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Three years follow-up of neoadjuvant chemoimmunotherapy in resectable non-small cell lung cancer

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Neoadjuvant chemoimmunotherapy plays a crucial role in resectable non-small cell lung cancer (NSCLC). Neoadjuvant chemotherapy before sleeve lobectomy was safe and feasible, but the impact of neoadjuvant chemoimmunotherapy before sleeve lobectomy was unclear. In our retrospective study, patients diagnosed as stage IIB to IIIB resectable NSCLC between December 1, 2018 and December 1, 2020 in the Department of Thoracic Surgery, Zhejiang Cancer Hospital were collected. We analyzed the efficacy and safety of neoadjuvant chemoimmunotherapy for resectable NSCLC patients and analyzed the impact of different types of surgery on postoperative complications, surgical difficulty, and long-term survival. In total, 56 patients were included in this retrospective study. With a median follow-up of 35 months, 1-year EFS, 2-year EFS, and 3-year EFS were 87.5%, 80.4%, and 76.7%, respectively. 1-year OS, 2-year OS, and 3-year OS were 96.4%, 91.1%, and 85.6%. respectively. Both median EFS and OS were not reached. The percentage of patients with pCR was 51.8%. 48 (85.7%) patients had nodal downstaging and primary tumor downstaging. In 40 (61.4%) patients occurred neoadjuvant chemoimmunotherapy-related adverse events (AEs), most of them of Grade 1 and 2. Postoperative complications occurred in 19 (33.9%) patients. Subgroup analysis showed that sleeve lobectomy was related to better survival and had no impact on operation duration, hospital stay, intraoperative blood loss, and postoperative complications. Neoadjuvant chemoimmunotherapy led to a high pCR rate, favorable 3-year survival rate, and acceptable AEs. Sleeve lobectomy was safe and related to better survival.

Key words: non-small cell lung cancer; neoadjuvant chemoimmunotherapy; sleeve lobectomy

Lung cancer is the second most common and the most fatal cancer worldwide in 2020, with an estimated 2.2 million new cases and 1.8 million deaths [1], and 85% is non-small cell lung cancer (NSCLC) [2]. Surgical resection is the optimal treatment for early-stage NSCLC, however, the 5-year survival rate ranges from 35% to 70% in all resectable stages [3], and both neoadjuvant chemotherapy and adjuvant chemotherapy can only improve 5-year survival rate by 5% [4, 5].

The immuno-checkpoint inhibitors (ICIs) including programmed death receptor-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors play a crucial role in advanced non-small cell lung cancer (aNSCLC) [6–8]. It has also been confirmed that PD-L1 inhibitor significantly improves survival of stage III unresectable lung cancer [9]. Neoantigens which were created along with tumor growth can influence the response to ICIs, $CD8^+$ tumor-infiltrating lymphocytes reactive to clonal neoantigens and high levels of PD-1 expression were observed in early-stage NSCLC, and early-stage NSCLC might be more sensitive to ICIs [10]. Since Forde et al. first reported that neoadjuvant nivolumab is associated with higher major pathological response (MPR) in resectable NSCLC and a favorable 5-year OS rate [11, 12], a growing number of studies confirmed that neoadjuvant immunotherapy can dramatically increase MPR and pCR as compared with neoadjuvant chemotherapy [4, 13–16]. Chemotherapeutic agents can stimulate anticancer immunity by depleting immunosuppressive cells, activating immune effector cells, and promoting the proliferation of immune cells [17]. Theoretically, the combination of chemotherapeutic agents will improve the efficacy of immunotherapy. Two multicenter single-arm phase II trials proclaimed that neoadjuvant chemoimmunotherapy shows much better pathological response and acceptable adverse events [18, 19].

CheckMate 816 was an open-label, phase 3 trial, it showed that the median event-free survival (EFS) and pCR rate of nivolumab plus chemotherapy are better than chemotherapy alone (EFS: 31.6 months vs. 20.8 months, pCR: 24% vs. 2.2%) [20].

For centrally located NSCLC, sleeve lobectomy and pneumonectomy were the main types of surgery. Nowadays, surgeons tend to prefer sleeve lobectomy, attributed to lower postoperative complications, mortality, and better long-term survival [21]. Sleeve lobectomy after neoadjuvant chemotherapy was safe, and neoadjuvant radiotherapy and chemoradiotherapy were associated with an increased risk of pulmonary and airway complications after sleeve lobectomy [22, 23]. The impact of neoadjuvant chemoimmunotherapy on patients who underwent sleeve lobectomy was unclear. Chen et al. retrospectively analyzed nine NSCLC patients who underwent sleeve lobectomy after neoadjuvant chemoimmunotherapy, four of the patients received two cycles of chemoimmunotherapy and five under sleeve lobectomy alone, the postoperative complications and surgical difficulty between the two groups were similar [24]. Another study also confirmed these results [25], sleeve lobectomy after neoadjuvant chemoimmunotherapy was safe and feasible. The impact on long-term survival of neoadjuvant chemoimmunotherapy after sleeve lobectomy was unclear.

