Original Article

The time-to-surgery interval and its effect on pathological response after neoadjuvant chemoimmunotherapy in non-small cell lung cancer: a retrospective cohort study

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Background: The time to surgery (TTS) after the completion of the final cycle of neoadjuvant chemoimmunotherapy in patients with non-small cell lung cancer (NSCLC) is inconsistent. Pathological complete response (pCR) and major pathological response (MPR) are associated with enhanced survival in those with NSCLC. The optimal TTS interval remains to be determined, some studies indicated that TTS ≤6 weeks has a vital role in NSCLC prognosis. Therefore, this study aimed to determine whether TTS is correlated with pathological outcomes and to identify the factors associated with TTS.

Methods: We retrospectively analyzed 82 individuals who had surgery after neoadjuvant chemoimmunotherapy for NSCLC between January 2020 and December 2023. Fifty participants were included in this study after inclusion and exclusion criteria. Participants were categorized into two groups: TTS ≤4 weeks and TTS >4 to 6 weeks. Univariate and multivariate regression analyses were employed to determine the impact of TTS on pathological response and to identify the variables associated with TTS. Variables that showed their P value <0.2 in univariate analyses were included in the multivariate analysis. Kaplan-Meier analysis was used to analyze disease-free survival (DFS).

Results: Our study evaluating 50 patients revealed that patients in the TTS ≤4 weeks group achieved pCR or MPR compared to patients in the >4 to 6 weeks group (P=0.01). In univariate analyses, TTS ≤4 weeks was more correlated with achieving pCR or MPR than TTS >4 to 6 weeks [odds ratio (OR) =0.211; 95% confidence interval (CI): 0.062–0.711; P=0.01] The multivariate analysis showed that cT1 stage (compared to cT4), and cN1 stage (compared to cN0) showed statistical correlation with achieving pCR or MPR. cN1 stage was independent predictor of achieving pCR or MPR (OR =27.817; 95% CI: 1.536–503.88; P=0.02). Concerning to the DFS, TTS ≤4 weeks group and TTS >4 to 6 weeks group showed no statistical differences (2-year DFS rate were 70.6% and 72.6%, respectively). Regarding the tendency of being patients' TTS ≤4 weeks, patients with ventilatory impairment (OR =0.203; 95% CI: 0.04–0.98; P=0.047) were more tending to prolong the TTS to >4 to 6 weeks.

Conclusions: TTS ≤4 weeks was associated with a significant improvement of pathological response. Therefore, patients with NSCLC should undergo surgery within 4 weeks after the last cycle of neoadjuvant chemoimmunotherapy.

Keywords: Non-small cell lung cancer (NSCLC); time to surgery (TTS); pathological response; neoadjuvant chemoimmunotherapy

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Introduction

Lung cancer continues to be the primary cause of cancer-related death globally and is responsible for 20% and 21% of deaths associated with cancer in males and females, respectively (1). Resection is the only therapy that has the potential to cure non-small cell lung cancer (NSCLC). However, only about 20% to 25% of individuals with NSCLC are eligible for this type of surgery (2,3). In the past few years, neoadjuvant immunotherapy has shown improved clinical response in NSCLC (4), Beattie *et al.* proved that lung resection after neoadjuvant immunotherapy is safe (5), profoundly changing the treatment paradigm for patients with NSCLC.

Pathological complete response (pCR) and major pathological response (MPR) are employed as pathological response endpoints in evaluating the effectiveness of neoadjuvant treatment and are linked to improved survival outcomes (6,7). Nuccio *et al.* found that individuals with NSCLC who received neoadjuvant chemoimmunotherapy experienced substantial increases in rates of pCR, MPR, overall survival (OS) and event-free survival (EFS) in comparison to neoadjuvant chemotherapy, and there was a significant correlation between pCR and EFS (8). Meanwhile, Alì *et al.* found that better pCR and MPR had significantly improved OS and EFS after neoadjuvant chemoimmunotherapy (9).

