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Surgery challenges and postoperative complications of lung cancer after neoadjuvant immunotherapy

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Abstract

Background: In China, real-world data on surgical challenges and postoperative complications after neoadjuvant immunotherapy of lung cancer are limited.

Methods: Patients were retrospectively enrolled from January 2018 to January 2023, and their clinical and pathological characters were subsequently analyzed. Surgical difficulty was categorized into a binary classification according to surgical duration: challenging or routine. Postoperative complications were graded using Clavien–Dindo grades. Logistic regression was used to identify risk factors affecting the duration of surgery and postoperative complications greater than Clavien–Dindo grade 2.

Results: In total, 261 patients were included. Of these, stage III patients accounted for 62.5% (163/261) at initial diagnosis, with 25.3% (66/261) at stage IIIB. Central-type non-small-cell lung cancer accounted for 61.7% (161/261). One hundred and forty patients underwent video-assisted thoracoscopic surgery and lobectomy accounted for 53.3% (139/261) of patients. Surgical time over average duration was defined as challenging surgeries, accounting for 43.7%. The postoperative complications rate of 261 patients was only 22.2%. Smoking history (odds ratio [OR] = 9.96, 95% [CI] 1.15–86.01, $p = 0.03$), chemoimmunotherapy (OR = 2.89, 95% CI 1.22–6.86, $p = 0.02$), and conversion to open surgery (OR = 11.3, 95% CI 1.38–92.9, $p = 0.02$) were identified as independent risk factors for challenging surgeries, while pneumonectomy (OR = 0.36, 95% CI 0.15–0.86, $p = 0.02$) was a protective factor. Meanwhile, pneumonectomy (OR = 7.51, 95% CI 2.40–23.51, $p < 0.01$) and challenging surgeries (OR = 5.53, 95% CI 1.50–20.62, $p = 0.01$) were found to be risk factors for postoperative complications greater than Clavien–Dindo grade 2.

Conclusions: Compared to immunotherapy alone or in combination with apatinib, neoadjuvant chemoimmunotherapy could increase the difficulty of surgery while the incidence of postoperative complications remained acceptable. The conversion to open surgery and pneumonectomy after neoadjuvant immunotherapy should be reduced.

KEYWORDS
immunotherapy, neoadjuvant, postoperative complications, surgical challenge

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide, with non-small-cell lung cancer (NSCLC) accounting for about 85% of lung cancer incidence.[1] Surgery remains the pivotal treatment strategy for early-stage NSCLC,[2,3] and adjuvant therapy after resection, including chemotherapy and radiotherapy, has been proven to improve the survival of patients.[4] However, it is not easy to achieve radical removal of some resectable lung cancers, especially in patients suffering from locally advanced lung cancer (stage III, N2/N3). These tumors are difficult to remove due to their large size, dangerous locations, involvement of metastatic lymph nodes, and altered anatomy. Worse still, the prognosis of these tumors remains poor even after their complete resection due to high recurrence and mortality rates. Nowadays, with the popularization of immunotherapy, neoadjuvant immunotherapy has provided new options for dealing with resectable NSCLC, enabling the radical removal of tumors.[5]

In recent years, many clinical trials have been conducted on neoadjuvant immunotherapy for NSCLC and some have already obtained results.[6–11] For example, CheckMate-816, a phase 3 trial,[9] demonstrated that neoadjuvant nivolumab plus chemotherapy, compared to chemotherapy alone, could lead to significantly longer event-free survival and a higher percentage of patients achieving a pathological complete response (pCR).

Nevertheless, accounts of challenging surgical procedures following neoadjuvant immunotherapy have been frequently reported in clinical practice. A notable example is the KEYNOTE-671 trial, which documented that up to 32 patients were unable to undergo complete resection after immunotherapy.[12] Antecedent studies have also suggested that neoadjuvant immunotherapy undoubtedly has a particular impact on thoracic surgery.[13–15] In these studies, perioperative conditions, especially intraoperative challenges and postoperative complications, were only described but not analyzed in detail due to their relatively small cohort sizes.[13–16] Currently, it is widely believed that the use of immune checkpoint inhibitors (ICIs) and the consequent chronic inflammatory reaction could cause tissue adhesion and fibrosis, and thus increase the difficulty of resection. However, the factors in this process remain to be further elucidated.

At present, the acceptance and application of immunotherapy in clinical settings are on the rise and numerous NSCLC patients in China have also benefited from neoadjuvant immunotherapy. Given the extensive prevalence of lung cancer in China, we are convinced that a substantial number of lung cancer patients who have undergone neoadjuvant immunotherapy could provide insights into the aforementioned problem. In the present study, we endeavored to present a relatively large real-world NSCLC cohort that underwent ICI therapy and aimed to investigate the risk factors associated with challenging surgeries and postoperative complications.

