in Asia [2]. Due to the insidious symptoms of early esophageal carcinoma, many patients are diagnosed with tumor at the late stage or locally advanced stage, even losing the opportunity for surgery. According to guidelines, neoadjuvant therapy followed by esophagectomy has recommended as the standard treatment strategy for locally advanced esophageal squamous cell carcinoma [3], which helps to reduce tumor volume, control micrometastasis of tumor, improve complete surgical resection rate and survival prognosis.

Immunotherapy combined with chemotherapy is an important means of neoadjuvant therapy for esophageal squamous cell carcinoma, the safety and efficacy of which have been reported in numerous clinical researches. It has been revealed to have manageable toxic and side effect, downstaging tumor, increasing complete resection rate and pathological complete response (pCR) rate [4, 5]. The local changes in the tumor lesions, systemic inflammatory response of body, and the patient's physical condition after neoadjuvant therapy can all influence the surgical outcomes. Notably, these factors may change over time. Therefore, the choice of surgical timing is particularly important for optimizing the effectiveness of tumor treatment. At present, there is no consensus on the optimal timing of surgery after neoadjuvant therapy for esophageal squamous cell carcinoma, and different studies have drawn inconsistent conclusions. Liu et al. [6] and Lee et al. [7] reported that a prolonged time interval from neoadjuvant chemoradiotherapy to surgery is related to a higher pCR rate, but it is not associated with survival prognosis. However, Nilsson et al. [8] pointed out in their clinical trial that prolonged interval between neoadjuvant chemoradiotherapy and surgery does not improve pCR rate, moreover, it is related with a trend towards poorer survival outcomes. Immunotherapy represented by PD-1/PD-L1 inhibitors blocks the interaction between PD-1 and PD-L1, relieving the inhibition of T cells and restoring their anti-tumor ability, whose tumor treatment mechanism is different from radiotherapy. Currently, the optimal surgical timing for neoadjuvant immunotherapy combined with chemotherapy has not been determined, despite many clinical trials on esophageal squamous cell carcinoma chose a time window of 4–6 weeks after the last neoadjuvant therapy for surgery [9–11]. In addition, there have been rare researches about the impact of prolonged time interval from neoadjuvant immunochemotherapy to surgery on tumor pathological response and survival prognosis in esophageal squamous cell carcinoma.

This study aimed to evaluate the impact of delayed surgery after immunotherapy combined with chemotherapy on pathological response and survival outcomes by comparing the clinicopathological and prognostic characteristics of esophageal squamous cell carcinoma patients with time interval from neoadjuvant immunochemotherapy to surgery time shorter than 6 weeks and longer than 6 weeks. This study provided evidence for determining the optimal surgical timing after neoadjuvant immunotherapy combined with chemotherapy in clinical practice.

Materials and methods

Study population

This research retrospectively reviewed esophageal squamous cell carcinoma patients receiving neoadjuvant immunotherapy combined with chemotherapy followed by esophagectomy between January 2021 and March 2024 in the First Affiliated Hospital of Xiamen University. Patients were included in this research if they met the following criteria: (1) patients diagnosed with esophageal squamous cell carcinoma on the basis of pathological examination; (2) patients undergoing neoadjuvant immunotherapy combined with chemotherapy followed by esophagectomy and lymphadenectomy; (3) patients with complete clinicopathological and follow-up information. The exclusion criteria were as follows: (1) patients who had or previously had other malignant tumors at the time of diagnosis of esophageal squamous cell carcinoma; (2) patients who received anti-tumor therapeutic strategies other than neoadjuvant immunotherapy combined with chemotherapy. The cases were divided into two groups based on time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery: timely surgery group (time interval $\leq$ 6 weeks) and delayed surgery group (time interval > 6 weeks).

Neoadjuvant therapy regimen and surgical process

The neoadjuvant chemotherapy regimens included albumin-bound paclitaxel plus nedaplatin, albumin-bound paclitaxel plus cisplatin, and albumin-bound paclitaxel

plus carboplatin. The immunotherapy drugs included Camrelizumab, Sintilimab, Pembrolizumab, Tislelizumab, Toripalimab, Nivolumab, and Penpulimab. The detailed neoadjuvant therapy protocols and drug dosage were shown in Table S1. All enrolled esophageal squamous cell carcinoma patients underwent esophagectomy via minimally invasive three-incision McKeown operation procedures with standard two-field lymphadenectomy. The indication criteria for adjuvant therapy were as follows: (1) patients who have not reached pCR and (2) patients with cT3-4 or cN + stage.

Patients follow-up

We performed follow-up evaluations every three months for the first two years after esophagectomy, and every six months thereafter. Enhanced computed tomography scans of the neck, chest, and abdomen were performed for every patients at each outpatient visit. The follow-up endpoint was the date of death or August 15, 2024.

Treatment response and survival outcome assessment

The imaging evaluation of tumor treatment response was performed by the enhanced computed tomography scans and the imaging efficacy evaluation was based on the criteria for Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [12]. The American Joint Committee on Cancer tumor-node-metastasis staging criteria (eighth edition) was used to determine the pathological stage of esophageal squamous cell carcinoma. The pCR was defined as the absence of evidence of residual tumor cells by pathological examination. The major pathological response (MPR) was defined as residual tumor cells of less than 10%. Additionally, the overall survival (OS) was defined as the time interval from the date of surgery to death or the date of last follow-up, and the disease-free survival (DFS) was defined as the time interval from the date of surgery to the recurrence of tumor or death.

Statistical analysis

Statistical analyses were performed using R 4.3.2 version and SPSS 26.0 software (SPSS Inc, Chicago, IL, USA). The chi-square test or Fisher exact probability test was conducted to compare categorical variables. Continuous variables were presented as means ± standard deviation and compared via independent sample t-test. In addition, the Kaplan–Meier method with the log-rank test were used to evaluate OS and DFS. The factors related to OS and DFS were determined through univariate and multivariate Cox proportional hazards regression models. A P value less than 0.05 was considered statistically significant.