The time to surgery (TTS) interval after completion of the last cycle of neoadjuvant therapy is inconsistent; for example, in the NADIM II trial (NCT03838159), checkmate 816 trial (NCT02998528), and AEGEAN trial (NCT03800134), surgery was conducted within 3–4 weeks, 6 weeks and 40 days after the completion of last cycle of neoadjuvant chemoimmunotherapy, respectively (10-12). While in the KEYNOTE-671 trial (NCT03425643), surgery was to be performed no later than 20 weeks after the first dose of neoadjuvant chemoimmunotherapy (13). Therefore, the optimal TTS interval remains to be determined. In fact, the effect of TTS on oncological outcomes after neoadjuvant therapy has been previously studied in various cancers. Nilsson *et al.* and Sutton *et al.* found that there was a strong correlation between prolonged TTS (>6 weeks) and adverse oncologic outcomes for oesophageal cancer and breast cancer after neoadjuvant therapy, respectively (14,15). According to the latest consensus, surgery is recommended 4–6 weeks following the final cycle of neoadjuvant immunotherapy in NSCLC (16); however, no studies have confirmed this recommendation. Gao *et al.* found that OS may be substantially worse in individuals with NSCLC who received surgery >6 weeks after neoadjuvant chemoradiation (17).

These studies indicated that TTS has a vital role in NSCLC prognosis, and a TTS ≤6 weeks may productive in exploring the TTS effect on oncological outcomes after neoadjuvant therapy in terms of pathological response. Therefore, this study primarily aimed to investigate whether TTS correlates with pathological outcomes after neoadjuvant chemoimmunotherapy in NSCLC and to identify the factors associated with TTS. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-781/rc).

Highlight box

Key findings

- A time to surgery (TTS) ≤4 weeks was associated with significantly improved pathological response in patients with non-small cell lung cancer (NSCLC) after neoadjuvant chemoimmunotherapy.

What is known and what is new?

- According to the latest consensus, surgery is recommended 4–6 weeks following the final cycle of neoadjuvant immunotherapy. However, no studies have confirmed this recommendation. The TTS interval after completing the last cycle of neoadjuvant therapy in NSCLC is still inconsistent. Several studies have examined conducting surgery within 6 weeks after neoadjuvant therapy and found that TTS <6 weeks is associated with a better prognosis, which indicates that TTS plays a vital role in NSCLC prognosis.
- In our study, a TTS ≤4 weeks was associated with significantly improved pathological responses after completion of the last cycle of neoadjuvant chemoimmunotherapy in NSCLC than TTS >4 to 6 weeks. Moreover, patients without ventilatory impairment were more tending to have a TTS ≤4 weeks.

What is the implication, and what should change now?

- Our findings suggest that patients with NSCLC should undergo surgery within 4 weeks after the last cycle of neoadjuvant chemoimmunotherapy.

Methods

Patients and study design

A total of 82 participants who underwent surgery after neoadjuvant chemoimmunotherapy for NSCLC at The First Affiliated Hospital of Ningbo University between January 2020 and December 2023 were included in this study. 50 participants were included in this study based on the following inclusion criteria: (I) age ≥18 years old; (II) eligible for surgical resection and deemed clinically operable by a multidisciplinary team; (III) no prior radiation or chemotherapy; (IV) no other tumors present; and (V) healthy organs and pulmonary function capable of withstanding lung resection operations. Meanwhile, the exclusion criteria were the following: (I) only administration of neoadjuvant chemotherapy; (II) only administration of neoadjuvant immunotherapy; (III) received combination of neoadjuvant chemotherapy and radiotherapy; (IV) administration of neoadjuvant targeted treatment; (V) use of multiple neoadjuvant regimens; and (VI) absence of information necessary for evaluating treatment response. The treatment regimen for patients in this study was immunotherapy plus platinum-based chemotherapy.

Participants were monitored every half a year until their death or their final follow-up date (December 31, 2023). The TTS interval was considered to be the duration between the completion of the last therapy cycle and surgery. The median TTS of 50 patients was 28 days (4 weeks). Therefore, we divided the patients into a TTS ≤4 weeks group and a TTS >4 to 6 weeks group. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by ethics board of The First Affiliated Hospital of Ningbo University (approval No. 2020-R229). The requirement for patient consent was waived due to the retrospective nature of this analysis.