METHODS

Patients

This study was approved by the National Cancer Center/Cancer Hospital ethics committee, Chinese Academy of Medical Sciences (approval number: 2022030911242202), on March 9, 2022. Patients' informed consent was waived due to the study's retrospective nature and no financial compensation was issued.

Patients were consecutively enrolled in our cohort study from our real-world prospective database (Department of Thoracic Surgery, National Cancer Center database) from January 2018 to January 2023. The inclusion criteria were patients who underwent ICI therapy and lung surgery. The exclusion criteria were: (1) having surgery before ICI therapy; (2) recipient of neoadjuvant radiotherapy; and (3) undergoing intrathoracic biopsy or incomplete resections.

All patients underwent standard pretreatment staging (before inducting treatment) examinations, including complete blood cell counts, serum biochemistry, serum tumor markers, electrocardiography, pulmonary function tests, and contrast-enhanced computed tomography (CT). In addition, CT-guided puncture or endobronchial biopsies were performed for pretreatment pathological diagnosis, and positron emission computed tomography (PET-CT) was recommended to exclude distant metastasis. If PET-CT was unavailable, brain magnetic resonance imaging (MRI) and radionuclide bone scans were mandatory. Notably, mediastinal lymph node staging was completed using mediastinoscopy in some cases and preoperative enhanced CT in others. Lymph nodes with the shortest diameter greater than 1.0 cm on preoperative enhanced CT were considered metastases. Due to the lack of pathological evidence, the accuracy of their N-stage is not 100% accurate for this group of patients.

Neoadjuvant treatment strategy

The patients in our cohort all came from real-world clinical practice and each received one of three types of neoadjuvant immunotherapy: immune monotherapy, chemoimmunotherapy, and immunotherapy combined with apatinib. Because it was real-world data, not every patient underwent Programmed Cell Death-Ligand 1 expression score testing. Clinicians decide whether to undergo neoadjuvant immunotherapy for patients based on guidelines and their own clinical experience. Generally speaking, patients need to meet the following conditions:

1. Clinical staging of stage II and above.
2. Diagnosed as squamous cell carcinoma or adenocarcinoma through biopsy. Some other types of NSCLC can continue to be used if immunotherapy is effective.

3. The patient's physical condition is appropriate, with an Eastern Cooperation Oncology Group (ECOG) score of 2 or above.
4. Patients should not have immune system diseases like hyperthyroidism, hypothyroidism, vitiligo, or other immune-related diseases.

The drugs used for immunotherapy were all Programmed cell Death protein-1 inhibitors, including sintilimab, camrelizumab, nivolumab, atezolizumab, and pembrolizumab. In the chemoimmunotherapy group, the chemotherapeutic agents administered varied by histological subtype: paclitaxel plus platinum was used for squamous carcinoma, pemetrexed plus platinum for adenocarcinoma, and etoposide for specific subtypes such as large-cell lung cancer. Apatinib is a drug that was independently developed and produced in China. This drug is a targeted anti-angiogenic drug with extensive applications in the treatment of cancer.[17]

Surgical procedures

All included patients underwent radical resection and systematic mediastinal lymph node dissection according to oncological principles. The resection strategies included lobectomy, bilobectomy (right middle lobe + right upper/lower lobe), sleeve resection, pneumonectomy, and extended lobectomy (lobectomy + partial lobectomy). Surgical approaches were either single-port video-assisted thoracic surgery (VATS) or open surgery.

Owing to the quality control standards for surgery at our center, the chief surgeon was required to manually record the surgical difficulty, which was based on intraoperative conditions, including the presence of dense adhesions, vascular events, and the difficulty of hilar dissection. We collected surgical records written by more than 10 different professors at our center. The average operative time was used to determine surgical difficulty and surgeries that exceeded the average duration were considered challenging surgeries.

Data collection

The baseline, perioperative, and surgical data were collected from our real-world database (Department of Thoracic Surgery, National Cancer Center database). Patients' baseline data included age, gender, smoking history, family cancer history, ECOG score,[18] Charlson Comorbidity Index (CCI),[19] clinical stage, and histological types before ICI treatment. The staging and pathological standards were in accordance with the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer Tumor region lymph Node and Metastasis staging for NSCLC.[20,21] Perioperative data encompass imaging characteristics, imaging response evaluated by Response Evaluation Criteria in Solid Tumors version 1.1,[22] duration between the end of immunotherapy and surgery, hospital stay, and postoperative complications. The postoperative complications were recorded and graded according to the Clavien–Dindo classification.[23] Follow-ups were conducted every 30 days by telephone calls or outpatient clinic visits. Surgical data comprised tumor location, resection strategy, surgical approach, operative time, blood loss, number of dissected lymph nodes, and other intraoperative events.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median combined with quartiles, while categorical variables are shown in percentages. Univariable and multivariable logistic regression analyses were performed to identify the independent risk factors of surgical challenges and postoperative complications. In all analyses, a two-sided p value <0.05 was considered statistically significant. All analyses were performed in SPSS software version 25 (IBM-SPSS Inc.) and R version 4.0.

