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The Safety and Efficacy of Preoperative Immunotherapy Combined with Chemotherapy in Patients with Stage IIIA-IIIB Lung Squamous Cell Carcinoma

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Abstract

Objective Data on preoperative immunotherapy combined with chemotherapy in potentially resectable lung squamous cell carcinoma (LUSC) remain scarce. This study was designed to investigate the safety and efficacy of preoperative immunotherapy and chemotherapy for stage IIIA-IIIB LUSC.

Methods This study consecutively enrolled stage IIIA-IIIB LUSC who received preoperative immunotherapy combined with chemotherapy between January 2019 and July 2021. Patients received two to four cycles of immunotherapy combined with platinum-based doublet chemotherapy (platinum + paclitaxel) before surgery. Patients were assessed radiographically every one to two cycles until surgery. Postoperative pathological evaluation was also performed. Follow-up was performed until at least 3 months after surgery.

Results Sixty-five patients with stage IIIA-IIIB LUSC were enrolled. The objective response rate was 78.46% (51/65), and no patients had progressive disease. Fifty-seven patients underwent surgery, and 55 patients achieved R0 resection. There were no perioperative deaths. The rate of pathological complete response (pCR) was 31.58% (18/57) and major pathological response was 68.42% (39/57). The incidence of grade 3 and 4 adverse reactions was 21.21 and 1.54%, respectively.

Conclusion Perioperative immunotherapy combined with chemotherapy followed by surgical resection for male patients with stage IIIA-IIIB LUSC was effective with a tolerable toxicity profile.

Keywords
- lung squamous cell carcinoma
- preoperative treatment
- immunotherapy
- chemotherapy
- surgery

Introduction

Lung cancer is still the most common malignant tumor in the world, accounting for approximately 22 to 23% of all cancer deaths, posing a huge threat to global health.[1] Almost 80 to 85% of lung cancer cases are pathologically categorized as non-small cell lung cancer (NSCLC), which is composed of lung adenocarcinoma, lung squamous cell carcinoma (LUSC), and large cell carcinoma.[2,3] Significant progress has been made in the treatment of lung adenocarcinoma due to the

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advent of targeted drugs, but drug therapy for LUSC still relies heavily on traditional chemotherapy.[4–7] In recent years, immunotherapy based on progressive disease (PD)-L1/PD-1 immune checkpoint inhibitors has played an important role in the treatment of solid tumors. The KEYNOTE-024, KEYNOTE-042, and IMPOWER-110 studies showed that immunotherapy has shown survival benefit over chemotherapy as first-line treatment for patients with metastatic or advanced NSCLC.[8–10] Results of the Checkmate-017 study showed that immunotherapy significantly outperformed chemotherapy in overall survival (OS) and progression-free survival (PFS) in previously treated patients with advanced LUSC.[11]

Immunotherapy combined with chemotherapy can yield better efficacy than chemotherapy alone. KEYNOTE-189, IMPOWER-130, and IMPOWER-150 studies revealed that the addition of immunotherapy to standard chemotherapy as first-line treatment for patients with metastatic or advanced NSCLC resulted in significantly improved OS and PFS compared with chemotherapy alone.[12–14] KEYNOTE-407 and IMPOWER-131 studies demonstrated that the combination of immunotherapy and chemotherapy produced significantly longer OS and PFS than chemotherapy alone in patients with previously untreated metastatic squamous NSCLC.[15,16] Furthermore, for patients with stage IB-IIIA resectable NSCLC, several studies have shown that immunotherapy with or without chemotherapy can help the majority of patients achieve major pathological responses with a high R0 resection rate and manageable treatment-related toxicities.[17–21] Radical surgery after chemoimmunotherapy also appears to be safe and effective in patients with unresectable stage IIIB NSCLC.[20–22] However, studies on whether patients with stage IIIA-IIIB potentially resectable LUSC can undergo surgery after immunotherapy combined with chemotherapy are still scarce. Therefore, this study aimed to investigate the safety and efficacy of preoperative immunotherapy combined with chemotherapy in patients with stage IIIA-IIIB LUSC.

