Original Article

Preoperative immunochemotherapy for locally advanced non-small cell lung cancer: an analysis of the clinical outcomes, optimal number of cycles, and peripheral immune markers

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Background: This retrospective study aimed to evaluate the real-world efficacy of neoadjuvant immunochemotherapy in locally advanced stage III non-small cell lung cancer (NSCLC), with a particular focus on analyzing the optimal treatment cycle and peripheral immune markers.

Methods: Eligible patients with biopsy-confirmed stage III NSCLC who underwent neoadjuvant immunochemotherapy between January 1st, 2018 and March 30th, 2021 were identified, and their oncological outcomes were collected.

Results: A total of 115 patients were identified, among whom 61, 51, and three cases were classified as clinical stage IIIA, IIIB, and IIIC at presentation, respectively. The objective response rate was 61.7% (71/115) after immunochemotherapy. The most frequent surgical procedure was lobectomy, performed in 91 (79.1%) cases, and all patients had microscopic-free margins. Major pathological response (MPR) was observed in 64 (55.7%) patients, among whom 44 (38.3%) achieved a complete pathological response; pathological-confirmed lymph node downstage (cN2-3 to ypN0-1) was described in 73.6% (67/91) of patients with cN2-3 diseases. The median disease-free survival (DFS) of all enrolled patients was 23.6 [95% confidence interval (CI): 15.9–31.3] months, while for patients with residual tumors of more than 10%, the median DFS was 18.1 (95% CI: 12.5–23.8) months. The post-hoc multivariable analysis showed that three [odds ratio (OR), 4.78; 95% CI: 1.17–19.55] and four (OR: 6.50; 95% CI: 1.12–37.54) cycles of neoadjuvant immunochemotherapy were prone to higher MPR rates compared to two cycles in patients that were classified as complete/partial response (CR/PR). However, adding over five cycles was not associated with a higher MPR rate (OR, 0.91; 95% CI: 0.15–5.47). The pretreatment lymphocyte count level (1.89±0.68 *vs.* 1.59±0.63, P=0.019) and monocyte count level (0.71±0.32 *vs.* 0.59, P=0.020) were significantly higher in MPR patients compared to non-MPR patients.

Conclusions: The present study confirmed a favorable real-world tumor downstage efficacy of neoadjuvant immunochemotherapy in locally advanced NSCLC. Even though CR/PR was achieved, it is still beneficial when extended into 3–4 cycles of neoadjuvant immunochemotherapy.

Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant immunochemotherapy; tumor downstage; treatment cycle; efficacy biomarker

Submitted Jun 09, 2022. Accepted for publication Nov 06, 2022.
doi: 10.21037/tlcr-22-439
View this article at: https://dx.doi.org/10.21037/tlcr-22-439

Introduction

Lung cancer remains the leading cause of cancer-associated deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of newly diagnosed cases (1), about one-third of which are locally advanced diseases at diagnosis (1,2). Multimodality therapies are currently considered the standard treatment (3) for stage III NSCLC; however, the therapeutic outcomes remain poor despite definitive concurrent chemoradiotherapy (4), with a median progression-free survival (PFS) of 13 months and a 3-year overall survival of just 30%. Furthermore, a significant number of locally advanced NSCLC cases eventually develop disease progression or locoregional relapse (5).

The emergence of immune checkpoint blockades (ICBs), which block the binding of the programmed cell death protein 1 (PD-1) receptor and its ligands (PD-L1/2) and subsequently reinvigorate an antitumor response due to T-cell activation, have already changed the treatment strategy (6) of advanced NSCLC in recent years. Long-term outcomes from phase III clinical trials of PD-1/PD-L1 inhibitors in previously treated patients with advanced NSCLC demonstrated a 2-year overall survival of 23–29% and 5-year overall survival of 16% (7,8). The subsequent PACIFIC (9) trials confirmed the survival benefit of the consolidation ICB strategy after concurrent chemoradiotherapy in locally advanced unresectable NSCLC and reported a 3-year overall survival (OS) of 57.0% in the durvalumab group versus 43.5% in the placebo group. Recently, more publications have focused on the role of immunotherapy plus chemotherapy (10-12) or dual checkpoint inhibition (13) in the neoadjuvant setting for resectable NSCLC. The NADIM trial (14) accessed the efficacy of neoadjuvant nivolumab combined with chemotherapy in stage IIIA NSCLC, and the major pathologic response (MPR) rate reached 85%, with a remarkable PFS rate of 95.7% at 12 months and 77.1% at 24 months. Unpublished results from the LCMC3 trial showed an MPR rate of 21% and pathologic complete response (pCR) rate of 7%, and about 43% of stage IIB-IIIB NSCLCs had a pathological downstage after neoadjuvant atezolizumab (15). The SAKK 16/14 trial (16) employing three cycles of neoadjuvant durvalumab combined with chemotherapy revealed an MPR rate of 62%. In the Checkmate816 trial (17), nivolumab plus platinum-based chemotherapy resulted in a significantly improved median event-free survival (31.6 *vs.* 20.8 months; P=0.005) and pCR rate (24.0% *vs.* 2.2%; P<0.001) compared with platin-chemotherapy alone. Theoretically, preoperative immunotherapy has the potential advantages of increasing operability and eradicating micrometastases (18,19), and may be able to induce long-term tumor regression and potentially cure locally advanced NSCLC. Despite the clinically established efficacy and safety of neoadjuvant immunochemotherapy, little is known about its long-term efficacy in a real-world setting.

Notably, two to four treatment cycles were administrated in most of the relevant phase II/III trials on neoadjuvant immunotherapy (15-17,20,21). Extended treatment cycles might result in the postponement of surgery, while a short course of treatment may not be sufficient for ICB to induce its effect. Nevertheless, the optimal cycle number of neoadjuvant immunotherapy could not be explored in the aforementioned trials because there were no head-to-head comparisons in the different cycle groups. Thus, further exploration of the correlation between the treatment cycle and treatment-induced pathological response is needed.

Herein, we assess the real-world efficacy of neoadjuvant immunochemotherapy for locally advanced stage III NSCLC, with a particular focus on analyzing the optimal treatment cycle and peripheral immune markers. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-439/rc).

Methods

Study design and patient inclusion

The present research is a retrospective and single-institutional study. The data of patients who underwent at least two cycles of PD-1 blockades (including Pembrolizumab, Nivolumab, Toripalimab, Tislelizumab, Camrelizumab, or Sintilimab) plus platinum-based chemotherapy followed by surgery after discussion and approval of the multidisciplinary team (MDT) approach at the First Affiliated Hospital of Guangzhou Medical University between May 1st, 2018 to March 30th, 2021 were retrospectively collected using a prospective follow-up database. The exclusion criteria were as follows: patients with small cell lung cancer; patients diagnosed with distant metastases or with other malignant tumors; patients who were previously treated; patients complicated with severe liver/renal dysfunctions, cardiovascular disease, or systemic immune disorders; and patients treated with other neoadjuvant therapies or participated in any clinical trials.

This real-world retrospective study was mainly conducted by assessing the patients' data in a prospective follow-up database maintained by our hospital. All patients signed the informed consent form for both the neoadjuvant regimen and the surgery. This study was carried out in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of The First Affiliated Hospital of Guangzhou Medical University (No.2020-122). The requirement for informed consent was waived due to the retrospective nature of the study.

