

**Original
Article**

Real-World Effectiveness and Prognostic Factors Analysis of Stages I–III Non-Small Cell Lung Cancer Following Neoadjuvant Chemo-Immunotherapy or Neoadjuvant Chemotherapy

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Purpose: Immune checkpoint inhibitors (ICIs) have been successfully used in many clinical trials related to immunotherapy. This study aimed to investigate the clinical efficacy of ICIs and prognostic factors in patients with resectable non-small cell lung cancer (NSCLC) following neoadjuvant therapy in the real world.

Methods: A total of 170 consecutive patients were finally selected and divided into two groups: the preoperative chemotherapy group (n = 91) and the chemo-immunotherapy group (n = 79). The primary endpoint was disease-free survival (DFS). The secondary endpoints were pathological response, clinical response, pathological nodal disease, and ability of multivariate Cox regression analysis to predict survival. Survival was estimated using Kaplan–Meier method and compared using log-rank test.

Results: There was a statistically significant difference in DFS between the two groups (log-rank test, P = 0.019). Multivariate Cox regression analysis showed that maximum tumor diameter (P = 0.016), higher lymph node stage (ypN1, P = 0.016; ypN2, P < 0.001), and major pathological response not achieved (non-major pathological response [MPR], P = 0.011) were independent prognostic factors for worse DFS.

Conclusion: Neoadjuvant chemo-immunotherapy yields better effects in pathological and clinical response than chemotherapy alone, which is also associated with longer DFS in the treatment of locally advanced NSCLC. Moreover, a larger tumor specimen diameter, higher ypN staging, and non-MPR after neoadjuvant therapy were associated with worse prognosis.

Keywords: immune checkpoint inhibitor, real-world effectiveness, non-small cell lung cancer, retrospective study, prognostic factor

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Introduction

Non-small cell lung cancer (NSCLC) is the main subtype of lung cancer, accounting for approximately 80%–85% of all lung cancers.¹⁾ Currently, surgery is the standard treatment to achieve cure for early NSCLC. In the past decades, for patients with locally advanced NSCLC, preoperative neoadjuvant chemotherapy (NCT) increased the chances of operation and improved the resection rate.

In previous research on platinum-based NCT regimens, compared with the surgery-only group, the advantages of the NCT group existed, but it did not show a

surprising expected advantage. Burdett et al. evaluated the results of a randomized controlled trial (RCT) describing the differences between surgery following preoperative chemotherapy and surgery alone, and concluded that the benefits of NCT were limited.^{2,3)} Preoperative chemotherapy can improve the survival rate, with a hazard ratio of 0.82 (95% confidence interval [CI], 0.69–0.97). It can merely increase the overall survival rate of all stages of the disease from 14% to 20% at 5 years, which is equivalent to an absolute benefit of 6%. Another meta-analysis of the NSCLC meta-analysis collaboration group included 2385 patients with stage IB–IIIA (15 RCTs) and showed that preoperative chemotherapy did benefit survival (hazard ratio [HR] 0.87, 95% CI 0.78–0.96), but the 5-year absolute survival rate could be increased from 40% to 45%.⁴⁾

In recent years, the emergence of immune checkpoint inhibitors (ICIs) for programmed cell death protein 1 (PD-1) and PD-ligand 1 has revolutionized the treatment of advanced NSCLC.⁵⁾ A number of studies have shown that ICIs can improve the overall survival rate of patients with advanced metastatic NSCLC compared to chemotherapy alone.^{6–9)} ICIs are now routinely used alone or in combination with chemotherapy in most patients with stage IV NSCLC. With the remarkable success of immunotherapy in advanced diseases, ICIs have been used to improve the prognosis of patients with resectable early lung cancer,¹⁰⁾ and surprising results have been preliminarily obtained with few side effects.¹¹⁾ However, the use of PD-1 inhibitors in neoadjuvant therapy for NSCLC is still in the research stage, and large-scale RCTs and real-world large retrospective studies are required.

In this study, we retrospectively analyzed 170 consecutive patients with stages I–III NSCLC who received NCT with or without PD-1 inhibitors to investigate the clinical efficacy of NCT plus ICIs in comparison with chemotherapy alone. In addition, prognostic factors of patients with resectable NSCLC following neoadjuvant therapy and radical surgery were explored in the real world.