Results

Baseline clinicopathological characteristics of the study cohort

A total of 133 esophageal squamous cell carcinoma patients who underwent neoadjuvant immunotherapy combined with chemotherapy followed by esophagectomy were finally included in this research. There were 106 males and 27 females, and the median age at the first time of neoadjuvant therapy was 60 years ranging from 44–79 years. As shown in Table 1 and Fig. 1, the median time interval between neoadjuvant immunochemotherapy and surgery was 5.14 weeks (range: 2.14–11.71 weeks). Except for more patients with cT4 stage were found in delayed surgery group ($P=0.017$), there were no statistically significant differences in terms of sex ($P=0.364$), age ($P=0.107$), smoking history ($P=0.909$), hypertension ($P=0.716$), diabetes ($P=0.569$), coronary atherosclerosis ($P=0.249$), tumor location ($P=0.971$), cN stage ($P=0.574$), imaging response ($P=0.445$), neoadjuvant therapy cycles ($P=0.768$), neoadjuvant therapy regimen ($P=0.350$), adjuvant therapy ($P=0.688$), tumor size ($P=0.175$), grade ($P=0.374$), ypT stage ($P=0.734$), and ypN stage ($P=0.829$) between the timely surgery group and the delayed surgery group.

Pathological response assessment

In the entire cohort, there were 85 patients achieving partial response and 48 patients assessed as stable disease on the basis of imaging examination, with an objective response rate of 63.9%. Moreover, 53 people (39.8%) achieved MPR, of which 27 people (20.3%) achieved pCR in this research (Table 2). There were 7 (17.9%), 8 (20.5%), 10 (25.6%), and 14 (35.9%) patients achieving TRG0, TRG1, TRG2, and TRG3 pathological response in the delayed surgery group compared with 25 (26.6%), 13 (13.8%), 29 (30.9%), and 27 (28.7%) patients in the timely surgery group, respectively. In addition, the pCR rates were 23.4% and 12.8% in the timely surgery group and the delayed surgery group, respectively, without significant statistical difference ($P=0.167$). And the MPR rates were 40.4% and 38.5% in these two cohorts without significant statistical difference either ($P=0.833$) (Fig. 2).

Adverse reactions and surgical outcomes

As shown in Table 3, there were no statistically significant differences between the timely surgery group and the delayed surgery group in terms of anemia ($P=0.898$), leukopenia ($P=0.645$), thrombocytopenia ($P=0.664$), liver dysfunction ($P=0.590$), renal dysfunction ($P=0.431$),

Table 1 Baseline characteristics of esophageal squamous cell carcinoma patients receiving neoadjuvant immunotherapy combined with chemotherapy followed by esophagectomy

Variable	Total ($n=133$)	Timely surgery ($n=94$)	Delayed surgery ($n=39$)	*P* value
Sex				0.364
Male	106 (79.7%)	73 (77.7%)	33 (84.6%)	
Female	27 (20.3%)	21 (22.3%)	6 (15.4%)	
Age				0.107
≤ 60 years	69 (51.9%)	53 (56.4%)	16 (41.0%)	
> 60 years	64 (48.1%)	41 (43.6%)	23 (59.0%)	
Smoking history				0.929
No	69 (51.9%)	49 (52.1%)	20 (51.3%)	
Yes	64 (48.1%)	45 (47.9%)	19 (48.7%)	
Hypertension				0.716
No	103 (77.4%)	72 (76.6%)	31 (79.5%)	
Yes	30 (22.6%)	22 (23.4%)	8 (20.5%)	
Diabetes				0.569
No	127 (95.5%)	90 (95.7%)	37 (94.9%)	
Yes	6 (4.5%)	4 (4.3%)	2 (5.1%)	
Coronary atherosclerosis				0.249
No	124 (93.2)	89 (94.7%)	35 (89.7%)	
Yes	9 (6.8)	5 (5.3%)	4 (2.6%)	
Tumor location				0.971
Upper	19 (14.3%)	13 (13.8%)	6 (15.4%)	
Middle	80 (60.2%)	57 (60.6%)	23 (59.0%)	
Lower	34 (25.6)	24 (25.5%)	10 (25.6%)	
cT stage				0.017
T2	2 (1.5%)	2 (2.1%)	0 (0)	
T3	128 (96.2%)	92 (97.9%)	36 (92.3%)	
T4	3 (2.3%)	0 (0)	3 (7.7%)	
cN stage				0.574
N0	63 (47.4%)	46 (48.9%)	17 (43.6%)	
N +	70 (52.6%)	48 (51.1%)	22 (56.4%)	
Imaging response				0.445
Partial response	85 (63.9%)	62 (66.0%)	23 (59.0%)	
Stable disease	48 (36.1%)	32 (34.0%)	16 (41.0%)	
Neoadjuvant therapy cycles				0.768
Two	88 (66.2%)	64 (68.1%)	24 (61.5%)	
Three	39 (29.3%)	26 (27.6%)	13 (33.3%)	
Four	6 (4.5%)	4 (4.3%)	2 (5.1%)	
Neoadjuvant therapy regimen				0.350
Camrelizumab + chemotherapy	68 (51.1%)	47 (50.0%)	21 (53.8%)	
Sintilimab + chemotherapy	32 (24.1%)	26 (27.7%)	6 (15.4%)	
Pembrolizumab + chemotherapy	14 (10.5%)	8 (8.5%)	6 (15.4%)	
Tislelizumab + chemotherapy	14 (10.5%)	11 (11.7%)	3 (7.7%)	
Toripalimab + chemotherapy	2 (1.5%)	1 (1.1%)	1 (2.6%)	
Nivolumab + chemotherapy	2 (1.5%)	1 (1.1%)	1 (2.6%)	
Penpulimab + chemotherapy	1 (0.8%)	0 (0)	1 (2.6%)	
Adjuvant therapy				0.688
No	18 (13.5%)	12 (12.8%)	6 (15.4%)	
Yes	115 (86.5%)	82 (87.2%)	33 (84.6%)	

Table 1 (continued)