Treatment strategy

All patients admitted to the hospital underwent a standard diagnostic work-up and staging for NSCLC. The baseline tumor staging included pretreatment bronchoscopy or computed tomography (CT)-guided fine-needle biopsy, positron-emission computed tomography (PET-CT), and contrast-enhanced CT or magnetic resonance imaging of the brain and chest to exclude distant metastases. The tumor, node, metastasis (TNM) classification of NSCLC was evaluated according to the AJCC (American Joint Committee on Cancer) Cancer Staging Manual (8th edition) (22). Specimens for cytological and histological examination were obtained via percutaneous needle biopsy or endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA). All patients were confirmed to have no targetable driven mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and c-ros oncogene 1, receptor tyrosine kinase (ROS1).

Each patient had their treatment decided after considering the following: (I) cancer staging and mutation test, (II) resectability of the tumor, and (III) the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of patients. Treatment was planned by a multidisciplinary tumor board. Patients with stage cIIIB/IIIC disease at presentation were considered for surgical resection, provided that they did not progress during induction immunochemotherapy and that all lesions were amenable to radical treatment without signs of direct tumor invasion to the great vessels, diaphragm, heart, trachea, and carina (23).

Neoadjuvant chemoimmunotherapy was performed after the consent of a MDT, which included thoracic oncologists, radiologists, and thoracic surgeons. The neoadjuvant immunochemotherapy strategy involved platinum-based doublet chemotherapy was prescribed every 21 days (24) with PD-1 inhibitors. Patients underwent venous blood cell analysis before each 21-day therapy cycle to monitor their complete blood cell counts and biochemical parameters. CT scans were performed every two cycles and at the last planned cycle of immunochemotherapy. The response to immunotherapy was graded according to the Immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) criteria (25).

The detailed criteria of resectability were as follows: (I) no bulky mediastinal mass; (II) no sign of direct tumor invasion to the great vessels, diaphragm, heart, trachea, and carina; and (III) no progression or distant metastasis (23). The workup was performed by the multidisciplinary tumor board.

Surgery was then performed by experienced thoracic surgeons. A thoracoscope was first indwelled for intraoperative exploration, which aimed to assess the nodal status, the extent of lymphovascular invasion, and possible adhesions in the fissure to re-evaluate resectability. Briefly, the procedures involved lobectomy/pneumonectomy with ipsilateral systematic hilar and mediastinal lymph node dissection. The resected lung and lymph node tissues were fixed in buffered 4% formaldehyde, embedded, sectioned, and stained with haematoxylin-eosin (HE), and the gross maximum diameter was then measured and analyzed by two senior pathologists. The percentage of viable tumor cells in each slide was measured, and MPR was defined as 10% or less viable tumor remaining on the postoperative pathological review (26), and pCR was defined as no residual tumor cells found in the dissected tissues and lymph node (26). The histologic subtype was determined by a review of biopsy specimens obtained before immunochemotherapy if there was no viable residual tumor in the surgical-resected specimens. Following surgery and a multidisciplinary board discussion regarding their initial response to chemotherapy and subsequent clinical conditions, all patients were provided with one of the following three regimens as an adjuvant treatment: (I) conventional chemotherapy, (II) PD-1 blockade monotherapy, or (III) chemotherapy combined with PD-1 blockade.

Data collection

The following outcomes were respectively collected: (I) baseline characteristics, including age, sex, histology, clinical TNM (cTNM) stage (subdivided into stage IIIA, and stage IIIB-IIIC subgroups), etc.; (II) baseline peripheral immune estimators before the first dose of immunochemotherapy,

including neutrophil count, lymphocyte count, blood platelet count, and monocyte count; (III) neoadjuvant treatment details, including agents, course of treatment, the interval between the last dose of immunochemotherapy and surgery, etc.; (IV) oncological outcomes, including radiological-regression rate, pathologic TNM (pTNM) stage, etc.; (V) surgical details, including surgical approach, surgical procedure, mortality, etc.; and (VI) survival outcomes: postoperative recurrence-free survival, which was defined as the time from primary tumor resection to the date of last follow-up or recurrence diagnosis.

Statistical analyses

To adjust for potential clinical factors influencing the outcomes, a multivariable binary logistic analysis for MPR (including factors such as age group, gender, histology type, clinical T stage, clinical N stage, and treatment cycle number) was conducted. Continuous data were presented as the mean and standard deviation and were analyzed with two-sample Student's t-tests for independent data. Categorical variables were presented as a count and percentage of patients and compared with the chi-squared test or Fisher's exact test. All tests were two-sided, with an a-level of 0.05. SPSS software (SPSS version 25.0; IBM Corp, Armonk, NY) was used for all statistical evaluations.

Results

Patients' characteristics

The detailed patient demographics are summarized in *Table 1*. A total of 115 patients were identified as having undergone lung resection after neoadjuvant immunochemotherapy for locally advanced stage III NSCLC, among whom 61 cases (53.0%) were classified as clinical stage IIIA, 51 cases (44.3%) with clinical stage IIIB, and three cases (2.6%) with clinical stage IIIC diseases at presentation. The median age of the entire cohort was 62 years [interquartile range (IQR), 55–67], and 102 (88.7%) patients were male. Also, 77 (67.0%) patients were current or ever smokers at enrolment. In terms of tumor histology, 74 (64.4%) patients were diagnosed with lung squamous cell carcinoma (LUSQ) and 26 (22.6%) with lung adenocarcinoma (LUAD). The pretreatment tumor stage assessment showed that 81 (70.4%) patients had N2 diseases, and 29 (25.2%) and 42 (36.5%) cases were at the T3 and T4 stage, respectively. Twenty-nine patients (25.2%) received two cycles of neoadjuvant immunochemotherapy, while 44 (38.3%) had three cycles, 27 (23.5%) had four cycles, and the remaining 15 had more than four cycles. The median interval between the last neoadjuvant treatment and surgery was 46 days (IQR, 36–55).

Efficacy of neoadjuvant immunochemotherapy

For all of the enrolled patients, after neoadjuvant immunochemotherapy, complete response (CR) was achieved in one (0.9%) patient, 70 (60.9%) patients achieved a partial response (PR), 38 (33.0%) had stable disease (SD), and one (0.9%) had progressive disease (PD) according to the RECIST 1.1 criteria (*Figure 1*). Seven patients were not available to radiologically evaluate the diameters of the target lesions due to central cancers with obstructive pneumonitis/atelectasis. No significant difference was identified between the stage cIIIA and stage cIIIB-C groups (P=0.274) (*Table 2*).

Outcomes of surgery after neoadjuvant immunochemotherapy

The most frequent surgical procedure was lobectomy, performed in 91 (79.1%) cases. Ten patients required a sleeve resection, including seven right upper sleeve resections with bronchoplastic and three left upper sleeve resections with angioplastic reconstruction. Bilobectomy was carried out in nine cases (7.8%), including right bilobectomy in six cases (5.2%) and left pneumonectomy in three cases (2.6%). Due to poor lung function, five cases only received wedge resection after immunochemotherapy. The video-assisted thoracoscopy (VATS) approach was used in 100 patients (87.0%) and thoracotomy in 12 (10.4%) patients. Three (2.6%) patients were converted to open from VATS intraoperatively. All patients underwent standard lymphadenectomy. The median number of N1 lymph nodes harvested was 7 (IQR, 4–13), while the median N2 lymph nodes harvested was 11 (IQR, 5–17).

