



Efficacy of neoadjuvant chemo-immunotherapy in non-small cell lung cancer: a real-world, multicenter, retrospective study

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Background: Resectable non-small cell lung cancer (NSCLC) patients have a high risk of recurrence. Multiple randomized controlled trials (RCTs) have shown that neoadjuvant chemo-immunotherapy brings new hope for these patients. The study aims to evaluate the safety, surgery-related outcomes and oncological outcomes for neoadjuvant chemo-immunotherapy in real-world setting with a large sample size and long-term follow-up.

Methods: Patients with clinical stage IB–IIIB NSCLC who received neoadjuvant chemo-immunotherapy at two Chinese institutions were included in this retrospective cohort study. Surgical and oncological outcomes of the enrolled NSCLC patients were collected and analyzed.

Results: There were 158 patients identified, of which 124 (78.5%) were at stage IIIA–IIIB and the remaining 34 (21.5%) were at stage IB–IIB. Forty-one patients (25.9%) received two cycles of neoadjuvant treatment, 80 (50.6%) had three cycles, and 37 (23.4%) had four cycles. Twenty-four patients (15.2%) experienced grade 3 or worse immune-related adverse events. The median interval time between the last neoadjuvant therapy and surgery was 37 [interquartile range (IQR), 31–43] days. Fifty-eight out of 96 (60.4%) central NSCLC patients who were expected to undergo complex surgery had the scope or the difficulty of operation reduced. Ninety-five (60.1%) patients achieved major pathologic response (MPR), including 62 (39.2%) patients with pathologic complete response (pCR). Multivariate regression analysis showed that no clinical factor other than programmed death-ligand 1 (PD-L1) expression was predictive of the pathological response. The median follow-up time from diagnosis was 27.1 months. MPR and pCR were significantly associated with improved progression-free survival (PFS) and overall survival (OS). Neither stage nor PD-L1 expression was significantly associated with long-term survival.

Conclusions: The neoadjuvant chemo-immunotherapy is a feasible strategy for NSCLC with a favorable rate of pCR/MPR, modified resection and 2-year survival. No clinical factor other than PD-L1 expression was predictive of the pathological response. pCR/MPR may be effective surrogate endpoint for survival in NSCLC patients who received neoadjuvant chemo-immunotherapy.

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Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant therapy; chemo-immunotherapy; programmed death-1/programmed death-ligand 1 (PD-1/PD-L1); surgical extent

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Introduction

Lung cancer is one of the most common malignant tumors with the highest cancer-related mortality worldwide and about 85% are non-small cell lung cancer (NSCLC) (1). For stage IA–IIIA NSCLC patients, complete surgical excision is the most promising curative-intent therapeutic method (2). Nowadays, the overall survival (OS) of NSCLC patients who have received curative surgery is not optimistic because 30% to 55% of them suffer from postsurgical recurrence (3,4). Neoadjuvant therapy is expected to treat resectable and potential resectable NSCLC to downstage the tumor and achieve better surgical outcomes, especially for borderline operable NSCLC patients. However, the improvement of the 5-year survival rate for neoadjuvant chemotherapy is only 5% (5,6).

In recent years, the immune-checkpoint inhibitors

(ICIs), especially programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors, have revolutionized the systemic treatment paradigm of advanced NSCLC with remarkable effectiveness and favorable safety and tolerability (7,8). Multiple phase II and III randomized controlled trials (RCTs) have also demonstrated that neoadjuvant immunotherapy could achieve better therapeutic effectiveness with manageable tolerability for resectable NSCLC, especially in combination with chemotherapy (5,9,10).

Though numerous studies have confirmed the promising application prospect of neoadjuvant chemo-immunotherapy for NSCLC, there are great differences in the efficacy of patients with different stages or different abundance of biomarkers. CheckMate 816 showed a pathologic complete response (pCR) benefit with chemo-immunotherapy across all stages (IB–IIIA), while the event-free survival (EFS) benefit for early stages (IB–II) is lower than locally advanced stage (IIIA) in subgroup analysis (9). Of course, this conclusion still needs to be verified by a longer follow-up. There is some evidence to support PD-L1 status as a predictive marker for treatment response and survival in neoadjuvant chemo-immunotherapy setting (9,11), however, PD-L1 and tumor mutation burden (TMB) were not significantly associated with survival in the NADIM trial (12). Investigation of the clinical prognostic factors associated with the therapeutic efficacy, such as pCR, major pathologic response (MPR), disease-free survival (DFS), and OS, could help us to identify the benefit-risk population for neoadjuvant chemo-immunotherapy.

