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Original Article

Comparison of perioperative outcomes among non-small cell lung cancer patients with neoadjuvant immune checkpoint inhibitor plus chemotherapy, EGFR-TKI, and chemotherapy alone: a real-world evidence study

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Background: The utilization of neoadjuvant immune checkpoint inhibitor (ICI) plus chemotherapy has increased significantly for resectable non-small cell lung cancer (NSCLC). It is still unclear whether such a treatment paradigm affects perioperative outcomes compared with other neoadjuvant treatment. We aimed to evaluate the perioperative outcomes of pulmonary resection after neoadjuvant ICI plus chemotherapy and to compare them with neoadjuvant epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) and neoadjuvant chemotherapy alone for resectable NSCLC.

Methods: A retrospective cohort including 194 stage IB–IIIB NSCLC underwent surgical resection after neoadjuvant treatment between 2018 and 2020 were reviewed. Perioperative complications were evaluated using the Common Terminology Criteria for Adverse Events, and were compared using one-way analysis of variance for continuous variables and Pearson chi-square test.

Results: There were 42, 54, and 98 patients in the neoadjuvant ICI plus chemotherapy, EGFR-TKI, and chemotherapy alone groups, respectively. The tumor size before neoadjuvant treatment was well balanced among the three groups (P=0.122). A shorter median surgical time was observed in the EGFR-TKI group than ICI plus chemotherapy group and chemotherapy group alone (120 *vs.* 150 *vs.* 146 min, P=0.041). Video-assisted thoracoscopic surgery was performed in 37 (88.1%), 49 (90.7%), and 57 (58.7%) patients in the three groups, respectively (P<0.001). A higher incidence of pneumonia (P=0.014) was found in the chemotherapy group. Perioperative mortality was observed in 1 patient (2.4%) in the ICI plus chemotherapy group and in 3 patients (3.1%) in the chemotherapy alone group (P=0.440). Patients in the ICI plus chemotherapy group had higher proportions of pathological complete response (40.5% *vs.* 11.1% *vs.* 6.1%, P<0.001) and downstaging of clinical N2 status (68.6% *vs.* 42.9% *vs.* 31.7%, P=0.012) than patients in EGFR-TKI group and chemotherapy alone group.

Conclusions: Surgical resection for NSCLC following neoadjuvant ICI plus chemotherapy was safe and feasible, the perioperative outcomes were similar with neoadjuvant EGFR-TKI and chemotherapy alone without

unexpected perioperative complications. Additional prospective studies are necessary to validate our findings.

Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant; immune checkpoint inhibitor (ICI); perioperative outcomes

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Introduction

Surgical resection remains the most effective treatment strategy for potentially resectable non-small cell lung cancer (NSCLC). The 5-year overall survival rates among surgically resected NSCLC range from 83% for stage IA disease to 26% for stage IIIB disease, with most mortality patients undergoing postoperative relapse (1). Utilizing neoadjuvant chemotherapy is one approach that attempts to augment the outcomes afforded by surgery alone. A limitation of this strategy, however, is that the actual proportion of patients achieving a pathological complete response (pCR) is low, and there is a considerable incidence of toxicity (2,3).

Immune checkpoint inhibitors (ICIs) that block the programmed death-1 (PD-1) pathway have revolutionized the cancer treatment landscape (4-6). The monotherapy of nivolumab accomplished a pCR in 15% resected tumor. Interestingly, the combination of ICI with chemotherapy has shown a significant survival advantage in metastatic NSCLC, generating considerable enthusiasm for the use of ICI plus chemotherapy when treating early-stage resectable NSCLC (7). Incorporating ICI and chemotherapy into the management of early-stage NSCLC is attractive because the primary tumor may release neoantigens from dying tumor cells and activate tumor-specific T cells before surgical resection (8,9). Previous clinical trials have found that neoadjuvant ICI plus chemotherapy were associated with a higher proportion of patients achieving pCR (10,11). Recently, the CheckMate 816 study, the first of several phase III trials evaluating neoadjuvant ICI plus chemotherapy, resulted in a significantly longer median event-free survival (31.6 *vs.* 20.8 months) and higher percentage of pCR (24.0% *vs.* 2.2%) than chemotherapy alone in resectable NSCLC (12). Furthermore, the treatment-related adverse events of neoadjuvant ICI were observed to be acceptable and not associated with surgery delays.