Pathological response and post-resection survival

All patients had microscopically free margins and no extracapsular extension of the tumor in resected lymph nodes. An MPR was observed in 64 patients (55.7%), among whom 44 (38.3%) were classified as pCR. Thirty-nine patients had lymph node involvement after surgery; among them, 24 (20.9%), and 15 (13.0%) cases had persistent metastasis region N2 and N1 disease,

Table 1 Baseline demographic and clinical characteristics of patients stratified by clinical stage at presentation

Characteristics	n (%)			P value
	Total (n=115)	Stage IIIA (n=61)	Stage IIIB-C (n=54)	
Age [median (IQR)] (years)	62 [55, 67]	63 [57, 67]	57 [54, 66]	0.024
≤70	101 (87.83)	53 (86.89)	48 (88.89)	0.966
>70	14 (12.17)	8 (13.11)	6 (11.11)	
BMI [median (IQR)] (kg/m^2)	23.3 [21.4, 25.3]	22.8 [20.7, 24.9]	23.7 [22.6, 25.3]	0.309
Sex				
Female	13 (11.30)	10 (16.39)	3 (5.56)	0.124
Male	102 (88.70)	51 (83.61)	51 (94.44)	
Smoking status				
Current or ever	77 (66.96)	31 (50.82)	36 (66.67)	0.085
Never	38 (33.04)	30 (49.18)	18 (33.33)	
Histology				
LUAD	26 (22.61)	13 (21.31)	13 (24.07)	0.854
LUSQ	74 (64.35)	38 (62.30)	36 (66.67)	
LCLC	2 (1.74)	1 (1.64)	1 (1.85)	
LELC	6 (5.22)	4 (6.56)	2 (3.70)	
LASC	6 (5.22)	4 (6.56)	2 (3.70)	
PMEC	1 (0.87)	1 (1.64)	0 (0.00)	
Clinical tumor stage				
T1	6 (5.22)	4 (6.56)	2 (3.70)	<0.001
T2	38 (33.04)	33 (54.10)	5 (9.26)	
T3	29 (25.22)	8 (13.11)	21 (38.89)	
T4	42 (36.52)	16 (26.23)	26 (48.15)	
Clinical nodal stage				
N0	8 (6.96)	8 (13.11)	0 (0.00)	<0.001
N1	16 (13.91)	16 (26.23)	0 (0.00)	
N2	81 (70.43)	37 (60.66)	44 (81.48)	
N3	10 (8.70)	0 (0.00)	10 (18.52)	
PD-1 blockades				
Camrelizumab	33 (28.70)	19 (31.15)	14 (25.93)	0.684
Nivolumab	12 (10.43)	8 (13.11)	4 (7.41)	
Pembrolizumab	15 (13.04)	7 (11.48)	8 (14.81)	
Sintilimab	40 (34.78)	18 (29.51)	22 (40.74)	
Tislelizumab	8 (6.96)	4 (6.56)	4 (7.41)	
Toripalimab	5 (4.35)	4 (6.56)	1 (1.85)	
Unknown	2 (1.74)	1 (1.64)	1 (1.85)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	n (%)			P value
	Total (n=115)	Stage IIIA (n=61)	Stage IIIB-C (n=54)	
Chemotherapy regimens (All with platinum[1])				
Docetaxel	3 (2.61)	2 (3.28)	1 (1.85)	0.748
Gemcitabine	3 (2.61)	1 (1.64)	2 (3.70)	
Paclitaxel	82 (71.30)	42 (68.85)	40 (74.07)	
Pemetrexed-disodium	27 (23.48)	16 (26.23)	11 (20.37)	
Interval time, days[2]				
≤42	45 (39.13)	24 (39.34)	21 (38.89)	1
>42	70 (60.87)	37 (60.66)	33 (61.11)	
Treatment cycle				
2 cycles	29 (25.22)	19 (31.15)	10 (18.52)	0.376
3 cycles	44 (38.26)	23 (37.70)	21 (38.89)	
4 cycles	27 (23.48)	13 (21.31)	14 (25.93)	
≥5 cycles	15 (13.04)	6 (9.84)	9 (16.67)	

[1], platinum-based agents include: carboplatin, nedaplatin, lobaplatin, and cisplatin. [2], the days between the final neoadjuvant therapy and surgery. BMI, body mass index; LUAD, Lung adenocarcinoma; LUSQ, Lung squamous cell carcinoma; LCLC, Large cell lung cancer; LELC, Lung lymphoepithelioma-like carcinoma; LASC, Lung adeno-squamous carcinoma; PMEC, Pulmonary mucoepidermoid carcinoma.

respectively. Pathologically-confirmed lymph node downstaging (cN2-3 to ypN0-1) was described in 73.6% (67/91) of patients with cN2-3 diseases. Twenty cases were (48.8%) classified as uncertain resection according to the International Association for the Study of Lung Cancer (IASLC) standards for lymphadenectomy (at least three N1 nodes plus at least three lobe-specific N2 stations, with station 7 in all cases), including 17 patients (41.4%) with fewer than three N1 nodes resected, and three patients having incomplete N2 lymphadenectomy. The detailed clinical-pathological outcomes of neoadjuvant immunochemotherapy are listed in *Table 2*.

Two typical cases of pathological response to neoadjuvant immunochemotherapy are shown in *Figure 2*. *Figure 2A* demonstrates the case of a patient (stage IIIB, T4N2M0, LUAD) who underwent two cycles of neoadjuvant immunochemotherapy and surgery, of which the surgically resected specimen of the primary tumor contained 30% residual tumor cells in the regression bed. *Figure 2B* presents the case of a patient (stage IIIC, T4N3M0, LUSQ) who underwent 10 cycles of neoadjuvant treatment and surgery. The surgically resected #2R lymph node specimens showed that there was a regression bed inside the lymph node and were characterized by features of cell death (cholesterol clefts, interstitial foamy macrophages) with no residual tumor cells.

At a median follow-up of 14.0 months (interquartile range: 11.9–16.1) from the day of surgery, 21 patients experienced a relapse postoperatively, among whom six patients had lymph nodes metastases (hilar, mediastinal, or axillary lymph node recurrence). Eleven patients had disease recurrence in the residual lung. No significant differences were identified between the stage IIIA and stage IIIB-C groups. Kaplan-Meier survival curves of DFS in all enrolled patients (*Figure 3A*) and stratified by pathological response (*Figure 3B*) are shown in *Figure 3*. Also, the median DFS of all enrolled patients was 23.6 [95% confidence interval (CI): 15.9–31.3] months. For patients that achieved MPR, the median DFS was not reached; while the median DFS of patients that had residual tumors of more than 10% was 18.1 (95% CI: 12.5–23.8) months.