Except the anti-oncology and safety outcomes, the benefits of the surgical approach and its extent are worth in-depth study for neoadjuvant chemo-immunotherapy. Given the high postoperative morbidity and mortality after complex and extensive surgery, such as pneumonectomy, bilobectomy, or sleeve lobectomy (13), efforts should be made to avoid these excisions for selected NSCLC. Nowadays, neoadjuvant chemo-immunotherapy has brought hope to reduce such excision. However, there is little research on whether neoadjuvant chemo-immunotherapy

Highlight box

Key findings

- The neoadjuvant chemo-immunotherapy is a feasible strategy for non-small cell lung cancer (NSCLC) with a favorable rate of pathologic response, modified resection and long-term survival.
- No clinical factor other than programmed death-ligand 1 (PD-L1) expression was predictive of the pathological response.
- Pathologic response may be effective surrogate endpoint for survival in NSCLC patients who received neoadjuvant chemo-immunotherapy.

What is known and what is new?

- Neoadjuvant chemo-immunotherapy has shown good efficacy for NSCLC in randomized controlled trials.
- The neoadjuvant chemo-immunotherapy is a feasible strategy for NSCLC in real clinical setting. Potential risk-benefit patients were identified. The relationship between pathological response and long-term survival was validated.

What is the implication, and what should change now?

- This study provides a reference for patient selection, efficacy evaluation and clinical application of neoadjuvant chemo-immunotherapy. It is feasible to modify the surgical procedure after neoadjuvant chemo-immunotherapy for selected patients.

has any effect on long-term survival.

Therefore, we performed a retrospective study with a relatively large sample size which contained 158 NSCLC patients who received neoadjuvant chemo-immunotherapy prior to radical excision from two Chinese institutions, with particular attention paid to evaluating the safety, identifying benefit-risk population and surgery-related outcomes for neoadjuvant chemo-immunotherapy in real-world setting. We present this article in accordance with the STROBE reporting checklist (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-24-17/rc>).

Methods

Ethical statement

The retrospective cohort study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by The Ethics Committee of Peking University People's Hospital (approved number: 2021-PHB271-001) and The Second Affiliated Hospital of Air Force Medical University (approved number: K-202211-32). Informed consent was waived because this study was a noninterventional study.

Study population

NSCLC patients who received neoadjuvant chemo-immunotherapy between January 2019 and June 2022 in Peking University People's Hospital and The Second Affiliated Hospital of Air Force Medical University were eligible for this study. The main criteria for neoadjuvant chemo-immunotherapy were T3–4 and N2 diseases. In addition, we also included early-stage patients whose tumors were close to the main bronchus and were seeking neoadjuvant therapy to reduce the extent of surgical resection. All patients who underwent neoadjuvant immunotherapy were reviewed by the multi-disciplinary team which included oncologists, radiologists, and thoracic surgeons. *EGFR* mutations and *ALK* rearrangements status analysis were not recommended routinely before treatment, while they were performed in some patients based on individual surgeon recommendations and patient wishes. Patients with *EGFR* mutations and *ALK* rearrangements were not excluded from neoadjuvant chemo-immunotherapy and our analysis. In general, the included criteria for this study were: (I) diagnosed as resectable or potentially resectable primary NSCLC, regardless of *EGFR* and *ALK* status;

(II) clinical stage IB to IIIB (American Joint Committee on Cancer, eighth edition) based on preoperative staging examination; (III) received two to four cycles of neoadjuvant PD-1/PD-L1 immune checkpoint inhibitors combined with platinum-based chemotherapy; (IV) received radical resection and systemic lymph node dissection. The exclusion criteria were: (I) N3 lymph node metastasis; (II) wedge resection of the primary tumor; (III) previous lung cancer; (IV) previous or concurrent other malignant tumors; and (V) involved in any clinical trials. Patients with missing values were excluded from the analysis.

According to the National Comprehensive Cancer Network guidelines, all the enrolled patients underwent routine pretreatment examinations, including contrast-enhanced chest computed tomography (CT) to evaluate the primary tumor; positron emission tomography-CT (PET-CT) or combination of abdomen CT, brain magnetic resonance imaging (MRI) and radionuclide bone scanning to evaluate tumor staging; fiberoptic bronchoscopy or subcutaneous needle biopsy and endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) to obtain pathologic tumor diagnosis and staging. All patients received two to four cycles of ICI combined with platinum-based chemotherapy in 21-day cycles according to the international consensus. The efficacy of neoadjuvant chemo-immunotherapy was evaluated after every two cycles according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Comprehensive preoperative evaluation which included the aforementioned radiological examinations (PET-CT or combination of chest CT, abdominal CT, brain MRI and radionuclide bone scanning) and fiberoptic bronchoscopy were performed to confirm the resectability of the tumor. The neoadjuvant treatment cycles were decided based on comprehensive consideration of patients' tolerance to drugs and imaging remission of lesions, and eventually decided by the multi-disciplinary team. Surgical approach, and surgical extent were also determined by the multi-disciplinary team. To investigate the change of surgical approach after neoadjuvant therapy, the extent of primary surgical resection prior to neoadjuvant treatment was evaluated by two experienced thoracic surgeons according to the outcomes of radiological examination and fiberoptic bronchoscopy prior to neoadjuvant regimen. Modified surgery referred to decreased complexity or reduced surgical extent for central tumor expected to undergo complex surgery, including pneumonectomy to sleeve lobectomy, bilobectomy, or lobectomy; bilobectomy to lobectomy; sleeve lobectomy

to lobectomy. The suspicious residual disease, such as bronchial or vascular margin, were excluded by frozen section evaluation.