Materials and Methods

Patients

A total of 170 consecutive patients with clinical stages IB–IIIB resectable NSCLC who received NCT with or without PD-1 inhibitors at Tianjin Cancer Hospital from August 2018 to September 2020 were included in this study. The inclusion criteria were as follows: (1) NSCLC, stages I–III confirmed by imaging and cytological

examination before surgery; (2) feasible neoadjuvant therapy after assessment; (3) no distant metastasis; (4) no previous history of radiotherapy and chemotherapy; (5) Karnofsky performance status, KPS score ≥ 80 ; (6) no previous lung tumor operation; and (7) complete resection. The exclusion criteria were as follows: (1) PD-1 inhibitors or chemotherapy intolerance; (2) complicated with other malignant tumors; (3) liver, kidney, or other organ dysfunction; (4) surgical contraindications; and (5) patients with preoperative neoadjuvant therapy as single immunotherapy. Finally, 79 and 91 cases were included in the observation and control groups, respectively. Staging was performed using computed tomography (CT), positron emission tomography (PET-CT), and/or bone scan. Magnetic resonance imaging (MRI) and/or CT were used to examine head involvement. Malignant tumors were staged according to the eighth edition of the TNM classification.¹²⁾

This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). The institutional review board of Tianjin Medical University Cancer Institute and Hospital gave ethical approval for this study.

Drug treatment and surgical methods

Patients were administered two to five cycles of chemotherapy with or without immunotherapy intravenously, and the specific regimen was determined according to the corresponding pathological type of the tumor (**Table 1**). Eighty-nine patients (93.7%) with squamous cell carcinoma, five patients (100%) with adenocarcinoma, seven patients (70%) with large cell carcinoma, and one patient (33.3%) with other types of pathology were administered albumin-bound paclitaxel or paclitaxel liposomes combined with platinum. Fifty-two patients (94.5%) with adenocarcinoma, three patients (30%) with large cell carcinoma, two patients (100%) with sarcomatoid carcinoma, and one patient (33.3%) with other types of pathology received pemetrexed combined with platinum chemotherapy. Four patients (2.4%) with squamous cell carcinoma and one patient (1.9%) with adenocarcinoma were administered docetaxel plus platinum chemotherapy, while two patients (1.2%) with squamous cell carcinoma, two patients (3.6%) with adenocarcinoma, and one patient (33.3%) with other types of pathology received gemcitabine plus platinum chemotherapy.

The immunotherapy drug was one of four kinds of PD-1 inhibitors, including pembrolizumab (34 patients, 2 mg/kg), nivolumab (20 patients, 3 mg/kg), sintilimab

Table 1 Baseline of clinical and sociodemographic characteristics

	Total n = 170 (%)	Type of neoadjuvant treatment		P-value
		NCT n = 91 (%)	NCIT n = 79 (%)	
Sex				0.846
Male, n (%)	141 (82.9)	75 (82.4)	66 (83.5)	
Female, n (%)	29 (17.1)	16 (17.6)	13 (16.5)	
Age				0.157
≥60 years, n (%)	100 (58.8)	49 (46.2)	51 (64.6)	
<60 years, n (%)	70 (41.2)	42 (53.8)	28 (35.4)	
Smoking history				0.846
Yes, n (%)	141 (82.9)	75 (82.4)	66 (83.5)	
No, n (%)	29 (17.1)	16 (17.6)	13 (16.5)	
MTD in imaging (cm)		4.0 (±2.2)	4.6 (±2.7)	0.300
Clinical T stage				0.434
cT1, n (%)	24 (14.1)	13 (14.3)	11 (13.9)	
cT2, n (%)	83 (48.8)	47 (51.6)	36 (45.6)	
cT3, n (%)	41 (24.1)	21 (23.1)	20 (25.3)	
cT4, n (%)	22 (12.9)	10 (11.0)	12 (15.2)	
Clinical N stage				0.665
N0, n (%)	35 (20.6)	18 (19.8)	17 (21.5)	
N1, n (%)	37 (21.8)	19 (20.9)	18 (22.8)	
N2, n (%)	87 (51.2)	48 (52.7)	39 (49.4)	
N3, n (%)	11 (6.5)	6 (6.6)	5 (6.3)	
Clinical TNM stage				0.754
IB, n (%)	12 (7.1)	4 (4.4)	8 (10.1)	
IIA, n (%)	8 (4.7)	3 (3.3)	5 (6.3)	
IIB, n (%)	29 (17.1)	19 (20.9)	10 (12.7)	
IIIA, n (%)	79 (46.5)	46 (50.5)	33 (41.8)	
IIIB, n (%)	42 (24.7)	19 (20.9)	23 (29.1)	
Tumor location				0.826
Left	79 (46.5)	43 (47.3)	36 (45.6)	
Right	91 (53.5)	48 (52.7)	43 (54.4)	
Surgical approach				0.015
Thoracotomy	142 (83.5)	81 (89.0)	61 (77.2)	
VATS	18 (10.6)	9 (9.9)	9 (11.4)	
RATS	10 (5.9)	1 (1.1)	9 (11.4)	
Approach to surgery				0.368
Local resection	3 (1.8)	1 (1.1)	2 (2.5)	
Lobectomy	103 (60.6)	55 (60.4)	48 (60.8)	
Pneumonectomy	23 (13.5)	16 (17.6)	7 (8.9)	
Bilobectomy	15 (8.8)	9 (9.9)	6 (7.6)	
Sleeve	20 (11.8)	8 (8.8)	12 (15.2)	
Others	6 (3.5)	2 (2.2)	4 (5.1)	
Pathological type				0.952
Squamous	95 (55.9)	52 (57.1)	43 (54.4)	
Adenocarcinoma	55 (32.4)	31 (34.1)	27 (34.2)	
Adenosquamous	5 (2.9)	1 (1.1)	1 (1.3)	
Large-cell	10 (5.9)	4 (4.4)	6 (7.6)	
Sarcomatoid	2 (1.2)	1 (1.1)	1 (1.3)	
Others	3 (1.8)	2 (2.2)	1 (1.3)	
Chemotherapy				0.495
Paclitaxel + platinum	102 (60)	52 (57.1)	50 (63.3)	
Pemetrexed platinum	58 (34.1)	32 (35.2)	26 (32.9)	
Others	10 (5.9)	7 (7.7)	3 (3.8)	
Treatment cycles				0.05
2 cycles	89 (53.5)	56 (61.5)	35 (44.3)	
3 cycles	48 (28.2)	20 (22.0)	28 (35.4)	
4 cycles	27 (15.9)	13 (14.3)	14 (17.7)	
5 cycles	4 (2.4)	2 (2.2)	2 (2.5)	
Median(IQR)		2 (±1)	3 (±1)	