RESULTS

Patient clinical and pathological characteristics

A total of 261 patients were included in this study, as shown in Figure 1. The data of patients who had undergone preoperative radiotherapy and non-R0 resection were eliminated, as these factors could have affected the surgical procedures and outcomes. The clinical and pathological characteristics of patients are shown in Table 1. Among the 261 patients, the median age was 61 years (55–66 years) and most were male (224/261, 85.8%). In addition, 189 patients had a smoking history (189/261, 72.4%) and 199 patients had no family cancer history (199/261, 76.2%). Furthermore, 78.8% of the patients (205/261) had an ECOG score of 0. Preoperative comorbidities were collected in the form of the CCI,

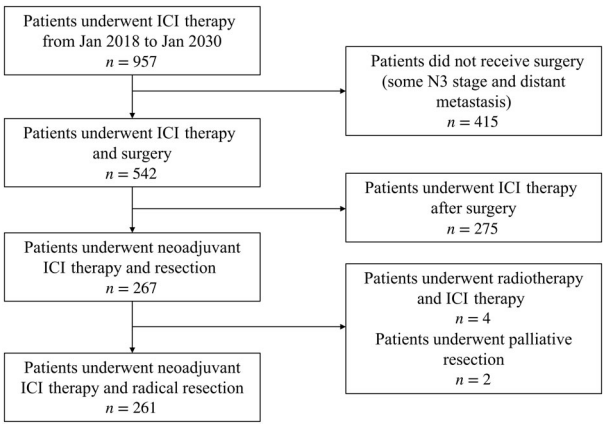

FIGURE 1 Flowchart for patient enrollment.

TABLE 1 Clinical and pathological characteristics of patients.

Variable	Total population ($n = 261$)
Age, median (range)	61 (55–66)
BMI, median (range)	24.5 (22.3–26.5)
Gender, *n* (%)	
Female	37 (14.2)
Male	224 (85.8)
Smoking history, *n* (%)	
Yes	189 (72.4)
No	72 (27.6)
Family cancer history, *n* (%)	
Yes	62 (23.8)
No	199 (76.2)
ECOG, *n* (%)	
0	206 (78.9)
1	55 (21.1)
CCI, *n* (%)	
0	6 (2.3)
1	21 (8.0)
2	72 (27.6)
3	106 (40.6)
4	49 (18.8)
5	6 (2.3)
6	1 (0.4)
Clinical stage, *n* (%)	
I	18 (6.9)
II	80 (30.7)
IIIA	97 (37.2)
T1/2/N2	56 (21.5)
T3N1	16 (6.1)
T4N0/1	25 (9.6)
IIIB	66 (25.3)
T3/4N2	60 (23.0)
T1/2N3	6 (2.3)
Histological subtype, *n* (%)	
Squamous cell carcinoma	195 (74.7)
Adenocarcinoma	63 (24.1)
Others	3 (1.1)
Immune strategy	
Immune monotherapy	38 (14.6)
Chemoimmunotherapy	168 (64.4)
Immune + apatinib	55 (21.1)
PD-L1 status	
<1%	61 (23.4)
>1%	103 (39.5)
Unknown	97 (37.2)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperation Oncology Group.

which could better reflect the situation. Notably, 62.5% (163/261) of the patients were initially diagnosed at stage III; more specifically, 25.3% (66/261) were at stage IIIB. Among these stage III patients, 74.8% (122/163) were staged as N2/3. From the perspective of neoadjuvant ICI therapy, there were 38 patients receiving immune monotherapy, 168 undergoing chemoimmunotherapy, and 55 receiving immunotherapy combined with apatinib. In the treatment cohort, lung squamous cell carcinoma was the most common histological subtype (195/261, 74.7%).

Operation-related characteristics of patients

The operation-related characteristics are summarized in Table 2. The tumor locations, resection protocols, and surgical approaches of the whole cohort are shown in Figure 2. Central-type NSCLC accounts for 61.7% (161/261) and tumors in the left upper lobe are the most common (30.7%, 80/261). In the entire cohort, lobectomy was performed on 53.3% (139/261) of the patients and VATS was the primary surgical approach (140/261, 53.6%). The median duration between the end of ICI therapy and surgery was 42 ± 17.4 days (6 weeks). The mean surgical duration and blood loss were 148.6 ± 53.0 min and 166.5 ± 108.3 mL, respectively. We recorded in detail the unexpected events during surgery and the top three intraoperative events are presented in Table 2: vascular events, dense adhesions, and complicated hilar anatomy. Other undisclosed cases include ruptured lymphatic ducts, pleural defects, nerve damage, etc. At the same time, Supporting Information Table S1 shows detailed information on the nine patients whose surgeries were intraoperatively converted to open surgeries: four cases due to vascular events, another four due to complicated hilar anatomy (frozen hilum), and one due to diffuse adhesions.