Methods

Patients

This study included stage IIIA-IIIB LUSC male patients who received preoperative immunotherapy combined with chemotherapy in the Thoracic Surgery Department of the First Affiliated Hospital of Zhejiang University School of Medicine from January 2019 to July 2021. This project was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (2021 IIT No. 844), and informed consent was obtained from patients so that we could use relevant medical record information of them. Patients with the following criteria were included: (1) Male patients over the age of 18 and under the age of 80; (2) histopathologically confirmed LUSC by bronchoscopy or lung aspiration; (3) pretreatment clinical stage IIIA-IIIB LUSC; (4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (5) adequate organ function, and sufficient pulmonary and cardiac function. The main exclusion criteria for patients were as follows: (1) lack of necessary pretreatment imaging examinations in our hospital; (2) imaging evaluations less than two times; (3) prior anticancer treatment, such as radiotherapy, interventional therapy, or drug treatment; (4) active autoimmune disease or infectious disease; (5) undergoing systemic immunosuppressive therapy; (6) clinically significant concurrent malignant tumor. We obtain clinicopathological data from patients through their regular examinations or treatment in our hospital. The follow-up period was at least 3 months after surgery.

Preoperative Treatment Procedures

The patient received two to four cycles (three weeks per cycle) of immunotherapy combined with platinum-based dual–drug chemotherapy (platinum + paclitaxel) before surgery. Immunotherapy regimens were camrelizumab 200 mg, nivolumab 3 mg/kg, pembrolizumab 100 or 200 mg, sintilimab 200 mg or tislelizumab 200 mg. The platinum drugs were cisplatin 75 mg/m^2, carboplatin AUC = 5 or nedaplatin 80 mg/m^2, and the paclitaxel regimen was nab-paclitaxel 260 mg/m^2 or paclitaxel 175 to 200 mg/m^2. After two cycles of neoadjuvant therapy, we would make an assessment on patients to see whether there was a surgical chance. If the treatment was intolerable for the patient, we would appropriately alter the treatment plan or put off it. If there was no obvious tumor regression, treatment would continue, with an evaluation of surgical possibility after one to two cycles. If there was disease progression, radiotherapy would be recommended.

Tumor Response Evaluation

Within 1 week prior to the immunotherapy and chemotherapy, patients were systematically assessed with imaging to obtain baseline data, including computed tomography (CT) of chest and abdomen, bronchoscopy and endoscopic ultrasound, positron emission tomography-CT, bone emission computed tomography, brain magnetic resonance imaging, and abdominal ultrasound. Moreover, chest CT scans were done for the patients every two cycles until surgery was performed or the patient withdrew from the treatment. Evaluation of tumor location, degree of differentiation, cTNM, ycTNM, and ypTNM was performed according to the 8^{th} edition of AJCC TNM staging.[23] We adopted the Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST 1.1) to assess the tumor treatment response in the presence of target lesions.[24] Complete response (CR) is defined as the vanishment of all target lesions; partial remission (PR) is defined as at least 30% shrinkage in the total diameter of target lesions; PD is defined as at least 20% increase in the total diameter of target lesions or the emergence of new lesions; stable disease (SD) is defined as neither CR, PR, nor PD.

Treatment-Related Adverse Events

Continuous evaluations were routinely performed to monitor treatment-related adverse events (AEs) during therapy procedure, with blood routine and blood biochemical examinations every week, and with myocardial enzyme spectrum, thyroid function, and coagulation function examinations every 3 weeks. We evaluated gastrointestinal reactions and skin reactions by patients' complaints.

Surgical Treatment

The surgical approach for LUSC is composed of open radical surgery, video-assisted thoracoscopic surgery (VATS), or robot-assisted thoracoscopic surgery (RATS) with systematic lymph node dissection. Detailed operation method includes wedge resection, lobectomy, sleeve lobectomy, and total pneumonectomy. Systematic lymph node dissection scope includes at least three groups of lymph nodes in the lung and three groups of mediastinal lymph nodes which must include subcarinal lymph nodes. On the left side, we generally dissect group 3, 4L, 5 to 13 lymph nodes and the right side we include 3a, 4R, 7 to 13 lymph nodes. Operation time, estimated blood loss, and length of hospital stay were fully recorded.