Effect of cycle number on pathological response

The pathological response outcome stratified by different neoadjuvant cycle numbers is shown in *Figure 4*. The MPR

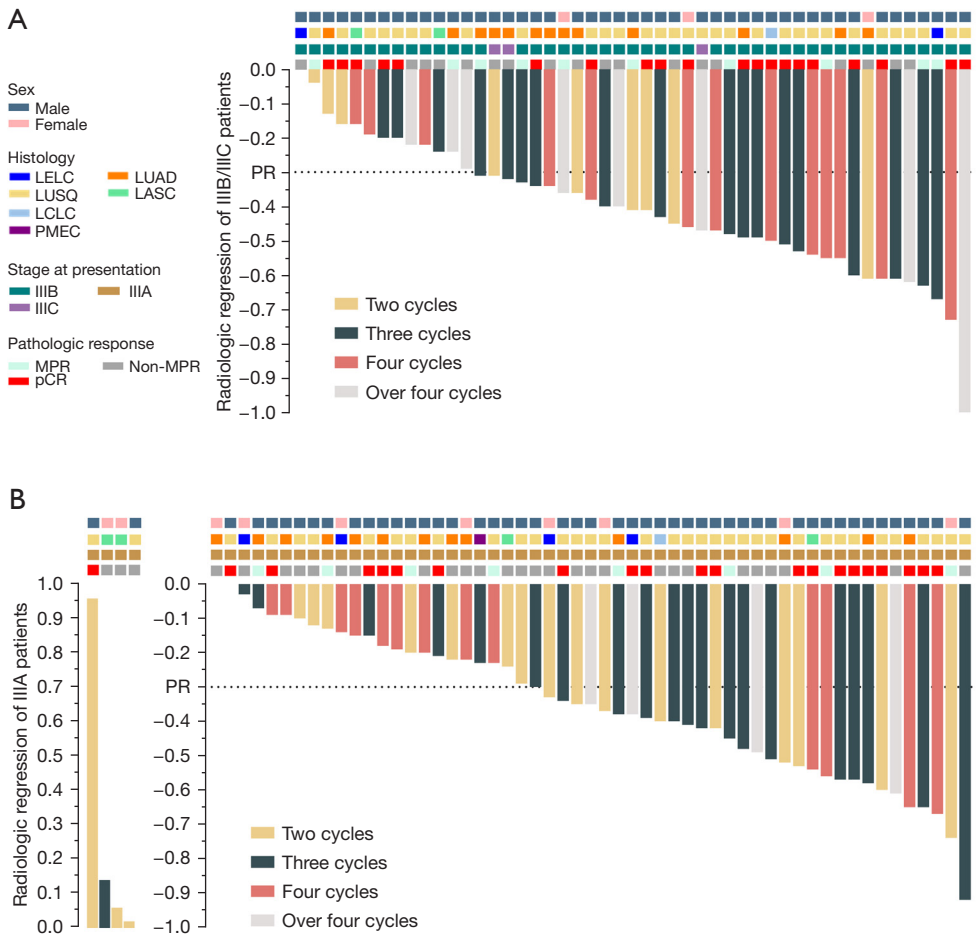

Figure 1 Radiological assessment of the response to neoadjuvant immunochemotherapy in locally advanced (A) cIIIB & cIIIC (n=49) and (B) stage cIIIA (n=59) patients. The black dashed line indicates the threshold for partial response (30% regression). The clinical-pathological features include sex, histology, clinical stages at presentation, and pathological response evaluation. Seven patients are not available in the figure due to central cancers with obstructive pneumonitis/atelectasis, and it was not feasible to radiologically assess the response of the target lesions. MPR, major pathologic response; pCR, pathologic complete response; PR, partial response.

Table 2 Oncological and surgical outcomes of neoadjuvant immunochemotherapy

Outcomes	n (%)			P value*
	Total (n=115)	Stage IIIA (n=61)	Stage IIIB-C (n=54)	
Clinical response				
CR	1 (0.87)	0 (0.00)	1 (1.85)	0.274
PR	69 (60.00)	33 (54.10)	36 (66.67)	
SD	37 (32.17)	24 (39.34)	13 (24.07)	
PD	1 (0.87)	1 (1.64)	0 (0.00)	
NA	7 (6.09)	3 (4.92)	4 (7.41)	

Table 2 (*continued*)

Table 2 (*continued*)

Outcomes	n (%)			P value*
	Total (n=115)	Stage IIIA (n=61)	Stage IIIB-C (n=54)	
Approach				
Thoracotomy	12 (10.43)	6 (9.84)	6 (11.11)	0.875
VATS	100 (86.96)	53 (86.89)	47 (87.04)	
VATS convert to thoracotomy	3 (2.61)	2 (3.28)	1 (1.85)	
Type of resection				
Lobectomy#	99 (86.09)	50 (81.97)	49 (90.74)	0.262
Pneumonectomy	1 (0.87)	0 (0.00)	1 (1.85)	
Sleeve resection	10 (8.70)	7 (11.48)	3 (5.56)	
Wedge resection	5 (4.35)	4 (6.56)	1 (1.85)	
Pathological outcomes				
MPR	20 (17.39)	9 (14.75)	11 (20.37)	0.661
pCR	44 (38.26)	23 (37.70)	21 (38.89)	
<90%	51 (44.35)	29 (47.54)	22 (40.74)	
Pathological nodal status				
N2	24 (20.87)	8 (13.11)	16 (29.63)	0.093
Single station	11 (9.57)	3 (4.92)	8 (14.81)	
Multiple station	13 (11.30)	5 (8.20)	8 (14.81)	
N1	15 (13.04)	6 (9.84)	9 (16.67)	
N0	76 (66.09)	45 (73.77)	31 (57.41)	
Overall nodal downstaging	80 (69.57)	42 (68.85)	38 (70.37)	0.646
Downstaging of N2 nodal status				
N2 to N2	21 (25.93)	8 (13.11)	13 (24.07)	0.704
N2 to N1	11 (13.58)	5 (8.20)	6 (11.11)	
N2 to N0	49 (60.49)	24 (39.34)	25 (46.30)	
Recurrent rate	28 (24.35)	14 (22.95)	14 (25.93)	–
Recurrent site				
Residual lung	11 (9.57)	4 (6.56)	7 (12.96)	0.677
Lymph node	6 (5.22)	3 (4.92)	3 (5.56)	
Bone metastasis	6 (5.22)	3 (4.92)	3 (5.56)	
Brain metastasis	3 (2.61)	2 (3.28)	1 (1.85)	
Spleen metastasis	1 (0.87)	1 (1.64)	0	
Systemic metastasis	1 (0.87)	1 (1.64)	0	

*, P value refers to the chi-square test P value; #, included bilobectomy. CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NA, not available; VATS, video-assisted thoracoscopic surgery; MPR, major pathologic response; pCR, pathologic complete response; <90%, pathologic regression <90%.