Variable	Total ($n=133$)	Timely surgery ($n=94$)	Delayed surgery ($n=39$)	*P* value
Tumor size				0.175
≤ 5 cm	125 (94.0%)	90 (95.7%)	35 (89.7%)	
> 5 cm	8 (6.0%)	4 (4.3%)	4 (10.3%)	
Grade				0.374
Highly	1 (0.8%)	1 (1.1%)	0 (0)	
Moderately	64 (48.1%)	48 (51.1%)	16 (41.0%)	
Poorly	26 (19.5%)	15 (16.0%)	11 (28.2%)	
Unknown	42 (31.6%)	30 (31.9%)	12 (30.8%)	
ypT stage				0.734
T0	30 (22.6%)	23 (24.5%)	7 (17.9%)	
T1	37 (27.8%)	27 (28.7%)	10 (25.6%)	
T2	20 (15.0%)	14 (14.9%)	6 (15.4%)	
T3	46 (34.6%)	30 (31.9%)	16 (41.0%)	
ypN stage				0.829
N0	94 (70.7%)	67 (71.3%)	27 (69.2%)	
N1	32 (24.1%)	23 (24.5%)	9 (23.1%)	
N2	4 (3.0%)	2 (2.1%)	2 (5.1%)	
N3	3 (2.3%)	2 (2.1%)	1 (2.6%)	

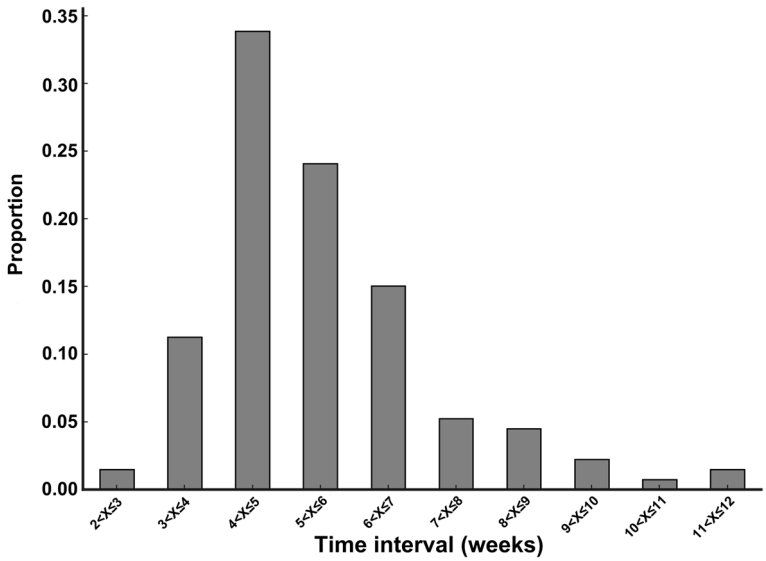

Fig. 1 Distribution histogram of time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery in esophageal squamous cell carcinoma

skin rash ($P=0.650$), and pneumonia ($P=0.150$). In addition, no statistically significant differences were found in terms of anastomotic fistula ($P=0.321$), pulmonary infection ($P=0.427$), chylothorax ($P=0.502$), and multiple organ dysfunction syndrome ($P=0.206$) between the two groups.

As shown in Table 4, there were no significant statistical differences between the timely surgery group and the delayed surgery group regarding operation time (309.04 ± 87.71 min vs. 296.92 ± 82.04 min, $P=0.359$), blood loss (149.68 ± 105.85 ml vs. 173.59 ± 159.08 ml, $P=0.093$), number of resected lymph nodes (25.01 ± 10.14 vs. 24.87 ± 7.23, $P=0.091$), and hospital stay (18.77 ± 11.95 days vs. 21.41 ± 6.96 days, $P=0.167$). Moreover, the R0 resection rates were 93.6% and 92.3% in the timely surgery group and the delayed surgery group, respectively, without statistically significant difference ($P=0.523$).

Table 2 The pathological response between timely surgery group and delayed surgery group in esophageal squamous cell carcinoma patients

Variable	Total ($n=133$)	Timely surgery ($n=94$)	Delayed surgery ($n=39$)	*P* value
TRG				0.503
0	32 (24.1%)	25 (26.6%)	7 (17.9%)	
1	21 (15.8%)	13 (13.8%)	8 (20.5%)	
2	39 (29.3%)	29 (30.9%)	10 (25.6%)	
3	41 (30.8%)	27 (28.7%)	14 (35.9%)	
pCR				0.167
No	106 (79.7%)	72 (76.6%)	34 (87.2%)	
Yes	27 (20.3%)	22 (23.4%)	5 (12.8%)	
MPR				0.833
No	80 (60.2%)	56 (59.6%)	24 (61.5%)	
Yes	53 (39.8%)	38 (40.4%)	15 (38.5%)	

TRG Tumor Response Grade, *pCR* pathological complete response, *MPR* major pathologic response

Factors related to survival prognosis

In the entire cohort, the median follow-up time of esophageal squamous cell cercinoma patients was 19 months (range: 2–47 months). As presented in Fig. 3, the 1-year, 2-year, and 3-year OS rates were 92.8%, 85.7%, and 77.5% in the timely surgery group, and 89.2%, 63.5%, and 63.5% in the delayed surgery group, respectively, with statistically significant differences ($P=0.046$). Additionally, The 1-year, 2-year, and 3-year DFS rates were 93.3%, 72.3%, and 59.1% in the timely surgery group, and 74.8%, 56.4%, and 38.4% in the delayed surgery group, respectively, also with statistically significant differences ($P=0.035$). Furthermore, we conducted subgroup analyses based on cN stage and tumor size (Fig. 4). In the cN + stage subgroup, patients in the delayed surgery group had significantly poorer overall survival prognosis compared to those in the timely surgery group ($P=0.035$). Additionally, delayed surgery significantly decreased OS ($P=0.040$) and DFS ($P=0.007$) in the subgroup of patients with tumor size larger than 5 cm.

We further performed univariate and multivariate Cox regression analyses to determine the independent prognostic factors for esophageal squamous cell carcinoma patients receiving neoadjuvant immunotherapy combined with chemotherrapy. As shown in Table 5, interval from neoadjuvant therapy to surgery ($P=0.049$) and ypN stage ($P=0.020$) were independent prognostic factors for OS. Moerover, interval from neoadjuvant therapy to surgery ($P=0.025$) and MPR status ($P=0.044$) were independent predictors for DFS.

