Original Article

Pathological responses of primary tumor and lymph nodes in non-small cell lung cancer after neoadjuvant chemoimmunotherapy: a retrospective real-world study

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Background: In patients with non-small cell lung cancer (NSCLC) receiving neoadjuvant chemoimmunotherapy (NCIT), inconsistent pathological responses between the tumor and lymph nodes (LNs) are often observed. There has been limited evidence comparing the different responses of tumors and LNs in those patients. This retrospective real-world analysis intended to evaluate the clinical and pathological response of primary tumors and LNs, and the long-term outcomes in NSCLC patients after NCIT.

Methods: We included resectable NSCLC patients who had received neoadjuvant therapy and had available clinicopathological records. The progression-free survival (PFS) and overall survival (OS) outcomes were analyzed using survival analysis.

Results: In total, 204 patients were included in the final analysis. Patients were predominantly male (85.8%) and ever-smokers (66.2%), with a median age of 63 years. No significant difference was observed in intraoperative bleeding (P=0.51 and P=0.54) and operation time (P=0.57 and P=0.58) between the major pathologic response (MPR) and pathological complete response (pCR) group, respectively. Patients who were male (pCR, P=0.01; MPR, P=0.004), with squamous cell carcinoma (SCC) (pCR, P=0.02; MPR, P=0.001), and overall response rate (ORR) (pCR, P<0.001; MPR, P<0.001) demonstrated significantly higher rates of pCR and MPR. The median follow-up time for all patients in this study was 23 months. Patients with MPR (P=0.004) and pCR (P=0.02) experienced prolonged PFS, but not OS (MPR, P=0.08; pCR, P=0.15). In terms of yield pathological tumor MPR (ypTMPR) and yield pathological LNs stage (ypN), Kaplan-Meier analyses demonstrated that there was a better PFS for the ypTMPR(+)/ypN(0) group, followed by ypTMPR(–)/ypN(0), ypTMPR(+)/ypN(0), and ypTMPR(–)/ypN(1+2) (P=0.01). The average PFS time was 35.7, 31.7, 29.4, and 28.7 months, respectively. After achieving MPR, the probability of local recurrence or distant metastasis was 7.3%, 25%, 23.5%, and 23.7%, respectively.

Conclusions: In this real-world study, the combination of tumor and LNs responses was significantly associated with prognosis, and we demonstrated that ypTMPR(+)/ypN(0) group had a better prognosis, followed by ypTMPR(–)/ypN(0), ypTMPR(+)/ypN(0), and ypTMPR(–)/ypN(1+2). We advocate for ypTMPR(+)/ypN(0) status as a better surrogate of PFS in resectable NSCLC patients after NCIT.

Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant chemoimmunotherapy (NCIT); clinical and pathological response; progression-free survival (PFS); real-world study

Submitted Jun 23, 2024. Accepted for publication Sep 06, 2024. Published online Oct 21, 2024.
doi: 10.21037/jtd-24-1011
View this article at: https://dx.doi.org/10.21037/jtd-24-1011

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in China and the world (1). Neoadjuvant chemotherapy (NCT) alone has been shown to have limited capability to improve the survival rate (2). For locally advanced NSCLC, the emergence of immune checkpoint inhibitors (ICIs) has thoroughly changed the neoadjuvant therapy regimen and the CheckMate 816 trial has demonstrated that neoadjuvant chemoimmunotherapy (NCIT) provides more survival benefits than NCT (3,4). Major pathologic response (MPR) is a common alternative endpoint in many ongoing or completed clinical trials evaluating neoadjuvant immunotherapy (NIT) for NSCLC (5). However, current clinical studies on NCIT have shown very different results for MPR, ranging from 36.9% in the CheckMate 816 study to 82.9% in the NADIM study (4,6).

In recent years, the association between primary tumor and lymph nodes (LNs) responses to neoadjuvant therapy and survival benefits has been investigated. It has been reported that the combined responses of primary tumor and LNs after NCT in patients with NSCLC showed favorable prognostic significance (7,8). The consistently good response observed in the primary tumor and LNs was associated with a good survival benefit. However, some studies have reported that 21.05–53.2% of patients still have differences in response between the primary tumor and LNs (4,6). There have been case reports of inconsistent response of LNs in patients who have achieved pathological complete response (pCR) of the primary tumor. There is limited evidence comparing different responses of primary tumor and LNs in patients with resectable NSCLC. Hence, this retrospective real-world analysis intended to evaluate the clinical and pathological responses of primary tumor and LNs, and long-term outcomes in NSCLC patients after NCIT. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1011/rc).

Highlight box

Key findings

- The combination of tumor and lymph nodes (LNs) responses is significantly associated with prognosis and we demonstrated that yield pathological tumor major pathologic response (ypTMPR) and yield pathological LNs stage (ypN) [ypTMPR(+)/ypN(0)] group had a better prognosis.

What is known and what is new?

- Recent clinical studies on neoadjuvant chemoimmunotherapy (NCIT) have shown that the results of major pathologic response are very different, ranging from 36.9% to 82.9%.
- ypTMPR(+)/ypN(0) group had a better prognosis.

What is the implication, and what should change now?

- We advocated for ypTMPR(+)/ypN(0) status as a better surrogate of progression-free survival in resectable non-small cell lung cancer patients after NCIT.