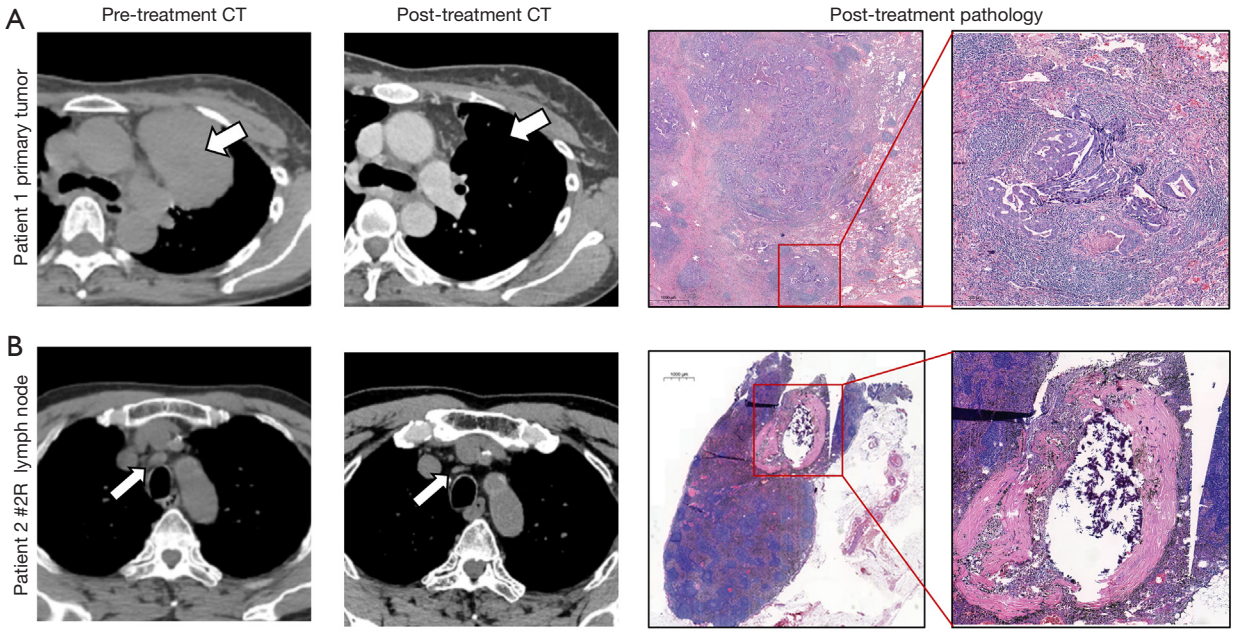

Figure 2 Typical cases of radiological and pathological response to neoadjuvant immunochemotherapy. (A, left 2 figures) Thorax CT image of the primary tumor from a 56-year-old female non-smoker patient diagnosed with stage IIIB (T4N2M0) lung adenocarcinoma before and after two cycles of neoadjuvant pembrolizumab + pemetrexed disodium + carboplatin. The white arrow represented the position of the primary tumor before and after neoadjuvant treatment. The patient then underwent left upper lobectomy. (A, right 2 figures) Representative sections of the primary tumor surgical resected specimen (HE staining, 10× and 40×) with 30% residual tumor cells in the regression bed. (B, left 2 figures) Thorax CT image of the #2R lymph node from a 63-year-old male patient with stage IIIC (T4N3M0) lung squamous cell carcinoma who received 10 cycles of neoadjuvant sintilimab + cisplatin + abraxane. The write arrow illustrates the swollen #2R lymph node before the treatment and its shrinkage after the treatment. The patient then underwent right upper lobectomy. (B, right 2 figures) Representative sections of the surgical resected #2R lymph node specimens (HE staining, 10× and 40×), showing a regression bed inside the lymph node, which is characterized by the features of cell death (cholesterol clefts and interstitial foamy macrophages are obvious in the regression bed). CT, computed tomography.

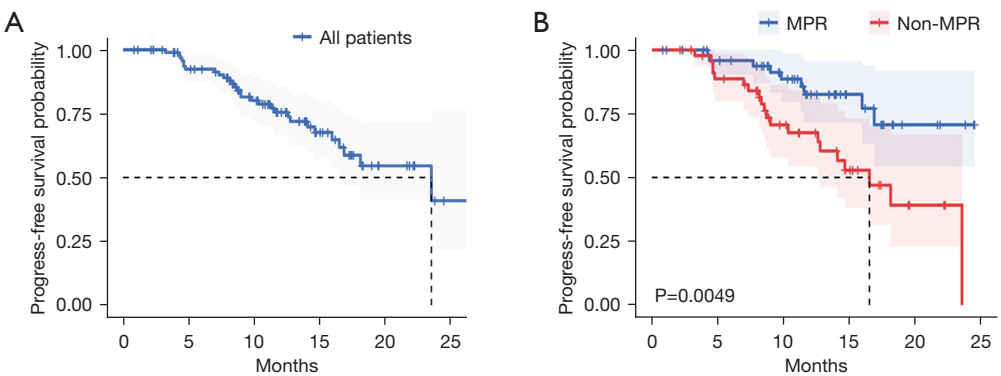

Figure 3 Kaplan-Meier survival curves of disease-free survival in (A) all enrolled patients and (B) patients stratified by pathological response (MPR and non-MPR). MPR, major pathologic response.

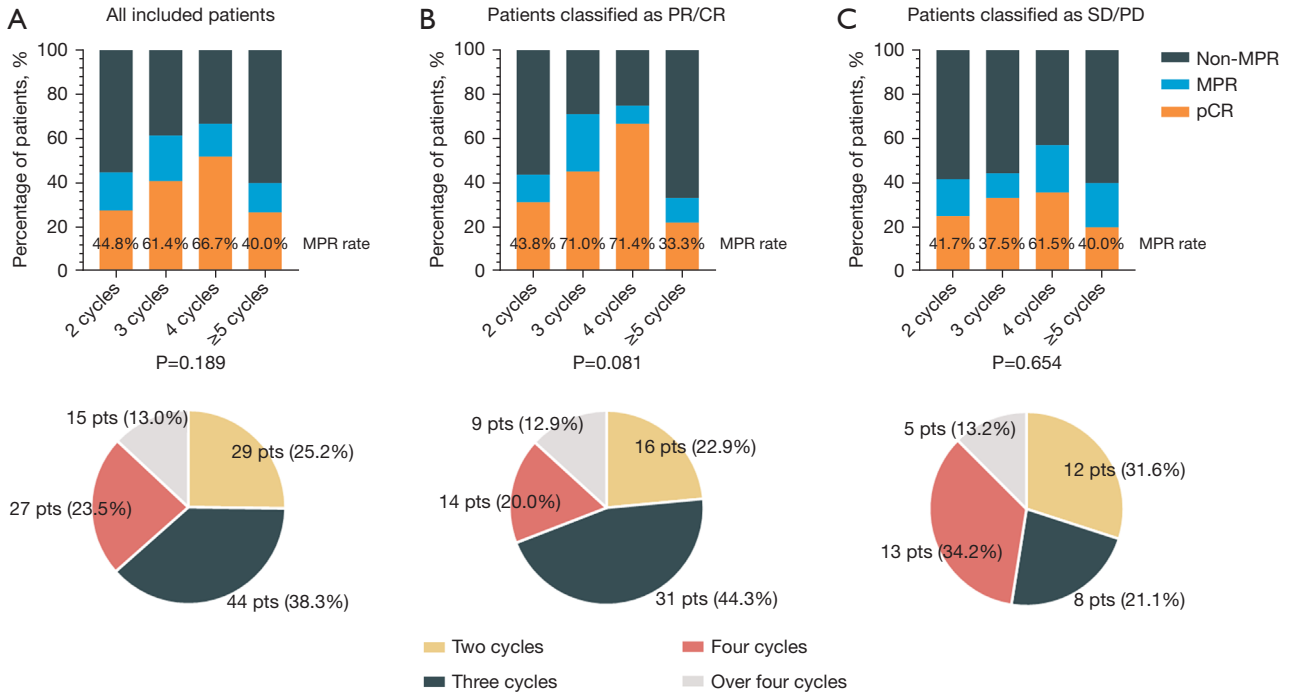

Figure 4 The pathological response outcome stratified by the different neoadjuvant cycle numbers. (A) All included patients, (B) patients classified as PR, and (C) patients classified as SD/PD. The pie chart displays the number of patients who received different neoadjuvant cycle numbers. PR, partial response; CR, complete response; SD, stable disease; PD, progression disease; MPR, major pathological response.