We divided these patients into two groups based on their surgical duration. Surgeries exceeding the cohort's average duration of 148.6 min were designated as challenging surgeries and those that did not were routine surgeries. This way, 43.7% (114/261) of the surgeries were categorized as challenging. In addition, the average number of lymph node stations resected was 7.4 ± 1.3 and the average number of lymph nodes resected was 25.5 ± 11.5. The mean hospital stay of all patients was 6.0 ± 2.9 days. However, 59 patients (22.6%) were discharged with chest tubes and some of them went to community hospitals for rehabilitation. Postoperatively, four patients (1.5%) died within 30 days and two patients (2.3%) passed away after 30 days but within 90 days. The causes of their death are shown in Supporting Information Table S2.

Risk factors for surgical difficulty

Since the standard of challenging surgeries has been established, we attempted to explore the factors that could affect

TABLE 2 Operation-related characteristics of patients.

Variable	Total population ($n = 261$)
Tumor location, *n* (%)	
RUL	67 (25.7)
RML	19 (7.3)
RLL	55 (21.1)
LUL	80 (30.7)
LLL	40 (15.3)
Central type, *n* (%)	
Yes	161 (61.7)
No	100 (38.3)
Extent of resection, *n* (%)	
Lobectomy	139 (53.3)
Bilobectomy	34 (13.0)
Sleeve resection	26 (10.0)
Pneumonectomy	43 (16.5)
Extended lobectomy	19 (7.3)
Approach, *n* (%)	
VATS	140 (53.6)
Open	112 (42.9)
Conversion to open	9 (3.4)
Duration to surgery (days)	42.0 ± 17.4
Surgical duration (min)	148.6 ± 53.0
Blood loss (mL)	166.5 ± 108.3
Lymph node station of dissection	7.4 ± 1.3
Lymph nodes of dissection	25.5 ± 11.5
Intraoperative event	
Vascular event	39 (14.9)
Dense adhesion	24 (9.2)
Difficult hilar anatomy	23 (8.8)
Challenging surgery	
No	147 (56.3)
Yes	114 (43.7)
Hospital stay	6.0 ± 2.9
Discharge with chest tube	59 (22.6)
30-day mortality	4 (1.5)
90-day mortality	6 (2.3)

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; VATS, video-assisted thoracic surgery.

surgical difficulty by univariable and multivariable logistic regression analyses. Table 3 shows the variables that could be risk factors for surgical difficulty.

Univariable logistic regression analyses revealed that chemoimmunotherapy (odds ratio [OR] = 3.22, 95% confidence interval [95% CI] 1.44–7.22, $p < 0.01$) and conversion to open surgery (OR = 11.3, 95% CI 1.38–92.9, $p = 0.02$) are risk factors for challenging surgeries, while pneumonectomy (OR = 0.32, 95% CI 0.14–0.72, $p < 0.01$) is a protective factor. Different from univariable logistic regression, multivariable logistic regression analysis revealed that, except for chemoimmunotherapy (OR = 2.89, 95% CI 1.22–6.86, $p = 0.02$) and conversion to open surgery (OR = 11.3, 95% CI 1.38–92.9, $p = 0.02$), a smoking history (OR = 9.96, 95% CI 1.15–86.01, $p = 0.03$) is also an independent risk factor for challenging surgeries and pneumonectomy (OR = 0.36, 95% CI 0.15–0.86, $p = 0.02$) remains a protective factor for challenging surgeries.

Postoperative complications and risk factors

Table 4 shows postoperative complications, graded according to the Clavien–Dindo classification. Only 22.2% (58/261) of patients had postoperative complications. However, among them, 34 had postoperative complications greater than Clavien–Dindo grade 2 that necessitated active intervention. The most common complications were pneumonia (5.4%, 14/261) and pleural effusion that warranted intervention (5.4%, 14/261).