In this retrospective study, we analyzed the efficacy and safety of neoadjuvant chemoimmunotherapy in resectable non-small cell lung cancer, and the impact of different types of surgery on postoperative complications, surgical difficulty, and long-term survival.

Patients and methods

Patients. Patients who were diagnosed as resectable NSCLC between December 1, 2018 and December 1, 2020 in the Department of Thoracic Surgery, Zhejiang Cancer Hospital were collected. The key inclusion criteria were as follows: 1) age ≥18, 2) pathologically confirmed squamous cell carcinoma and adenocarcinoma, 3) underwent radical lobectomy and systemic lymph node dissection, 4) normal organ function, 5) clinical stage IIB–IIIB, 6) Eastern Cooperative Oncology Group performance-status score 0–1, 7) received neoadjuvant chemoimmunotherapy. The key exclusion criteria were: 1) ongoing systemic immunosuppressive therapy, 2) active cancer, 3) autoimmune or serious infectious diseases.

The adverse events of neoadjuvant therapy were evaluated according to the National Cancer Institute Common Toxicity Criteria (CTCAE) version 5.0. Evaluation of efficacy after neoadjuvant therapy was according to the Response Evaluation Criteria in Solid Tumors Group 1.1 (RECIST1.1). Clinical staging was according to the American Joint Committee on Cancer staging system 8th edition. pCR was defined as no residual viable tumor cells in the primary tumor and lymph nodes. It was evaluated by a pathologist. Event-free survival (EFS) was defined as the time from pathological diagnosis to recurrence, metastasis, or death from any cause. Overall survival (OS) was defined as the time from pathological diagnosis to death from any cause. Interval time was defined as the time from the last neoadjuvant therapy to surgery. Delay of surgery was defined as more than 30 days past planned surgical time (4–6 weeks after the last neoadjuvant therapy).

This study was approved by the ethics committee of Zhejiang Cancer Hospital (No: IRB-2023-414). Due to the retrospective nature of this study, the ethics committee waived the patients' informed consent forms.

Treatments. The neoadjuvant chemoimmunotherapy scheme was PD-1/PD-L1 inhibitors combined with platinum-based dual-drug chemotherapy. PD-1/PD-L1 inhibitors and chemotherapeutic agents were given intravenously every 3 weeks. The operation was performed 4–6 weeks after the last chemoimmunotherapy. The operation scheme was planned based on the patient's condition and the thoracic surgeons' experience. Postoperative complications that occurred within one month were recorded.

Follow-up. All patients were followed up every three months in the first two years, every six months from the third to fifth year, and once a year thereafter. Medical history, physical examination, blood test, computer tomography (CT) scan, and ultrasound examination were performed every follow-up. Brain magnetic resonance imaging (MRI), bronchoscopy, or positron emission tomography CT (PET-CT) were performed if necessary. The last follow-up date was March 18, 2023.

Statistical analysis. Statistical analysis was performed with SPSS software (22.0). Graphs were drawn using GraphPad Prism (9.5.1). Median follow-up time was calculated by the reverse Kaplan-Meier (KM) method, OS and EFS were calculated by the KM method, log-rank test was used to test the difference among different types of surgery. Categorical variables were analyzed using Fisher's exact or χ^2 tests. Categorical variables were presented as absolute and relative frequencies and numerical variables as median (range). Kruskal-Walli's test was used to analyze the difference in operation duration, hospital stay, postoperative hospital stays, and blood loss among sleeve lobectomy, lobectomy, and pneumonectomy. The p-values < 0.05 were considered to be statistically significant, p-values were all two-tailed.