We conducted additional analysis based on different cutoff values of time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery, namely 4-week, 5-week, 7-week, and 8-week. We observed similar trends in baseline clinicopathological characteristics, pathological response, adverse reactions, surgical outcomes, and survival outcomes as when the cutoff value was set at 6-week (Table S2-S9 and Figure S1).

Discussion

Neoadjuvant therapy has been recommended as the standard treatment for locally advanced esophageal squamous cell carcinoma, and its optimal strategy and specific details have always been the focus of clinical researches. Among numerous related issues, the optimal surgical timing after neoadjuvant therapy has not been well elucidated. There have been many studies reporting

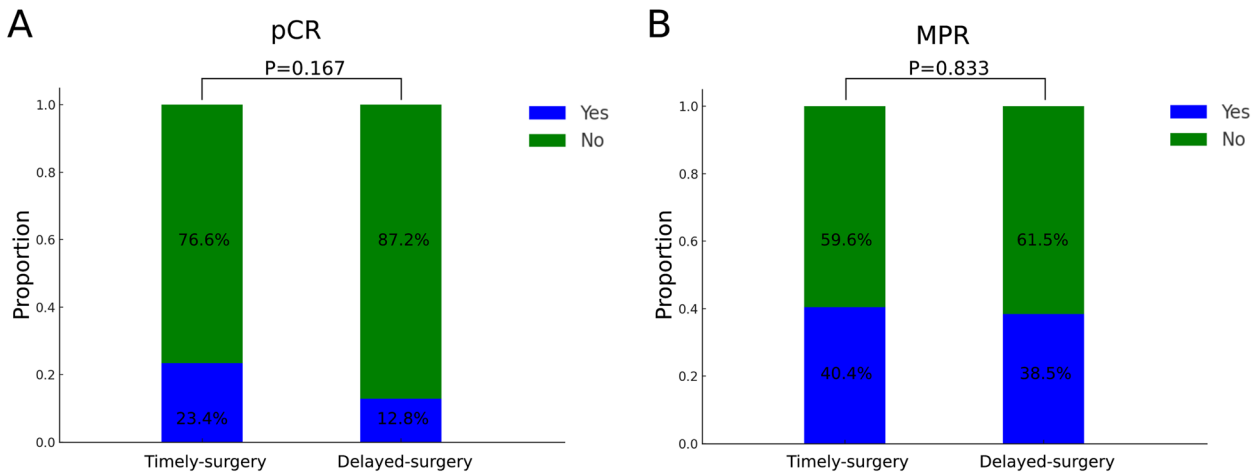

Fig. 2 The distribution condition of pathological complete response (**A**) and major pothalogical response (**B**) between the timely surgery group and the delayed surgery group

Table 3 Adverse reactions and postoperative complications between timely surgery group and delayed surgery group in esophageal squamous cell carcinoma patients

Variable	Total ($n=133$)	Timely surgery ($n=94$)	Delayed surgery ($n=39$)	*P* value
Adverse reactions during neoadjuvant therapy				
Anemia				0.898
No	110 (82.7%)	78 (83.0%)	32 (82.1%)	
Yes	23 (17.3%)	16 (17.0%)	7 (17.9%)	
Leukopenia				0.645
No	113 (85.0%)	79 (84.0%)	34 (87.2%)	
Yes	20 (15.0%)	15 (16.0%)	5 (12.8%)	
Thrombocytopenia				0.664
No	129 (97.0%)	91 (96.8%)	38 (97.4%)	
Yes	4 (3.0%)	3 (3.2%)	1 (2.6%)	
Liver dysfunction				0.590
No	122 (91.7%)	86 (91.5%)	36 (92.3%)	
Yes	11 (8.3%)	8 (8.5%)	3 (7.7%)	
Renal dysfunction				0.431
No	125 (94.0%)	89 (94.7%)	36 (92.3%)	
Yes	8 (6.0%)	5 (5.3%)	3 (7.7%)	
Skin rash				0.650
No	130 (97.7%)	92 (97.9%)	38 (97.4%)	
Yes	3 (2.3%)	2 (2.1%)	1 (2.6%)	
Pneumonia				0.150
No	128 (96.2%)	92 (97.9%)	36 (92.3%)	
Yes	5 (3.8%)	2 (2.1%)	3 (7.7%)	
Postoperative complications				
Anastomotic fistula				0.321
No	122 (91.7%)	85 (90.4%)	37 (94.9%)	
Yes	11 (8.3%)	9 (9.6%)	2 (5.1%)	
Pulmonary infection				0.427
No	111 (83.5%)	80 (85.1%)	31 (79.5%)	
Yes	22 (16.5%)	14 (14.9%)	8 (20.5%)	
Chylothorax				0.502
No	131 (98.5%)	93 (98.9%)	38 (97.4%)	
Yes	2 (1.5%)	1 (1.1%)	1 (2.6%)	
MODS				0.206
No	130 (97.7%)	93 (98.9%)	37 (94.9%)	
Yes	3 (2.3%)	1 (1.1%)	2 (5.1%)	

MODS multiple organ dysfunction syndrome

the impact of time interval between neoadjuvant chemoradiotherapy and surgery on the pathological response and survival prognosis in esophageal carcinoma, but the conclusions of these studies vary greatly. Some researches found that the time interval from neoadjuvant chemoradiotherapy to surgery is not associated with pCR rate or OS in esophageal carcinoma [13, 14]. Nilsson et al. [8] and Chiu et al. [15] even revealed that prolonged time interval does not improve pCR rate, and may indicate a worse survival prognosis. However, some studies reported that prolonged time interval is associated with a higher pCR rate, despite no improvement in survival prognosis is found [7, 16–18]. Immunotherapy combined with chemotherapy is an important neoadjuvant therapeutic strategy for esophageal squamous cell carcinoma with a tumor treatment mechanism different from chemoradiotherapy, the optimal surgical intervention timing after which has not been fully understood. Whether delayed surgery has an impact on tumor pathological response and survival outcomes remains unknown. Moreover, there are fewer researches clarifying this issue.