NCT: neoadjuvant chemotherapy; NCIT: neoadjuvant chemo-immunotherapy; MTD: maximum tumor diameter; RATS: robot-assisted thoracoscopic surgery; VATS: video-assisted thoracic surgery; IQR: interquartile range

(13 patients, 200 mg), and camrelizumab (12 patients, 200 mg) (intravenous drip on the first day, 21 days as a cycle). Sintilimab¹³⁾ and camrelizumab are recombinant humanized anti-PD-1 monoclonal antibodies made in China that block interactions between PD-1 and its ligands, which have been tested for safety and activity in patients with advanced stage solid tumor therapy.^{14,15)} They were respectively approved for the treatment of lymphoma by the Chinese Center for Drug Evaluation in China in 2018 and 2019, and have shown encouraging efficacy in resectable NSCLC patients in China.^{10,16)} Hematological and imaging examinations were performed regularly during medication.

Surgical methods include local resection, anatomical lobectomy, sleeve resection, or pneumonectomy plus ipsilateral and mediastinal hilar lymph node dissection. All patients underwent surgery 16–24 days after the last treatment cycle and achieved R0 resection. After surgery, different adjuvant treatment schemes were adopted according to the individual clinical condition of the patient, the side effects of drugs, and the pathological effect under the discussion of the attending physicians.

Evaluation of efficacy

Tumor response to neoadjuvant therapy was assessed through changes in size on preoperative CT or PET-CT imaging by chief thoracic surgeons, in accordance with Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).¹⁷⁾ The indicators included complete response (CR), partial response (PR), stable disease (SD), disease progression (PD), and objective response rate (ORR). Pathologic responses to neoadjuvant therapy were verified by re-reviewing the pathologic slides and confirmed by two experienced pathologists in our hospital. Major pathological response (MPR) was defined as $\geq 90\%$ necrosis of the tumor. Pathological complete response (pCR) was defined as tumor regression with no residual tumor on pathology. If the above two conditions were not achieved after neoadjuvant therapy, it was defined as MPR not reached (non-MPR). Furthermore, in our study, nodal downstaging was defined as the change between the clinical N stage at first visit and ypN stage after surgery.

In the first 2 years after treatment, the patients were observed at 1- to 3-month intervals, and in the third year, they were followed up every 6 months. During follow-up, the endpoint events were defined as disease recurrence, metastasis, or death due to any cause. The last follow-up time was May 2021.

Statistical analysis

Descriptive statistics were used to calculate the percentage, mean, standard deviation, and median for the selected demographic and clinical parameters. Comparisons between the groups were analyzed using Student's t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The Mann–Whitney U-test was used for grade data and the data that did not obey parameter distribution. Disease-free survival (DFS) was defined as the period from surgery to the time of first recurrence or metastasis, death from any cause, or the last follow-up. Kaplan–Meier DFS curves were plotted using R software version 4.0.3 and compared using a log-rank test. The meaningful variables in the univariate analysis were incorporated into the multivariate Cox proportional hazard regression model. The P-values were two-sided, and the significance level was set at 0.05. Statistical analyses were performed using SPSS version 25 (IBM, Armonk, NY, USA).