Univariable and multivariable logistic regression analyses were also used to identify risk factors for postoperative complications greater than Clavien–Dindo grade 2, as shown in Table 5. Univariable logistic regression analysis brought to light that thoracotomy (OR = 2.71, 95% CI 1.24–5.89, $p = 0.01$), pneumonectomy (OR = 4.50, 95% CI 1.82–11.16, $p < 0.01$), challenging surgeries (OR = 3.65, 95% CI 1.67–8.00, $p < 0.01$), and blood loss (OR = 1.004, 95% CI 1.001–1.007, $p < 0.01$) are risk factors for postoperative complications greater than Clavien–Dindo grade 2. On the other hand, in partial agreement with this finding, multivariable logistic regression analysis indicated that only pneumonectomy (OR = 7.51, 95% CI 2.40–23.51, $p< 0.01$) and challenging surgeries (OR = 5.53, 95% CI 1.50–20.62, $p = 0.01$) are risk factors for postoperative complications greater than Clavien–Dindo grade 2. No protective factor was found.

Outcomes of the neoadjuvant immunotherapy

Supporting Information Table S3 displays the outcomes of the neoadjuvant immunotherapy. Over half of the patients (137/261, 52.5%) achieved major pathological response (MPR) after neoadjuvant immunotherapy, which clearly shows the curative effect of it. However, the pCR rate (79/261, 30.3%) remains unsatisfactory. It is worth mentioning that, after using immunotherapy drugs, 72.8% of patients experienced a downstaging of their T stage and 49.0% underwent a downstaging of their N stage. Supporting Information Table S4 shows the pathological response of three treatment groups. We found that the MPR rate in the apatinib group was significantly higher than in the immunochemotherapy group (32.7% vs. 16.7%, $p = 0.02$), and the pCR rate in the chemoimmunotherapy group was significantly higher than in the immunotherapy group (53.0% vs. 39.5%, $p < 0.01$).

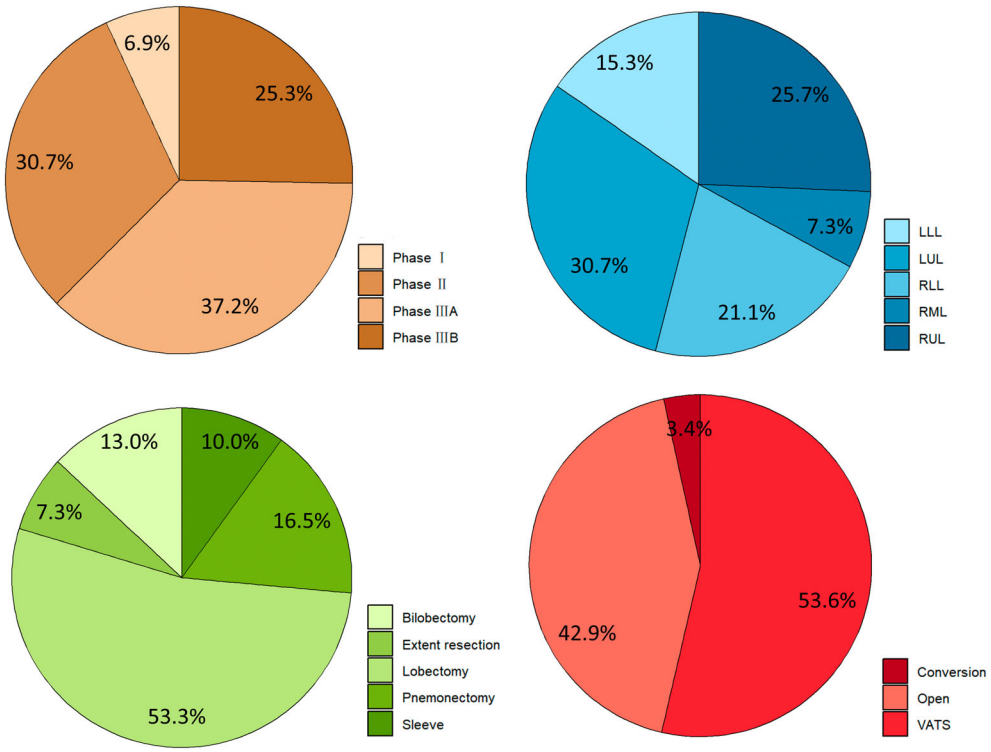

FIGURE 2 Pie charts of patients' stages, tumor locations, surgical procedures, and approaches. It can be seen that 62.5% of patients were at stage III and the left upper lobe is the most common place of tumor occurrence, 53.3% of patients underwent lobectomy after neoadjuvant immunotherapy, and 53.6% of patients underwent video-assisted thoracic surgery (VATS). LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

DISCUSSION

In this study, we continuously enrolled 261 patients who received neoadjuvant immunotherapy at the Chinese National Cancer Center from January 2018 to January 2021. All patients 'perioperative variables, especially surgical difficulty and postoperative complications, were analyzed. Surgeries were classified as routine or challenging based on whether they exceeded the mean surgical duration. Univariable and multivariable logistic regression analyses were performed to identify risk factors for challenging surgeries and postoperative complications greater than Clavien–Dindo grade 2.