Results

Patient's characteristics. 56 patients were in this retrospective study and the baseline characteristics are summarized in Table 1. Most of the patients were males (91.1%), age ≥60 (62.5%), having a smoking history (76.8%), and never drinking (66.1%). 92.9% of the patients were pathologically confirmed as squamous cell carcinoma. IIIA (44.6%) was the main stage. The chemotherapy scheme included albumin-bound Paclitaxel+Platinum (87.5%),

Paclitaxel+Platinum (5.3%), Gemcitabine+Platinum (3.6%), Pemetrexed+Platinum (3.6%). PD-1/PD-L1 inhibitors included Camrelizumab (23.2%), Durvalumab (10.7%), Nivolumab (1.8%), Pembrolizumab (46.4%), Sintilimab (10.7%), and Tirelizumab (7.2%). Most of the patients received two cycles of neoadjuvant chemoimmunotherapy (78.6%). 36 (64.3%) patients received at least one cycle of adjuvant therapy. 45 (75%) patients underwent radical surgery within six weeks after the last neoadjuvant chemoimmunotherapy.

Surgical information. The surgical information is summarized in Table 2. More patients (57.1%) underwent a video-assisted thoracoscopy approach (VATS). 41 (73.2%) patients underwent lobectomy, 12 (21.4%) underwent sleeve lobectomy, 3 (5.4%) underwent pneumonectomy (all left). The median number of lymph node dissection was 17.5 (range: 4–40) and lymph node stations were 7 (range: 3–12). The median operation duration was 166.5 minutes (range: 96–342) and the median blood loss was 200 ml (range: 50–1000). The median postoperative hospital stay was 6 days (range: 2–24). The median hospital stay was 12 days (range: 5–45). The median interval time was 5.07 weeks (range: 2–10). No surgery delay happened.

Efficacy evaluation and long-term outcome. Tumor response was evaluated after neoadjuvant chemoimmunotherapy by CT scan in all patients. According to RECIST 1.1 criteria, 2 patients showed complete response (CR), 37 patients showed partial response (PR), and 17 patients showed stable disease (SD), no one had disease progression (Figure 1A). According to the postoperative pathology, the percentage of patients with pCR was 51.8%. Patients with CR and PR had a higher probability of pCR (59% vs. 35.3%) but with no statistical significance (p=0.103; Figure 1B). 48 (85.7%) patients had nodal downstaging and primary tumor downstaging (Figures 2A, 2B).

With a median follow-up of 35 months, 11 patients had disease progression, six patients died, five died of tumor progression and one died of COVID-19. 1-year EFS, 2-year EFS, and 3-year EFS were 87.5%, 80.4%, and 76.7%, respectively; 1-year OS, 2-year OS, and 3-year OS were 96.4%, 91.1%, and 85.6%, respectively (Figures 3A, 3B). Both median EFS and OS were not reached.

Adverse events and postoperative complications. In 40 (61.4%) patients occurred neoadjuvant chemoimmunotherapy-related adverse events (AEs), most of them were of Grade 1 and Grade 2. In Grade 1 and Grade 2 AEs, anemia (26.8%), increased transaminase (23.2%), leukopenia (19.6%), neutropenia (17.9%), and thrombocytopenia (17.9%) were the top five AEs. Grade 3 AEs included neutropenia (5.4%), leukopenia (7.1%), thrombocytopenia (1.8%), arrhythmias (1.8%), and vomiting (1.8%). None of the AEs was associated with surgery delay or death. No Grade 4 and Grade 5 AEs occurred (Table 3).

In 19 (33.9%) patients occurred postoperative complications, of which, pneumothorax (8.9%), hydropneumothorax

Table 1. Clinical characteristics of all patients.

Clinical characteristics	n (%)
Age	
<60	21 (37.5%)
≥60	35 (62.5%)
Gender	
Male	51 (91.1%)
Female	5 (8.9%)
Smoking	
Never	13 (23.2%)
Ever or current	43 (76.8%)
Drinking	
Never	37 (66.1%)
Ever or current	19 (33.9%)
Pathological type	
Adenocarcinoma	4 (7.1%)
Squamous cell carcinoma	52 (92.9%)
Neoadjuvant chemoimmunotherapy	
1 cycle	1 (1.7%)
2 cycles	44 (78.6%)
3 cycles	8 (14.3%)
4 cycles	3 (5.4%)
Chemotherapy agents	
Albumin-bound Paclitaxel+Platinum	49 (87.5%)
Paclitaxel+Platinum	3 (5.3%)
Paclitaxel+Platinum	2 (3.6%)
Pemetrexed+Platinum	2 (3.6%)
Immuno-checkpoint inhibitors	
Camrelizumab	13 (23.2%)
Durvalumab	6 (10.7%)
Nivolumab	1 (1.8%)
Pembrolizumab	26 (46.4%)
Sintilimab	6 (10.7%)
Tirelizumab	4 (7.2%)
Adjuvant therapy	
Yes	32 (57.1%)
No	24 (42.9%)
Interval time	
≥6 weeks	20 (35.7%)
<6 weeks	36 (64.3%)
T-stage	
1	3 (5.4%)
2	22 (39.3%)
3	19 (33.9%)
4	12 (21.4%)
N-stage	
0	1 (1.8%)
1	27 (48.2%)
2	28 (50%)
cTNM	
IIB	14 (25%)
IIIA	25 (44.6%)
IIIB	17 (30.4%)