Pathologic evaluation

Surgical specimens, including primary tumors and dissected lymph nodes, were evaluated by two senior histopathologists. Pathological response was assessed by calculating the mean percentage of viable tumor cells. The pCR was defined as the absence of residual viable tumor cells in the primary tumor and dissected lymph nodes. The MPR was defined as $\leq 10\%$ residual viable tumor.

Follow-up and endpoints

Follow-up information was obtained from the medical records, postoperative visits, and telephone calls. The loss of follow-up was recorded according to the last follow-up status. The follow-up data included not only survival information to assess the therapeutic effect but also adverse events to evaluate the safety of the neoadjuvant regimen. The primary endpoint was pCR. The secondary endpoints were objective response rate (ORR), MPR, progression-free survival (PFS), OS, and safety. Safety included immunotherapy-related adverse events, 30-day mortality, and complications during the first 30 days after surgery. Postoperative complications were graded according to the Clavien-Dindo classification (14).

Statistical analysis

Statistical analysis was carried out with the R version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>). The Kaplan-Meier method with a log-rank test was used to evaluate the survival differences. Continuous variables were presented as median [interquartile range (IQR)] or mean [standard deviation (SD)], and categorical variables were presented as percentages. The Shapiro-Wilk test was used to analyze the normal distribution of the continuous variables. Student's *t*-test was used to compare variables with normal distributions. Non-normally distributed variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. To investigate the predictors of pCR and MPR, the odds ratio (OR) and its 95% confidence interval (CI) were estimated using a logistic regression model.

Variables were included in multivariate analysis when $P < 0.2$ in univariate analysis. Two-sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of the patients

As shown in [Figure S1](#), 158 patients eventually met our inclusion and exclusion criteria and were divided into early-stage group (stage IB–IIB) and locally advanced-stage group (stage IIIA–IIIB). Patients' baseline characteristics are presented in [Table 1](#). The patient cohort consisted predominantly of males (143, 90.5%), with a high prevalence of former or current smokers (123, 77.8%) and exhibiting central type (119, 75.3%) and squamous cell carcinoma (115, 72.8%). PD-L1 expression levels at diagnosis were examined in 73 individuals. Forty-one patients (25.9%) received two cycles of neoadjuvant treatment, while 80 (50.6%) had three cycles, and the left 37 (23.4%) had four cycles. Immunotherapy and chemotherapy drugs and treatment regimens are shown in [Table S1](#). In general, no significant difference was identified between early-stage and locally advanced-stage groups. Adjuvant treatment was received by 22.8% of the patients ([Table S2](#)). The rate of adjuvant therapy was significantly lower in patients who received four cycles of neoadjuvant therapy than in those who received three cycles of neoadjuvant therapy (0.8% *vs.* 30.0%, $P = 0.04$). While there was no significant difference in the proportion of adjuvant therapy in other pairwise comparisons (two cycles *vs.* three cycles: 17.1% *vs.* 30.0%, $P = 0.18$; two cycles *vs.* four cycles: 17.1% *vs.* 10.8%, $P = 0.64$).

Surgery summary

As shown in [Table 2](#), the median interval time between the last neoadjuvant therapy and surgery was 37 (IQR, 31–43) days. The mean operation duration and median blood loss were 166.7 (SD 52.9) minutes and 100 (IQR, 50–200) mL, respectively. Video-assisted thoracoscopic surgery (VATS) was performed in 89 (56.3%) patients. Fifty-eight out of 96 (60.4%) central NSCLC patients expected to undergo complex surgery underwent the aforementioned modified surgery. The proportion of surgical modification was significantly higher in locally advanced-stage patients (52/77, 67.5%) than in early-stage patients (6/19, 31.6%, $P = 0.009$). Other aspects of the modified surgery have been

Table 1 Baseline demographics and clinical characteristics of the NSCLC patients treated with neoadjuvant chemo-immunotherapy