Variables

MPR was considered as the finding of ≤10% of viable tumor cells found in tumor bed of resected primary tumor in postoperative pathological examination, while pCR was considered as complete excision of tumor cell in resected lung and dissected lymph nodes. In this study, disease-free survival (DFS) was the primary outcome, which was the period between the date of surgery and the date when the recurrence was firstly detected or the date of death from any causes. Objective response rate (ORR) was the secondary outcomes of this study. ORR defined as the sum of the proportion of patients with complete response (CR) and partial response (PR) based on the RECIST version 1.1. Information was collected on patient's basic characteristics including age, smoking history, body mass index (BMI), treatment cycle, ventilatory impairment [defined as forced expiratory volume in 1 s predicted value (FEV1%) <80%], and Charlson-Deyo score. We combined BMI <18.5 kg/m^2 group and 18.5 to <25 kg/m^2 group into one group because only 4 patients in the BMI <18.5 kg/m^2 group and the BMI divided into <25 kg/m^2 group and ≥25 kg/m^2 group, accordingly. Surgery types included pneumonectomy or lobectomy; the surgical approach included thoracotomy or video-assisted thoracoscopy surgery (VATS); the TNM stage were classified based on the American Joint Committee on Cancer 8th (AJCC8) edition (18). ycT stage defined as "clinical tumor stage after neoadjuvant chemoimmunotherapy" and ycN stage defined as "clinical nodal stage after neoadjuvant chemoimmunotherapy" in this study. ycT3 and ycT4 stage were combined into one group because only two patients had an ycT4 stage. Treatment-related adverse events (TRAEs) were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The pathological response was categorized as "pCR or MPR" and "others" (a patient did not achieve pCR or MPR).

Statistical analysis

The investigation employed χ^2 tests to compare categorical variables and independent samples *t*-tests to compare continuous variables. Univariate and multivariate regression analyses were employed to verify the predictors of achieving pCR or MPR and TTS ≤4 weeks. Variables that showed their P value <0.2 in univariate analyses were included in the multivariate analysis. The results are reported as odds ratio (OR) with 95% confidence-interval (CI). The Kaplan-Meier method was used for calculating DFS, and the statistical variation was assessed with the log-rank test. SPSS version 23 (IBM Corp, Armonk, NY, USA) and R version 4.0.5 (The R Foundation of Statistical Computing; https://www.r-project.org/) were used for statistical analyses. A P value <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

This study examined a cohort of 50 patients who received

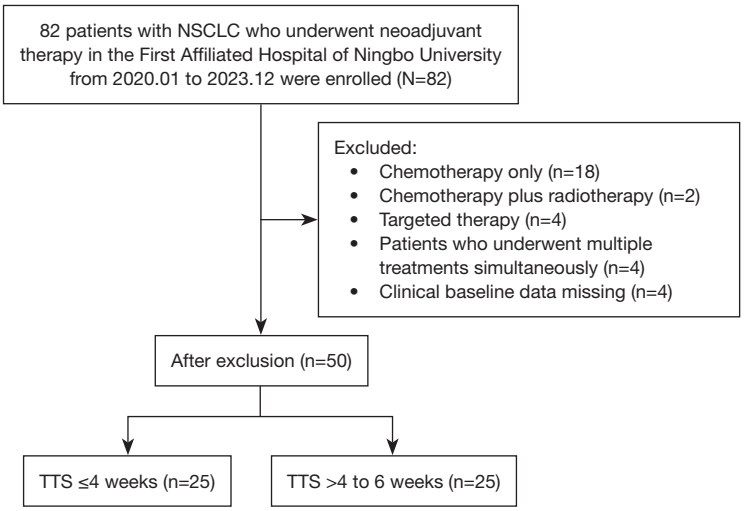

Figure 1 Flowchart of patient selection. NSCLC, non-small cell lung cancer; N, number; TTS, time to surgery.

neoadjuvant chemoimmunotherapy, with 25 patients in the TTS ≤4 weeks group and 25 patients in the TTS >4 to 6 weeks group, respectively. *Figure 1* shows a flowchart of patient selection.