In this research, we found that there were no statistically significant differences in MPR rate and pCR rate between the delayed surgery group and the timely surgery group. However, it was worth noting that the pCR rate in the delayed surgery group was 12.8%, lower than that of 23.4% in the timely surgery group. In a study investigating the impact of time interval from neoadjuvant immunotherapy to surgery for esophageal squamous cell carcinoma, Yang et al. [19] revealed that the rate of pCR is 34.1% in the timely surgery group and 24.6% in the delayed surgery group, despite no statistically significant difference is found. The results of this study was consistent with our findings. However, Liu et al. [20] pointed out that the pCR rate in the long-interval group is slightly higher than that in the short-interval group without statistically significant difference for esophageal squamous cell carcinoma patients receiving neoadjuvant camrelizumab combined with chemotherapy. On the basis of previous literature and our research findings, we speculate that prolonged time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery is not beneficial for improving the pCR rate in esophageal squamous cell carcinoma. Considering that a longer time interval may pose a risk of local lesion progression, tumor patients should avoid delaying surgery as much as possible.

There were abundant evidences regarding the relationship between the timing of surgery after neoadjuvant chemoradiotherapy and survival outcomes. Many researchers believed that prolonged time interval from neoadjuvant chemoradiotherapy to surgery is not conducive to improving the survival prognosis of esophageal carcinoma patients [6, 8, 21]. However, there was also literature that proposed a different viewpoint. Ruol et al. [22] pointed out that delaying surgery up to 90 days can reduce recurrence of tumor, and may improve OS in thoracic esophageal squamous cell carcinoma patients

Table 4 Operative characteristics between timely surgery group and delayed surgery group in esophageal squamous cell carcinoma patients

Variable	Total ($n=133$)	Timely surgery ($n=94$)	Delayed surgery ($n=39$)	*P* value
Operation time (min)	305.49 ± 85.96	309.04 ± 87.71	296.92 ± 82.04	0.359
Blood loss (ml)	156.69 ± 123.69	149.68 ± 105.85	173.59 ± 159.08	0.093
Number of resected lymph nodes	24.97 ± 9.35	25.01 ± 10.14	24.87 ± 7.23	0.091
Hospital stay (day)	19.54 ± 10.77	18.77 ± 11.95	21.41 ± 6.96	0.167
R0 resection				0.523
No	9 (6.8%)	6 (6.4%)	3 (7.7%)	
Yes	124 (93.2%)	88 (93.6%)	36 (92.3%)	

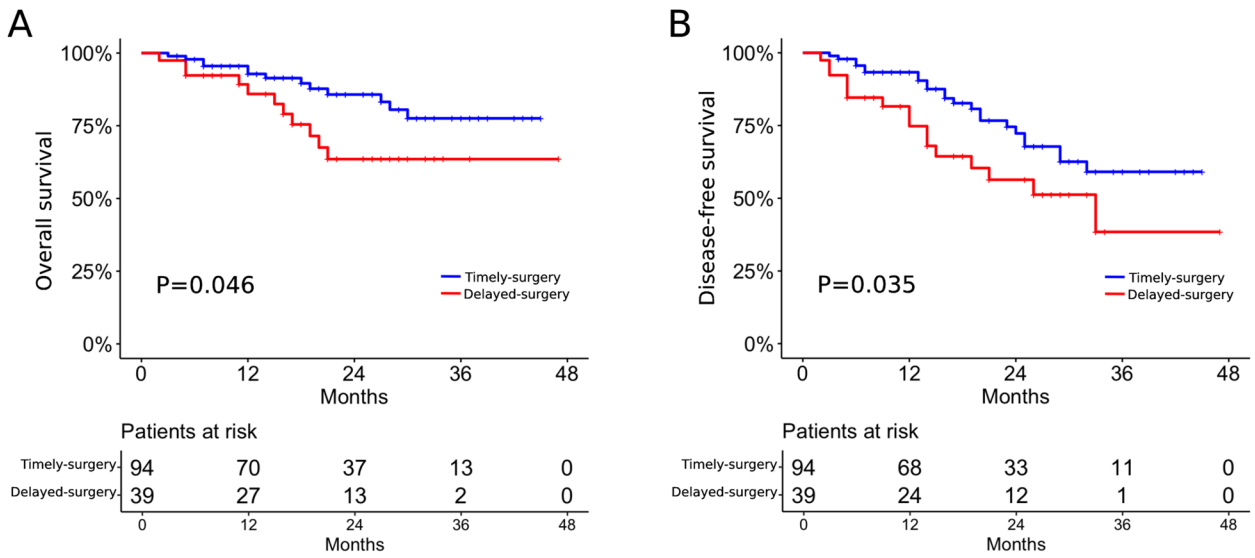

Fig. 3 Kaplan–Meier survival analysis of overall survival (**A**) and disease-free survival (**B**) between the timely surgery group and the delayed surgery group

with R0 resection surgery. At present, there were limited reports on the optimal surgery timing after neoadjuvant immunotherapy combined with chemotherapy in esophageal squamous cell carcinoma. Existing literature all revealed that a longer time interval from neoadjuvant immunochemotherapy to surgery is associated with poorer survival outcomes [19, 20]. One reason for this result may be that patients often experience delayed surgery due to their poor physical condition, which is an important factor affecting survival outcomes. Except that 29 patients who received delayed surgery due to personal reasons, in our research, there were 3, 4, 2, and 1 patients with time interval from neoadjuvant therapy to surgery over 6 weeks due to pulmonary inflammation, leukopenia, liver dysfunction, and kidney dysfunction, respectively, which may affect the clinical

(See figure on next page.)