Variables	All patients (N=158)	Stage IB–IIB (N=34)	Stage IIIA–IIIB (N=124)	P
Age (years), median [IQR]	62 [56, 66]	63 [57, 67]	61 [55, 66]	0.47
Gender, N (%)				
Male	143 (90.5)	33 (97.1)	110 (88.7)	0.25
Female	15 (9.5)	1 (2.9)	14 (11.3)	
Smoking status, N (%)				
Current or ever	123 (77.8)	29 (85.3)	94 (75.8)	0.34
Never	35 (22.2)	5 (14.7)	30 (24.2)	
Tumor location, N (%)				
Central	119 (75.3)	29 (85.3)	90 (72.6)	0.19
Peripheral	39 (24.7)	5 (14.7)	34 (27.4)	
Histology, N (%)				
Squamous	115 (72.8)	25 (73.5)	90 (72.6)	0.54
Adenocarcinoma	38 (24.1)	7 (20.6)	31 (25.0)	
Adenosquamous	5 (3.2)	2 (5.9)	3 (2.4)	
Tumor PD-L1 TPS, N (%)				
<1%	18 (11.4)	6 (17.6)	12 (9.7)	0.49
1–49%	26 (16.5)	4 (11.8)	22 (17.7)	
≥50%	29 (18.4)	5 (14.7)	24 (19.4)	
Unknown	85 (53.8)	19 (55.9)	66 (53.2)	
Treatment cycles, N (%)				
Two	41 (25.9)	9 (26.5)	32 (25.8)	0.32
Three	80 (50.6)	14 (41.2)	66 (53.2)	
Four	37 (23.4)	11 (32.4)	26 (21.0)	

NSCLC, non-small cell lung cancer; IQR, interquartile range; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

reported previously (15).

Efficacy

According to the RECIST 1.1 criteria, 10 (6.3%) patients achieved complete response (CR), 101 (63.9%) with partial response (PR), 44 (27.8%) with stable disease (SD), and three (1.9%) with radiographic progressive disease (PD). Ninety-five (60.1%) patients achieved MPR, including 62 (39.2%) patients with pCR. As shown in *Figure 1*, all ten patients with clinical CR achieved pCR; all three patients with PD were judged to be pathologically non-MPR; 15 (34.1%) of 44 patients with SD and 37 (36.6%) of 101 patients with PR achieved pCR. The postoperative

pathological downstaging of tumor-node-metastasis (TNM) stage and N stage is shown in *Figure S2*. None of the eight patients with known *EGFR* mutations achieved MPR.

Multivariate regression analysis revealed that no clinical factors such as age, gender, smoking history, tumor type, initial tumor size, N2 lymph node metastasis, neoadjuvant cycles adverse reactions, and radiological response (CR and PR) were associated with pCR or MPR. Meanwhile, patients with high PD-L1 tumor proportion score (TPS) level were more likely to achieve MPR (*Tables 3,4*).

The median follow-up time from diagnosis was 27.1 (IQR, 22.0–34.6) months with six (3.8%) patients were lost. The median duration of PFS and OS was not reached (*Figure S3*). The 2-year PFS and OS were 80.6% (95%

Table 2 Perioperative outcomes after neoadjuvant chemo-immunotherapy for NSCLC

Variables	All patients	Stage IB–IIB	Stage IIIA–IIIB	P
Clinical response				0.86
Complete response	10 (6.3)	2 (5.9)	8 (6.5)	
Partial response	101 (63.9)	20 (58.8)	81 (65.3)	
Stable disease	44 (27.8)	11 (32.4)	33 (26.6)	
Progressive disease	3 (1.9)	1 (2.9)	2 (1.6)	
Interval time to surgery (day), median [IQR]	37 [31, 43]	35 [30, 42]	38 [32, 43]	0.46
Type of operation, N (%)				0.005
VATS	89 (56.3)	26 (76.5)	63 (50.8)	
Thoracotomy	50 (31.6)	3 (8.8)	47 (37.9)	
Convert to thoracotomy	19 (12.0)	5 (14.7)	14 (11.3)	
Surgical approach, N (%)				0.04
Lobectomy	95 (60.1)	26 (76.5)	69 (55.6)	
Sleeve lobectomy	21 (13.3)	4 (11.8)	17 (13.7)	
Bilobectomy	20 (12.7)	4 (11.8)	16 (12.9)	
Pneumonectomy	22 (13.9)	0	22 (17.7)	
Operative duration (min), mean (SD)	166.7 (52.9)	154.6 (56.6)	170.0 (51.6)	0.13
Blood loss (mL), median [IQR]	100 [50, 200]	100 [50, 200]	135 [50, 200]	0.28
Pathologic response, N (%)				0.06
pCR	62 (39.2)	19 (55.9)	43 (34.7)	0.04 ^a
MPR	95 (60.1)	23 (67.6)	72 (58.1)	0.41 ^b
Non-MPR	63 (39.9)	11 (32.4)	52 (41.9)	
Change in pN stage, N (%)				<0.001
N0 to N0	31 (19.6)	20 (58.8)	11 (8.9)	
N1 to N1	5 (3.2)	4 (11.8)	1 (0.8)	
N1 to N0	19 (12.0)	6 (17.6)	13 (10.5)	
N2 to N2	18 (11.4)	0	18 (14.5)	
N2 to N1	8 (5.1)	0	8 (6.5)	
N2 to N0	69 (43.7)	0	69 (55.6)	
Progress	8 (5.1)	4 (11.8)	4 (3.2)	
Modified surgery, N (%)				0.01
Yes	58 (36.7)	6 (17.6)	52 (41.9)	0.009
No	38 (24.1)	13 (38.2)	25 (20.2)	
Uninvolved	62 (39.2)	15 (44.1)	47 (37.9)	

^a, comparison of pCR and non-pCR; ^b, comparison of MPR and non-MPR. NSCLC, non-small cell lung cancer; IQR, interquartile range; VATS, video-assisted thoracoscopic surgery; SD, standard deviation; pCR, pathologic complete response; MPR, major pathologic response.