In contrast to traditional platinum-based neoadjuvant chemotherapy, ICI that regulate the immune-inhibitory pathway of patients to release their own anti-tumor immunity has attracted special attention on the perioperative outcomes. The unique mechanism of neoadjuvant ICI plus chemotherapy may increase the risk of pneumonitis and adhesion, which can, theoretically, lead to technical challenges for lung resections (13). However, reports regarding the surgical technique and the perioperative outcomes of surgical resection after neoadjuvant ICI plus chemotherapy in NSCLC, especially in comparison with traditional neoadjuvant chemotherapy, are scarce. Moreover, epidermal growth factor receptor (EGFR) mutation is present in 39% to 59% NSCLC patients in East Asia population, which are predictive of response to EGFR-tyrosine kinase inhibitors (TKI) (14-17). Zhong *et al.* reported that patients with neoadjuvant EGFR-TKI have significantly longer progression-free survival versus neoadjuvant chemotherapy (18).

Therefore, the objective of this study was to evaluate the perioperative complications and mortalities of surgical resection after neoadjuvant ICI plus chemotherapy and comprehensively compare these outcomes with neoadjuvant EGFR-TKI and neoadjuvant chemotherapy alone in patients with resectable NSCLC. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-476/rc).

Methods

Ethical statement

This is a retrospective, sing-center study. We retrospectively enrolled patients who underwent neoadjuvant ICI plus chemotherapy, neoadjuvant EGFR-TKI, and neoadjuvant chemotherapy alone from Shanghai Pulmonary Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Shanghai Pulmonary Hospital (No. L21-224), and written informed consent was waived due to the retrospective nature of the study.

Study population and procedures

A total of 42 patients with NSCLC who received neoadjuvant ICI plus chemotherapy between January 2018 and December 2020 were reviewed. Patients with history of previous cancer, positive tumor driver mutation, and ICI-only neoadjuvant therapy were excluded. All enrolled patients were diagnosed with clinical stage IB to IIIB disease according to the 8th edition of the tumor, node, metastasis (TNM) classification for lung cancer. To compare the perioperative outcomes of neoadjuvant ICI plus chemotherapy with neoadjuvant EGFR-TKI and neoadjuvant chemotherapy, 54 patients who received neoadjuvant EGFR-TKI and 98 patients who received neoadjuvant chemotherapy during the same period also were evaluated.

All patients underwent a standard staging workup before treatment, including a chest computed tomography (CT) scan, abdominal CT scan, and magnetic resonance imaging of the brain. Positron emission tomography (PET)/CT scan and endobronchial ultrasound (EBUS)-guided transbronchial needle aspirations were also performed when necessary. Patients with central tumor and hilar or mediastinal lymphadenopathy on CT scan were required to undergo a PET-CT scan or EBUS examination for precise staging before neoadjuvant treatment. In addition, a tumor biopsy was mandatory for histological diagnosis and mutation detection before neoadjuvant treatment. The strategy of neoadjuvant treatment was decided upon patients' profile, driver mutation status, and discussion by a group of oncologists, surgeons, and radiologists together. Patients in the chemotherapy alone group received 2–4 of cycles of platinum-based doublet chemotherapy before surgery. Additionally, the same regimens of adjuvant chemotherapy for two cycles were performed after complete resection or until disease progression or unacceptable toxicity. For patients harboring EGFR mutations (EGFR-TKI group), standard doses of EGFR-TKIs, such as gefitinib, icotinib, erlotinib, and afatinib, were administered daily during 3 to 6 weeks before surgery. Postoperative adjuvant treatment using either EGFR-TKI or platinum-based chemotherapy was chosen on the basis of the patient's condition and the clinical experience of the medical oncologist.

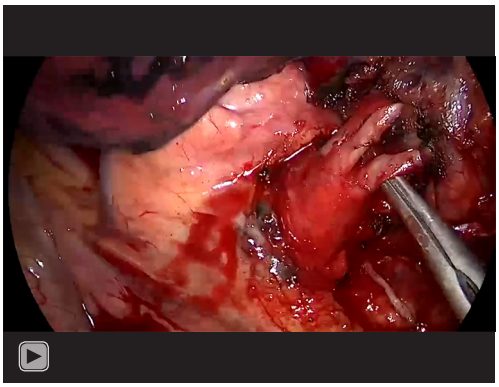
Eligible patients in the neoadjuvant ICI group received pembrolizumab (200 mg) and platinum-based doublet chemotherapy on day 1 of each 21-day cycle, with a total of 2–4 cycles before surgical resection. Generally, surgery was performed approximately 4 weeks after the 1st day of the last treatment cycle. When patients were unable to tolerate the treatment-related adverse effects, or there was local disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), the patients were taken immediately to surgery. A repeat chest CT scan and pulmonary function test were required within 7 days before surgery. Resection of the primary tumor and systematic mediastinal lymph node (LN) dissection were performed. Postoperative ICI plus chemotherapy or chemotherapy alone was administered within 3 to 8 weeks after complete resection were administered. The pathological response was assessed using routine hematoxylin and eosin staining by measuring the percentage of residual viable tumor in the resected primary tumor. Major pathologic response (MPR) was defined as no more than 10% viable tumor cells in the resected primary tumor (19).