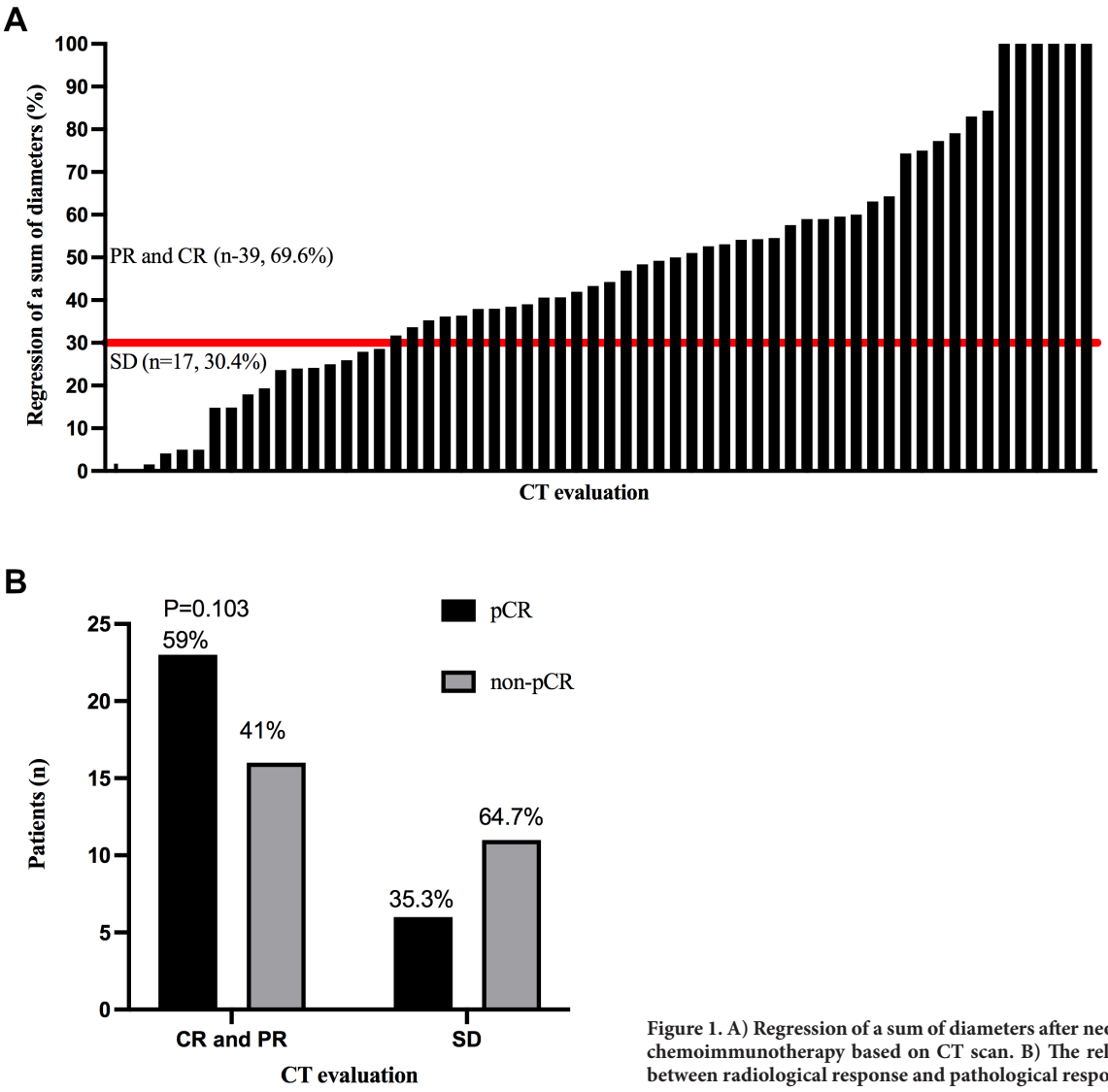

Figure 1. A) Regression of a sum of diameters after neoadjuvant chemoimmunotherapy based on CT scan. B) The relationship between radiological response and pathological response.