CI: 74.5–87.3%) and 89.5% (95% CI: 84.5–94.7%), respectively. During the follow-up period, postoperative recurrence occurred in 25 (15.8%) patients, of whom eight (5.1%) had local recurrence and 17 (10.8%) had distant metastasis. Notably, one patient who reached pCR without adjuvant treatment was found to have intracranial metastasis

13 months after surgery. Seventeen (10.8%) patients died, including nine from tumor progression, four from perioperative complications, one from severe side effects (immune myocarditis) of postoperative immunotherapy, one from pulmonary infection, and two from other causes. The patient who died from immune myocarditis received three cycles of neoadjuvant chemo-immunotherapy and achieved pCR. Immune myocarditis occurred one month after the first cycle of adjuvant chemo-immunotherapy.

As for subgroup analysis, both PFS and OS in pCR and MPR groups were significantly higher than those in non-pCR and non-MPR groups (Figure 2). Moreover, there was no statistically significant difference on PFS or OS between early-stage group and locally advanced-stage group, and no significant association was found between PD-L1 TPS level and PFS or OS (Figure S4).

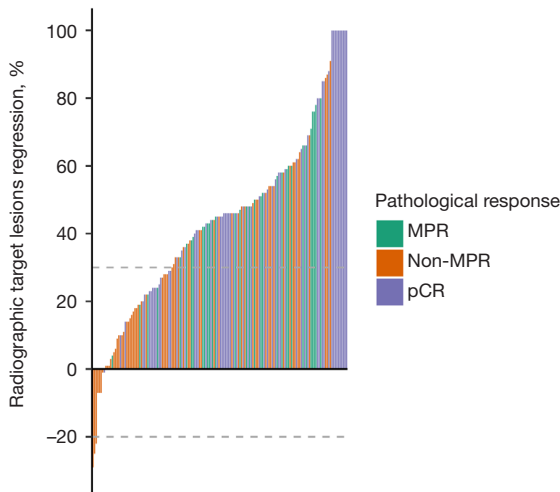


Figure 1 Imaging remission after neoadjuvant chemo-immunotherapy. MPR, major pathologic response; pCR, pathologic complete response.

Safety and surgical complications

As shown in Figure S1, among 177 patients who were assessed for eligibility, 19 (10.7%) patients without radical resection were excluded. Of these, five cases (2.8%) were because the tumor was deemed unresectable or the surgical risk was too high; three (1.7%) were denied surgery because of poor lung function or other serious underlying diseases; two (1.1%) because of severe immunotherapy-associated

Table 3 Univariate and multivariate logistic analysis of predictive factors for achieving pCR

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (≥65 years)	1.10	0.55–2.19	0.78			
Gender (female)	0.21	0.05–0.98	0.04			
Smoke history (yes)	3.24	1.31–7.97	0.01	1.85	0.46–9.33	0.41
Tumor size (≥4 cm)	0.58	0.29–1.14	0.11	0.33	0.10–1.03	0.05
Tumor location (peripheral)	0.96	0.46–2.01	0.90			
Histological type (non-SCC)	0.76	0.37–1.56	0.45			
cN stage (N2)	0.52	0.27–1.01	0.05	0.42	0.14–1.24	0.12
Neo-adjuvant cycle (≥C3)	0.88	0.43–1.82	0.73			
PD-L1 (high)	3.17	1.15–8.75	0.02	4.13	1.38–13.58	0.01
irAE (yes)	0.56	0.19–1.66	0.29			
Radiographic remission (ORR)	1.57	0.76–3.22	0.22			

Gender was not included in the multivariate analysis to avoid overfitting given the paucity of data (only 2/13 patients achieved pCR). pCR, pathologic complete response; OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinomas; PD-L1, programmed death-ligand 1; irAE, immune-related adverse events; ORR, objective response rate.