Surgical techniques

Video-assisted thoracoscopic surgery (VATS) was the preferred surgical approach at our center. Detailed surgical procedures for VATS lobectomy and pneumonectomy have been described in our previous studies (20,21). Sleeve lobectomy generally was performed at our center for centrally located tumors to avoid pneumonectomy (22,23). For uniportal VATS sleeve lobectomy, a 3–5 cm incision at the 4th intercostal space of the anterior axillary line was drawn. An intraoperative frozen section was required to confirm that the tumor was free of proximal and distal margins. A systematic hilar and mediastinal LN dissection was performed before the anastomosis. The inferior pulmonary ligament was always released to reduce anastomotic tension. Subsequently, end-to-end bronchial anastomosis was performed using continuous sutures with a 3-0 Prolene running suture (*Video 1*).

Variables studied and statistical analysis

The demographic information, clinical and pathologic characteristics, data about neoadjuvant therapy, surgical outcomes, and perioperative complications were collected from the medical record system. All clinical and pathological classifications were recorded in accordance with the 8th edition of the TNM staging system (1). A peripheral tumor was defined as a tumor located in the outer 3rd of the lung on the CT scan. The Charlson Comorbidity Index (CCI) was used to describe comorbidities (24). Perioperative mortality



Video 1 Uniportal VATS sleeve lobectomy for left upper lobe. VATS, video-assisted thoracoscopic surgery.

was defined as death from any cause within 30 days after surgery. Prolonged air leakage was defined as lasting for more than 7 days after surgery. Postoperative complications were evaluated using the Common Terminology Criteria for Adverse Events (version 5.0).

Continuous variables are presented as the mean ± standard deviation or the median value with the interquartile range (IQR). Categorical variables are presented as frequency and percentage. Baseline characteristics and perioperative outcomes were compared among the ICI plus chemotherapy group, EGFR-TKI group, and chemotherapy alone group using 1-way analysis of variance for continuous variables and Pearson chi-square test or Fisher exact test for categorical variables. A 2-sided P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 26.0 (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics

Between January 2018 and December 2020, 42 patients received neoadjuvant ICI plus chemotherapy followed by surgical resection. During the same period, 54 patients received neoadjuvant EGFR-TKI and 98 patients received neoadjuvant chemotherapy alone followed by surgical resection. The baseline characteristics of these three groups are listed and compared in *Table 1*.

Patients in the ICI plus chemotherapy group and chemotherapy alone group had higher proportions of male patients (95.2% *vs.* 84.7% *vs.* 44.4%, P<0.001), higher proportions of smoking history (57.1% *vs.* 46.9% *vs.* 18.5%, P<0.001), more centrally located tumors (54.8% *vs.* 44.9% *vs.* 16.7%, P<0.001), and more advanced clinical TNM stages (stage II to III, 97.6% *vs.* 94.9% *vs.* 87.0%, P=0.003) compared with patients in the EGFR-TKI group. In addition, patients in the ICI plus chemotherapy and chemotherapy alone groups had and compared with patients in the EGFR-TKI group. Patients in the ICI plus chemotherapy group and EGFR-TKI group had similar radiologic tumor size with chemotherapy alone group before neoadjuvant treatment (4.7 *vs.* 3.9 *vs.* 4.2 cm, P=0.122), but significantly smaller tumor size after neoadjuvant treatment (3.5 *vs.* 2.6 *vs.* 2.6 cm, P=0.005). According to RESCIST version 1.1 criteria, 25 (59.5%), 23 (42.6%), and 22 (22.4%) patients achieved radiological response (P=0.001) in the ICI, EGFR-TKI, and chemotherapy groups, respectively. Representative radiologic images of the lesion before and after the neoadjuvant ICI plus chemotherapy treatment are shown in *Figure 1*. There were no significant differences among the three groups in terms of age, forced expiratory volume in 1 second of predicted value, body mass index, and CCI.