Table 2. Surgical information.

Surgical information	
Surgical approach (n%)	
VATS	32 (57.1%)
Thoracotomy	24 (42.9%)
Type of surgery (n%)	
Lobectomy	41 (73.2%)
Sleeve lobectomy	12 (21.4%)
Pneumonectomy	3 (5.4%)
Lymph node dissection, median (range)	17.5 (4–40)
Lymph node stations, median (range)	7 (3–12)
Interval time (weeks), median (range)	5.07 (2–10)
Operation duration (minutes), median (range)	166.5 (96–342)
Hospital stays (days), median (range)	12 (5–45)
Postoperative hospital stays (days), median (range)	6 (2–24)
Blood loss (ml), median (range)	200 (50–1000)

(8.9%), pneumonia (8.9%) were the most common. No one died of postoperative complications (Table 4).

Patterns of failure. In total, 11 patients had disease progression on March 18, 2023, 54.5% had distant metastasis, 27.3% had regional lymph node recurrence, and 18.2% had distant metastasis and regional lymph node recurrence (Figure 2C). The brain was the most common site of metastasis (four patients), followed by liver (two patients), pleura (one patient), adrenal (one patient), spleen (one patient).

Subgroup analysis. Subgroup analysis showed that age, gender, smoking history, drinking history, cycles of neoadjuvant chemoimmunotherapy, adjuvant immunotherapy, interval time, pathological response, and surgical approach had no significant impact on EFS and OS (Table 5).

Type of surgery was associated with survival: sleeve lobectomy had better EFS (3-year EFS rate: 91.7%) and OS (3-year

Table 3. Adverse events of neoadjuvant chemoimmunotherapy.

Events	n (%)					
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	15 (26.8%)	10 (17.9%)	5 (8.9%)	0 (0%)	0 (0%)	0 (0%)
Pneumonia	3 (5.4%)	2 (3.6)	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)
Neutropenia	10 (17.9%)	1 (1.8%)	6 (10.7%)	3 (5.4%)	0 (0%)	0 (0%)
Leukopenia	11 (19.6%)	3 (5.4%)	4 (7.1%)	4 (7.1%)	0 (0%)	0 (0%)
Thrombocytopenia	10 (17.9%)	9 (16.1%)	0 (0%)	1 (1.8%)	0 (0%)	0 (0%)
Hypothyroidism	1 (1.8%)	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased transaminase	13 (23.2%)	12 (21.4%)	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)
Increased bilirubin	2 (3.6%)	2 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased creatinine	6 (10.7%)	6 (10.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	2 (3.6%)	0 (0%)	1 (1.8%)	1 (1.8%)	0 (0%)	0 (0%)
Increased amylase	2 (3.6%)	2 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fever	2 (3.6%)	1 (1.8%)	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)
Arrhythmias	6 (10.7%)	5 (8.9%)	0 (0%)	1 (1.8%)	0 (0%)	0 (0%)

Table 4. Postoperative complications.

Complication	n (%)
All	19 (33.9%)
Hydrothorax	3 (5.4%)
Pneumothorax	5 (8.9%)
Atelectasis	3 (5.4%)
Pneumonia	5 (8.9%)
Hydropneumothorax	5 (8.9%)
Arrhythmias	2 (3.6%)
Acute exacerbation of COPD	1 (1.8%)
Bleeding	2 (3.6%)

OS rate: 91.7%) than lobectomy (3-year EFS rate: 74.7%, 3-year OS rate: 87.5%) and pneumonectomy (3-year EFS rate: 33.30%, 3-year OS rate: 33.30%) (Figures 4A, 4B). Operation duration, hospital stay, postoperative hospital stays, blood loss, and postoperative complications among sleeve lobectomy, lobectomy, pneumonectomy had no significant statistical difference (Table 6).

Discussion

The purpose of neoadjuvant therapy is to improve pathologic downstaging, complete resection, and overall survival. In the era before immunotherapy, the median pCR rate of neoadjuvant chemotherapy was 4% (range 0–16%) [15]. Compared with neoadjuvant chemotherapy, neoadjuvant concurrent chemoradiotherapy could improve nodal downstaging (53% vs. 22%) and pCR rate (21% vs. 0%), but not 3-year OS rate (27% vs. 23%) [26, 27].