Table 4 Univariate and multivariate logistic analysis of predictive factors for achieving MPR

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age (≥ 65 years)	0.94	0.48–1.88	0.87			
Gender (female)	0.55	0.19–1.59	0.26			
Smoke history (yes)	1.58	0.74–3.37	0.23			
Tumor size (≥ 4 cm)	1.03	0.52–2.03	0.92			
Tumor location (peripheral)	1.69	0.78–3.65	0.18	2.98	0.76–13.78	0.13
Histological type (non-SCC)	0.49	0.24–0.99	0.04	0.43	0.11–1.61	0.21
cN stage (N2)	0.54	0.28–1.05	0.06	0.48	0.14–1.61	0.24
Neo-adjuvant cycle ($\geq C3$)	1.64	0.80–3.36	0.17	0.84	0.20–3.34	0.81
PD-L1 (high)	5.26	1.70–16.28	0.004	6.98	2.12–28.22	0.003
irAE (yes)	0.81	0.30–2.18	0.67			
Radiographic remission (ORR)	3.65	1.79–7.45	<0.001	3.16	0.91–11.94	0.07

MPR, major pathologic response; OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinomas; PD-L1, programmed death-ligand 1; irAE, immune-related adverse events; ORR, objective response rate.

pneumonia. In three cases (1.7%), the reason was that the patients met the operation conditions but they explicitly refused the operation. In six cases (3.4%), only wedge resection or palliative resection was performed considering the patient's physical condition and the patient's wish. Twenty-four patients (15.2%) experienced grade 3 or worse immune-related adverse events, including immune-related pneumonitis, myelosuppression, and skin lesions.

Perioperative complications are statistically analyzed and shown in [Table S3](#). A total of 32 (20.3%) patients experienced grade 2–5 postoperative complications, and there was no significant difference between the different neoadjuvant treatment cycles (21.9% for two cycles, 20% for three cycles and 18.9% for four cycles, $P=0.94$). The most frequent complications were excessive hemorrhage (>400 mL, 18, 11.4%), pneumonia (7, 4.4%), chylothorax (3, 1.9%), and respiratory failure (3, 1.9%). Four (2.5%) patients died within the first 30 days after surgery, three from pneumonia and one from acute heart attack accompanying respiratory failure.

Discussion

We presented 158 cases of NSCLC patients who had received neoadjuvant chemo-immunotherapy prior to radical excision from two Chinese academic institutions.

Compared to most previous studies on neoadjuvant therapy for lung cancer (5,9), more locally advanced-stage NSCLC (54.3% IIIA and 24.3% IIIB) were enrolled in our cohort. Stage IIIB or above is generally considered unsuitable for surgical treatment. However, the results of chemo-immunotherapy RCTs have revolutionized the therapeutic landscape for locally advanced-stage NSCLC patients (stage III) with promising effectiveness, favorable safety, and tolerability (9,16).

Deng and colleagues reported that 60.1% (31/51) of clinical IIIB patients successfully converted from initial unresectable to radical resection after neoadjuvant chemo-immunotherapy with favorable DFS compared to those without surgery (17). However, the involvement of N3 lymph nodes (supraclavicular and contralateral mediastinal lymph nodes), bulky N2 lymph nodes and direct invasion to heart, great vessels, diaphragm, trachea, or carina after neoadjuvant therapy were still regarded as unresectable disease (18). In our study, of the 42 patients with stage IIIB disease, 40 achieved stage IIIA or better after neoadjuvant therapy. This series provides evidence that surgery after neoadjuvant chemo-immunotherapy, even in those with later-stage disease is effective, with tolerable perioperative mortality and complication rates.

The pCR and MPR were identified as potential surrogate endpoints for survival in NSCLC patients who received