Pathological Examination

Based on the pathology report and pathological photographs, two investigators independently assessed the pathological results, from which we could obtain information such as pathological type, degree of differentiation, depth of invasion, resection margin, lymph node metastasis, and degree of tumor regression. By calculating the approximate percentage of residual viable tumor cells in the original tumor area, we defined pathological complete response (pCR) as no residual viable cancer cells, major pathological response (MPR) as residual viable cancer cells $\leq$10%.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages, and differences between groups were compared using the Chi-square test. Continuous variables were expressed as median and interquartile range (IQR), and differences between groups were compared using *t*-test or Wilcoxon test. All analyses were performed using R software (version 4.1.2). A two-sided p <0.05 was considered significant.

Results

Patients and the Treatment Process

A total of 65 patients were included in this study, and an overview of the of preoperative treatment process is shown in ►**Fig. 1A**. The operation rate was approximately 87.69% (57/65), and five patients with a PR were reluctant to undergo surgery and chose radiotherapy.

Response to Preoperative Immunotherapy Combined with Chemotherapy

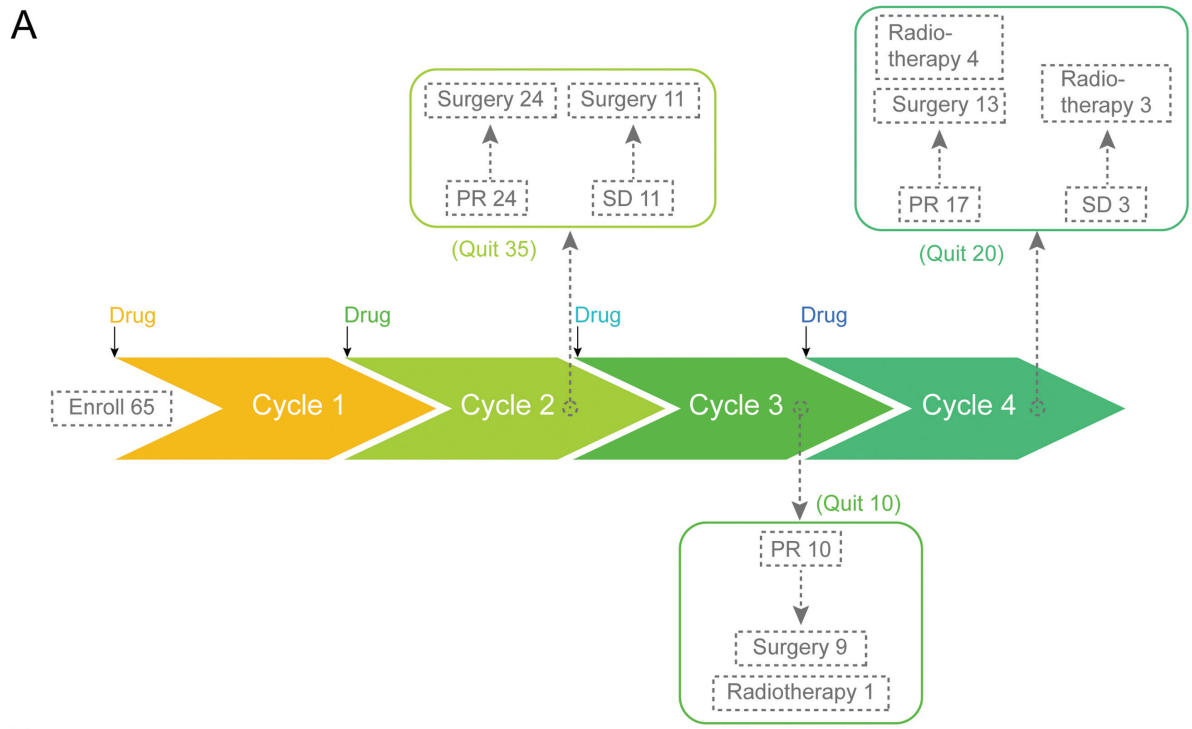
The treatment response of 65 patients evaluated according to RECIST version 1.1 was listed below: 51 patients presented with a PR, 14 patients presented with an SD, and no PD or CR occurred. The baseline clinical characteristics of patients grouped according to treatment response were shown in ►**Table 1**. The results showed that three to four cycles of treatment produced more PR responses than two cycles of treatment, but the difference was not statistically significant ($p = 0.071$). No significant differences between the PR and SD groups were found with regard to age, sex, ECOG performance status, smoking status, drinking status, comorbidities, pathological grade, tumor location, clinical stage, or immunotherapy regimens.