In our retrospective study, the percentage of patients who had pCR, node and primary tumor downstaging was 51.8%, 85.7%, and 85.7% respectively, which was much higher than historical neoadjuvant chemotherapy and chemoradiotherapy. Many open-label, single-arm, phase II, multi-center

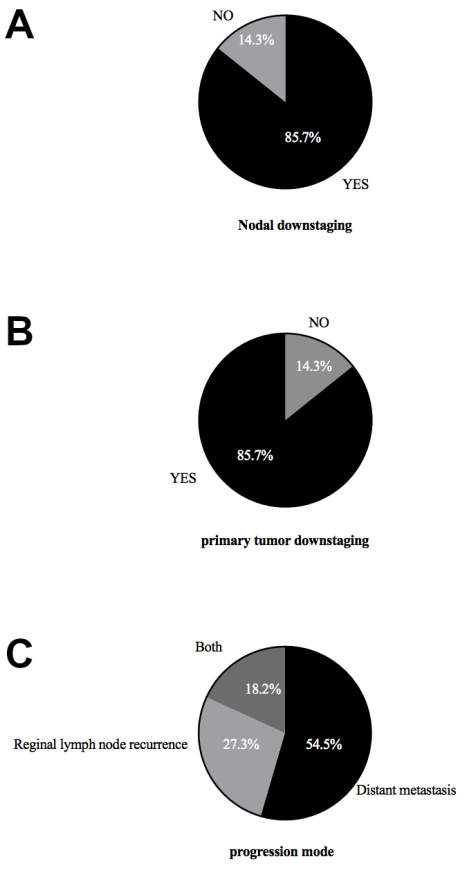

Figure 2. A) Nodal downstaging after neoadjuvant chemoimmunotherapy. B) Primary tumor downstaging after neoadjuvant chemoimmunotherapy. C) Patterns of failure.

clinicals of neoadjuvant chemoimmunotherapy for resectable NSCLC have been published recently. The results showed that the pCR rate ranged from 18% to 63.4% and 67% of patients had nodal downstaging [18, 28–30]. CheckMate 816

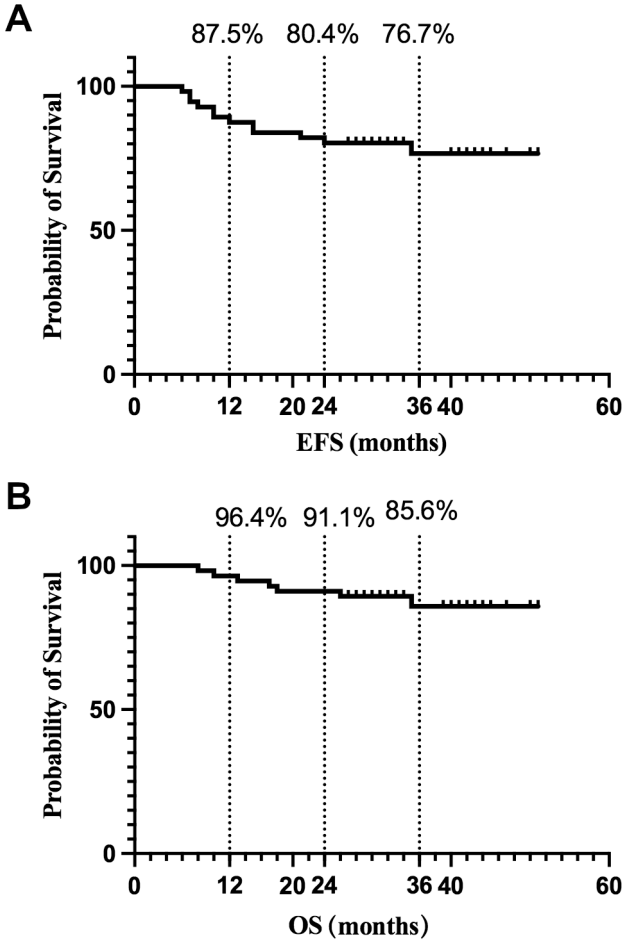

Figure 3. A) 1-year, 2-year, and 3-year EFS rates. B) 1-year, 2-year, and 3-year OS rates.

Table 5. Subgroup analysis for 3-year EFS and OS rate of different groups.