Results

Patients' characteristics

From August 2018 to September 2020, 170 consecutive eligible patients were selected in the study population, of whom 79 received neoadjuvant chemo-immunotherapy (NCIT) and 91 received NCT; the clinical and sociodemographic characteristics are shown in **Table 1**. The N2 or N3 status of patients was mainly evaluated by preoperative imaging examination, including PET-CT or CT, and 22 patients in our cohort were classified as clinical T4 because of the huge tumor bulk. The baseline features of patients in the two treatment groups were basically balanced, except for differences in the surgical approach.

Efficacy comparison

We retrospectively analyzed the clinical and pathological data of the two groups of patients and compared their efficacy (**Table 2**). Under naked eye measurement, the maximum tumor diameter (MTD) of specimen in the observation group was 2.5 (± 1.9) cm, which was 3.0 (± 2.0) cm in the control group, but the difference was not statistically significant ($P = 0.088$). There was also no significant statistical difference in ypT stage between the two groups ($P = 0.082$). However, in terms of ypN staging and lymph node descending rate, the ypN staging grade of the observation group tended to be lower ($P = 0.019$), and the incidence of lymph node descending stage was inclined to be higher ($P = 0.019$). Regarding the evaluation of the response, the ORR value of the

Table 2 Efficacy comparison

	Total n = 170 (%)	Type of neoadjuvant treatment		P-value
		NCT n = 91 (%)	NCIT n = 79 (%)	
MTD of specimen (cm)		3.0 (±2.0)	2.5 (±1.9)	0.088
ypT stage				0.082
T0	14 (8.2)	4 (4.4)	10 (12.7)	
T1	87 (51.2)	47 (51.6)	40 (50.6)	
T2	47 (27.6)	25 (27.5)	22 (27.8)	
T3	17 (10.0)	10 (11.0)	7 (8.9)	
T4	5 (2.9)	5 (5.5)	0 (0)	
ypN stage				0.019
N0	109 (64.1)	51 (56.0)	58 (73.4)	
N1	11 (6.5)	7 (7.7)	4 (5.1)	
N2	50 (29.4)	33 (36.3)	17 (21.6)	
Nodal downstaging				0.019
Yes	86 (50.6)	40 (44)	49 (62)	
No	84 (49.4)	51 (56)	30 (38)	
Clinical response				0.001
CR	6 (3.5)	1 (1.1)	5 (6.3)	
PR	93 (54.7)	42 (46.2)	51 (64.6)	
SD	66 (38.8)	44 (48.4)	22 (27.8)	
PD	5 (2.9)	4 (4.4)	1 (1.3)	
Pathological response				<0.001
pCR + MPR	55 (32.4)	13 (14.3)	42 (53.2)	
Non-MPR	115 (67.6)	78 (85.7)	37 (46.8)	

NCT: neoadjuvant chemotherapy; NCIT: neoadjuvant chemo-immunotherapy; MTD: maximum tumor diameter; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease; pCR: pathological complete response; MPR: major pathological response; non-MPR: major pathological response not reached

observation group was 70.9%, which was significantly higher than that of the control group (47.3%) ($P = 0.001$). The pathological remission rate (including pCR and MPR rates) in the observation group was 53.2%, while it was 14.3% in the control group ($P < 0.001$).

DFS outcomes and prognostic factors

Over a median potential follow-up time of 17.0 months (95% CI: 15.54–18.47), 65 (38.2%) patients in the whole cohort experienced end point events, including 44 (48.3%) patients in the NCT group, and 21 (26.6%) patients in the NCIT group. The patterns of failure after surgery are shown in **Supplementary Table 1** (All Supplementary Tables are available Online). The most common site of relapse was the ipsilateral lung (33.8%), followed by the mediastinal (23.1%) and bone metastases (10.8%). Log-rank analysis showed that a better outcome could be expected in patients with NCIT if compared with patients with NCT in terms of mean DFS survival (13.28 ± 6.34 months vs. 12.60 ± 7.13 months) and 2-year DFS rates (67.2% vs. 39.5%, log-rank $P = 0.019$), as reported in **Fig. 1A**. For the whole population, univariate Cox analysis demonstrated that the type of neoadjuvant