rates in patients that had two cycles, three cycles, four cycles, and more than four cycles of neoadjuvant treatment were 44.8%, 61.4%, 66.7%, and 40.0% (P=0.189), respectively. Notably, even in patients that already had PR, the MPR rates in the two cycles, three cycles, four cycles, and more than four cycles subgroups were 43.8%, 71.0%, 71.4%, and 33.3% (P=0.081), respectively. Meanwhile, for patients that were classified as SD/PD, the MPR rates were 41.7%, 37.5%, 61.5%, and 40.0% (P=0.654) in the two-, three-, four-, and more than four-cycle subsets, respectively.

In the univariable analysis (*Table 3*), three cycles [odds ratio (OR), 3.14; 95% CI: 0.90–11.03] and four cycles (OR: 3.21, 95% CI: 0.70–14.74) of neoadjuvant immunochemotherapy were found to be prone to higher MPR rates compared to the conventional two cycles in patients that were classified as CR/PR, indicating that even if CR/PR is achieved, it is still beneficial when extended into 3–4 cycles. However, adding more cycles (≥5) was not associated with a higher MPR rate (OR, 0.64; 95% CI: 0.12–3.53). In addition, for patients that had SD/PD after immunochemotherapy, three (OR, 0.84; 95% CI: 0.13–5.26) or four cycles (OR, 2.24; 95% CI: 0.45–11.11) had little effect on the MPR rate, and no statistical significance was reached (P=0.662).

To adjust for potential clinical factors that influence the outcomes, multivariable binary logistics analysis for MPR, including the factors as follows: age group, gender, histology type, clinical T stage, clinical N stage, and treatment cycle number, were conducted (*Table 3*). In the multivariable analysis, the treatment cycle was associated with the MPR rate (P=0.045), and three cycles (OR, 4.78; 95% CI: 1.17–19.55) and four cycles (OR, 6.50; 95% CI: 1.12–37.54) appeared to have a superior pathological response than two cycles.

Peripheral immune estimators and pathological response

To explore the potential role of peripheral immune estimators in predicting the pathological response after neoadjuvant immunochemotherapy, a two-independent sample *t*-test was conducted to examine the differences in pretreatment peripheral immune markers levels between patients who achieved MPR and those that did not (non-MPR) (*Figure 4*). The pretreatment neutrophil count level (P=0.122, *Figure 5A*) showed no statistically significant relationship with the MPR rate, while the pretreatment

Table 3 Univariable and multivariable logistic regression of predictors for major pathologic response

Variables	Univariable		Multivariable	
	HR (95% CI)	P value	OR (95% CI)	P value
Patients classified as CR/PR				
Age		0.173		
≤70 years	ref.			
>70 years	0.39 (0.10–1.52)			
Gender		0.338		
Female	ref.			
Male	2.17 (0.45–10.53)			
Histology subtype		0.678		
LUSQ	ref.			
Non-LUSQ	0.81 (0.29–2.22)			
cT stage at presentation		0.495		0.171
T1–T2[1]	ref.		ref.	
T3	0.74 (0.21–2.62)		0.43 (0.10–1.85)	
T4	0.51 (0.16–1.57)		0.27 (0.07–1.06)	
cN stage at presentation		0.688		
N0	ref.			
N1	0.83 (0.08–8.24)			
N2	1.81 (0.23–14.12)			
N3	1.50 (0.15–15.46)			
Treatment cycle		0.095		0.045
2 cycles	ref.		ref.	
3 cycles	3.14 (0.90–11.03)		4.78 (1.17–19.55)	
4 cycles	3.21 (0.70–14.74)		6.50 (1.12–37.54)	
≥5 cycles	0.64 (0.12–3.53)		0.91 (0.15–5.47)	
Patients classified as SD/PD[2]				
Histology subtype		0.105		0.105
LUSQ	ref.		ref.	
Non-LUSQ	0.33 (0.09–1.26)		0.33 (0.09–1.26)	
cT stage at presentation		0.774		
T1–T2[1]	ref.			
T3	1.43 (0.30–6.88)			
T4	1.71 (0.37–7.92)			
cN stage at presentation		0.986		
N0	ref.			
N1	1.00 (0.06–16.0)			
N2	0.88 (0.11–7.05)			

Table 3 (*continued*)

Table 3 (*continued*)

	Univariable		Multivariable	
	HR (95% CI)	P value	OR (95% CI)	P value
Treatment cycle		0.662		
2 cycles	ref.			
3 cycles	0.84 (0.13–5.26)			
4 cycles	2.24 (0.45–11.11)			
≥5 cycles	0.93 (0.11–7.82)			

[1], only three patients classified as PR were staged as T1 and three patients classified as SD/PD were staged as T1. [2], only four patents with age >70, and only six patients were female; thus, age group and gender were not selected as the potential factors for adjusting the outcome. LUSQ, Lung squamous cell carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