Table 1 illustrates the baseline, tumor, and treatment features of the patients. Most patients were over 65 years old (56%), BMI at 18.5 to <25 kg/m^2 (72%), had a smoking history (64%), underwent two cycles of neoadjuvant treatment (62%), had ventilatory impairment (70%), and had a Charlson-Deyo score ≥1 (70%). Most patients underwent lobectomy (82%) and underwent with VATS approach (68%). Among the 50 patients, 8 (16%) had a cT1 stage, 12 (24%) had a cT2 stage, 20 (40%) had a cT3 stage, 10 (20%) had a cT4 stage, 13 (26%) had a cN0 stage, 9 (18%) had cN1 stage, 28 (56%) had a cN2 stage. After receiving neoadjuvant chemoimmunotherapy, 18 (36%) patients had a ycT1 stage, 21 (42%) had a ycT2 stage, 9 (18%) had a ycT3 and 2 (4%) had a ycT4 stage. 21 (42%) had an ycN0 stage, 6 (12%) had a ycN1 stage and 23 (46%) had a ycN2 stage. Seventeen (34%) patients experienced grade 1 adverse events, 18 (36%) and 15 (30%) experienced grade 2 and grade 3 adverse events, respectively. There was no grade 4 TRAEs observed in any of the 50 patients. Twenty-nine (58%) patients achieved pCR or MPR. The ORR of the total patients, TTS ≤4 weeks group and TTS >4 to 6 weeks group were 58%, 60% and 56%, respectively.

Table 2 summarizes the patient characteristics of the two groups. In the TTS ≤4 weeks group, 19 (76%) patients achieved pCR or MPR, whereas 6 (24%) patients did not. In the >4 to 6 weeks group, 10 patients (40%) achieved pCR or MPR, and 15 (60%) did not. Therefore, more patients achieved pCR or MPR in TTS ≤4 weeks group than in the >4 to 6 weeks group (P=0.01). We observed no variation between the two groups in terms of age (P=0.57), BMI (P=0.07), smoking status (P=0.56), cycles of treatment (P=0.15), ventilatory impairment (P=0.47), Charlson-Deyo score (P=0.36), surgery type (P=0.71), surgical approach (P=0.54), cT stage (P=0.68), cN stage (P=0.62), ycT stage (P=0.84), ycN stage (P=0.32) and adverse events (P=0.30).

Factors associated with achieving pCR or MPR

The univariate regression (*Table 3*) indicated that TTS ≤4 weeks was more correlated with achieving pCR or MPR than TTS >4 to 6 weeks (OR =0.211; 95% CI: 0.062–0.711; P=0.01). According to the results from univariate analyses, TTS, age, clinical tumor stage and clinical nodal stage were included in the multivariate regression. According to the results, TTS ≤4 weeks compared to TTS >4 to 6 weeks (OR =0.116; 95% CI: 0.023–0.57; P=0.008) had a statistically significant correlation with achieving pCR or MPR. cT4 stage (OR =0.043; 95% CI: 0.002–0.965; P=0.047) was less achieving pCR or MPR than cT1. Although it was not found to be statistically significant, cT3 stage may suggest a less likelihood of achieving pCR or MPR (OR =0.096; 95% CI: 0.008–1.211; P=0.07) than cT1. cN1 stage (OR =27.817; 95% CI: 1.536–503.88; P=0.02) was independent predictor of achieving pCR or MPR. No significant differences in age