Methods

Patient population

We included resectable NSCLC patients who had received neoadjuvant therapy and had available clinicopathological data from March 2021 to June 2023 at the Department of Thoracic Surgery, Shandong Cancer Hospital and Institute. The flow chart of study design is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the Shandong Cancer Hospital and Institute (No. SDTHEC2024002005). The requirement for individual consent for this retrospective analysis was waived. The inclusion criteria were as follows: (I) age 18 years or older; (II) no previous treatment for lung cancer; (III) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (IV) underwent NCIT and surgery; and (V) histologically confirmed NSCLC. The exclusion criteria were as follows: (I) history of malignancies in the past 5 years; (II) previous local radiotherapy or any systemic antitumor therapy; (III) unstable systemic disease; (IV) history or current diagnosis of interstitial lung disease (ILD); and (V) exploratory thoracotomy.

This study was based on the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) primary tumor, regional LNs involvement, and distant metastases (TNM) staging system. All patients received multi-disciplinary treatments (MDTs) to assess their condition and determine an appropriate protocol before starting treatment. The main preoperative regimens consisted of platinum-based dual-drug chemotherapy and programmed cell death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) inhibitors every 3 weeks.

The clinical responses of the primary tumor and LNs were evaluated after every two NCIT cycles according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (9). The evaluation of the target lesions was

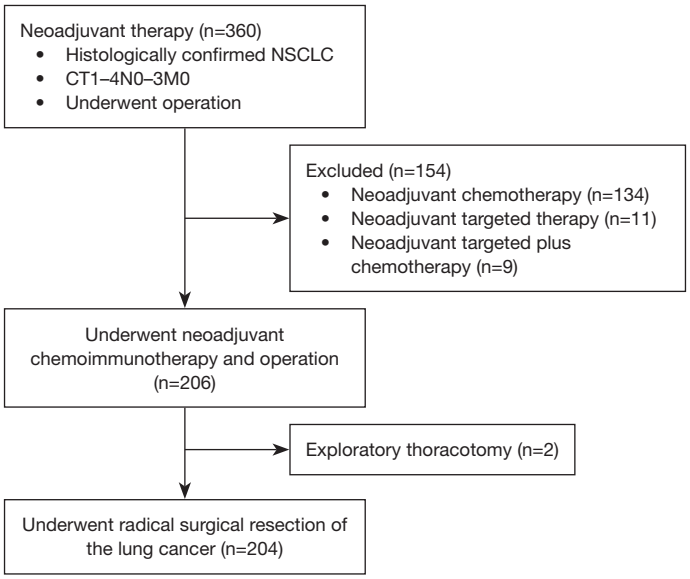

Figure 1 Flow chart of study design. NSCLC, non-small cell lung cancer.

divided into complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and overall response (OR).

All patients underwent radical surgical resection of lung cancer 4–6 weeks after the last NCIT. The pulmonary lesion was excised via lobectomy, sublobectomy, sleeve lobectomy, or pneumonectomy. Surgical specimens were histopathologically examined, and the activity of the tumor and LNs was evaluated by two pathologists. T and N downstaging were defined as T or N category declines. MPR was defined as residual viable tumor cells less than 10%, and pCR was defined as no residual viable tumor (including primary tumor and LNs) (10). Yield pathological tumor MPR (ypTMPR) was defined as residual viable primary tumor cells less than 10%, and yield pathological tumor pCR (ypTpCR) was defined as no residual viable primary tumor. All selected patients received a regular outpatient review and telephone follow-up. The follow-up ended on 1 March 2023. Overall survival (OS) was defined as the time from the initial diagnosis to death from any cause and progression-free survival (PFS) was defined as the time from the initial diagnosis to progression of disease, recurrence of disease, or death from any cause.

Statistical analysis

Categoric variables were expressed as numbers or percentages and evaluated with Chi-squared or Fisher's exact test. Continuous data were presented as mean [interquartile range (IQR)] or mean ± standard deviation and were compared using the two-sample Student's *t*-test. The Kaplan-Meier method was used to estimate median PFS and OS and two-sided 95% confidence intervals (CIs) for time to event. We estimated hazard ratios (HRs) and 95% CIs using a Cox proportional hazards regression model. All P values were reported by two-sided analyses, and the statistical significance level was set at less than 0.05. Subgroup analysis adjusted by T stage and N stage was adopted to investigate the impact of adjuvant treatment on survival outcomes. Statistical analysis was performed with SPSS 25.0 software (IBM Corp., Armonk, NY, USA).