►**Fig. 1B** showed the percentage change from baseline for the diameter of the maximum target lesion. The results also showed that compared with two cycles of treatment, the tumor shrinkage was more obvious after three to four cycles of treatment, mainly in the right half of the figure. Furthermore, to assess the relationship between the number of treatment cycles and the treatment effect, we compared tumor diameters for each two cycles (►**Fig. 2**). Tumor diameters shrunk significantly at the end of cycles 2 (►**Fig. 2A**), 3 (►**Fig. 2B**), and 4 (►**Fig. 2C**) compared with baseline. Tumor diameters were also reduced after treatment in the third cycle (►**Fig. 2D**) and the fourth cycle (►**Fig. 2E**) compared with the end of the second cycle.

The changes of the clinical stage of LUSC patients before (cStage) and after (ycStage) preoperative immunotherapy combined with chemotherapy were shown in ►**Table 2**. We found that T staging was significantly different before and after treatment (p <0.001), which was reflected in the decrease in T4, T3, and T2b patients after treatment, while the increase in T1 and T2a patients. N3 and N2 patients decreased, while N0 and N1 patients increased, but there was no significant difference in N stage changes before and after treatment ($p = 0.064$). There was also a significant difference in total stage changes before and after treatment ($p = 0.017$), and the results showed that the number of inoperable stage IIIb patients was significantly reduced, and the number of operable stage I, II, and IIIa patients was significantly increased.

Surgery and Pathological Response

Among the 65 patients, surgery eventually was performed in 57 patients. Outcomes of surgery and the pathological response of the 57 patients who received surgical treatment were listed in ►**Table 3**. The median time from the last treatment to surgery was approximately 30.0 days (IQR, 28.0–33.0 days). The most common operation method was lobectomy, accounting for 29 cases, followed by sleeve resection in 19 cases, pneumonectomy in seven cases, and wedge resection in one case. In another case, exploratory thoracotomy was performed because the tumor was too tightly adhered to the surrounding blood vessels. Of the 57 patients, 44 underwent thoracotomy, two underwent RATS, six underwent VATS, and five underwent VATS conversion to thoracotomy due to severe thoracic adhesions. The median operation time was 151.5 minutes (IQR 116.8–202.0 minutes). The median estimated intraoperative blood loss was 50 mL (IQR 20–100 mL). The median number of lymph node dissections during surgery was 15.5 (IQR 11.0–23.5). Fifty-five patients (96.49%) achieved R0 resection, one patient had R1 resection, and one patient had R2 resection. The median length of hospitalization stay was 21 days (IQR 17–24.3 days). There were no perioperative deaths and severe postoperative complications. Finally, 18 patients (31.58%) achieved pCR, and 39 patients (68.42%) achieved MPR.