Fig. 4 Kaplan–Meier survival analysis according to cN stage and tumor size between the timely surgery group and the delayed surgery group. **A** Comparison of overall survival between the two groups for patients with cN0 stage. **B** Comparison of overall survival between the two groups for patients with cN + stage. **C** Comparison of disease-free survival between the two groups for patients with cN0 stage. **D** Comparison of disease-free survival between the two groups for patients with cN + stage. **E** Comparison of overall survival between the two groups for patients with tumor size less than 5 cm. **F** Comparison of overall survival between the two groups for patients with tumor size larger than 5 cm. **G** Comparison of disease-free survival between the two groups for patients with tumor size less than 5 cm. **H** Comparison of disease-free survival between the two groups for patients with tumor size larger than 5 cm

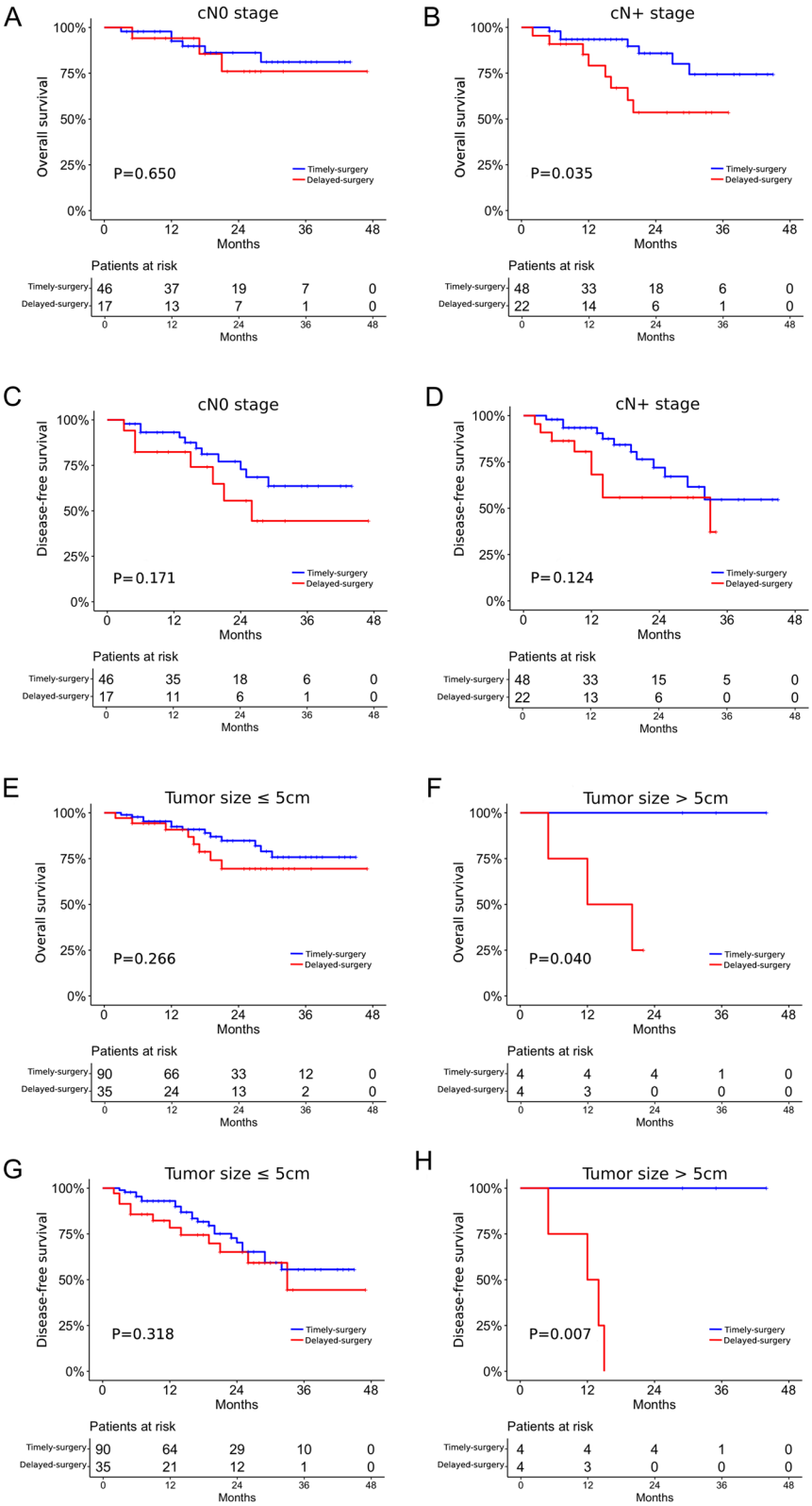

Fig. 4 (See legend on previous page.)

Table 5 Univariate and multivariate Cox regression analyses of overall survival and disease-free survival for esophageal squamous cell carcinoma patients

Variable	Overall survival				Disease-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Sex		0.219				0.794		
Male	Reference				Reference			
Female	0.468 (0.140–1.571)	0.219			0.950 (0.644–1.401)	0.794		
Age		0.444				0.935		
≤ 60 years	Reference				Reference			
> 60 years	0.728 (0.323–1.641)	0.444			0.974 (0.519–1.827)	0.935		
Smoking history		0.254				0.559		
No	Reference				Reference			
Yes	1.597 (0.714–3.572)	0.254			1.208 (0.641–2.274)	0.559		
Neoadjuvant therapy cycles		0.062						
Two	Reference							
Three	1.154 (0.445–2.993)	0.768						
Four	4.506 (1.282–15.83)	0.019						
Interval from neoadjuvant therapy to surgery		0.047		0.049		0.040		0.025
Timely surgery	Reference		Reference		Reference		Reference	
Delayed surgery	2.210 (1.010–4.940)	0.047	2.186 (1.002–4.910)	0.049	1.951 (1.030–3.697)	0.040	2.101 (1.096–4.026)	0.025
Adjuvant therapy		0.564						
No	Reference							
Yes	0.729 (0.249–2.133)	0.564						
Tumor size		0.341				0.482		
≤ 5 cm	Reference				Reference			
> 5 cm	1.803 (0.536–6.057)	0.341			1.450 (0.514–4.091)	0.482		
ypT stage		0.032		0.073		0.049		0.220
T0	Reference		Reference		Reference		Reference	
T1	1.282 (0.306–5.366)	0.734	1.382 (0.328–5.814)	0.659	0.967 (0.335–2.791)	0.951	0.433 (0.106–1.774)	0.245
T2	0.485 (0.050–4.667)	0.531	0.355 (0.034–3.645)	0.383	1.237 (0.377–4.055)	0.725	0.310 (0.054–1.796)	0.191
T3	3.507 (1.014–12.13)	0.047	2.946 (0.831–10.45)	0.094	2.546 (1.021–6.351)	0.045	0.720 (0.154–3.358)	0.676
ypN stage		0.020		0.041		0.063		
N0	Reference		Reference		Reference			
N1	2.653 (1.125–6.256)	0.026	2.549 (1.076–6.038)	0.034	1.585 (0.787–3.193)	0.197		
N2	7.578 (1.649–34.82)	0.009	5.017 (1.046–24.06)	0.044	3.508 (0.819–15.03)	0.091		
N3	3.845 (0.495–29.90)	0.198	7.234 (0.811–64.54)	0.076	4.862 (1.129–20.94)	0.034		
Imaging response		0.698				0.449		
Partial response	Reference				Reference			
Stable disease	1.174 (0.521–2.647)	0.698			1.277 (0.678–2.408)	0.449		
TRG		0.353				0.073		
0	Reference				Reference			
1	1.425 (0.287–7.071)	0.665			0.646 (0.161–2.588)	0.537		
2	2.061 (0.533–7.977)	0.295			1.979 (0.752–5.210)	0.167		
3	2.913 (0.812–10.45)	0.101			2.471 (0.972–5.280)	0.057		
pCR		0.175				0.249		
No	Reference				Reference			
Yes	0.367 (0.086–1.561)	0.175			0.576 (0.225–1.473)	0.249		
MPR		0.108				0.011		0.044
No	Reference				Reference		Reference	
Yes	0.468 (0.186–1.182)	0.108			0.380 (0.180–0.802)	0.011	0.266 (0.073–0.964)	0.044
R0 resection		0.179				0.646		
No	Reference				Reference			
Yes	0.435 (0.129–1.463)	0.179			0.758 (0.233–2.466)	0.646		