Results

Patients

We excluded two patients who underwent NCIT because they had only undergone exploratory thoracotomy. In total, 204 patients met the inclusion criteria (*Figure 1*). *Table 1* summarizes the clinical and pathological characteristics of patients. The patients were predominantly male (85.8%) and ever-smokers (66.2%), with a median age of 63 (IQR, 56–67.75) years and a median body mass index (BMI) of 23.94 (IQR, 21.80–25.97) kg/m^2. The main pathology was primary squamous cell carcinoma (SCC) (141, 69.1%). More than half of the patients (137, 67.2%) received

Table 1 Characteristics of the patients at baseline

Variables	N or median	% or IQR
Age (years)	63	56–67.75
Sex		
Male	175	85.8
Female	29	14.2
BMI (kg/m^2)	23.94	21.80–25.97
Smoking history		
Yes	135	66.2
No	69	33.8
Tumor position		
LUL	53	26.0
LLL	51	25.0
RUL	50	24.5
RML	8	3.9
RLL	42	20.6
Resection scope		
Lobectomy	149	73.0
Pneumonectomy	6	2.9
Sublobectomy	2	1.0
Sleeve lobectomy	21	10.3
RM/LL or RM/UL	26	12.7
Operation time (min)	120	90–148.75
Cycle		
1	5	2.5
2	137	67.2
3	53	26.0
4	8	3.9
5	1	0.5
Pathology		
SCC	141	69.1
AD	54	26.5
SCC/AD	5	2.5
Sarcomatoid carcinoma	3	1.5
BCLC	1	0.5
cT		
1	16	7.8
2	97	47.5
3	51	25.0
4	40	19.6
cN		
0	50	24.5
1	48	23.5
2	103	50.5
3	3	1.5
cTNM		
IA	4	2.0
IB	1	0.5
IIA	18	8.8
IIB	41	20.1
IIIA	95	46.6
IIIB	43	21.1
IIIC	2	1.0
ycT		
0	18	8.8
1	55	27.0
2	88	43.1
3	32	15.7
4	11	5.4
ycN		
0	67	32.8
1	43	21.1
2	93	45.6
3	1	0.5
ycTNM		
0	10	4.9
IA	15	7.4
IB	3	1.5
IIA	25	12.3
IIB	41	20.1
IIIA	91	44.6
IIIB	18	8.8
IIIC	1	0.5
SD		
Yes	77	37.7
No	127	62.3

Table 1 *(continued)*

Table 1 *(continued)*

Variables	N or median	% or IQR
PR		
Yes	96	47.1
No	108	52.9
CR		
Yes	19	9.3
No	185	90.7
PD		
Yes	12	5.9
No	192	94.1
ORR		
Yes	115	56.4
No	89	43.6
ypT		
0	83	40.7
T1a	59	28.9
T1b	11	5.4
T1c	18	8.8
T2a	12	5.9
T2b	14	6.9
T3	3	1.5
T4	4	2.0
ypN		
0	149	73.0
1	20	9.8
2	35	17.2
ypTNM		
0	77	37.7
IA1	45	22.1
IA2	7	3.4
IA3	4	2.0
IB	6	2.9
IIA	7	3.4
IIB	19	9.3
IIIA	37	18.1
IIIB	2	1.0
MPR		
Yes	127	62.3
No	77	37.7

Table 1 *(continued)*

Variables	N or median	% or IQR
pCR		
Yes	77	37.7
No	127	62.3
T stage		
Yes	188	92.2
No change	15	7.4
Up	1	0.5
N stage		
Yes	118	57.8
No change	45	22.1
Up	41	20.1
cN→pN		
0→0	41	20.1
2→0	73	35.8
1→0	33	16.2
2→1	9	4.4
3→0	2	1.0
3→2	1	0.5
2→2	21	10.3
1→1	8	3.9
1→2	7	3.4
0→2	6	2.9
0→1	3	1.5

IQR, interquartile range; BMI, body mass index; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; RM/LL or RM/UL, right middle and lower lobe or right middle and upper lobe; SCC, squamous cell carcinoma; AD, adenocarcinoma; BCLC, big cell lung cancer; cT, clinical stage of primary tumor; cN, clinical stage of regional lymph nodes; cTNM, clinical stage of primary tumor, regional lymph nodes involvement, and distant metastases; ycT, yield clinical stage of primary tumor; ycN, yield clinical stage of regional lymph nodes; ycTNM, yield clinical stage of primary tumor, regional lymph nodes involvement, and distant metastases; SD, stable disease; PR, partial response; CR, complete response; PD, progressive disease; ORR, overall response rate; ypT, yield pathological of primary tumor; ypN, yield pathological of regional lymph nodes; ypTNM, yield pathological of primary tumor, regional lymph nodes involvement, and distant metastases; MPR, major pathologic response; pCR, pathological complete response; pN, pathological of regional lymph nodes.

2 cycles of NCIT. Most patients received lobectomy (149, 73.0%), with a smaller proportion undergoing bilobectomy (26, 12.7%), sleeve lobectomy (21, 10.3%), or pneumonectomy (6, 2.9%). No significant difference was observed in intraoperative bleeding (P=0.51 and P=0.54) and operation time (P=0.57 and P=0.58) between the MPR and pCR groups, respectively.