Table 1 Baseline, tumor, and treatment characteristics of patients

Variable	N [%]
Age, years	
≤65	22 [44]
>65	28 [56]
BMI, kg/m^2	
<18.5	4 [8]
18.5 to <25	36 [72]
25 to <30	9 [18]
Smoking history	
No	18 [36]
Yes	32 [64]
Immunotherapy regimen	
Pembrolizumab	24 [48]
Tislelizumab	11 [22]
Camrelizumab	6 [12]
Sintilimab	5 [10]
Durvalumab	2 [4]
Slulizumab	2 [4]
Cycles of treatment	
2	31 [62]
3	17 [34]
4	2 [4]
Time-to-surgery, weeks	
≤2	1 [2]
>2 to 4	24 [48]
>4 to 6	25 [50]
Ventilatory impairment	
No	15 [30]
Yes	35 [70]
Charlson-Deyo score	
0	15 [30]
1	23 [46]
2	9 [18]
3	2 [4]
4	1 [2]
Surgery type	
Pneumonectomy	9 [18]
Lobectomy	41 [82]
Surgical approach	
Thoracotomy	16 [32]
VATS	34 [68]
cT stage	
cT1	8 [16]
cT2	12 [24]
cT3	20 [40]
cT4	10 [20]
cN stage	
cN0	13 [26]
cN1	9 [18]
cN2	28 [56]
ycT stage	
ycT1	18 [36]
ycT2	21 [42]
ycT3	9 [18]
ycT4	2 [4]
ycN stage	
ycN0	21 [42]
ycN1	6 [12]
ycN2	23 [46]
Adverse events grade	
1	17 [34]
2	18 [36]
3	15 [30]
Pathological response	
pCR or MPR	29 [58]
Others	21 [42]
Objective response rate (%)	
TTS ≤4 weeks	60 (15/25)
TTS >4 to 6 weeks	56 (14/25)
Pooled	58 (29/50)

N, number; BMI, body mass index; VATS, video-assisted thoracoscopy surgery; T, tumor; N, nodal; pCR, pathological complete response; MPR, major pathological response; TTS, time to surgery.

Table 2 Patients characteristics in the TTS ≤4 weeks group and TTS >4 to 6 weeks group

Characteristics	TTS ≤4 weeks, n [%]	TTS >4 to 6 weeks, n [%]	P
Age, years			0.57
≤65	10 [40]	12 [48]	
>65	15 [60]	13 [52]	
BMI, kg/m^2			0.07
<25	23 [84]	18 [72]	
≥25	2 [16]	7 [28]	
Smoking history			0.56
No	10 [40]	8 [32]	
Yes	15 [60]	17 [68]	
Cycles of treatment			0.15
≤2	18 [72]	13 [52]	
>2	7 [28]	12 [48]	
Ventilatory impairment			0.47
No	10 [40]	5 [20]	
Yes	15 [60]	20 [80]	
Charlson-Deyo score			0.36
0	9 [36]	6 [24]	
≥1	16 [64]	19 [76]	
Surgery type			0.71
Pneumonectomy	5 [20]	4 [16]	
Lobectomy	20 [80]	21 [84]	
Surgical approach			0.54
Thoracotomy	9 [36]	7 [28]	
VATS	16 [64]	18 [72]	
cT stage			0.68
cT1	4 [16]	4 [16]	
cT2	7 [28]	5 [20]	
cT3	8 [32]	12 [48]	
cT4	6 [24]	4 [16]	
cN stage			
cN0	8 [32]	5 [20]	0.62
cN1	4 [16]	5 [20]	
cN2	13 [52]	15 [60]	
ycT stage			0.84
ycT1	10 [40]	8 [32]	
ycT2	10 [40]	11 [44]	
ycT3 + T4	5 [20]	6 [24]	
ycN stage			0.32
ycN0	13 [52]	8 [32]	
ycN1	3 [12]	3 [12]	
ycN2	9 [36]	14 [56]	
Adverse events grade			0.30
1	11 [44]	6 [24]	
2	7 [28]	11 [44]	
3	7 [28]	8 [32]	
Pathological response			0.01*
pCR or MPR	19 [76]	10 [40]	
Others	6 [24]	15 [60]	

*, P<0.05. TTS, time to surgery; BMI, body mass index; VATS, video-assisted thoracoscopy surgery; T, tumor; N, nodal; pCR, pathological complete response; MPR, major pathological response.

(P=0.22) were detected.

DFS

The rates of 2-year DFS were 70.6% and 72.6% in the TTS ≤4 and TTS >4 to 6 weeks groups, respectively (*Figure 2*). The two groups were no different in terms of DFS (P=0.96).