therapy (HR = 1.922, 95% CI: 1.142–3.233, $P = 0.014$), MTD of the specimen (HR = 1.244, 95% CI: 1.101–1.403, $P < 0.001$), lymph node staging after neoadjuvant therapy (ypN1–2) (HR = 2.811, 95% CI: 1.214–6.511, $P = 0.016$; HR = 4.426, 95% CI: 2.609–7.508, $P < 0.001$), clinical efficacy evaluation (HR = 2.576, 95% CI: 1.567–4.232, $P < 0.001$), and pathological efficacy evaluation (HR = 4.336, 95% CI: 2.067–9.093, $P = 0.021$) were all correlated with DFS outcomes (**Table 3**). Multivariate Cox regression analysis revealed that the MTD of the specimen (HR = 1.177, 95% CI: 1.031–1.345, $P = 0.016$), higher lymph node stage after neoadjuvant therapy (ypN1–2) (HR = 2.825, 95% CI: 1.212–6.585, $P = 0.016$; HR = 3.360, 95% CI: 1.945–5.804, $P < 0.001$), and non-MPR result by pathological evaluation (HR = 2.930, 95% CI: 1.278–6.719, $P = 0.011$) remained independent factors affecting poor prognosis.

Pathological response and pathological lymph node status

Since pathological response and ypN staging were independent factors affecting the prognosis of the whole

Table 3 Univariate and multivariate Cox regression analyses

Variate	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Therapy		0.014		
Chemotherapy	1.922 (1.142–3.233)			
Chemo-immuno	1			
Clinical TNM stage				
IB	1			
IIA + IIB	1.890 (0.418–8.530)	0.409		
IIIA	3.237 (0.777–13.488)	0.096		
IIIB	3.128 (0.721–13.580)	0.129		
Surgery approach				
Thoracotomy	1			
VATS	0.952 (0.445–2.143)	0.976		
RATS	0.549 (0.134–2.253)	0.405		
Approach to surgery	–	0.811		
Pathological type				
Squamous	1			
Adenocarcinoma	1.639 (0.978–2.745)	0.061		
Adenosquamous	2.385 (0.323–17.633)	0.394		
Large-cell	1.497 (0.526–4.258)	0.45		
Sarcomatoid	2.225 (0.302–16.387)	0.432		
Others	0.858 (0.117–6.309)	0.881		
MTD of specimen (cm)	1.244 (1.101–1.403)	<0.001	1.177 (1.031–1.345)	0.016
ypN stage				
N0	1		1	
N1	2.811 (1.214–6.511)	0.016	2.825 (1.212–6.585)	0.016
N2	4.426 (2.609–7.508)	<0.001	3.360 (1.945–5.804)	<0.001
Clinical effect		<0.001		
CR + PR	1			
SD + PD	2.576 (1.567–4.232)			
Pathological effect		<0.001		0.011
pCR + MPR	1		1	
Non-MPR	4.336 (2.067–9.093)		2.930 (1.278–6.719)	

MTD: maximum tumor diameter; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; pCR: pathological complete response; MPR: major pathological response; non-MPR: major pathological response not reached

cohort, we respectively evaluated the association between DFS and the two varieties (**Fig. 1B** and **1C**).

In total, 58 (50.4%) of the 115 non-MPR patients and 7 (12.7%) of the 55 pCR + MPR patients experienced endpoint events until the last follow-up. Among the seven patients with pCR + MPR who experienced endpoint events, two patients were in the chemotherapy group. One patient's pathological lymph node disease was ypN2, and the lumbar vertebrae was involved 5 months after the operation. The other patient's pathological lymph node disease was ypN1 and developed recurrence at the original operation site 16 months after the operation. Five patients who reached endpoint events in the chemo-immunotherapy group all had ypN0. Two patients developed recurrence at the original operation site 18 months after the operation. One patient developed

cervical lymph node metastasis 3 months after the surgery. Two patients died of severe pulmonary infection respectively 3 or 4 months after the operation. In the Kaplan–Meier survival analysis of pathological evaluation (**Fig. 1C**), median DFS was 17.0 months (95% CI: 11.67–22.3 months) in the non-MPR group, which was not reached in pCR + MPR group (2 years DFS rate: 81.8% vs. 37.3%, log-rank $P < 0.001$).

In the DFS survival analysis of ypN staging, there were respectively 22.9% (25/109) in the ypN0 group, 63.6% (7/11) in the ypN1 group, and 66.0% (33/50) in the ypN2 group who experienced endpoint events. Kaplan–Meier survival curves revealed differences among the different ypN staging groups (log-rank $P < 0.0001$). The median DFS time was significantly shortest in the ypN2 group (8 months [95% CI: 4.59–11.41 months]),