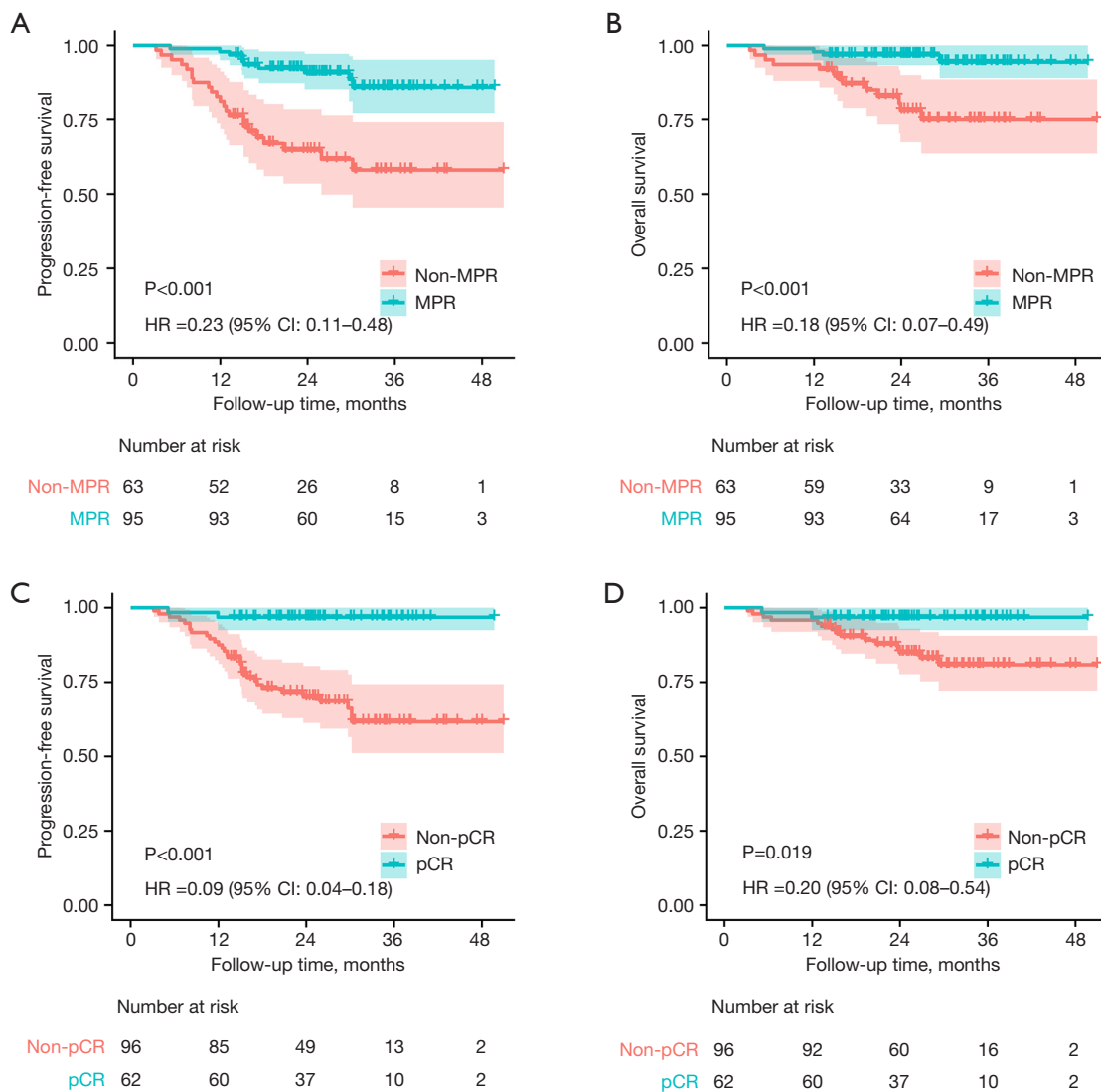


Figure 2 Kaplan-Meier survival curves according to the pathological response. (A) Progression-free survival comparisons: MPR *vs.* non-MPR; (B) overall survival comparisons: MPR *vs.* non-MPR; (C) progression-free survival comparisons: pCR *vs.* non-pCR; (D) overall survival comparisons: pCR *vs.* non-pCR. HR, hazard ratio; CI, confidence interval; MPR, major pathologic response; pCR, pathologic complete response.

neoadjuvant therapy. For those who achieved MPR, it was reported that there was a two-time improvement of 5-year OS (85.0% *vs.* 40.0%, $P<0.001$) compared to the absence of MPR (19). However, historical data showed that pCR and MPR rates were relatively low in the era of neoadjuvant chemotherapy, with a pCR rate of 4% and an MPR rate of 20%, respectively (20). There was no doubt that the combination of chemotherapy and immunotherapy increased the pathological responses, and multiple RCTs showed that the pCR rate could range from 18% to 63%, and 36.9% to 85% for MPR rate (20). Consistent with

previous trials, our study demonstrated promising anti-oncology outcomes resulting in a pCR rate of 39.2% and an MPR rate of 60.1%, respectively. Meanwhile, we demonstrated that there was no local recurrence or distant metastasis among the patients who achieved pCR. And the 2-year PFS and OS rates were significantly higher for patients who achieved pCR and MPR, which reinforced the relevance of the pathological response as a potential survival surrogate.

Nowadays, there is still controversy on the clinical predictive factors for therapeutic effect of patients who

received neoadjuvant chemo-immunotherapy (5,9). Indeed, although in some trials, PD-L1, biomarker in adjuvant immunotherapy, was found to have the potential to predict radiologic and pathologic response of neoadjuvant chemo-immunotherapy (11,21), PD-L1 and TMB were not significantly associated with survival in the NADIM trial (12). In the CheckMate 816 trial, although the EFS benefit of neoadjuvant chemo-immunotherapy was observed in all PD-L1 subgroups, the benefits were greater in the PD-L1 $\geq 50\%$ group [hazard ratio (HR), 0.24] and PD-L1 $\geq 1\%$ group (HR 0.41) compared with PD-L1 $< 1\%$ group (HR, 0.85) (9). In the whole group of our study, we found that no clinical factor could predict the pCR or MPR status but PD-L1 staining levels. Patients with high PD-L1 staining levels seemed to have better PFS and OS (HR 0.44 & 0.42). Larger scale cohorts and longer follow-up time are still required to confirm the clinical predictive factors for pathological response and survival outcomes.