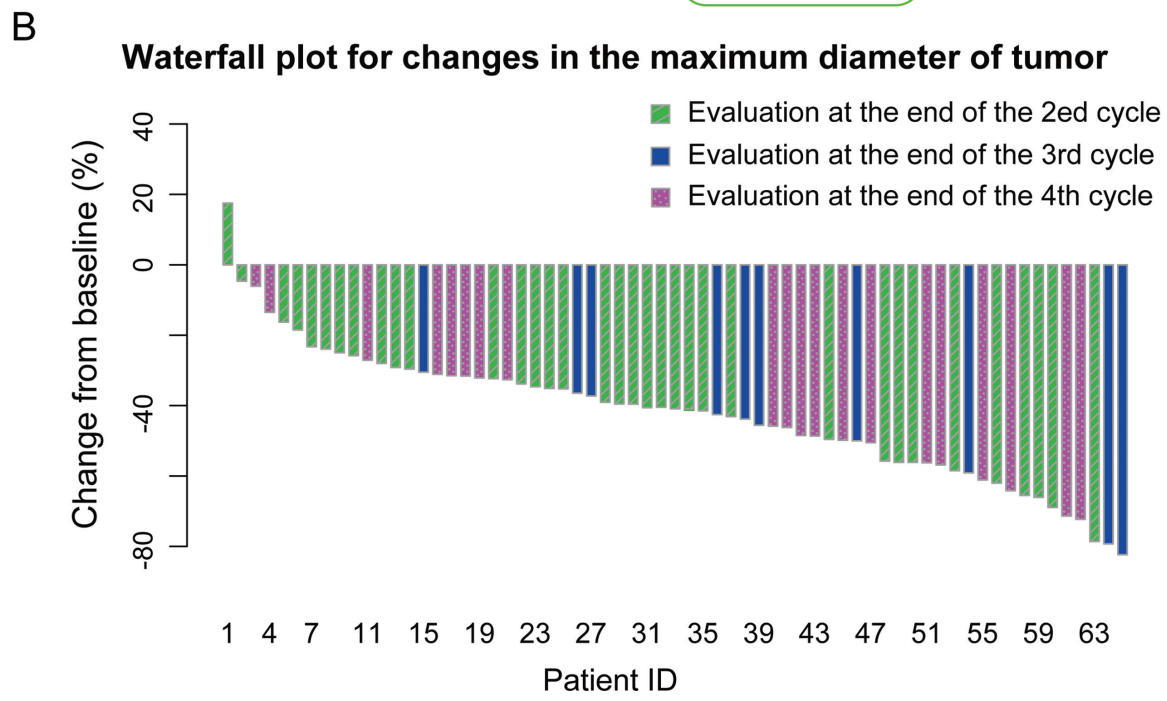


Fig. 1 Overview of preoperative treatment process and outcomes. (**A**) Overview of preoperative treatment process; (**B**) The percentage change from baseline for the diameter of the maximum target lesion.

Toxicity

No patients withdrew from the therapy process because of intolerable toxic effects and there were no previously undocumented toxicities that occurred in our study. The toxic effects were summarized in ►**Table 4**. Grade 3 to 4 adverse reactions were mainly distributed in three cases of leukopenia, two cases of agranulocytosis, three cases of anemia, two cases of constipation, two cases of hepatic injury, and three cases of skin reaction. The adverse reactions of these patients improved after symptomatic treatment.

Discussion

In recent years, several clinical centers have conducted studies of preoperative immunotherapy for NSCLC. Forde et al

Table 1 Characteristics of the patients at baseline, according to treatment response ($n = 65$)

Characteristic	Total, $n = 65$	PR, $n = 51$	SD, $n = 14$	p-Value
Median age (IQR), years	67.0 (62.0–71.0)	66.0 (62.0–72.0)	67.0 (65.0–70.5)	0.712
Sex, *n* (%)				
Male	65 (100.00)	51 (100.00)	14 (100.00)	
ECOG performance status				
0	39 (60.00)	30 (58.82)	9 (64.29)	0.712
1	26 (40.00)	21 (41.18)	5 (35.71)	
Smoking status, *n* (%)				
Never	16 (24.62)	11 (21.57)	5 (35.71)	0.276
Ever	49 (75.38)	40 (78.43)	9 (64.29)	
Drinking status, *n* (%)				
Never	39 (60.00)	33 (64.71)	6 (42.86)	0.139
Ever	26 (40.00)	18 (35.29)	8 (57.14)	
Comorbidities, *n* (%)				
Pulmonary disease	21 (32.31)	15 (28.85)	6 (42.86)	0.341
Cardiac disease	5 (7.69)	5 (9.62)	0 (0)	0.223
Diabetes mellitus	6 (9.23)	5 (9.62)	1 (7.14)	0.761
Hypertension	23 (35.38)	17 (32.69)	6 (42.86)	0.509
Pathological grade, *n* (%)				
G1	1 (1.54)	1 (1.96)	0 (0)	0.357
G2	14 (21.54)	13 (25.49)	1 (7.14)	
G3	20 (30.77)	15 (29.41)	5 (35.71)	
Unknown	30 (46.15)	22 (43.14)	8 (57.14)	
Tumor location, *n* (%)				
Hilum of left lung	2 (3.08)	2 (3.92)	0 (0)	0.489
Inferior lobe of left lung	7 (10.77)	6 (11.76)	1 (7.14)	
Inferior lobe of right lung	14 (21.54)	13 (25.49)	1 (7.14)	
Middle lobe of right lung	2 (3.08)	1 (1.96)	1 (7.14)	
Superior lobe of left lung	20 (30.77)	14 (27.45)	6 (42.86)	
Superior lobe of right lung	20 (30.77)	15 (29.41)	5 (35.71)	
Clinical stage, *n* (%)				
IIIa	38 (58.46)	31 (60.78)	7 (50.00)	0.468
IIIb	27 (41.54)	20 (39.22)	7 (50.00)	
Immunotherapy regimes, *n* (%)				
Camrelizumab	17 (26.15)	14 (27.45)	3 (21.43)	0.239
Nivolumab	15 (23.08)	13 (25.49)	2 (14.29)	
Pembrolizumab	12 (18.46)	9 (17.65)	3 (21.43)	
Sintilimab	6 (9.23)	6 (11.76)	0 (0)	
Tislelizumab	15 (23.08)	9 (17.65)	6 (42.86)	
Treatment cycle, *n* (%)				
2	35 (53.85)	24 (47.06)	11 (78.57)	0.071
3	10 (15.38)	10 (19.61)	0 (0)	
4	20 (30.77)	17 (33.33)	3 (21.43)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PR, partial remission; SD, stable disease.