Clinical and pathological response

Most patients were classified as clinical T2 (cT2) (97, 47.5%) and clinical N2 (cN2) (103, 50.5%). After NCIT, 96 (47.1%) achieved PR and 19 (9.3%) had a CR, resulting in an OR rate (ORR) of 56.4%. As shown in *Table 1*, 77 (37.7%) patients achieved pCR and 127 (62.3%) patients achieved MPR. Patients who were male (pCR, P=0.01; MPR, P=0.004), had SCC (pCR, P=0.02; MPR, P=0.001), and ORR (pCR, P<0.001; MPR, P<0.001) demonstrated significantly higher rates of pCR and MPR (*Table 2*). There was no significant correlation between pathological response and clinical stage of tumor (cT) (pCR, P=0.75; MPR, P>0.99), clinical stage of LNs (cN) (pCR, P=0.54; MPR, P=0.09), or clinical stage of TNM (cTNM) (pCR, P=0.79; MPR, P=0.20). However, there was a significant difference between pathological response and yield clinical stage of primary tumor (ycT) (pCR, P<0.001; MPR, P=0.004). In terms of re-staging after treatment, stage ycIII accounted for the highest proportion (53.9%), but postoperative pathology confirmed that stage ypIII only accounted for (19.1%), re-staging to ypI accounted for the greatest proportion (37.7%). A total of 188 patients (92.2%) had T downstaging and 118 patients (57.8%) had N downstaging. Only 1 patient (0.5%) had T upstaging, but 41 patients (20.1%) had N upstaging. Pathological N upstaging was observed in only 9 (4.4%) patients. The detailed stages [cTNM, yield clinical stage of TNM (ycTNM), yield pathological stage of TNM (ypTNM)] are shown in *Figure 2A-2C*.

Survival outcomes

The median follow-up time for all patients in this study was 23 months. The survival analyses for OS (*Figure 3A,3B*) and PFS (*Figure 4A,4B*) compared MPR and pCR. Patients with MPR (P=0.004) and pCR (P=0.02) experienced prolonged PFS, but no extension of OS (MPR, P=0.08; pCR, P=0.15). Survival analysis also showed that compared to the yield pathological LNs stage (ypN)(1+2) group, the ypN(0) group had a longer PFS (*Figure 5A,5B*) (P=0.043). Rates of progression among patients with MPR and non-MPR were 9.4% (12/127) and 24.7% (19/77) (P=0.003), and those among patients with pCR and non-pCR were 7.8% (6/77) and 19.7% (25/127) (P=0.12). A total of 31 (15.2%) patients experienced local recurrence or distant metastasis, and 24 (11.8%) patients died. The death rate among patients with MPR and non-MPR was 8.7% (11/127) and 16.9% (13/77) (P=0.08), respectively, and that among patients with pCR and non-pCR was 7.8% (6/77) and 14.2% (18/127) (P=0.17), respectively.

ypT versus ypN

The overall ypTMPR rate was 62.3%, ypTpCR rate was 40.7%, and the ypN0 rate was 73%. LNs downstaging to ypN0 was observed in 107 of 204 (52.5%) patients, with two cases downstaging from N3 to N0, 73 cases from N2 to N0, and 33 cases from N1 to N0 (*Table 1*). Notably, we found a significant association between ypTMPR/pCR and ypN. After obtaining ypTMPR, 86.6% (110/127) of patients achieved ypN0, whereas only 50.6% (39/77) of patients in the non-ypTMPR group achieved ypN0 (P<0.001). After obtaining ypTpCR, 92.8% (77/83) of patients achieved ypN0, whereas only 59.5% (72/121) of patients in the non-ypTpCR group achieved ypN0 (P<0.001).

In terms of ypTMPR and ypN (*Figure 6A*), Kaplan-Meier analyses demonstrated the better PFS for the ypTMPR(+)/ypN(0) group, followed by ypTMPR(–)/ypN(0), ypTMPR(+)/ypN(0), and ypTMPR(–)/ypN(1+2). The average PFS time for these groups was 35.7, 31.7, 29.4, and 28.7 months, respectively. After achieving MPR, the probability of local recurrence or distant metastasis was 7.3%, 25%, 23.5%, and 23.7%, respectively. The results showed that the PFS of the ypTMPR(+)/ypN(0) group was significantly better than that of the other groups (P=0.01). In terms of ypTpCR and ypN (*Figure 6B*), survival analysis showed better PFS for the ypTpCR(+)/ypN(0) group, followed by ypTpCR(–)/ypN(0), ypTpCR(+)/ypN(0), and ypTpCR(–)/ypN(1+2).

To specifically assess the responses of primary tumor and LNs, survival analyses were performed to understand outcomes between groups. Using ypTMPR and ypN status (*Figure 6A*), four groups were reviewed in assessing PFS: ypTMPR(+)/ypN(0), ypTMPR(+)/ypN(1+2), ypTMPR(–)/ypN(0), and ypTMPR(–)/ypN(1+2). Similarly, using ypTpCR and ypN status, four groups were reviewed in assessing PFS: ypTpCR(+)/ypN(0), ypTpCR(+)/ypN(1+2),