TRG Tumor Response Grade, *pCR* pathological complete response, *MPR* major pathologic response

outcomes. In addition, a longer time interval after neoadjuvant therapy may be a risk factor for tumor progression and metastasis [15]. In our research, we also found that a time interval longer than 6 weeks is significantly related with worse OS and DFS. Further subgroup analysis results showed that prolonged time interval was significantly associated with poor survival prognosis in patients with higher clinical lymph node staging and larger tumor lesion. Thus, we conclude that esophageal squamous cell carcinoma patients should avoid delaying surgery after neoadjuvant immunotherapy combined with chemotherapy, especially for those with more severe local tumor lesions.

In our study, we did not find a significant correlation between time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery and surgical difficulty or incidence of postoperative complications. Liu et al. [20] also indicated that there is no significant differences in the postoperative complications between the delayed surgery and timely surgery groups in esophageal squamous cell carcinoma. However, Overtoom et al. [23] revealed that prolonged time to surgery increases the risk of postoperative respiratory complications for esophageal carcinoma patients after neoadjuvant chemoradiotherapy. Wang et al. [24] found that a longer time interval from neoadjuvant chemoradiotherapy to surgery is related to higher risk of anastomotic fistula. This issue requires further clinical trials to investigate.

There have some limitations in our research. Firstly, this was a retrospective study, and potential bias was inevitable. Secondly, the sample size of our research was not large and it is a single center study, which may lead to a decrease in statistical power. Thirdly, the cut-off points of the time interval from neoadjuvant therapy to surgery for various researches were not the same. We set the cut-off point of 6 weeks, used by most clinical trials, which may lead to potential bias. Finally, the follow-up time in our research was relatively short, and further study is required to investigate the long-term survival outcomes.

Conclusion

Prolonged time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery did not improve pCR rate for esophageal squamous cell carcinoma. Instead, delayed surgery after neoadjuvant immunochemotherapy was significantly associated with worse OS and DFS. Esophageal squamous cell carcinoma patients should avoid delaying surgery if their physical conditions permit.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03802-5.

Supplementary Material 1: Figure S1. Kaplan–Meier survival analysis according to different time interval from neoadjuvant immunotherapy combined with chemotherapy to surgery. (A) Comparison of overall survival between patients with time interval ≤ 4 weeks and patients with time interval > 4 weeks. (B) Comparison of disease-free survival between patients with time interval ≤ 4 weeks and patients with time interval > 4 weeks. (C) Comparison of overall survival between patients with time interval ≤ 5 weeks and patients with time interval > 5 weeks. (D) Comparison of disease-free survival between patients with time interval ≤ 5 weeks and patients with time interval > 5 weeks. (E) Comparison of overall survival between patients with time interval ≤ 7 weeks and patients with time interval > 7 weeks. (F) Comparison of disease-free survival between patients with time interval ≤ 7 weeks and patients with time interval > 7 weeks. (G) Comparison of overall survival between patients with time interval ≤ 8 weeks and patients with time interval > 8 weeks. (H) Comparison of disease-free survival between patients with time interval ≤ 8 weeks and patients with time interval > 8 weeks.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

Supplementary Material 6.

Supplementary Material 7.

Supplementary Material 8.

Supplementary Material 9.

Supplementary Material 10.

Supplementary Material 11.

Acknowledgements

This study was supported by Natural Science Foundation of Fujian Province (No. 2022J05301 and No.2021J05284).

Authors' contributions

Guanzhi Ye: Conceptualization; Literature selection; Data curation; Writing-review and editing. Gaojian Pan: Data extraction; Data curation; Software. Xiaolei Zhu: Conceptualization; Data curation; Writing-review and editing. Hongming Liu: Methodology; Literature selection. Ning Li: Data extraction; Literature selection. Guojun Geng: Conceptualization; Supervision; Writing-review and editing. Jie Jiang: Conceptualization; Supervision.All authors read and approved the final manuscript.

Funding

This study was supported by Natural Science Foundation of Fujian Province (No. 2022J05301 and No.2021J05284).

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University on 26 February 2024 (protocol number: XMYY-2024KYSB090). Due to the retrospective character of this analysis and the approval by the Ethics Committee of the First Affiliated Hospital of Xiamen University, the need for informed consent to participate was unnecessary.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Thoracic Surgery, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, No 55, Zhenhai Road, Xiamen, Fujian 361003, China.