Perioperative outcomes

All patients underwent R0 resection and no intraoperative deaths were observed. *Table 2* shows the perioperative outcomes of the three groups. The median interval times from last treatment to surgery were 36 (IQR, 31–41), 12 (IQR, 5–21), and 37 (IQR, 30–49) days for the ICI, EGFR-TKI, and chemotherapy groups (P<0.001), respectively. No treatment-related surgical delay was observed. Patients in the ICI plus chemotherapy group and chemotherapy alone group were associated with higher proportions of sleeve lobectomies compared with those in the EGFR-TKI group (33.3% *vs.* 21.4% *vs.* 11.1%, P=0.001). There were 37 cases (88.1%), 49 cases (90.7%), and 57 cases (58.2%) resected via VATS approach in the ICI, EGFR-TKI, and chemotherapy groups, respectively (P<0.001).

Patients in the ICI plus chemotherapy group and chemotherapy alone group had longer operative time than those in the EGFR-TKI group (150 *vs.* 146 *vs.* 120 minutes, P=0.041). The number of examined LNs, estimated blood loss, rates of postoperative transfusion, and postoperative hospital stay were evenly distributed among the three groups. The perioperative mortality within 30 days was 2.4%, 0%, and 3.1% for the ICI, EGFR-TKI, and chemotherapy groups, respectively (P=0.440). One patient in the ICI plus chemotherapy group died due to bronchopleural fistula after sleeve lobectomy. Three

Table 1 Comparison of baseline characteristics among the three groups

Variables	ICI plus chemotherapy (N=42)	EGFR-TKI (N=54)	Chemotherapy alone (N=98)	P value
Age (years), mean ± SD	61.3±9.1	59.3±9.2	60.7±7.3	0.470
Gender, n (%)				<0.001
Male	40 (95.2)	24 (44.4)	83 (84.7)	
Female	2 (4.8)	30 (55.6)	15 (15.3)	
Smoking history, n (%)				<0.001
Never	18 (42.9)	44 (81.5)	52 (53.1)	
Current/former	24 (57.1)	10 (18.5)	46 (46.9)	
BMI (kg/m^2), mean ± SD	25.2±3.0	24.6±3.5	23.6±3.0	0.043
FEV1% (of predicted), mean ± SD	89.1±23.6	91.1±15.2	88.8±17.2	0.742
Preoperative staging, n (%)				
PET-CT	34 (81.0)	29 (53.7)	42 (42.9)	<0.001
EBUS	24 (57.1)	21 (38.9)	52 (53.1)	0.143
Tumor location, n (%)				0.241
Upper lobe	26 (61.9)	33 (61.1)	60 (61.2)	
Middle lobe	2 (4.8)	7 (13.0)	4 (4.1)	
Lower lobe	14 (33.3)	14 (25.9)	34 (34.7)	
Central/peripheral lesion, n (%)				<0.001
Central	23 (54.8)	9 (16.7)	44 (44.9)	
Peripheral	19 (45.2)	45 (83.3)	54 (55.1)	
Radiologic tumor size (cm), mean ± SD				
Before neoadjuvant treatment	4.7±2.1	3.9±1.5	4.2±1.8	0.122
After neoadjuvant treatment	2.6±1.3	2.6±1.0	3.5±1.8	0.005
Clinical TNM stage, n (%)				0.003
I	1 (2.4)	7 (13.0)	5 (5.1)	
II	1 (2.4)	2 (3.7)	18 (18.4)	
III	40 (95.2)	45 (83.3)	75 (76.5)	
Radiologic response (RESCIST 1.1 criteria), n (%)				0.001
Partial response	25 (59.5)	23 (42.6)	22 (22.4)	
Stable disease	9 (21.4)	21 (38.9)	48 (49.0)	
Progressive disease	0 (0)	3 (5.6)	8 (8.2)	
Unavailable	8 (19.0)	7 (13.0)	20 (20.4)	
Histology, n (%)				<0.001
Adenocarcinoma	8 (19.0)	53 (98.1)	37 (37.8)	
Squamous cell carcinoma	29 (69.0)	0 (0)	53 (54.1)	
Other/unspecific	5 (11.9)	1 (1.9)	8 (8.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	ICI plus chemotherapy (N=42)	EGFR-TKI (N=54)	Chemotherapy alone (N=98)	P value
Charlson Comorbidity Index, n (%)				0.568
0	5 (11.9)	9 (16.7)	9 (9.2)	
1	9 (21.4)	13 (24.1)	14 (14.3)	
2	19 (45.2)	22 (40.7)	46 (46.9)	
3	5 (11.9)	8 (14.8)	18 (18.4)	
4	4 (9.5)	2 (3.7)	11 (11.2)	

ICI, immune checkpoint inhibitor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; SD, standard deviation; BMI, body mass index; FEV1, forced expiratory volume in one second; PET-CT, positron emission tomography-computed tomography; EBUS, endobronchial ultrasound; TNM, tumor, node, metastasis.