Table 2 Comparison of MPR and pCR between groups

Variables	MPR			pCR		
	Yes	No	P value	Yes	No	P value
Age (years)	62.72±7.51	60.27±8.14	0.03	62.34±8.38	61.46±7.48	0.44
Sex			0.004			0.01
Male	116	59		72	103	
Female	11	18		5	24	
BMI (kg/m^2)	23.96±3.02	24.35±3.23	0.38	23.64±3.08	24.38±3.09	0.10
Smoking history			0.13			0.75
Yes	89	46		52	83	
No	38	31		25	44	
Smoking index	625.43±612.84	527.27±632.99	0.28	634.94±630.51	560.16±615.62	0.41
Tumor position			0.43			0.48
LUL	34	19		23	30	
LLL	30	21		17	34	
RUL	35	15		22	28	
RML	3	5		3	5	
RLL	25	17		12	30	
Resection scope			0.059			0.21
Lobectomy	100	49		63	86	
Pneumonectomy	2	4		1	5	
Sublobectomy	0	2		0	2	
Sleeve lobectomy	10	11		5	16	
RM/LL or RM/UL	15	11		8	18	
Operation time (min)	123.24±35.45	120±44.2	0.57	120.14±34.47	123.15±41.46	0.58
Bleed loss (mL)	122.83±102.38	139.1±247.63	0.51	119.48±74.57	134.72±210.06	0.54
Cycle			0.80			0.96
1	3	2		2	3	
2	88	49		52	85	
3	31	22		20	33	
4	4	4		3	5	
5	1	0		0	1	
Pathology			0.001			0.02
SCC	100	41		62	80	
AD	21	33		16	38	
SCC and AD	3	2		0	5	
Sarcomatoid carcinoma	2	1		0	3	
BCLC	1	0		0	1	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	MPR			pCR		
	Yes	No	P value	Yes	No	P value
cT			>0.99			0.87
1	10	6		6	10	
2	60	37		37	60	
3	32	19		21	30	
4	25	15		13	27	
cN			0.09			0.57
0	28	22		18	32	
1	31	17		19	29	
2	68	35		40	63	
3	0	3		0	3	
cTNM			0.20			0.81
IA	1	3		1	3	
IB	0	1		0	1	
IIA	11	7		6	12	
IIB	27	14		18	23	
IIIA	58	37		35	60	
IIIB	30	13		17	26	
IIIC	0	2		0	2	
ycT			0.004			<0.001
0	18	0		15	3	
1	37	18		21	34	
2	51	37		31	57	
3	16	16		8	24	
4	5	6		2	9	
ycN			0.44			0.21
0	43	24		31	36	
1	24	19		12	31	
2	60	33		34	59	
3	0	1		0	1	
ycTNM			0.27			0.007
0	10	0		10	0	
IA	8	7		5	10	
IB	2	1		1	2	
IIA	16	9		10	15	
IIB	25	16		15	26	
IIIA	56	35		32	59	
IIIB	10	8		4	14	
IIIC	0	1		0	1	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	MPR			pCR		
	Yes	No	P value	Yes	No	P value
SD			<0.001			0.001
Yes	36	41		18	59	
No	91	36		59	68	
PR			0.02			0.10
Yes	68	28		42	54	
No	59	49		35	73	
CR			<0.001			<0.001
Yes	19	0		16	3	
No	108	77		61	124	
PD			0.03			0.03
Yes	4	8		1	11	
No	123	69		76	116	
ORR			<0.001			<0.001
Yes	87	28		58	57	
No	40	49		19	70	
ypN			<0.001			<0.001
N0	110	39		77	72	
N1	7	13		0	20	
N2	10	25		0	35	
Progression			0.003			0.02
Yes	12	19		6	25	
No	115	58		71	102	
Status			0.08			0.17
Alive	116	64		71	109	
Dead	11	13		6	18	

Data are presented as n or mean ± standard deviation. MPR, major pathologic response; pCR, pathological complete response; BMI, body mass index; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; RM/LL or RM/UL, right middle and lower lobe or right middle and upper lobe; SCC, squamous cell carcinoma; AD, adenocarcinoma; BCLC, big cell lung cancer; cT, clinical stage of primary tumor; cN, clinical stage of regional lymph nodes; cTNM, clinical stage of primary tumor, regional lymph nodes involvement, and distant metastases; ycT, yield clinical stage of primary tumor; ycN, yield clinical stage of regional lymph nodes; ycTNM, yield clinical stage of primary tumor, regional lymph nodes involvement, and distant metastases; SD, stable disease; PR, partial response; CR, complete response; PD, progressive disease; ORR, overall response rate; ypN, yield pathological of regional lymph nodes.

ypTpCR(–)/ypN(0), and ypTpCR(–)/ypN(1+2).

The average PFS time was 35.6, 34.5, 31, and 28.5 months, respectively (P=0.09). After achieving pCR, the probability of local recurrence or distant metastasis was 7.8%, 16.7%, 16.7%, and 24.5%, respectively.

Discussion

Many clinical trials (NADIM, CheckMate 816, and Keynote-671) have demonstrated superior PFS, OS, MPR, and pCR rates of NSCLC after NICT (4,6,11). We demonstrated a higher rate of patients with a pCR (37.7%)