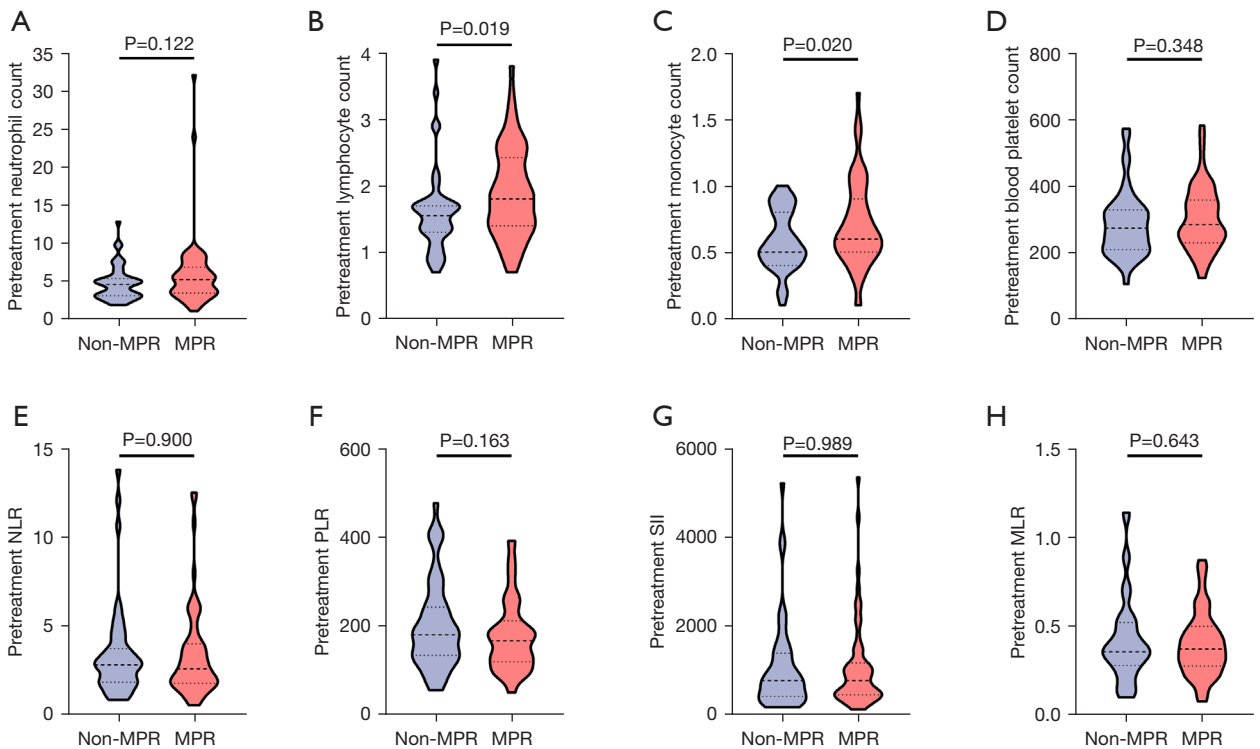

Figure 5 Pretreatment peripheral immune markers level in patients who achieved MPR/non-MPR. (A) Neutrophil count level; (B) Lymphocyte count level; (C) Monocyte count level, (D) Blood platelet count level, (E) NLR level; (F) PLR level; (G) SII level; (H) MLR level. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; MLR, monocyte to lymphocyte ratio.

lymphocyte count level (1.89±0.68 *vs.* 1.59±0.63, P=0.019, *Figure 5B*) and monocyte count level (0.71±0.32 *vs.* 0.59, P=0.020, *Figure 5C*) were significantly higher in patients that had MPR compared those of the non-MPR group. In addition, our data also demonstrated that the blood platelet count level (P=0.348, *Figure 5D*), neutrophil to lymphocyte ratio (NLR) level (P=0.900, *Figure 5E*), platelet to lymphocyte ratio (PLR) level (P=0.163, *Figure 5F*), systemic immune-inflammation index (SII) level (P=0.989, *Figure 5G*), and monocyte to lymphocyte ratio (MLR) level

(P=0.643, *Figure 5H*) did not appear to be associated with the MPR rate.

Discussion

In the present study, we retrospectively evaluated the clinical outcomes of locally advanced stage III NSCLC patients. Our study yielded promising results, with objective response rate (ORR), MPR, and pCR rates of 61.7% (71/115), 55.7% (64/115), and 38.3% (44/115), respectively. In comparison, the SAKK16/14 study (27) reported a similar MPR rate (62.0% *vs.* 55.7%), and a lower pCR rate (18.0% *vs.* 38.3%). Also, the NADIM trial (14) demonstrated a much higher MPR rate (85.4% *vs.* 55.7%). This difference might be because about 44% of the patients included in this study were with stage IIIB/IIIC NSCLC, while the NADIM trial (14) only enrolled patients with IIIA (N2) NSCLC; also, potential micro-metastases tend to be accompanied by more advanced stage tumors.

The choice of cycle number remains an unresolved conundrum in the neoadjuvant immunochemotherapy setting for NSCLC. A short course of immunochemotherapy may not be adequate to induce an effect; however, extended treatment cycles could be ineffective or delay surgery. From the evidence of pre-clinical studies, Zhang *et al.* (28) reported that a proportion of the top 1% of intra-tumor clonotypes shared with the peripheral T-cell receptor repertoire significantly increased after the second cycle of the preoperative immunotherapy, and the upward trend side remained the same. Trials such as CheckMate159 (21), NEOSTAR (29), LCMC3 (30), CHICTR-OIC-17013726 (31), NEOMUN (32), and TOP1501 (33), which studied neoadjuvant mono-immunotherapy (single agent) in early-stage NSCLC administered two treatment cycles. Neoadjuvant immunochemotherapy regimens trials, including the NADIM (14), SAKK16/14 (16), NCT02716038 (10), NCT04304248 (34), and CheckMate816 (17) trials, were performed for three to four cycles. Although limited data are available on the optimal treatment cycles of neoadjuvant immunochemotherapy in NSCLC, evidence regarding other cancer types is available. In patients with breast cancer, Steger *et al.* (35) reported that doubling the neoadjuvant chemotherapy cycle number from three to six cycles contributed to a higher pCR rate. These results reinforced the necessity to extend the neoadjuvant immunochemotherapy cycle for achieving MPR.

In this study, we demonstrated that 3–4 cycles of neoadjuvant immunochemotherapy before radical surgery was necessary to achieve a better pathological response, as commencing immunochemotherapy with fewer cycles (two cycles) was comparatively ineffective. This result was consistent with those of the neoSCORE (36) trial, which indicated that three cycles of neoadjuvant treatment achieved a numerically higher MPR rate compared with two cycles. We also demonstrated that adding more than four cycles was not associated with the presence of MPR (*Table 4*). However, only 15 (13.04%) patients had received more than four cycles (with only three receiving more than six cycles). Among these patients, five were extended for additional cycles as they had still not met the surgical indications (persistent N2) after neoadjuvant treatment. Therefore, although this study concluded that more than four cycles were ineffective compared to fewer cycles (2–4 cycles), there may have been bias due to the small sample size and inclusion of such patients. Thus, further larger sample studies with a sufficient number of patients receiving more than four cycles are needed to verify the conclusion. Moreover, considering that in the real-world setting, standard cycles may be halted during the therapy period if the tumor size improves sufficiently, as the historic objective of neoadjuvant treatment is to render inoperable cancers operable or to shrink tumors to facilitate surgical feasibility (37), we stratified patients into those classified as CR/PR and SD/PD to adjust for the influence of subjectively shortening the treatment cycles due to the significant efficacy of tumor downstage. The results suggest that patients with locally advanced lung cancer should complete at least a three-cycle (or four-cycle) neoadjuvant immunochemotherapy regimen, even for patients classified as PR. However, as there was no significant pathological response benefit in patients with SD, continuation or switching approaches might be reasonable choices that require further investigation. To comprehensively and visually demonstrate the impact of the treatment cycle, we conducted a review of the current published neoadjuvant immunochemotherapy randomized controlled trials (RCTs), which is shown in *Table 4*. The majority of RCTs administered three cycles of neoadjuvant immunochemotherapy (12,14,16,17,34,36,38,39), with the MPR rate ranging from 36.9% to 73.9%, pCR rate ranging from 18.0% to 56.9% [excluding one phase I trial NCT03480230 (12)].