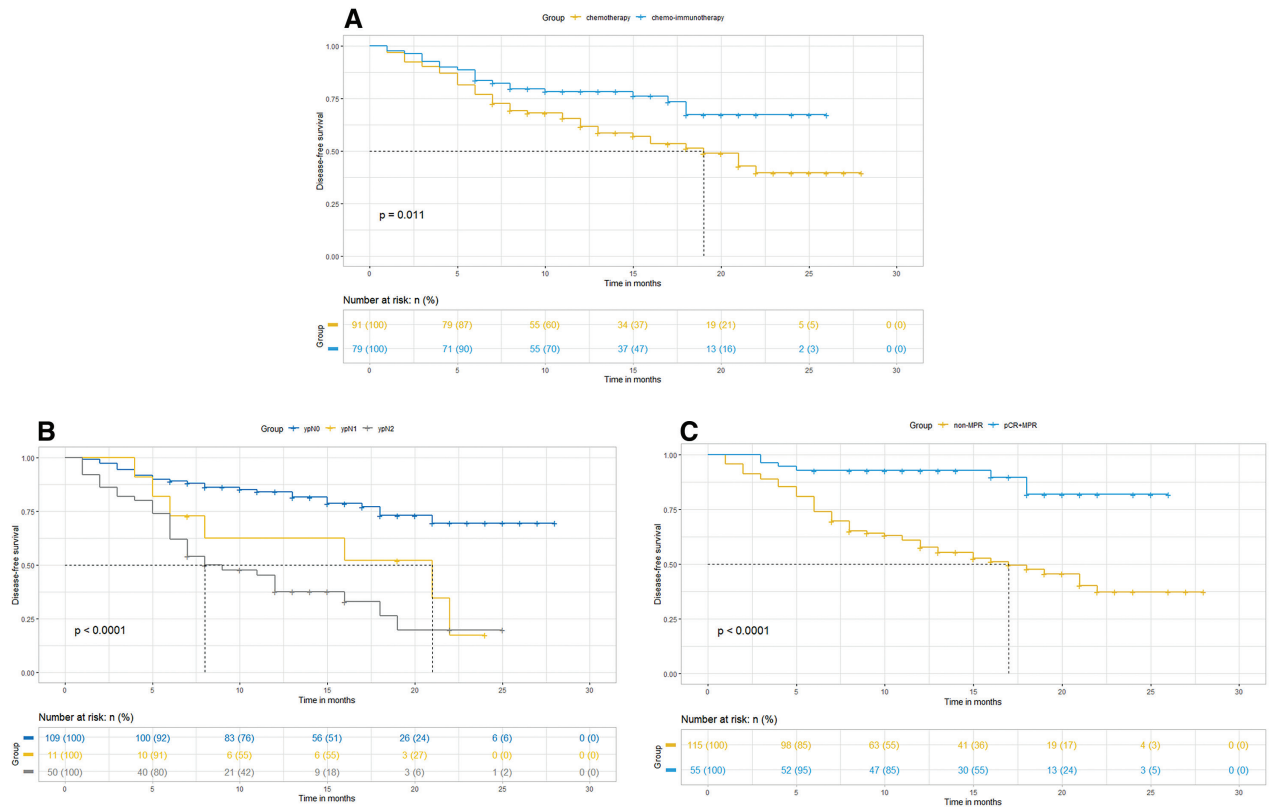


Fig. 1 (A) Disease-free survival (DFS) according to different neoadjuvant therapy type. (B) DFS among patients with ypN0 (blue), ypN1 (yellow), and ypN2 (gray) disease ($P < 0.0001$). (C) DFS among patients who achieved pathological complete response or major pathological response (pCR + MPR, blue) in comparison to those with residual disease (non-MPR, yellow) ($P < 0.0001$).

while it was 21 months (95% CI: 4.83–37.1 months) in the ypN1 group, which was not achieved in the ypN0 group (Fig. 1B). These results highlight the importance of nodal disease in lung cancer outcomes, in addition to the primary tumor response to systemic therapy.

To further explore whether ICIs increased survival benefits in comparison with chemotherapy alone, when the results of pathological evaluation were the same, we performed Kaplan–Meier survival analyses on the non-MPR and pCR + MPR groups, respectively (Fig. 2A and 2B). When considering only 55 patients in the non-MPR group and 115 patients in the pCR + MPR group, there were no statistically significant differences between chemo-immunotherapy and chemotherapy two subgroups (log-rank $P = 0.702$; log-rank $P = 0.587$).

The relationship between the pathological efficacy and clinical efficacy of the entire cohort is shown in **Supplementary Table 2**. We found that the ORR (CR + PR) of patients in the pathological remission (pCR + MPR) group was relatively higher, reaching 89.1%, but not all patients who achieved pathological remission achieved

clinical remission. For example, in this cohort, 6 of the 55 patients with pathological remission failed to achieve PR, although the tumor size was smaller than that before neoadjuvant therapy. Among the three chemotherapy regimens, the paclitaxel plus platinum regimen had the highest pathological response rate (38.2%), but the difference was not statistically significant ($P = 0.116$). In the pathological remission group, the proportion of patients with squamous cell carcinoma was the highest (65.5%).