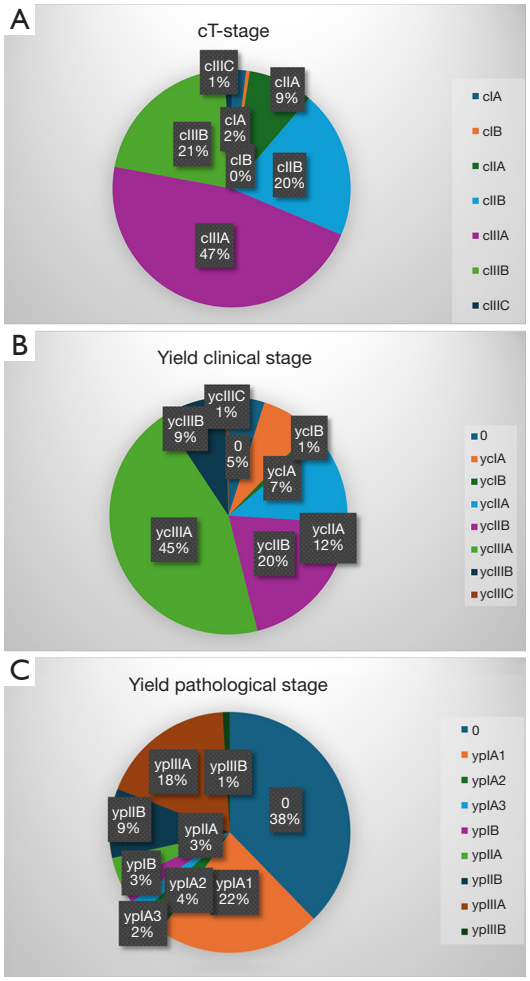

Figure 2 Changes in stages. (A) cTNM; (B) ycTNM; (C) ypTNM. cTNM, clinical stage of primary tumor, regional lymph nodes involvement, and distant metastases; ycTNM, yield clinical stage of primary tumor, regional lymph nodes involvement, and distant metastases; ypTNM, yield pathological stage of primary tumor, regional lymph nodes involvement, and distant metastases.

than the CheckMate 816 trial (24%), which was similar to that in the NADIM II trial (37%). In clinical trials, more reliable LNs sampling and pathological assessments were carried out at baseline, whereas in routine clinical practice, simplified radiological evaluation was more common for N stage patients, resulting in more early-stage patients undergoing NCIT. In addition, clinical trials have typically excluded stage I patients, and among the patients who received NCIT in our cohort, 2.5% of patients were diagnosed as stage I at the time of diagnosis. The above

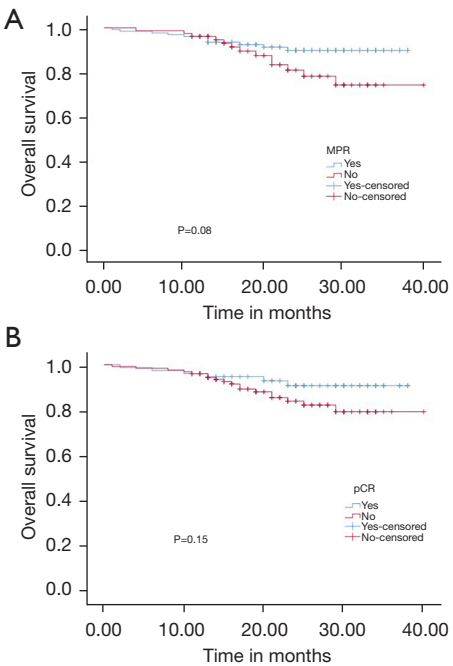

Figure 3 OS among patients with MPR (A) and pCR (B). MPR, major pathologic response; pCR, pathological complete response; OS, overall survival.

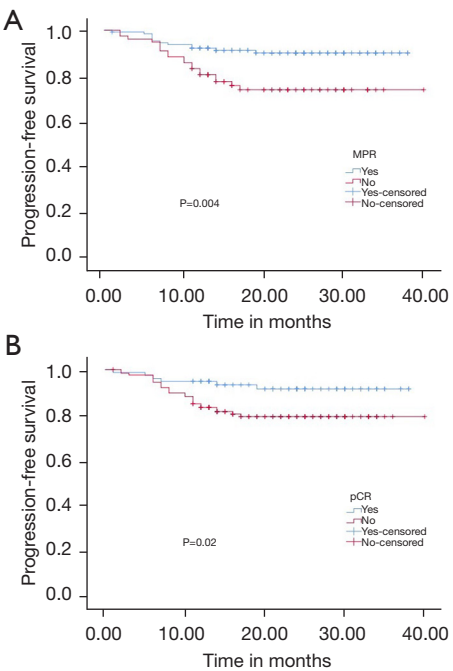

Figure 4 PFS among patients with MPR (A) and pCR (B). MPR, major pathologic response; pCR, pathological complete response; PFS, progression-free survival.

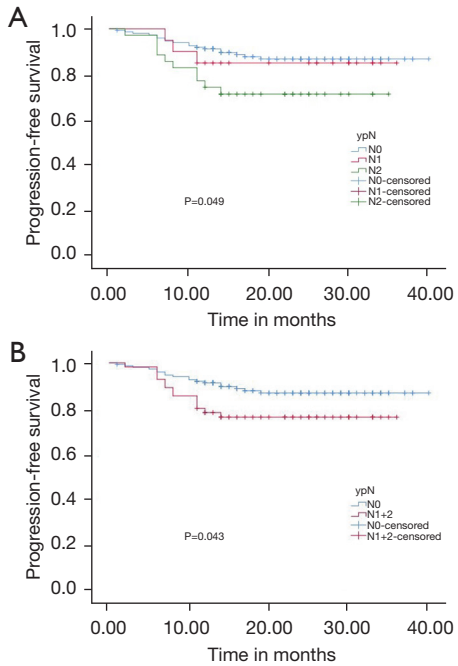

Figure 5 PFS among patients with ypN (A,B). ypN, yield pathological of regional lymph nodes; PFS, progression-free survival.