Notably, two patients had radiological PD (≥20% increase in the nadir of the sum of target lesions) during-or-after the administration of immunochemotherapy. The first case was a 56-year-old male former smoker patient with an initial stage cIIIA (T4N0M0) LUSQ who

Table 4 Characteristic of current published neoadjuvant immunochemotherapy randomized controlled trials

Trial	Tumor stage	Phase	Regimen	Cycle	Sample size	Surgery patients	ORR rate	MPR rate	pCR rate	Recurrence rate/survival
neoSCORE (36), (NCT04459611)	Stage IB-IIIA	2	Sintilimab + platinum-based chemotherapy × 2 cycles; Sintilimab + platinum-based chemotherapy × 3 cycles	2	30	26	55.2%	26.9%	19.2%	–
				3	30	29	50.0%	41.4%	24.1%	–
NADIM (14), (NCT03081689)	IIIA	2	Nivolumab + paclitaxel and carboplatin	3	46	41	76%	73.9%	56.9%	PFS: 77.1% [24 months]
CheckMate-816 (17), (NCT02998528)	IB (≥4 cm) –IIIA	3	Nivolumab + platinum-based chemotherapy × 3 cycles	3	179	141	–	36.9%	24.0%	mEFS: 31.6 months
SAKK 16/14 (16), (NCT02572843)	IIIA (N2)	2	Durvalumab + cisplatin + docetaxel × 3 cycles	3	67	55	43%	62.0%	18.0%	mEFS: not reached [28.6 months]
NADIM II (37), (NCT03838159)	IIIA, resectable IIIB	2	Nivo + carboplatin/paclitaxel × 3 cycles	3	90	87	75.4%	52 %	36.2%	–
NeoTAP01 (33), (NCT04304248)	IIIA or T3-4N2 IIIB	2	Toripalimab + carboplatin + pemetrexed/nab-paclitaxel × 3 cycles	3	33	30	87.9%	60.6%	45.5%	2 patients [10.13 months]
NCT03366766 (38)	IB (≥4cm)-IIIA	2	Nivolumab + cisplatin and + pemetrexed/gemcitabine × 3 cycles	3	13	13	46.2%	46.2%	38.5%	0 patients [10 months]
NCT03480230 (12)	IB-IIIA	1	Avelumab + cisplatin/ carboplatin + gemcitabine/ pemetrexed × 3 cycles	3	15	11	26.7%	18.1%	9.1%	–
NCT02716038 (10)	IB–IIIA	2	Atezolizumab + carboplatin + nab-paclitaxel	4	30	29	63.0%	57.0%	33.0%	mDFS: 17.9 months [12.9 months]

mEFS, median event-free survival; mDFS, median disease-free survival; PFS, progression-free survival.

received two cycles of neoadjuvant Abraxane + Carboplatin + Camrelizumab. The tumor in this case increased by 92%; however, the surgical specimens showed pCR. The second case was a 67-year-old male patient with stage IIIA (T2N2M0) lymphoepithelioma-like carcinoma (LELC). During treatment with six cycles of pemetrexed disodium + carboplatin + sintilimab + bevacizumab, the tumor diameter increased from 4.0 to 5.7 cm after the second cycle of treatment, and shrunk to 2.5 cm after the last cycle of treatment. Pathological examination in this case exhibited a pCR in the primary tumor. This is perhaps most significant in relation to lymphocytic infiltration, tissue fibrosis hyperplasia, and tumor-infiltrating inflammation occupying the peritumoral site after tumor shrinkage (40), or the tumor growing until a sufficient immune response occurs (41). This pseudo progression possibly occurs during immunotherapy and was previously reported by Tanizaki *et al.* and Bott *et al.* (42,43). Regarding the pseudo-progression rate, Gettinger *et al.* (44) reported that 4.6% of patients with NSCLC treated with nivolumab experienced pseudo-progression; Ferrara *et al.* (45) also reported a similar rate of 4.7%. In summary, this study indicated that a proportion of patients can exhibit pseudo-progression after neoadjuvant immunochemotherapy; thus, CT features, re-biopsy, or other methods are recommended to discern pseudo-progression from true progression. Also, these patients should not miss the opportunity for subsequent surgery.

Surgical treatment represents a valid choice in cases that have an excellent response to immunotherapy, with regression of nodal metastases and direct invasion to the great vessels/diaphragm/heart/trachea/carina (23), but a persistent primary lesion. Published case reports have detailed the

outcomes of surgery following immunochemotherapy for stages IIIB–IV lung cancer that achieved a clinical downstaging (23,46-50). Furthermore, a few cohort studies involving patients with IIIB diseases (15,23,34,51-53) demonstrated that surgeons in experienced centers can safely operate on advanced NSCLCs that re-enter resectability after immunotherapy or its combination with chemotherapy. Moreover, postoperative survival dramatically improved in these patient cohorts compared to those that did not receive surgery (23,53). Similar to the aforementioned articles, nearly half of the included patients in the present study had stage IIIB/IIIC diseases (IIIB: n=51; IIIC: n=3). These patients were deemed as "potentially resectable" or "temporarily unresectable", which have the potential to be transformed into resectable. The inclusion of these patients was more consistent with real-world clinical practice as opposed to a clinical trial setting. The following reasons explain why these patients did not receive the standard of care "PACIFIC pattern": (I) patients had contraindications to radiotherapy; (II) patients could not tolerate radiotherapy-related adverse events; or (III) patients refused to undergo radiotherapy. Although neoadjuvant immunochemotherapy is currently not the standard of care for stage IIIB NSCLC, the current study supports the integration of surgery in these patients, and it is likely to change the treatment pattern for stage IIIB NSCLC in the future.

This study had some limitations that should be noted. Firstly, we did not investigate the immune-related adverse events of immunochemotherapy, which influence the tolerance of neoadjuvant immunochemotherapy. Secondly, PD-L1 expression was detected in some but not all of the patients. Thirdly, the postoperative follow-up time is short, leading to certain limitations in long-term survival and postoperative functional results. Fourth, due to the innate characteristics of retrospective setting, this study may have inherent weak points for inhomogeneity of patient's characteristics.

Taken together, our findings support the real-world administration of surgery in the treatment plan of patients undergoing immunochemotherapy in those with locally advanced stage III NSCLC. We also recommend prolonging immunochemotherapy into 3–4 cycles to achieve higher MPR rates. However, larger prospective randomized studies are needed to confirm the clinical results of our study.

Conclusions

Neoadjuvant immunochemotherapy was efficacious for tumor and nodal downstaging in locally advanced stage III NSCLC. Prolonged cycles of immunochemotherapy (3–4 cycles) were more appropriate for achieving higher MPR rates in stage III NSCLC than the conventional two cycles, even when PR was obtained.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-439/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-439/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-439/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. This study was carried out in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of The First Affiliated Hospital of Guangzhou Medical University (No. 2020-122). The requirement for informed consent was waived due to the retrospective nature of the study.

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(English Language Editor: A. Kassem)

Cite this article as: Deng H, Liang H, Chen J, Wang W, Li J, Xiong S, Cheng B, Li C, Chen Z, Wang H, Zheng J, Guo Z, He J, Liang W. Preoperative immunochemotherapy for locally advanced non-small cell lung cancer: an analysis of the clinical outcomes, optimal number of cycles, and peripheral immune markers. Transl Lung Cancer Res 2022;11(12):2364-2381. doi: 10.21037/tlcr-22-439