Discussion

From a theoretical point of view, the neoadjuvant therapy in locally advanced NSCLC should lead to facilitating the possibility of curative resection by downstaging lung cancer, reducing the local and distance recurrence rate by controlling microscopic distant metastatic spread, and increasing the overall survival. Robust evidence suggests that better survival outcomes could be expected after surgery in patients who presented with downstaging after neoadjuvant therapy (i.e., mediastinal downstaging).^{18,19} This was also a significant reason that the

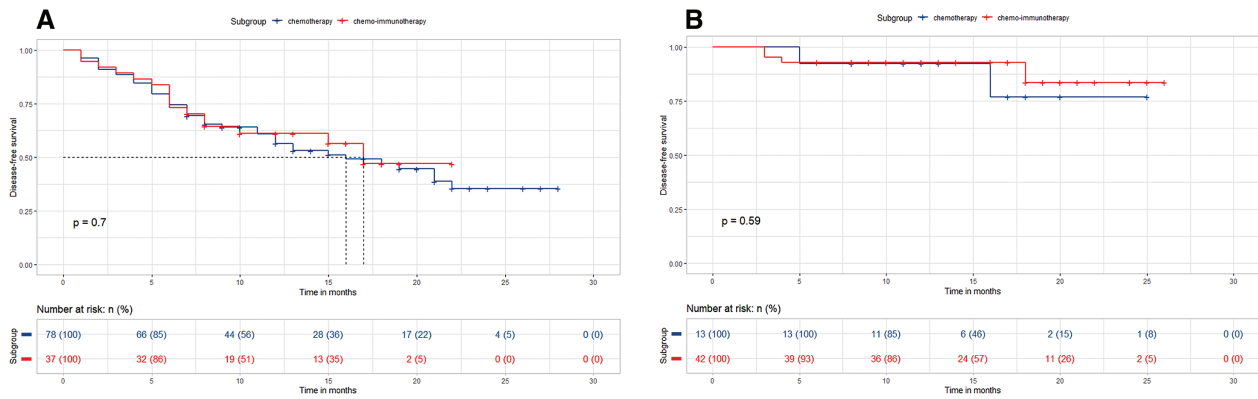


Fig. 2 (A) Subgroup analysis in patients who were with residual disease (non-MPR) ($P = 0.7$). (B) Subgroup analysis in patients who achieved pathological complete response or major pathological response (pCR + MPR) ($P = 0.59$).

prognosis of the NCIT group was better than that of the NCT group.

In this study, the pathological remission rate of the NCIT group was 53.2% (42/79), which was significantly higher than that in the NCT group (14.3% [13/91]). This suggested that ICIs indeed showed promising efficacy in a real-world setting. However, compared with the results of previous clinical trials, the pathological remission rate in the real world may be slightly different. For example, Mariano et al. reported a pathological remission rate of 83% (34/41) in their phase II, single-arm, open-label multicenter clinical trials.²⁰ The reason may be that 46 patients included in this clinical trial all had stage IIIA2 and received three cycles of nivolumab and paclitaxel plus carboplatin neoadjuvant therapy. However, 79 patients observed in this retrospective study had a wider range of clinical stages, ranging from stage IB to stage IIIB, and the choice of immune drugs was also not limited to one immune drug (nivolumab). Generally, reviewing the largest clinical series reported in the literature, the rates of pCR for patients with locally advanced NSCLC treated with neoadjuvant therapy range from 8% to 45%, with acceptable treatment-related toxicity and surgical morbidity rates, depending on the neoadjuvant therapy approach used.^{18,19,21–23} In the process of neoadjuvant therapy, safety of the therapy is also a problem worthy of attention. Usually, the various adverse reactions in the course of drug treatment are graded according to the American National Cancer Institute Common Terminology Criteria for Adverse Event. In the therapy of immunotherapy, ICIs' specific side effects include immune hepatitis, immune pneumonia, hypothyroidism, and so on. Treatment-related toxicity was acceptable in our study and no surgery was delayed due to severe adverse drug reactions.

Regarding DFS outcomes, in this study, although the median duration of follow-up for the entire cohort was only 17.0 months (95% CI: 15.54–18.47) and it may be immature, a statistical difference in DFS between the two groups was observed (log-rank $P = 0.0019$). On one hand, the reason for the short median follow-up time is related to the late emergence time of ICIs; on the other hand, the patients in stages cIIIA and cIIIB accounted for 71.2% (121/170) of the whole cohort, and such patients were more prone to suffer from recurrence and metastasis.