Preoperative factors associated with TTS

To explore the patients whose TTS tends to prolong over 4 weeks, we further evaluated the factors associated with TTS (*Table 4*). Univariate regression included age, BMI, smoking, treatment cycles, ventilatory impairment, Charlson-Deyo score, clinical tumor stage, clinical nodal stage and adverse events, but no significant differences were found. However, according to the results of the multivariate regression analysis, which included BMI, treatment cycles, ventilatory impairment and adverse events, patients whose BMI 25 to

Table 3 Predictors of achieving pCR or MPR

Predictors	Univariate regression		Multivariate regression	
	OR (95% CI)	P	OR (95% CI)	P
TTS, weeks				
≤4	Ref		Ref	
>4 to 6	0.211 (0.062–0.711)	0.01*	0.116 (0.023–0.57)	0.008*
Age, years				
≤65	Ref		Ref	
>65	2.533 (0.798–8.038)	0.12	3.149 (0.506–19.598)	0.22
BMI, kg/m^2				
<25	Ref			
≥25	0.885 (0.207–3.791)	0.87		
Smoking history				
No	Ref			
Yes	0.818 (0.252–2.655)	0.74		
Cycles of treatment				
≤2	Ref			
>2	0.993 (0.312–3.158)	0.99		
Ventilatory impairment				
No	Ref			
Yes	1.571 (0.453–5.45)	0.48		
Charlson-Deyo score				
0	Ref			
≥1	1.934 (0.569–6.580)	0.29		
Clinical tumor stage				
cT1	Ref		Ref	
cT2	0.286 (0.026–3.196)	0.31	0.101 (0.006–1.692)	0.11
cT3	0.107 (0.011–1.033)	0.053	0.096 (0.008–1.211)	0.07
cT4	0.179 (0.015–2.119)	0.17	0.043 (0.002–0.965)	0.047*
Clinical nodal stage				
cN0	Ref		Ref	
cN1	9.333 (0.892–97.619)	0.06	27.817 (1.536–503.88)	0.02*
cN2	1.346 (0.360–5.036)	0.66	2.923 (0.396–21.582)	0.29
Adverse events grade				
1	Ref			
2	0.857 (0.217–3.386)	0.83		
3	0.477 (0.115–1.976)	0.31		

*, P<0.05. pCR, pathological complete response; MPR, major pathological response; TTS, time to surgery; OR, odds ratio; CI, confidence interval; BMI, body mass index; T, tumor; N, nodal.

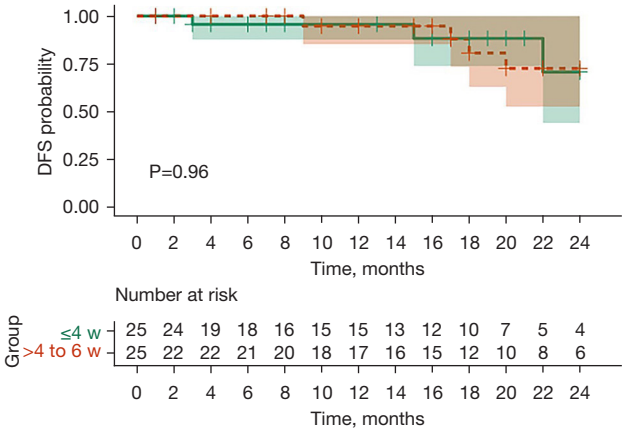

Figure 2 The DFS curves of TTS ≤4 weeks and TTS >4 to 6 weeks. DFS, disease-free survival; TTS, time to surgery; w, weeks.

<30 kg/m^2 (OR =0.1; 95% CI: 0.013–0.781; P=0.03) or with ventilatory impairment (OR =0.203; 95% CI: 0.042–0.98; P=0.047) were more tending to prolong the TTS to >4 to 6 weeks after neoadjuvant chemoimmunotherapy.