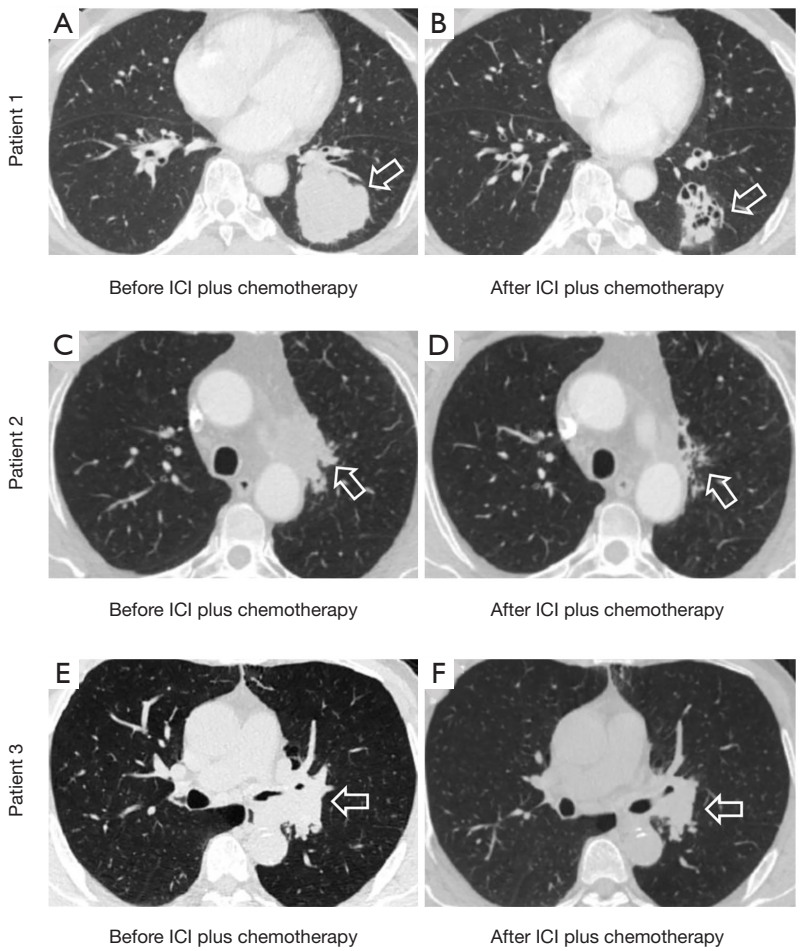


Figure 1 Representative radiologic changes before neoadjuvant ICI plus chemotherapy and before surgery. (A,B) Radiologic imaging before and after neoadjuvant ICI plus chemotherapy of patient 1, who finally underwent lobectomy; (C,D) radiologic imaging before and after neoadjuvant ICI plus chemotherapy of patient 2, who finally underwent sleeve lobectomy; (E,F) radiologic imaging before and after neoadjuvant ICI plus chemotherapy of patient 3, who finally underwent pneumonectomy. The arrows indicate tumor lesion. ICI, immune checkpoint inhibitor.