Received: 10 November 2024 Accepted: 18 March 2025
Published online: 04 April 2025

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca-Cancer J Clin. 2024;74:229–63.
2. Morgan E, Soerjomataram I, Rumgay H, Coleman HG, Thrift AP, Vignat J, et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from globocan 2020. Gastroenterology. 2022;163:649–58.
3. Ajani JA, D'Amico TA, Bentrem DJ, Cooke D, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, version 2.2023, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Ne. 2023;21:393–422.
4. Yang W, Xing X, Yeung SJ, Wang S, Chen W, Bao Y, et al. Neoadjuvant programmed cell death 1 blockade combined with chemotherapy for resectable esophageal squamous cell carcinoma. J Immunother Cancer. 2022;10: e003497.
5. Ge F, Huo Z, Cai X, Hu Q, Chen W, Lin G, et al. Evaluation of clinical and safety outcomes of neoadjuvant immunotherapy combined with chemotherapy for patients with resectable esophageal cancer: a systematic review and meta-analysis. Jama Netw Open. 2022;5: e2239778.
6. Liu J, Zeng X, Zhou X, Xu Y, Ding Z, Hu Y, et al. Longer interval between neoadjuvant chemoradiotherapy and surgery is associated with improved pathological response, but does not accurately estimate survival in patients with resectable esophageal cancer. Oncol Lett. 2023;25:155.
7. Lee A, Wong AT, Schwartz D, Weiner JP, Osborn VW, Schreiber D. Is there a benefit to prolonging the interval between neoadjuvant chemoradiation and esophagectomy in esophageal cancer? Ann Thorac Surg. 2016;102:433–8.
8. Nilsson K, Klevebro F, Sunde B, Rouvelas I, Lindblad M, Szabo E, et al. Oncological outcomes of standard versus prolonged time to surgery after neoadjuvant chemoradiotherapy for oesophageal cancer in the multicentre, randomised, controlled NeoRes II trial. Ann Oncol. 2023;34:1015–24.
9. Yang Y, Liu J, Liu Z, Zhu L, Chen H, Yu B, et al. Two-year outcomes of clinical N2–3 esophageal squamous cell carcinoma after neoadjuvant chemotherapy and immunotherapy from the phase 2 NICE study. J Thorac Cardiov Sur. 2024;167:838–47.
10. Liu J, Yang Y, Liu Z, Fu X, Cai X, Li H, et al. Multicenter, single-arm, phase II trial of camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced esophageal squamous cell carcinoma. J Immunother Cancer. 2022;10(3):e004291.
11. Yan X, Duan H, Ni Y, Zhou Y, Wang X, Qi H, et al. Tislelizumab combined with chemotherapy as neoadjuvant therapy for surgically resectable esophageal cancer: a prospective, single-arm, phase II study (TD-NICE). Int J Surg. 2022;103: 106680.
12. Schwartz LH, Litiere S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. Recist 1.1-update and clarification: from the recist committee. Eur J Cancer. 2016;62:132–7.
13. Klevebro F, Nilsson K, Lindblad M, Ekman S, Johansson J, Lundell L, et al. Association between time interval from neoadjuvant chemoradiotherapy to surgery and complete histological tumor response in esophageal and gastroesophageal junction cancer: a national cohort study. Dis Esophagus. 2020;33:doz078.
14. Tessier W, Gronnier C, Messager M, Hec F, Mirabel X, Robb WB, et al. Does timing of surgical procedure after neoadjuvant chemoradiation affect outcomes in esophageal cancer? Ann Thorac Surg. 2014;97:1181–9.
15. Chiu CH, Chao YK, Chang HK, Tseng CK, Chan SC, Liu YH, et al. Interval between neoadjuvant chemoradiotherapy and surgery for esophageal squamous cell carcinoma: does delayed surgery impact outcome? Ann Surg Oncol. 2013;20:4245–51.
16. Shaikh T, Ruth K, Scott WJ, Burtness BA, Cohen SJ, Konski AA, et al. Increased time from neoadjuvant chemoradiation to surgery is associated with higher pathologic complete response rates in esophageal cancer. Ann Thorac Surg. 2015;99:270–6.
17. Haisley KR, Laird AE, Nabavizadeh N, Gatter KM, Holland JM, Vaccaro GM, et al. Association of intervals between neoadjuvant chemoradiation and surgical resection with pathologic complete response and survival in patients with esophageal cancer. Jama Surg. 2016;151: e162743.
18. Maramara T, Shridhar R, Blinn P, Huston J, Meredith K. Timing after neoadjuvant therapy predicts mortality in patients undergoing esophagectomy: a propensity score-matched analysis. J Gastrointest Surg. 2023;27:2342–51.
19. Yang G, Hong Y, Zhang X, Zeng C, Tan L, Zhang X. Impact of the interval between neoadjuvant immunotherapy and surgery on prognosis in esophageal squamous cell carcinoma (ESCC): a real-world study. Cancer Immunol Immun. 2024;73:202.
20. Liu J, Zhu L, Huang X, Lu Z, Wang Y, Yang Y, et al. Does the time interval from neoadjuvant camrelizumab combined with chemotherapy to surgery affect outcomes for locally advanced esophageal squamous cell carcinoma? J Cancer Res Clin. 2024;150:161.
21. Tie H, He F, Shen J, Zhang B, Ye M, Chen B, et al. Prolonged interval between neoadjuvant chemoradiotherapy and esophagectomy does not benefit the outcome in esophageal cancer: a systematic review and meta-analysis. Dis Esophagus. 2018;31:1–9.
22. Ruol A, Rizzetto C, Castoro C, Cagol M, Alfieri R, Zanchettin G, et al. Interval between neoadjuvant chemoradiotherapy and surgery for squamous cell carcinoma of the thoracic esophagus: does delayed surgery have an impact on outcome? Ann Surg. 2010;252:788–96.
23. Overtoom H, Eyck BM, van der Wilk BJ, Noordman BJ, van der Sluis PC, Wijnhoven B, et al. Prolonged time to surgery in patients with residual disease after neoadjuvant chemoradiotherapy for esophageal cancer. Ann Surg. 2024. https://doi.org/10.1097/SLA.0000000000006488. Epub ahead of print.
24. Wang J, de Jongh C, Wu Z, de Groot EM, Alexandre C, Markar SR, et al. Impact of preoperative time intervals for neoadjuvant chemoradiotherapy on short-term postoperative outcomes of esophageal cancer surgery: a population-based study using the dutch upper gastrointestinal cancer audit (DUCA) data. Ann Surg. 2024;280:808–16.

Publisher's Note