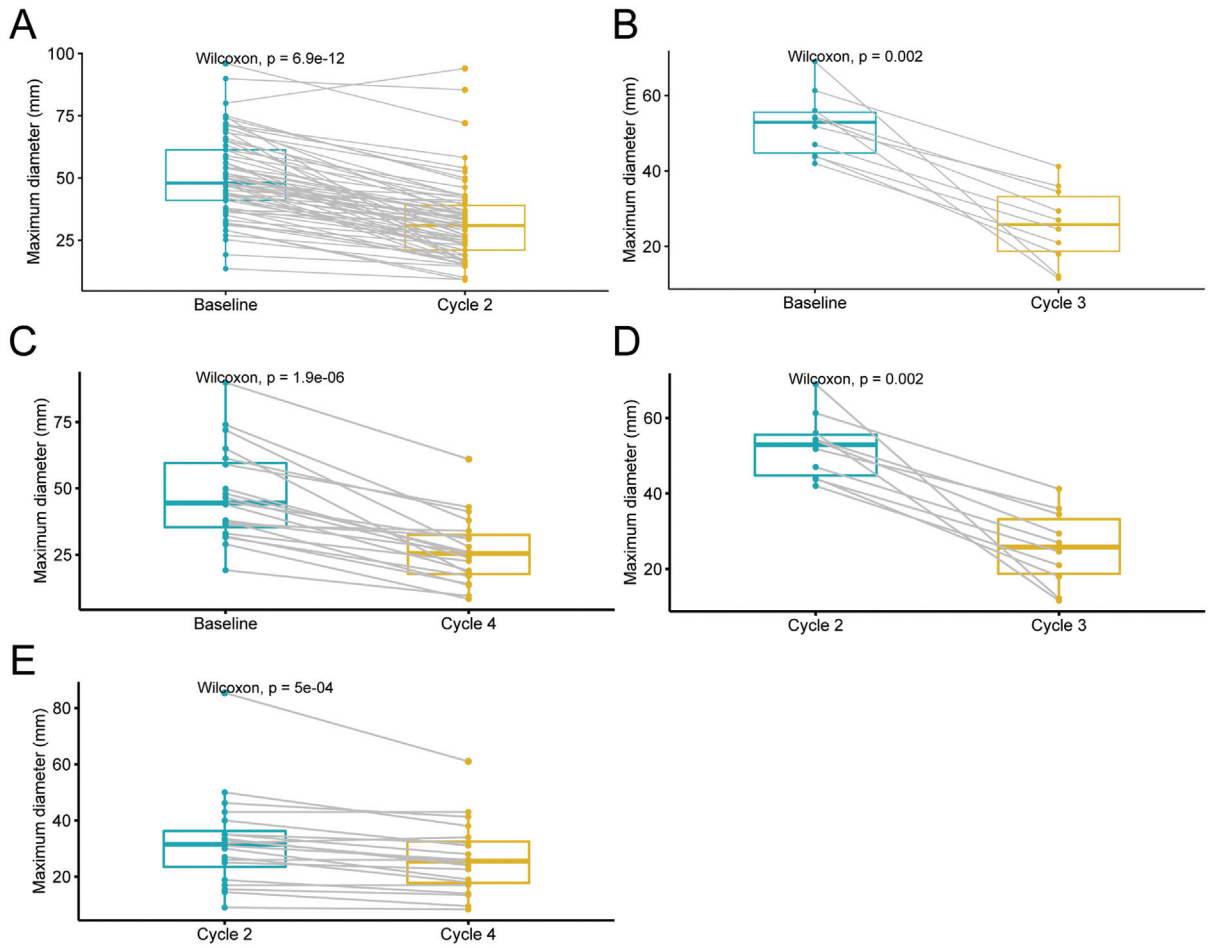


Fig. 2 Changes in the maximum transverse diameter of the tumor during neoadjuvant therapy. (**A**) The change in the maximum transverse diameter of the tumor from baseline to the end of the second cycle of neoadjuvant therapy; (**B**) The change in the maximum transverse diameter of the tumor from baseline to the end of the third cycle of neoadjuvant treatment; (**C**) The change in the maximum transverse diameter of the tumor from baseline to the end of the fourth neoadjuvant therapy; (**D**) The change in the maximum transverse diameter of the tumor from the end of the second cycle to the end of the third cycle of neoadjuvant therapy; (**E**) The change of the maximum transverse diameter of the tumor from the end of the second cycle to the end of the fourth cycle of neoadjuvant therapy.

performed two cycles of neoadjuvant therapy (nivolumab) in patients with resectable stage I-IIIA NSCLC, with MPR and pCR rates of 45 and 15%, respectively.[17] Shen et al used 2 cycles of neoadjuvant therapy (pembrolizumab) in patients with resectable stage IIB-IIIB LUSC, and the MPR rate was 64.7%.[20] In the NADIM study, patients with resectable stage IIIA NSCLC had an MPR rate of 76.1% and a pCR rate of 54.3% after three cycles of neoadjuvant therapy (nivolumab).[18] Shu et al performed two to four cycles of neoadjuvant therapy (atezolizumab) in patients with resectable stage IB-IIIA NSCLC, the MPR rate was 57%, and the pCR rate was 33%.[19] Our study found that preoperative immunotherapy combined with chemotherapy in patients with potentially resectable stage III A-B LUSC had a high objective response rate (78.46%) and manageable adverse effects. The MPR and pCR rates in this study were 68.42 and 31.58%, respectively, which were similar to the above studies. Compared with the use of two cycles of immunotherapy combined with