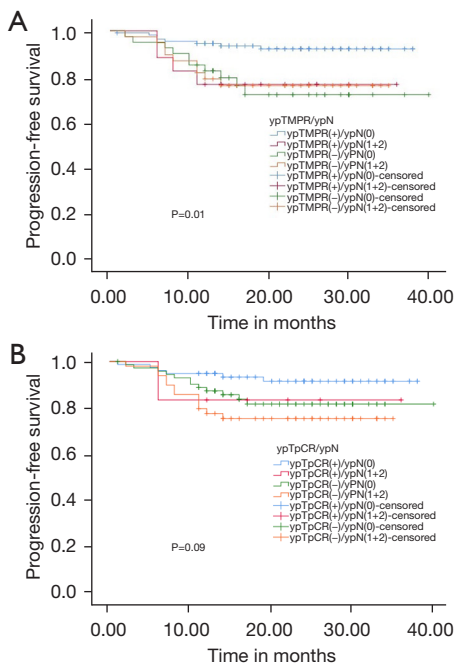

Figure 6 PFS among patients with ypTMPR/ypN (A) and ypTpCR/ypN (B). ypTMPR, yield pathological tumor major pathologic response; ypN, yield pathological of regional lymph nodes; ypTpCR, yield pathological tumor pathological complete response; PFS, progression-free survival.

reasons led to a higher pCR rate in our study. The ability of NCIT to induce MPR (P=0.001) and pCR (P=0.02) in SCC was significantly higher than that in other pathological types. This also confirmed the clinical preference for NCIT in patients with SCC (9).

Although pCR was a more accurate predictive indicator, its application in NCIT was often limited by its infrequent occurrences. Currently, MPR has become an acceptable surrogate of predicting the effect of NCT and has been used as a prognostic index in some clinical trials of NIT (12,13). The MPR rate was 62.3%, and the result was similar to the pooled analysis of Zhai *et al.* (14). PFS in patients who achieved pCR and MPR was better than it was those who achieved non-pCR (P=0.02) and non-MPR (P=0.004). For OS, no significant difference was observed between the MPR (P=0.08) and pCR (P=0.15). It seemed that for patients who have obtained MPR or pCR, PFS was a better endpoint indicator than OS. Therefore, we adopted PFS as the end point indicator in the subgroup analysis.

Previous studies have shown that the pathological benefit (MPR or pCR) was better in patients with stage III than in patients with stage I or II (15,16). However, in our results, pathological type was the significant factor affecting pathological benefits and had little to do with clinical TNM staging.

We further compared the pathological responses of primary tumors and LNs in NSCLC patients who received NCIT. We demonstrated a significant association between ypTMPR/pCR and ypN0. We found that about 50% of patients achieved ypN0, but the primary tumor did not reach MPR or pCR. This might be because we included more patients with baseline cN0 (24.5%). Ye *et al.* believed that *in situ* immune patterns of T cells and cytotoxic T cells were different between primary tumor and metastasis LNs in NSCLC. The heterogeneity of the *in situ* immune patterns might result in different immune-mediated responses to NIT (17). Hence, after NCIT, it was not reliable to establish an absolute correlation between ypTMPR/pCR and ypN0. Similarly, Forde *et al.* and Gao *et al.* concluded that ypN0 could not simply be present in patients with ypTpCR (16,18).

Betticher *et al.* and van Meerbeeck *et al.* have demonstrated a positive association between LNs downstaging and improvement in OS in patients with pathologically confirmed stage IIIA NSCLC after NCT (19,20). The association between LNs responses to NCIT and OS has also been investigated (6). LNs downstaging was widely recognized as an independent prognostic factor, reflecting both radical resection of NSCLC and the

effectiveness of NCIT (21). The impact of ypN status on PFS was statistically significant in this study. The ypN0 was significantly correlated with better PFS, followed by ypN1 and ypN2. Our research showed a promising result about LNs response, with a high LNs downstaging rate (57.9%) and ypN0 status (73%). As expected, LNs, a recognized organ that promotes anti-tumor immunity, was more responsive to immunotherapy.

In order to further evaluate the combined response of an NCIT regimen to primary tumor and LNs response, we conducted subgroup analysis. In this real-world study, we demonstrated that the ypTMPR(+)/ypN(0) group had a better prognosis, followed by ypTMPR(–)/ypN(0), ypTMPR(+)/ypN(0), and ypTMPR(–)/ypN(1+2). The results indicated that compared to primary tumor regression, LNs downstaging was more likely to predict PFS. It was found that the combination of ypTMPR(+) and ypN0 was associated with good PFS and should be regarded as a reliable indicator to predict the prognosis of NSCLC patients after NCIT. Corsini *et al.* found that MPRypN0 represented the most favorable end point after NCT (22). They emphasized that MPRypN0 was the most effective end point and should be considered as an alternative end point in future neoadjuvant trials. We validated their outcomes in the environment of NCIT, which provided more evidence for ypTMPR(+)/ypN(0) as the end point.

Moreover, our study found a significant difference between ycTNM and ypTNM. A recent report has shown that there was inconsistency between radiological and pathological assessments of tumor response in the real-world settings (23). We believed that RECIST version 1.1, which was currently available, was not timely enough to distinguish between radiological and true pathological responses. Further research was needed to establish new radiological standards that did not rely solely on CT to better reflect the efficacy of NCIT.