Discussion

TTS has been inconsistent in phase II–III clinical trials of neoadjuvant chemoimmunotherapy in NSCLC, with most of the patients undergoing surgery within 6 weeks (19,20). Xu *et al.* reported that a shorter TTS duration was associated with a more favorable objective response (P=0.01) and pCR (P=0.01) in individuals with NSCLC who received neoadjuvant immunotherapy (median TTS of 33.5 days) and those who did not (median TTS of 45 days) (21). However, the optimal TTS interval after neoadjuvant chemoimmunotherapy remains unknown. This study found that TTS ≤4 weeks can achieve a significantly greater possibility of pCR or MPR than TTS >4 to 6 weeks, which indicate that patients with NSCLC should undergo surgery within 4 weeks after the last cycle of neoadjuvant chemoimmunotherapy.

Chen *et al.* examined the connection between TTS interval and pathological outcomes in patients with NSCLC. Their findings revealed that TTS exerted no significant impact on the pathological response at ≤4, >4 to 6, and >6 weeks in an analysis of MPR and pCR as separate variables (22). The median TTS of 50 patients was 28 days (4 weeks), therefore, the patients of our study were categorized into two groups depending on their TTS: TTS ≤4 weeks and TTS >4 to 6 weeks. In this study, participants with a TTS ≤4 weeks had a higher probability of achieving pCR or MPR than did those with a TTS >4 to 6 weeks, suggesting that these patients may have potentially better survival. However, the rates of 2-year DFS were 70.6% in the TTS ≤4 group and 72.6% in the TTS >4 to 6 weeks groups, respectively. The DFS showed no difference between two groups (P=0.96), possibly due to the short interval between the time of surgery and the last follow-up. Therefore, whether patients with TTS ≤4 weeks can experience improved survival remains to be verified. According to the multivariate regression, cT4 stage was significantly less associated with achieving pCR or MPR than cT1 stage, and there was a trend that the possibility of achieving pCR or MPR was decreasing with the upgrading of cT stage. Ling *et al.* observed that the tumor size of patients who achieved pCR/MPR was much smaller than the patients who achieved no pCR/MPR (23). Topalian and colleagues found that greater tumor burden (sum of tumor lesion diameters) was correlated with lower 5-year survival (24). Forde *et al.* also showed that compared to the patients with advanced stage (stage IIIA) NSCLC, the pCR/MPR rate was much higher in the patients with early stage (stage I–II) (25). These findings from the studies were consistent with our findings. Moreover, according to our study, cN1 stage suggested a greater likelihood of achieving pCR or MPR than cN0 and cN2 stage, which was also consistent with recent research conducted by Ling *et al.* (23), which showed that the patients with N1 stage NSCLC achieved a higher rate of pCR of lymph node (6/19 versus 1/7 patients) and inflamed morphological phenotype than N2 stage. But the reason for this difference is unclear and still need to be verified. To guide clinicians in selecting appropriate patients for surgery within 4 weeks after the last cycle of neoadjuvant chemoimmunotherapy, we further analyzed which factors may be associated with TTS and found that patients whose BMI ≥25 kg/m^2 were more tending to prolong the TTS to >4 to 6 weeks, this indicates that patients whose BMI <25 kg/m^2 were more likely to undergo surgery within 4 weeks after neoadjuvant chemoimmunotherapy. However, Icard *et al* found that BMI >25 kg/m^2 statistically positively affected long-term survival after lung resection for NSCLC (26). Kim *et al.* also showed that a lower BMI was independent risk factor of postoperative pulmonary complications after neoadjuvant chemoradiotherapy for NSCLC (27). Therefore, whether the effect of BMI on TTS associate with better survival and postoperative clinical outcomes still need to be verified. In addition, patients without ventilatory impairment were