chemotherapy, the diameter of tumor lesions was still reduced after the third to fourth cycles of treatment, suggesting a sustained tumor regression effect under prolonged treatment course. Therefore, for patients who do not achieve the ideal therapeutic effect after receiving two treatment cycles, it is feasible to appropriately increase the treatment cycle.

Stage IIIB NSCLC is generally regarded as unresectable. Initially, 41.54% of patients with stage IIIB were enrolled, and after preoperative drug treatment, the proportion of patients with stage IIIB was only 7.69%. Ultimately, 87.69% (57/65) of patients ultimately underwent surgery, and 96.49% (55/57) of patients achieved R0 resection. In this study, 77.19% of the patients underwent thoracotomy, and another 8.77% of the patients were converted from VATS to thoracotomy, suggesting that preoperative drug therapy or the tumor itself may lead to increased thoracic adhesions and increase difficulty of surgery. However, in the study conducted by Shen et al, thoracotomy only accounted for 32.4%.[20] The obvious difference between the two centers may be related to the different drug regimens used or the habits of the surgeons.

Table 2 Changes of clinical stage of LUSC patients before (cStage) and after (ycStage) preoperative immunotherapy combined with chemotherapy

Characteristic	cStage ($n=65$)	ycStage ($n=65$)	*p*-Value
T stage, *n* (%)			
T1a	0 (0)	4 (6.15)	<0.001
T1b	2 (3.08)	15 (23.08)	
T1c	4 (6.15)	19 (29.23)	
T2a	9 (13.65)	14 (21.54)	
T2b	19 (29.23)	7 (10.77)	
T3	20 (30.77)	4 (6.15)	
T4	11 (16.92)	2 (3.08)	
N stage, *n* (%)			
N0	0 (0)	2 (3.08)	0.064
N1	6 (9.23)	16 (24.62)	
N2	57 (87.69)	47 (72.31)	
N3	2 (3.08)	0 (0)	
Stage, *n* (%)			
Ib	0 (0)	1 (1.54)	0.017
IIa	0 (0)	1 (1.54)	
IIb	0 (0)	15 (23.08)	
IIIa	38 (58.46)	43 (66.15)	
IIIb	27 (41.54)	5 (7.69)	

Abbreviation: LUSC, lung squamous carcinoma.