Table 2 Comparisons of surgical outcomes

Perioperative outcomes	ICI plus chemotherapy (N=42)	EGFR-TKI (N=54)	Chemotherapy alone (N=98)	P value
Time from last treatment to surgery (days), median [IQR]	36 [31–41]	12 [5–21]	37 [30–49]	<0.001
Extent of resection, n (%)				0.001
Lobectomy	19 (45.2)	45 (83.3)	49 (50.0)	
Bilobectomy	6 (14.3)	1 (1.9)	19 (19.4)	
Sleeve lobectomy	14 (33.3)	6 (11.1)	21 (21.4)	
Pneumonectomy	3 (7.1)	2 (3.7)	9 (9.2)	
Surgical approach, n (%)				<0.001
VATS	37 (88.1)	49 (90.7)	57 (58.2)	
Thoracotomy	4 (9.5)	4 (7.4)	36 (36.7)	
VATS convert to thoracotomy	1 (2.4)	1 (1.9)	5 (5.1)	
Total number of examined LNs, mean ± SD	15.3±8.4	14.1±7.4	16.2±7.9	0.271
Examined N1 nodes	7.7±4.5	6.4±4.2	7.3±4.0	0.249
Examined N2 nodes	9.6±5.3	8.3±4.2	9.4±5.3	0.335
Surgical time (min), median [IQR]	150 [120–180]	120 [99–167]	146 [120–180]	0.041
Estimated blood loss (mL), median [IQR]	50 [50–100]	50 [50–100]	100 [50–150]	0.846
Required for postoperative transfusion, n (%)	5 (11.9)	8 (14.8)	6 (6.1)	0.197
Postoperative stay (days), median [IQR]	5 [4–7]	3 [3–6]	5 [4–7]	0.164
Perioperative mortality, n (%)	1 (2.4)	0 (0)	3 (3.1)	0.440
Postoperative complications, n (%)				
Any complications	7 (16.7)	3 (5.6)	24 (24.5)	0.013
Bronchopleural fistula	2 (4.8)	0 (0)	1 (1.0)	0.144
Hemothorax	0 (0)	0 (0)	2 (2.0)	0.372
Chylothorax	0 (0)	0 (0)	2 (2.0)	0.372
Prolonged air leak	2 (4.8)	1 (1.9)	3 (3.1)	0.714
Pneumonia	3 (7.1)	1 (1.9)	16 (16.3)	0.014
Pulmonary embolism	0 (0)	1 (1.9)	0 (0)	0.272

ICI, immune checkpoint inhibitor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; IQR, interquartile range; VATS, video-assisted thoracoscopic surgery; LN, lymph node; SD, standard deviation.

patients in the chemotherapy alone group died due to chylothorax, food aspiration, and hemothorax, respectively.

The overall postoperative complications were significantly higher in the ICI plus chemotherapy group and chemotherapy alone group than the EGFR-TKI group (16.7% *vs.* 24.5% *vs.* 5.6%, P=0.013). Patients in the ICI plus chemotherapy group and EGFR-TKI group were associated with a significantly lower rate of pneumonia than patients in the chemotherapy alone group (7.1% *vs.* 1.9% *vs.* 16.3%, P=0.014). Hemothorax, chylothorax, prolonged air leak, and pulmonary embolism were similar among the three groups. Bronchopleural fistula occurred more frequently in the ICI plus chemotherapy group than the EGFR-TKI and chemotherapy alone groups (4.8% *vs.* 0% *vs.* 1.0%), but the difference was not statistically significant (P=0.144).

Table 3 Tumor response according to different neoadjuvant treatment strategy

Variables	ICI plus chemotherapy (N=42)	EGFR-TKI (N=54)	Chemotherapy alone (N=98)	P value
Pathologic response, n (%)				<0.001
Pathologic complete response	17 (40.5)	6 (11.1)	6 (6.1)	
Major pathologic response	30 (71.4)	11 (20.4)	14 (14.3)	
<90% response	12 (28.6)	43 (79.6)	84 (85.7)	
yp TNM stage, n (%)				0.002
I	29 (69.0)	27 (50.0)	33 (33.7)	
II	3 (7.1)	6 (11.1)	23 (23.5)	
III	10 (23.8)	21 (39.9)	42 (42.8)	
Pathological tumor size (cm), mean ± SD	2.9±1.7	2.6±1.0	3.4±1.7	0.018
Downstaging of nodal status for N2 disease , n (%)				0.012
N2 to pN0	24 (68.6)	15 (42.9)	19 (31.7)	
N2 to pN1	1 (2.8)	4 (11.4)	9 (15.0)	
N2 to pN2	10 (28.6)	16 (45.7)	32 (53.3)	

ICI, immune checkpoint inhibitor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; TNM, tumor, node, metastasis; SD, standard deviation.

Tumor response to neoadjuvant treatment

A higher proportion of patients in the ICI plus chemotherapy group achieved pCR (17/42, 40.5%) and MPR (30/42, 71.4%) compared with patients in the EGFR-TKI group (pCR: 6/54, 11.1%; MPR: 11/54, 20.4%) and chemotherapy alone group (pCR: 6/98, 6.1%; MPR: 14/98, 14.3%) (*Table 3*). Furthermore, the proportion of downstaging of nodal status from clinical N2 disease to pathologic N0 disease was significantly higher in the ICI group (68.6%, 42.9%, and 31.7% for the ICI, EGFR-TKI, and chemotherapy groups, respectively, P=0.012).