Subgroups	3-year EFS rate	p-value	3-year OS rate	p-value
Age				
<60	66.7%	0.113	85.7%	0.841
≥60	81.8%		84.9%	
Gender				
Male	82.4%		84.4%	0.387
Female	60.0%		100%	
Smoking				
Never	69.2%	0.369	90.1%	0.143
Ever or current	79.3%		78.9%	
Drinking				
Never	81.7%	0.158	90.9%	0.129
Ever or current	68.0%		80.0%	
Neoadjuvant chemoimmunotherapy				
1–2 cycles	80.0%	0.671	91.1%	0.108
3–4 cycles	65.5%		65.5%	
Adjuvant therapy				
Yes	78.1%	0.812	90.6%	0.527
No	77.8%		82.0%	
Interval time				
≥6 weeks	70.0%	0.215	80.0%	0.169
<6 weeks	81.3%		89.9%	
Pathological response				
pCR	75.0%	0.856	81.5%	0.741
Non-pCR	77.8%		89.0%	
Surgical approach				
VATS	75.0%	0.966	84.6%	0.955
Thoracotomy	79.2%		87.5%	
Type of surgery				
Lobectomy	74.7%	0.020	87.5%	0.004
Sleeve lobectomy	91.7%		91.7%	
Pneumonectomy	33.3%		33.3%	

was an open-label, phase 3 trial, 358 patients were randomly assigned in a 1:1 ratio to receive neoadjuvant nivolumab plus chemotherapy or chemotherapy alone, nivolumab plus chemotherapy group had a higher pCR rate than chemotherapy alone (24% vs. 2.2%) [20]. The different pCR rates among these researches might be attributed to different PD-1/PD-L1 inhibitors, cycles of neoadjuvant chemoimmunotherapy, and PD-L1 expression levels. Three cycles of neoadjuvant chemoimmunotherapy might result in a higher pCR than one or two cycles [29–31]. PD-1 inhibitors might result in a higher pCR than PD-L1 inhibitors [18, 28, 32]. PD-L1 expression ≥1% might result in a higher rate of pCR than PD-L1 expression <1% [33].

In our study, with a median follow-up time of 35 months, 1-year EFS, 2-year EFS, and 3-year EFS were 87.5%, 80.4%, and 76.7%, 1-year OS, 2-year OS, and 3-year OS were 96.4%, 91.1%, and 85.6%, both the median EFS and OS were not reached. So far, there have been few reports about the long-term survival of resectable NSCLC patients who received neoadjuvant chemoimmunotherapy. Only NADIM and CheckMate 816 had long-term survival data available. NADIM reported that in the pre-protocol population, with a median follow-up of 38 months, 3-year progression-free survival (PFS) is 81.1% and 3-year OS is 91% [30]. Checkmate 816 reported that the nivolumab plus chemotherapy group had better survival than chemotherapy alone (median EFS: 31.6 vs. 20.8 months, 1-year EFS: 76.1% vs. 63.4%, 2-year EFS: 63.8% vs. 45.3%) [20].

In a retrospective study, patients who achieved pCR had better OS and DFS [34] and this conclusion was also been proved in Checkmate 816 [20]. However in our study, pCR was not associated with better EFS, and NADIM confirmed the same conclusion [30]. Food and Drug Administration (FDA) approved atezolizumab as an adjuvant therapy in PD-L1 expression ≥1% stage II–IIIA NSCLC patients [35]. However, there was no consensus on whether adjuvant

immunotherapy was necessary for NSCLC patients who had received neoadjuvant chemoimmunotherapy. In our study, both EFS and OS were not affected by adjuvant immunotherapy. The ongoing phase III AEGEAN trial will reveal the impact of adjuvant immunotherapy on NSCLC patients who had received neoadjuvant chemoimmunotherapy [36].

For centrally located NSCLC, sleeve lobectomy is more suitable than pneumonectomy. It has been reported that sleeve lobectomy is safer and has a better prognosis than pneumonectomy after neoadjuvant chemotherapy [37]. Chen et al. reported that sleeve lobectomy after neoadjuvant chemoimmunotherapy is also safe and effective [24]. A recent multicenter retrospective study reported that compared with the chemotherapy group, sleeve lobectomy did not increase surgical difficulty and postoperative complications in the chemoimmunotherapy group [25]. Sleeve lobectomy was safe and feasible after neoadjuvant chemoimmunotherapy, but whether it had a better prognosis was unclear. In our study, 92.9% were squamous cell carcinoma which mostly occurs in the central position. Operation duration, hospital stay, postoperative hospital stays, blood loss, and postoperative complications among sleeve lobectomy, lobectomy, pneumonectomy had no significant statistical difference. The sleeve lobectomy group had better EFS and OS, followed by lobectomy and pneumonectomy. Further studies were needed to confirm these.