Table 4 Predictors of TTS ≤4 weeks

Predictors	Univariate regression		Multivariate regression	
	OR (95% CI)	P	OR (95% CI)	P
Age, years				
≤65	Ref			
>65	1.385 (0.451–4.246)	0.57		
BMI, kg/m^2				
<25	Ref		Ref	
25 to <30	0.224 (0.041–1.21)	0.08	0.1 (0.013–0.781)	0.03*
Smoking history				
No	Ref			
Yes	0.706 (0.221–2.252)	0.56		
Cycles of treatment				
≤2	Ref		Ref	
>2	0.421 (0.130–1.363)	0.15	0.334 (0.083–1.345)	0.12
Ventilatory impairment				
No	Ref		Ref	
Yes	0.286 (0.075–1.086)	0.07	0.203 (0.042–0.98)	0.047*
Charlson-Deyo score				
0	Ref			
≥1	0.561 (0.164–1.918)	0.36		
Clinical tumor stage				
cT1	Ref			
cT2	1.40 (0.232–8.464)	0.71		
cT3	0.667 (0.128–3.47)	0.63		
cT4	1.50 (0.23–9.796)	0.67		
Clinical nodal stage				
cN0	Ref			
cN1	0.50 (0.089–2.807)	0.43		
cN2	0.542 (0.142–2.072)	0.37		
Adverse events grade				
1	Ref		Ref	
2	0.347 (0.088–1.371)	0.13	0.479 (0.098–2.338)	0.36
3	0.477 (0.115–1.976)	0.31	0.318 (0.063–1.602)	0.17

*, P<0.05. TTS, time to surgery; OR, odds ratio; CI, confidence interval; BMI, body mass index; T, tumor; N, nodal.

also having a greater likelihood of TTS ≤4 weeks according to the results of the multivariate regression analysis. Laurent *et al.* showed that preoperative training can reduce pulmonary-related complications for NSCLC (28). Therefore, most of the patients with ventilatory impairment had received respiratory exercise before surgery, which may account for the postponement of TTS. Dai *et al.* found that sleeve resection was feasible and the perioperative outcomes between the VATS and thoracotomy were comparable after neoadjuvant chemoimmunotherapy in NSCLC (29). Stafinski *et al.* identified eight strategies in reducing the wait time before surgery (30). The effect of TTS on perioperative outcomes needs to be further studied.

Several clinical trials have confirmed that neoadjuvant chemoimmunotherapy improves the response in patients with NSCLC, however, the specific molecular mechanisms underlying this remain unclear. Kaira *et al.* found that the tumor microenvironment-related surface markers comprised an increase in $CD8^+$ and $CD4^+$ T cells could be optimal predictors for pCR (31). Hui *et al.* discovered that an increase in the number of B cells and $CD4^+$ T cells was linked with a favorable clinical outcome in patients receiving neoadjuvant chemoimmunotherapy (32). Interleukin 21 (IL-21), produced by infiltrating T follicular helper cells, stimulates B cells to undergo class switching to produce antitumor immunoglobin (Ig)G1 and IgG3 isotypes, a process crucial in the immune response against tumors. Consequently, IL-21 combined with immune checkpoint inhibitors may improve antitumor immunity. According to Hui *et al.*, IL-21 can predict clinical response to neoadjuvant chemoimmunotherapy in NSCLC (32). Based on these findings, the relationship between IL-21 and TTS warrants further examination. In addition, the optimized timing for effector cells to exert their impact may correlate with the cycle of T-cell amplification and help determine an optimal TTS interval, but the related mechanism remains unclear.

The limitations of this study include: (I) its retrospective design and limited sample size; (II) the fact that the majority of patients had surgery mostly in 2022 or 2023, which did not allow for a longer period of follow-up of DFS or overall survival; and (III) the limited types of pathology, such as adenocarcinoma or squamous cell carcinoma, which could not be examined independently owing to the small sample of enrolled participants.

Conclusions

This study analyzed the effect of TTS ≤4 weeks and TTS >4 to 6 weeks on pathological responses and found that TTS ≤4 weeks was associated with a significantly improved pathological response than TTS >4 to 6 weeks. cT4 stage was less achieving pCR or MPR than cT1 stage, while cN1 stage was independent predictor of achieving pCR or MPR. Finally, patients without ventilatory impairment were more tending to have a TTS ≤4 weeks after neoadjuvant chemoimmunotherapy. Therefore, patients with NSCLC should undergo surgery within 4 weeks after the last cycle of neoadjuvant chemoimmunotherapy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-781/coif). A.R. serves as an unpaid editorial board member of *Translational Lung Cancer Research* from November 2022 to October 2024. A.R. owns stock options by IQVIA Holdings Inc. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by ethics board of The First Affiliated Hospital of Ningbo University (approval No. 2020-R229). The requirement for patient consent was

waived due to the retrospective nature of this analysis.

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