Discussion

Incorporating ICI plus chemotherapy into the management of early-stage resected NSCLC is now an area of active investigation (7,10,11). However, concerns about the feasibility and safety of surgical resection after neoadjuvant ICI still exist as mediastinal or hilar inflammation/fibrosis might develop in response to treatment. In this study, we reviewed 42 patients who received neoadjuvant ICI plus chemotherapy followed by surgical resection and found that neoadjuvant ICI was associated with a higher rate of achieving MPR and a similar postoperative mortality and morbidity compared with neoadjuvant EGFR-TKI and neoadjuvant chemotherapy alone in resectable NSCLC. To the best of our knowledge, this is the first study to comprehensively evaluate perioperative outcomes after neoadjuvant ICI plus chemotherapy and compare it to other neoadjuvant regimens.

Neoadjuvant ICI in resected NSCLC was first reported in 2018. Two doses of nivolumab were associated with 45% of cases achieving MPR and 10% of cases achieving pCR (7). Recent phase II trials also have shown that 57–74% of patients experience MPR after neoadjuvant ICI, and without treatment-related surgical delays (10,11). In this study, the proportion of patients achieving MPR was 71.4% in the neoadjuvant ICI plus chemotherapy group, which was significantly higher than in the neoadjuvant EGFR-TKI and neoadjuvant chemotherapy alone groups, and no treatment-related surgical delay was observed. The effectiveness and safety of neoadjuvant ICI plus chemotherapy have been corroborated by the CheckMate 816 study (12). The perioperative outcomes after neoadjuvant ICI plus chemotherapy have not been evaluated comprehensively and compared with standard neoadjuvant chemotherapy alone, despite the emergence of numerous clinical trials using neoadjuvant ICI (25).

Yang *et al.* first evaluated surgical outcomes after neoadjuvant ipilimumab plus chemotherapy for stage II-IIIA

NSCLC based on a phase II trial (TOP1201), demonstrating the safety and feasibility of surgical resection (26). Bott *et al.* reported perioperative outcomes after neoadjuvant nivolumab based on a randomized trial and concluded that the surgery, while challenging, could be accomplished safely (13). Minimally invasive resections have been shown to be performed safely following monotherapy of ICI. However, more than half of VATS or robotic cases were converted to thoracotomy often because of hilar inflammation and fibrosis. In the current study, all patients were completely resected and most of the tumors (88.1%) were resected via VATS after neoadjuvant ICI plus chemotherapy, which is higher than previous reports (26,27). There was only one patient in the ICI plus chemotherapy group converted to thoracotomy due to severe hilar fibrosis. It is worth noting that patients in the chemotherapy alone group had a larger tumor size before surgery, which can explain a lower use of VATS resections and thereby a higher proportion of postoperative pneumonia associated with thoracotomies. Ultimately, this study showed that neoadjuvant ICI plus chemotherapy was not associated with unexpected perioperative mortality or postoperative complications compared with neoadjuvant EGFR-TKI and neoadjuvant chemotherapy alone.

Thomas *et al.* reported that neoadjuvant chemotherapy increased treatment-related mortality compared to patients without neoadjuvant chemotherapy, especially in patients undergoing a pneumonectomy (14% *vs.* 6%), which led to the absence of a progression-free survival benefit (28). In this study, 7.3% of patients underwent pneumonectomy after neoadjuvant treatment, and the associated perioperative mortality was 7.1%. One patient in the chemotherapy group experienced food aspiration, leading to severe pneumonia and ongoing hypoxemia and eventually, death. In this study, neoadjuvant treatment was not associated with a higher rate of perioperative mortality after pneumonectomy compared with those without neoadjuvant treatment, which is consistent with the findings of a previous study (29).

Sleeve lobectomy is an optional surgical procedure to improve postoperative quality of life compared with pneumonectomy for centrally located NSCLC, but it remains challenging, especially via VATS (30). Yang *et al.* reported that sleeve lobectomy achieved superior perioperative outcomes and equivalent oncological efficacies compared with pneumonectomy (31). In this study, 76 patients with centrally located NSCLC received neoadjuvant treatment, and 41 patients eventually were resected by sleeve lobectomy. Additionally, sleeve lobectomy was associated with a shorter hospital stay and similar postoperative complications compared with pneumonectomy (Table S1). Our previous study also found double sleeve lobectomy after neoadjuvant chemotherapy is safe and no perioperative mortality in patients with centrally-located NSCLC than those without neoadjuvant chemotherapy (32). In the current study, one (7.1%) sleeve lobectomy patient in the ICI plus chemotherapy group experienced bronchopleural fistula and eventually die. We believe that the safety of sleeve lobectomy after ICI plus chemotherapy need more evidence to verify.