As China's official national cancer center, we have admitted lung cancer patients from different cities in the country. From the results, it could be easily found that the majority of lung cancer patients receiving neoadjuvant immunotherapy were clinically at stage III (62.5%), with approximately two-fifths of them even at stage IIIB. Among these stage III patients, 74.8% were staged as N2/3. Through these patients, who would normally stand a slim chance of radical resection, neoadjuvant immunotherapy has shown excellent results in the treatment of locally advanced lung cancer. In the near future, neoadjuvant immunotherapy followed by surgical resection might become a standard treatment for patients with lymph node metastases at N2 or N3 stations.[24] Remarkably, the proportion of squamous cell carcinoma patients in our cohort was notably high at 74.7%, which might be due to the fact that EGFR mutation is common in Chinese patients with lung adenocarcinoma.[25] In our clinical routine, before the commencement of treatment, patients with lung adenocarcinoma were, and continue to be, subjected to genetic testing at our center, and we did not, and still do not, recommend immunotherapy for patients diagnosed with an EGFR mutation.

From the perspective of surgery-related variables, central-type lung cancer accounts for 61.7% of the cohort, which is often located at the opening of the lobar or segmental bronchus and is in the immediate vicinity of pulmonary arteries and veins. The intricate location of this type of tumor often leads to changes in the structure of the pulmonary hilum, making it difficult to dissect. The relatively high proportion of central-type tumors in the current study might result from doctors' desire to use neoadjuvant immunotherapy to shrink the tumor, reduce changes in hilar anatomy, and facilitate a smooth operation. Given the inherently complicated hilar anatomy in patients with central-type lung cancer, no research to date, however, has demonstrated that neoadjuvant immunotherapy could effectively simplify hilar dissection in these patients and we believe this is an issue that can be further studied. In subgroup analysis, we found that central-type lung cancer accounted for 75.4% (86/114) of all challenging surgeries. Despite this, tumor types were not included in the logistic regression analysis because we could not determine whether the intrinsic difficulty of operating on the central type itself or the severe fibrosis in the hilum caused by neoadjuvant immunotherapy was responsible for the surgical challenges. We believe a comparative study needs to be conducted to determine the exact cause and effect relationship therein.

This article defined surgical duration as a cut-off to distinguish between challenging and routine surgeries. As we

TABLE 3 Risk factors for challenging surgeries.

	Univariable			Multivariable		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Age	1.01	0.98–1.04	0.57	1.00	0.97–1.03	0.98
Gender (female/male)	1.52	0.74–3.13	0.26			
Smoking history (no/yes)	1.67	0.95–2.94	0.07	1.93	1.05–3.53	0.03*
Clinical stage						
I	Reference					
II	0.81	0.28–2.36	0.70			
IIIA	0.90	0.46–1.73	0.74			
IIIB	1.10	0.59–2.07	0.76			
Histological types						
Squamous carcinoma	Reference					
Adenocarcinoma	0.61	0.34–1.11	0.10			
Others	0.57	0.05–6.41	0.65			
Neoadjuvant strategy						
Immune alone	Reference			Reference		
Chemoimmunotherapy	3.22	1.44–7.22	<0.01*	2.89	1.22–6.86	0.02*
Immune + anlotinib	1.99	0.79–5.02	0.15	1.53	0.56–4.18	0.40
Duration to operation (>42 days)	1.43	0.87–2.35	0.16			
Lymph node dissection number	0.99	0.98–1.02	0.79	1.01	0.98–1.03	0.94
Surgical approach						
VATS	Reference			Reference		
Thoracotomy	1.06	0.64–1.75	0.82	1.23	0.71–2.14	0.46
Conversion to open	11.3	1.38–92.9	0.02*	9.96	1.15–86.01	0.04*
Resection strategy						
Lobectomy	Reference			Reference		
Bilobectomy	1.21	0.57–2.56	0.62	1.19	0.54–2.63	0.67
Sleeve resection	1.65	0.71–3.84	0.25	1.59	0.65–3.90	0.31
Pneumonectomy	0.32	0.14–0.72	<0.01*	0.36	0.15–0.86	0.02*
Lobectomy combined with sublobar resection	1.34	0.51–3.50	0.55	1.21	0.45–3.28	0.71
Pathological response						
Non-MPR	Reference					
MPR	0.65	0.35–1.23	0.19			
pCR	1.05	0.53–2.06	0.90			

Abbreviations: CI, confidence interval; OR, odds ratio; MPR, major pathological response; pCR, pathological complete response; VATS, video-assisted thoracic surgery.
*p value <0.05, which means statistically significant.