In the Cox multivariate proportional hazard model of DFS outcomes, we found that the type of neoadjuvant therapy was not an independent factor affecting the prognosis, but the evaluation of pathological effects ($P = 0.011$), ypN staging ($P = 0.016$; $P < 0.001$), and MTD of the specimen ($P = 0.016$) were deemed to be more important factors. Undoubtedly, in our efficacy analysis of neoadjuvant therapy, NCIT significantly improved the pathological effect ($P < 0.001$) and ypN staging ($P = 0.019$), and other significant statistical differences were also observed in nodal downstaging ($P = 0.019$) and clinical response ($P = 0.001$). Accordingly, the type of neoadjuvant therapy had an indirect effect on the prognosis of patients in our study.

In multivariate analysis, pathological remission could improve DFS, which was also a common view supported by previous studies.^{20,24–26} As reported in **Table 3**, a 2.93 times higher relative risk of disease recurrence or metastasis (95% CI: 1.278–6.719, $P = 0.011$) was estimated in the Cox regression analysis for patients with non-MPR after surgery. Specifically, even in the pCR + MPR group, there is still the potential for recurrence and metastasis. This phenomenon is currently uncommon, but it exists in the real world and deserves attention. This

reminds us of the importance of regular follow-up in clinical practice. In addition, we speculated that, since a significantly higher pathological remission rate was observed in the NCIT group, whether ICIs could reduce the tumor burden to some extent and increase the survival benefit, even in the condition that pCR or MPR was not achieved by neoadjuvant therapy. However, this hypothesis was not supported by our observations (**Fig. 2A** and **2B**), which means that ICIs may not bring survival benefits to this group of people who are insensitive to them. Accordingly, a reasonable selection of a suitable population for ICIs is still necessary.

In multivariate Cox analysis, ypN staging is an independent risk prognostic factor for DFS, and the survival prognosis of patients with ypN2 staging is still poor. The influence of ypN staging on prognosis has also been explored in the recent survival analysis of NCT followed by surgery.^{27,28} Erin M. Corsini et al. demonstrated that MPR in the primary tumor alone may incompletely characterize the response to neoadjuvant therapy, with significant implications for long-term survival. In their study, they have identified that, among patients with MPR, those with ypN0 could obtain more survival gains from NCT compared to those patients with ypN+.²⁹ We believe that this outcome is also suitable for explaining the role of ypN stage in the prognosis analysis of NCIT and adding ypN0 status and pathological remission together to the best surrogate of DFS and overall survival in resectable NSCLC is also necessary.

In our study, among the 55 patients in the pCR + MPR group, only 6 patients (10.9%) achieved CR by preoperative clinical evaluation, 43 patients achieved PR (78.2%), and 6 patients remain SD (10.9%). It is a common phenomenon for the discordant rates between the pathologic and RECIST responses in neoadjuvant therapy. Although MTD after neoadjuvant therapy is an independent risk prognostic factor for DFS in our study, MTD may not reflect the true tumor size after neoadjuvant therapy in reality. Because when sufficient cycles of neoadjuvant therapy are completed, many types of tumor necrosis, tissue fibrosis, and inflammatory response contribute to maintaining tumor bulk,³⁰ which also caused the discrepancy of images and pathology and the certain bias in independently predicting the survival of patients by MTD.

The limitations of this study need to be addressed. This was a retrospective study conducted at a single institution, which may limit the generalizability of the results. Although a statistically significant difference has been observed in DFS between the two neoadjuvant therapy

groups, due to the short median follow-up time in this study, the relevant data of the overall survival could not be provided. When it came to the last follow-up time, some patients were censored and endpoint events were not observed. Furthermore, although the immune drugs used in this study were all PD-1 inhibitors and had the same pharmacological effects theoretically, whether there were some differences in the efficacy and safety of different drugs in fact? No detailed baseline matching or subgroup analysis was performed. Finally, in our study, the efficacy comparison and prognostic analysis of neoadjuvant therapy were the primary research purpose; although adverse drug effects and the incidence of perioperative complications were still acceptable, the specific differences in safety between the two groups were not systematically clarified.

Certainly, prospective comparative and longer follow-up trials are needed to confirm the long-term outcomes of this novel treatment and to reach definitive conclusions.

Conclusion

In terms of efficacy, the combination of ICIs and chemotherapy yields better effects in pathological and clinical response compared with chemotherapy alone, which is also associated with longer DFS in the treatment of resectable stages IB–IIIB NSCLC. Moreover, a larger tumor specimen diameter, higher ypN staging, and non-MPR after neoadjuvant therapy seem to be associated with worse prognosis in locally advanced NSCLC.

Disclosure Statement

The authors have no conflicts of interest to declare.

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