This study had several limitations. First, the smaller sample size for the neoadjuvant ICI patients may have limited the statistical power, and the effect of the surgical extent and surgical approach on perioperative outcomes were not available. Second, the results were derived from retrospective study, using a single-center database, with inevitable selection bias. Some clinicopathologic factors, such as gender, smoking history, histologic subtype, and treatment cycles may not be well balanced. Prospective multicenter clinical trials are required to provide more evidence. Third, the baseline characteristics among the three groups were imbalanced. The results of additional forthcoming prospective studies on this topic should address this issue.

Conclusions

Surgical resection after neoadjuvant ICI plus chemotherapy appeared to be safe and feasible without unexpected perioperative complications and mortalities for patients with resected NSCLC compared with neoadjuvant EGFR-TKI and neoadjuvant chemotherapy alone, and our experience suggested that most of these procedures could be accomplished with VATS approach. Additional prospective randomized studies using larger patient cohorts are necessary to validate our findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-476/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-476/coif). FG serves in Ad Hoc Advisory Boards/Consultations (last 3 years) to Eli Lilly, Roche, Boehringer Ingelheim, AstraZeneca, Pierre Fabre, BMS, MSD, Novartis, Merck, Otsuka, Novartis, Takeda. FG also received Research Funding (last 3 years) from AstraZeneca, BMS, MSD and received honoraria (last 3 years) from Eli Lilly, Roche, Boehringer Ingelheim, AstraZeneca, Pierre Fabre, AMGEN, Celgene, BMS, MSD. AK received support from Roche Genentech and Medtronic and serves as Advisory Board for neoadjuvant immunotherapy trials for Roche Genentech. The other 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). This study was approved by the Institutional Review Board of the Shanghai Pulmonary Hospital (No. L21-224), and written informed consent was waived due to the retrospective nature of the study.

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Supplementary

Table S1 Comparisons of perioperative outcomes between sleeve lobectomy and pneumonectomy after neoadjuvant treatment

Variables	Sleeve lobectomy (N=41)	Pneumonectomy (N=14)	P value
Age (years), mean ± SD	61.1±7.1	59.9±6.9	0.592
Gender, n (%)			0.601
Male	36 (87.8)	13 (92.9)	
Female	5 (12.2)	1 (7.1)	
Radiologic tumor size (cm), mean ± SD			
Before neoadjuvant treatment	4.5±2.0	4.8±1.7	0.708
Before surgery	3.3±1.8	3.4±1.4	0.951
Clinical TNM stage			0.453
I	3 (7.3)	0 (0)	
II	3 (7.3)	2 (14.3)	
III	35 (85.4)	12 (85.7)	
Neoadjuvant agents			0.646
ICI plus chemotherapy	14 (34.1)	3 (21.4)	
EGFR-TKI	6 (14.6)	2 (14.3)	
Chemotherapy alone	21 (51.2)	9 (64.3)	
Surgical approach			0.066
VATS	29 (70.7)	5 (35.7)	
Thoracotomy	9 (22.0)	7 (50.0)	
VATS convert to thoracotomy	3 (7.3)	2 (14.3)	
Number of total examined LNs, mean ± SD	18.3±7.1	17.6±6.0	0.778
Examined N1 nodes	8.5±4.6	7.2±4.5	0.392
Examined N2 nodes	9.8±5.4	10.4±4.7	0.698
Surgical time (minutes), median (IQR)	212 (160–240)	141 (120–195)	0.079
Estimated blood loss (mL), median (IQR)	100 (50–200)	100 (50–300)	0.845
Required for postoperative transfusion, n (%)	5 (12.2)	5 (35.7)	0.049
Postoperative stay (days), median (IQR)	6 (4–7)	8 (7–12)	0.009
Perioperative mortality, n (%)	2 (4.9)	1 (7.1)	0.747
Postoperative complications, n (%)			
Any complications	11 (26.8)	5 (35.7)	0.527
Bronchopleural fistula	2 (4.9)	0 (0)	0.400
Hemothorax	1 (2.4)	0 (0)	0.555
Chylothorax	1 (2.4)	1 (7.1)	0.417
Prolonged air leak	2 (4.9)	0 (0)	0.400
Pneumonia	5 (12.2)	4 (28.6)	0.153

SD, standard deviation; TNM, tumor, node, metastasis; ICI, immune checkpoint inhibitor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitors; VATS, video-assisted thoracoscopic surgery; LN, lymph node; IQR, interquartile range.

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