know, a few studies have described the difficulty of surgeries after immunotherapy. Boris et al.[26] were the first to report surgical difficulty after immunotherapy in the original article, and they let eight surgeons grade surgical difficulties as purely subjective from level 1 to 4. Their results suggested that about 40% of surgeries were challenging, and they believe objectively describing the difficulty is complex. We have provided a detailed record of the top three intraoperative accidents in the cohort. Supporting Information Table S1 also shows the reasons for the unexpected conversion to thoracotomy. These events undoubtedly could prolong surgical durations but could not be objectively analyzed. Although various factors influence it, the time for difficult surgery is inevitably greater than that for simple surgery. Our results demonstrate that vascular accidents and complex hilar anatomy were the most common surgical difficulties (62/261) and the most common reasons for intraoperative conversion to thoracotomy (8/9). Furthermore, it should be pointed out that the proportion of patients discharged with tubes may be higher than in other studies. There were 59 patients discharged with chest tubes and 31 of them underwent challenging surgery. It seems that challenging surgery is not the reason for discharge with tubes. Of the 59 patients, 19 were discharged to community hospitals because of postoperative complications. China is gradually promoting a hierarchical diagnosis and treatment

TABLE 4 Postoperative complications of patients based on Clavien–Dindo classification.

Variable	Total population ($n = 261$)
Postoperative complications	
No	203 (77.8)
Yes	58 (22.2)
Clavien–Dindo classification (grade >2)	
No	227 (87.0)
Yes	34 (13.0)
Complications	
Clavien–Dindo I	
Persistent pulmonary leakage (<7 days)	3 (1.1)
Others[a]	13 (5.0)
Clavien–Dindo II	
Persistent pulmonary leakage (>7 days)	6 (2.3)
Pneumonia	14 (5.4)
Aerodermectasia	7 (2.7)
Arrhythmia	8 (3.1)
Atelectasis needing suction	6 (2.3)
Clavien–Dindo III	
Pleural effusion needing intervention	14 (5.4)
Postoperative hemothorax needing intervention	8 (3.1)
Chylothorax	3 (1.1)
Clavien–Dindo IV	
Respiratory failure	4 (1.5)
Return to ICU	4 (1.5)
Pulmonary embolism	3 (1.1)
Clavien–Dindo V	
Death	4 (1.5)

Abbreviation: ICU, intensive care unit.
[a]Other grade 1 complications contain constipation, diarrhea, electrolyte disturbances and wound infections.

system, and to save medical resources, more and more patients will be transferred to community hospitals for further treatment. The other 35 patients came from another city and requested to return to their own city to rehabilitate without postoperative complications.

Meanwhile, logistic regression analysis indicated that smoking history, chemoimmunotherapy, and conversion to open surgery are risk factors for the increase in surgical difficulty, while pneumonectomy was a protective factor. Our findings are similar to those of previous research.[16,27,28] Smoking would reduce lung tissue compliance, while chemoimmunotherapy could increase tissue fibrosis through chronic inflammatory responses possibly caused by the use of ICIs. Drugs used for immunotherapy may increase the inflammatory response of intrathoracic tissues, which could cause fibrosis and decrease the flexibility and compliance thereof. Previous studies have shown that preoperative chemoimmunotherapy could increase the difficulty of surgery and the occurrence of postoperative complications.[16] Kinan et al. were the first to compare preoperative chemotherapy's impact with neoadjuvant immunotherapy's impact on surgical difficulty using real-world data.[29] They found that ICIs were associated with tissue fibrosis and inflammation, particularly in centrally located lung tumors, which would augment the difficulty of resection. Nowadays, chemoimmunotherapy has become the main method of neoadjuvant immunotherapy. Further research should be conducted to explore how this treatment induces changes in the lung environment and how to cancel its impact on subsequent surgery. In our practice, rarely was right pneumonectomy performed due to its intraoperative risks and postoperative complications.[30] In comparison, left pneumonectomy is a relatively simple surgery, and some have reported the average surgical time for left pneumonectomy is 59 min, which is similar to ours.[28] However, left pneumonectomy might also bring about postoperative complications. Table 5 suggests that pneumonectomy and longer surgical time (challenging surgery) are independent risk factors for postoperative complications, which is consistent with the results of previous studies.[31,32] Foster et al.[31] believe that a surgical duration greater than 150 min significantly increases the complications of the surgery, similar to the threshold of 148.6 min used for surgical difficulty appraisal in the present study. Jiang et al.[32] reckon that, compared to sleeve resection, pneumonectomy has a higher 30- and 90-day mortality rates, and the overall incidence of postoperative complications, inclusive of bronchopleural fistula and acute respiratory distress syndrome, is significantly increased.