Immunotherapy-related adverse reactions vary widely among reported studies. In the NADIM study, 30.4% of patients experienced at least grade 3 adverse reactions.[18] The study by Shen et al showed an approximately 10.8% incidence of grade 3 AEs and no grade 4 adverse reactions.[20] The incidence of grade 3 and 4 AEs in this study was 21.21 and 1.54%, respectively. Differences in the incidence of adverse reactions between these studies may be due to differences in the number of treatment cycles and the use of different immunotherapies.

Limitations of our study include small sample size, retrospective nature, short postoperative follow-up, and heterogeneity of treatment regimens. These factors may limit the statistical power of this study. We included consecutive patients who met the study criteria, which eliminated selection bias to a certain extent and made the results representative.

In conclusion, neoadjuvant immunotherapy combined with chemotherapy followed by surgical resection for male patients with stage III A-B LUSC was effective and safe with a high MPR rate, as well as manageable adverse reactions. However, the effectiveness of our findings requires larger randomized controlled trials to confirm. And further follow-ups in the future are needed to confirm whether this preoperative therapy regimen can result in a survival benefit.

Table 3 Outcomes of LUSC patients undergoing surgery ($n=57$)

Outcomes	Patients, $n=57$
Time from last neoadjuvant therapy to surgery, median (IQR), day	30.0 (28.0–33.0)
Operation method, *n* (%)	
Wedge resection	1 (1.75)
Lobectomy	29 (50.88)
Sleeve lobectomy	19 (33.33)
Exploratory thoracotomy	1 (1.75)
Total pneumonectomy	7 (12.28)
Surgical approach, *n* (%)	
Open	44 (77.19)
RATS	2 (3.51)
VATS	6 (10.53)
VATS-Open	5 (8.77)
Operation time, median (IQR), min	151.5 (116.8–202.0)
Estimated blood loss, median (IQR), mL	50.0 (20.0–100.0)
Total number of lymph node dissections during surgery, median (IQR), *n*	15.5 (11.0–23.5)
Surgical margin, *n* (%)	
R0 resection	55 (96.49)
R1 resection	1 (1.75)
R2 resection	1 (1.75)
Length of hospital stay, median (IQR), day	14.0 (11.0–17.0)
ypTNM stage, *n* (%)	
Ia1	27 (47.37)
Ia2	2 (3.51)
Ia3	2 (3.51)
Ib	2 (3.51)
IIa	1 (1.75)
IIb	13 (22.81)
IIIa	10 (17.54)
Pathological response, *n* (%)	
No viable tumor cells	18 (31.58)
0 < viable tumor cells ≤10%	21 (36.84)
Viable tumor cells >10%	18 (31.58)

Abbreviations: IQR, interquartile range; LUSC, lung squamous carcinoma; RATS, robot-assisted thoracoscopic surgery; TRG, tumor regression grade; VATS, video-assisted thoracoscopic surgery.

Authors' Contribution

Y.W. and C.H. contributed toward conceptualization, data curation, formal analysis, software, visualization, and writing – original draft. J.L. and S.W. contributed toward

Table 4 Toxicities

Toxicities	None	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic					
Leukopenia	33	21	8	3	0
Agranulocytosis	50	10	3	1	1
Anemia	25	29	8	3	0
Thrombocytopenia	62	1	2	0	0
Gastrointestinal					
Nausea	62	2	1	0	0
Emesis	62	2	1	0	0
Diarrhea	62	2	1	0	0
Constipation	48	12	3	2	0
Hepatic injury	42	17	4	2	0
Renal injury	63	2	0	0	0
Skin reaction	44	11	7	3	0
Hypothyroidism	61	1	3	0	0
Coagulation disorders	64	1	0	0	0

conceptualization, methodology, investigation, data curation, visualization, writing – original draft. S.W. contributed toward conceptualization, methodology, investigation, data curation, visualization, and writing – original draft. X.H. did the investigation and data curation. L.Z., W.S., and C.G. did the data curation and visualization. Y.W. worked on methodology and visualization. L.Z. and J.H. did the conceptualization, data curation, funding acquisition, project administration, resources, supervision, validation, writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of Interest
None declared.

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