The main concerns about neoadjuvant chemoimmunotherapy were surgery delay for AEs, technical difficulty of surgical resection, postoperative complications, or disease progression during neoadjuvant chemoimmunotherapy. To date, surgery after neoadjuvant chemoimmunotherapy was a tolerable strategy for NSCLC, with a high VATS rate (20–73%) [28, 38], acceptable serious adverse events (SAEs) rate (24%) [39], low rate of surgery delay for AEs (0–4%) [20, 31], and complication rate (3.3–39%) [40, 41]. Commonly, operation duration, hospital stay, blood loss, and VATS proportion were used to evaluate the technical difficulty of surgical resection. In our study, operation duration, hospital stay, and blood loss were all acceptable, VATS rate was 57.1%, 40 (61.4%) patients occurred neoadjuvant chemoimmunotherapy related adverse events (AEs), SAEs included neutropenia (5.4%), leukopenia (7.1%), thrombocytopenia (1.8%), arrhythmias (1.8%), and vomiting (1.8%). None of the AEs was associated with surgery delays or deaths, the postoperative complication rate was 33.9%, and no one died of postoperative complications.

Neoadjuvant chemoimmunotherapy can significantly improve pCR and survival rate but not all patients can benefit from it. Several phase III clinical trials have indicated that PD-L1 expression ≥50% can guide single-agent immunotherapy or combination regimens for aNSCLC [42–44]. There were many controversies on tumor mutation burden (TMB) as a predictor for aNSCLC treated with ICIs [45]. The predictive value of PD-L1 expression and TMB in neoadjuvant chemoimmunotherapy was controversial. It is urgent to

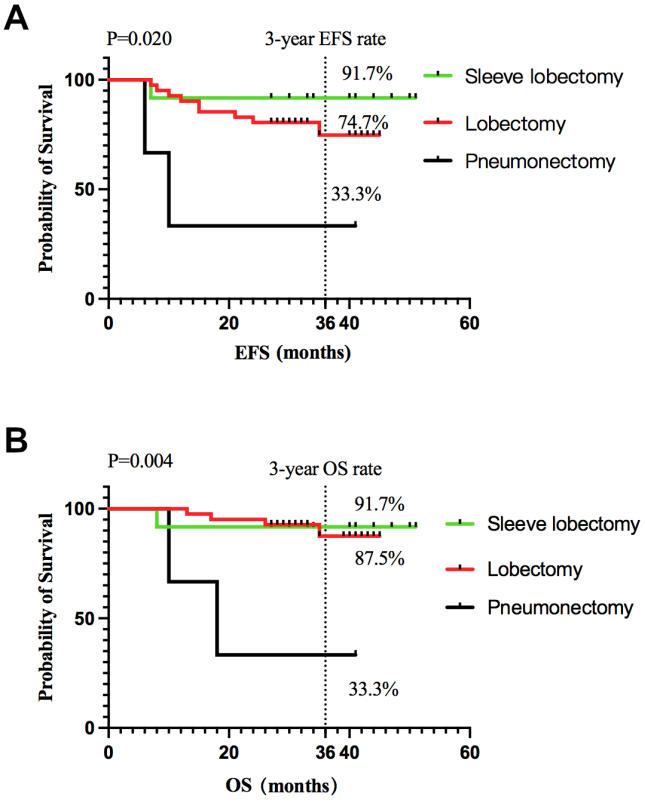

Figure 4. A) EFS among different types of surgery. B) OS among different types of surgery.

Table 6. Surgical difficulties and postoperative complications among different type of surgery.

	Lobectomy	Sleeve lobectomy	Pneumonectomy	p-value
Operation duration (minutes), median (range)	161 (97–321)	213.5 (96–342)	151 (134–195)	0.303
Hospital stays (days), median (range)	12 (5–45)	11.5 (8–22)	14 (10–15)	0.786
Postoperative hospital stays (days), median (range)	6 (2–24)	7 (4–15)	7 (5–11)	0.692
Blood loss (ml), median (range)	200 (50–900)	200 (50–1000)	200 (200–600)	0.427
Postoperative complications				
Yes	12 (29.3%)	5 (41.7%)	3 (100%)	0.077
No	29 (70.7%)	7 (58.3%)	0 (0%)	

find biomarkers for predicting the efficacy of neoadjuvant chemoimmunotherapy.

In conclusion, neoadjuvant chemoimmunotherapy led to a high pCR rate, favorable 3-year survival rate, and acceptable adverse events. The focus of future research was to identify whether neoadjuvant chemoimmunotherapy is the optimal strategy and define the appropriate PD-1/PD-L1 inhibitors, cycles of neoadjuvant chemoimmunotherapy, interval time, adjuvant immunotherapy, and find predictive biomarkers. To date, many phase III clinical trials are still ongoing [36, 46–48].

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