To our satisfaction, the use of ICIs does not seem to increase the incidence of postoperative complications. We did not see any significant increase in complications in our cohort, with the incidence of complications accounting for 22.2% of our cohort. This deviation from previous studies[16,29] might be explained by recent improvements in surgical skills, which allow doctors nowadays to complete such surgeries much more quickly. As reported by Li et al.,[33] neoadjuvant immunotherapy would not increase the incidence of postoperative complications after sleeve resection. In this study, the complication rates are lower than Li et al.'s, which supports our aforementioned conjecture.

Because of the retrospective nature and real-world database use, certain limitations exist in the present study. First, mean surgical duration may not be a perfect variable to reflect on the difficulties in operation, so some subjective obvious factors should be considered in the future. Second, our database is not perfect, lacking data such as preoperative immune-related adverse events, whose supplement could further enrich this research. Third, we did not make a comparison with patients who had no preoperative treatment or only underwent neoadjuvant chemotherapy, therefore we could not exactly determine to what extent ICIs would affect surgery. Finally, a large-scale prospective multicenter randomized controlled trial is still needed to study the impact of different immunotherapy strategies on subsequent

TABLE 5 Risk factors for postoperative complications exceeding Clavien–Dindo grade 2.

	Univariable			Multivariable		
Variable	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Age	0.98	0.94–1.03	0.48	0.99	0.9401.04	0.71
Gender (female/male)	1.28	0.42–3.86	0.67			
Smoking history (no/yes)	1.55	0.64–3.73	0.33	1.07	0.40–2.86	0.89
Clinical stage						
I	Reference					
II	0.65	0.12–3.51	0.62			
IIIA	1.24	0.266–6.02	0.79			
IIIB	1.96	0.40–9.63	0.41			
Histological type						
Squamous carcinoma	Reference					
Adenocarcinoma	0.37	0.13–1.10	0.08			
Other	0	0	1			
Neoadjuvant strategy						
Immune alone	Reference			Reference		
Immunochemotherapy	0.63	0.25–1.62	0.34	0.81	0.26–2.60	0.73
Immune + anlotinib	0.54	0.17–1.76	0.31	0.69	0.17–2.17	0.59
Duration to operation (>42 days)	0.79	0.38–1.65	0.52			
Lymph node dissection number	1.01	0.98–1.04	0.4			
Surgical approach						
VATS				Reference		
Thoracotomy	2.71	1.24–5.89	0.01*	1.92	0.81-4.54	0.14
Convert	3.35	0.62–18.12	0.16	1.82	0.15–22.33	0.64
Resection strategy						
Lobectomy	Reference			Reference		
Bilobectomy	2.50	0.85–7.31	0.10	2.42	0.77–7.59	0.13
Sleeve lobectomy	2.12	0.62–7.24	0.23	1.74	0.47–6.48	0.41
Pneumonectomy	4.50	1.82–11.16	<0.01*	7.51	2.40-23.51	<0.01*
Lobectomy combined with sublobar resection	0.65	0.08–5.31	0.69	0.61	0.07–5.24	0.65
Challenging surgeries	3.65	1.67–8.00	<0.01*	5.53	1.50-20.62	0.01*
Blood loss	1.004	1.001–1.007	<0.01*	1.00	1.00–1.01	0.80
Pathological response						
non-MPR	Reference					
MPR	0.93	0.35–2.44	0.88			
pCR	1.44	0.54–3.86	0.47			

Abbreviations: CI, confidence interval; OR, odds ratio; MPR, major pathological response; pCR, pathological complete response; VATS, video-assisted thoracic surgery.
*p value <0.05, statistically significant.

surgeries, identify the most significant risk factors affecting intraoperative events and postoperative complications, and enhance our preparedness for future surgery planning and perioperative management.

CONCLUSIONS

In summary, the impact of neoadjuvant immunotherapy on surgery cannot be ignored. Although immunotherapy could increase surgical difficulty, the incidence of complications remains acceptable. For those who have undergone neoadjuvant chemoimmunotherapy to reduce surgical duration and postoperative complications, the preoperative resection strategy should be well designed, and cautious operation should be taken to avoid the occurrence of intraoperative events, conversion to open thoracic surgery and pneumonectomy.

AUTHOR CONTRIBUTIONS

Conceptualization: B.G. and G.S. Methodology: B.G., J.Y., and G.S. Formal analysis: B.G. and Y.Z. Data curation: B.G.,

C.X., P.Y., J.Y., B.F., L.Y., and Y.Z. Writing – original draft: B.G. Software: C.X. Visualization: B.G., C.X., and L.Y. Funding acquisition: Y.Z. and G.S. Writing – review and editing: B.G. and G.S.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The clinical data in this article are partially available after publication, but the consent of the author is required. The sequencing data in this paper is not public.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patients for publication of this research and any accompanying images.

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