Another important note was that the rate of cN2 descending to pN0 was the highest, indicating that NCIT had a greater ability to descend mediastinal LNs. Ling *et al.* demonstrated that the percentage of inflammatory morphology and phenotype in the N1 LN was higher than that in the N2 LN in the enrolled patients (8).

Limitations

In the course of our above research, there were some small findings, but this study has several limitations. Firstly, as a single institution experience from a large, regional cancer hospital, our report might lack generalizability to other populations. Secondly, the postoperative follow-up is short. In the future, we hope to observe the 5-year PFS and OS after NCIT in a larger patient cohort. Thirdly, the efficacy of different chemotherapeutic and immunological drugs vary slightly, which might have an impact on the outcome. Finally, it is the use of a scheme used outside standard clinical practice as set out in clinical guidelines. We need more data to confirm these results.

Conclusions

Patients who achieved pCR and MPR had a better PFS than those with non-pCR and non-MPR, but OS did not. In the real-world study, we demonstrated that ypTMPR(+)/ypN(0) group had a better prognosis, followed by ypTMPR(–)/ypN(0), ypTMPR(+)/ypN(0), and ypTMPR(–)/ypN(1+2). The results demonstrated that, among patients with ypTMPR(+), those with ypN0 status could acquire better benefits from NCIT. We advocate for ypTMPR(+)/ypN(0) status as a better surrogate of PFS in resectable NSCLC patients after NCIT.

Acknowledgments

We gratefully acknowledge the role of all our colleagues, nurses, and others involved in the care of these patients.
Funding: This study was supported by the Taishan Scholar Project Special Fund (No. tsqn202312367).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1011/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1011/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1011/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1011/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). The study was approved by the Ethics Committee of the Shandong Cancer Hospital and Institute (No. SDTHEC2024002005). The requirement for individual consent for this retrospective analysis was waived.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Pisters KM, Vallières E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol 2010;28:1843-9.
3. de Miguel M, Calvo E. Clinical Challenges of Immune Checkpoint Inhibitors. Cancer Cell 2020;38:326-33.
4. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
5. Hellmann MD, Chaft JE, William WN Jr, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol 2014;15:e42-50.
6. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:1413-22.
7. Pataer A, Weissferdt A, Vaporciyan AA, et al. Evaluation of Pathologic Response in Lymph Nodes of Patients With Lung Cancer Receiving Neoadjuvant Chemotherapy. J Thorac Oncol 2021;16:1289-97.
8. Ling Y, Li N, Li L, et al. Different pathologic responses to neoadjuvant anti-PD-1 in primary squamous lung cancer and regional lymph nodes. NPJ Precis Oncol 2020;4:32.
9. Yang Z, Wang S, Yang H, et al. Treatment patterns and clinical outcomes of patients with resectable non-small cell lung cancer receiving neoadjuvant immunochemotherapy: A large-scale, multicenter, real-world study (NeoR-World). J Thorac Cardiovasc Surg 2024;168:1245-58.e17.
10. Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. J Thorac Oncol 2020;15:709-40.
11. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:491-503.
12. Cascone T, William WN, Weissferdt A, et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. J Clin Oncol 2019;37:8504.
13. Pataer A, Weissferdt A, Correa AM, et al. Major Pathologic Response and Prognostic Score Predict Survival in Patients With Lung Cancer Receiving Neoadjuvant Chemotherapy. JTO Clin Res Rep 2022;3:100420.
14. Zhai WY, Zhao ZR, Chen S, et al. Response of primary tumor and lymph node in non-small cell lung cancer after neoadjuvant immunotherapy: a pooled analysis. J Immunother Cancer 2022;10:e005160.
15. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
16. Forde PM, Chaft JE, Pardoll DM. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med 2018;379:e14.
17. Ye ZH, Long H, Zhao ZR. Different In Situ Immune Patterns between Primary Tumor and Lymph Node in Non-Small-Cell Lung Cancer: Potential Impact on Neoadjuvant Immunotherapy. J Immunol Res 2022;2022:8513747.
18. Gao S, Li N, Gao S, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol 2020;15:816-26.
19. Betticher DC, Hsu Schmitz SF, Tötsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003;21:1752-9.
20. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus

radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-50.
21. Detterbeck FC, Boffa DJ, Kim AW, et al. The Eighth Edition Lung Cancer Stage Classification. Chest 2017;151:193-203.
22. Corsini EM, Weissferdt A, Pataer A, et al. Pathological nodal disease defines survival outcomes in patients with lung cancer with tumour major pathological response following neoadjuvant chemotherapy. Eur J Cardiothorac Surg 2021;59:100-8.
23. Tazdait M, Mezquita L, Lahmar J, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer 2018;88:38-47.

Cite this article as: Shao W, Zhao C, Li H, Sun J, Li B, Liu Z, Chen F, Liu J, Guo X, Guo H. Pathological responses of primary tumor and lymph nodes in non-small cell lung cancer after neoadjuvant chemoimmunotherapy: a retrospective real-world study. J Thorac Dis 2024;16(10):6427-6440. doi: 10.21037/jtd-24-1011