Most of the earlier neoadjuvant studies (such as NADIM and SAKK16/14) specifically focused on advanced stage disease. However, CheckMate 816 showed a consistent pCR benefit with chemo-immunotherapy across all stages (IB–IIIA). Although the EFS benefit was not evident in lower stages (IB–IIB) compared with IIIA in subgroup analysis (9). Our study showed that pCR was more likely to be achieved in early-stage patients compared to locally advanced patients, while MPR rates were not significantly different. The EFS and OS curves also did not show significant differences between the early-stage and locally advanced-stage patients. Although there are potential differences of the benefits in patients with different stages for neoadjuvant chemo-immunotherapy, the relevant results need to be confirmed by further follow-up because of the low incidence of outcome events in early stage.

There is still a controversy about therapeutic effectiveness of immunotherapy in NSCLC with *EGFR*-sensitizing mutations. The tumor microenvironment (TME) of the NSCLC with *EGFR* mutations is mainly in non-inflammatory state which contains weak lymphocytic infiltration and low anti-tumor inflammatory response. Thus, this TME state would decrease the effectiveness of immunotherapy for NSCLC with *EGFR* mutations, theoretically (22). In the LCMC3 trial, two neoadjuvant cycles atezolizumab (a PD-L1 inhibitor) monotherapy was administered in resectable stage NSCLC. For patients without known *EGFR* or *ALK* alterations, 6.8% achieved pCR and 20.4% achieved MPR, while there was no MPR among the patients with *EGFR* mutations (23). However,

Zhang and colleagues reported that the pCR rate was 11.1% (2/18) and the MPR rate was 44.4% (8/18) with neoadjuvant chemo-immunotherapy for NSCLC with *EGFR* mutation (24). Though, our study also suggested low pCR and MPR rates for patients with gene mutations after neoadjuvant chemo-immunotherapy. We believe that as the sample size increases, the clinical feasibility and value of combination therapy for patients with *EGFR* or *ALK* mutations would be identified by larger cohorts.

Complex surgery, such as pneumonectomy, bilobectomy, sleeve lobectomy, lobectomy with bronchoplasty or arterioplasty, are usually needed for patients with extensive invasion tumors (i.e., invasion of trachea, carina, main bronchus, fissure, or main pulmonary artery). However, it was reported that pneumonectomy was associated with worse long-term survival, quality of life and non-oncologic death than lobectomy because of high postoperative morbidity and mortality (10). Thus, there is an urgent need to investigate whether the surgical feasibility and surgical extent could be changed after neoadjuvant therapy.

Chen and colleagues first demonstrated that the feasibility and safety of using chemo-immunotherapy before sleeve lobectomy were similar to those of sleeve lobectomy alone in a small sample study (25). Wu and colleagues reported that pneumonectomy was avoided in 80% (20/25) NSCLC after chemo-immunotherapy (26). Combined with the above literature and our findings, we believe that it is feasible to perform modified resection for pulmonary preservation among selected cases, benefiting from remarkable tumor regression after neoadjuvant chemo-immunotherapy.

In the CheckMate 816 study, the 2-year EFS rate was 63.8% with nivolumab plus chemotherapy and 45.3% with chemotherapy alone, and a better median EFS was observed in the combined treatment group (31.6 vs. 20.8 months; HR, 0.65; 95% CI: 0.47–0.90). Zhang and colleagues reported in a retrospective analysis that the 2-year DFS rate in the PD-1 plus chemotherapy group was higher than that of the chemotherapy group (79.3% vs. 60.2%, $P=0.04$) (27). The 2-year PFS rate of our series in the real world is comparable to previous RCT studies and adds to the evidence for the clinical use of this treatment modality.

There are several limitations in our research. Firstly, the patient selection biases were inevitable for this was a real-world retrospective study and only NSCLC patients who have received radical surgery after neoadjuvant immunotherapy were enrolled. Secondly, though patients from two centers were included in the current study, larger scale

cohorts should be needed to verify our results. Thirdly, the follow-up duration was relatively short, the long-term OS should be investigated in further study. In addition, as a one-arm study, comparing with neoadjuvant chemotherapy was not performed, so the pathological benefit of immunotherapy should be interpreted with caution. Finally, clinical factors were taken into consideration to identify the predictive factors for pCR and MPR, the TME and molecular characteristics were not involved in the current study.

Conclusions

The neoadjuvant chemo-immunotherapy is a feasible strategy for NSCLC with a favorable rate of pCR/MPR, modified resection and PFS. No clinical factor other than PD-L1 expression was predictive of the pathological response. pCR/MPR may be effective surrogate endpoints for survival in NSCLC patients who received neoadjuvant chemo-immunotherapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://tclr.amegroups.com/article/view/10.21037/tclr-24-17/rc>

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <https://tclr.amegroups.com/article/view/10.21037/tclr-24-17/coif>). The 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) and approved by The Ethics Committee of Peking University People's Hospital (approved number: 2021-PHB271-001) and The Second Affiliated Hospital of Air Force Medical University (approved number: K-202211-32). Informed consent was waived because this study was a noninterventional study.

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