Original Article

Preliminary experience of surgery after neoadjuvant immunotherapy combined with chemotherapy for stage-IIIB non-small cell lung cancer

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Background: Previously, stage-IIIB non-small cell lung cancer (NSCLC) has been considered inoperable. In recent years, neoadjuvant immunotherapy has shown encouraging efficacy in the treatment of advanced stage NSCLC in several trials. However, the effectiveness and safety of neoadjuvant immunotherapy in treating stage-IIIB NSCLC are still unknown. Therefore, we conducted this retrospective study to examine the outcomes of surgery after neoadjuvant immunotherapy combined with chemotherapy for stage-IIIB NSCLC.

Methods: Thirty patients with stage-IIIB NSCLC who were treated at the Department of Thoracic Surgery of Renji Hospital from January 2019 to September 2021 were analyzed retrospectively. Neoadjuvant immunotherapy combined with chemotherapy was administered prior to surgery. The curative effect was evaluated by imaging and pathological examinations.

Results: The objective response rate (ORR) and disease control rate (DCR) of the patients after neoadjuvant therapy evaluated by imaging studies were 70% and 86.7%, respectively. Of the 30 patients, 19 (63%) underwent surgical resection, in which all achieved a complete R0 resection. The median operative time was 168 minutes (range, 75–295 minutes), and the average intraoperative blood loss was 215.3±258.4 mL. The median postoperative hospital stay was 8 days (range, 4–59 days). The major pathological response (MPR) rate was 73.7% (14/19), and the pathological complete response rate was 47.4% (9/19); 2/30 patients (6.7%) had postoperative complications, including two who developed bronchopleural fistulas and one mortality, from a postoperative pulmonary infection. The treatment-related adverse reactions were mainly grades 1–2. Only two patients had grade 3 anemia, and no grade 4 adverse reactions were observed.

Conclusions: Neoadjuvant immunotherapy and chemotherapy combined with surgery in patients with stage-IIIB NSCLC is safe and feasible. The patient outcomes and optimal number of neoadjuvant treatment cycles need to be explored and studied further.

Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant therapy; immunotherapy; surgery

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Introduction

Lung cancer is the malignant tumor with the highest incidence and mortality rate worldwide (1,2). Non-small cell lung cancer (NSCLC) accounts for 80–85% of new lung cancer cases, with adenocarcinoma and squamous cell carcinoma as the most common subtypes (3). The treatment of NSCLC depends on the stage of the tumor. According to the 8th edition of lung cancer staging, stage-IIIB NSCLC includes local invasion of the tumor and metastasis in mediastinal or extrapulmonary regional lymph nodes (T3/4N2 or T1/2N3) (4). Stage-IIIB NSCLC belongs to locoregionally advanced lung cancer. Previously, stage-IIIB NSCLC has been considered inoperable, and curative-intent radiotherapy and chemotherapy have been its standard treatment. However, in recent years, the emergence of immunotherapy and its excellent effect in treating unresectable NSCLC has inspired novel treatment strategies (5,6).

Trial data have reported improved 3-year overall survival of stage-III NSCLC patients following durvalumab consolidation treatment after radical radiotherapy and chemotherapy (57.0% *vs.* 43.5%) (7). Forde *et al.* (8) analyzed the efficacy of neoadjuvant therapy with nivolumab in 21 patients with resectable NSCLC in stages I–IIIA, and found that the major pathological response (MPR) rate was 45%, and the incidence of adverse events (AEs) was low. Forde *et al.*'s study (8) was the first to propose the use of immunotherapy in the neoadjuvant treatment of NSCLC. Neoadjuvant immunotherapy combined with chemotherapy has also been shown to be more effective than neoadjuvant chemotherapy alone (9,10). However, for unresectable stage-IIIB NSCLC, further research needs to be conducted to determine whether neoadjuvant immunotherapy combined with chemotherapy can transform tumor into resectable NSCLC and to examine the long-term postoperative outcomes, including disease-free and overall survival. Additionally, a number of studies have suggested that neoadjuvant immunotherapy combined with chemotherapy increases the difficulty of surgery (11,12).

In this study, we retrospectively analyzed 30 patients with stage-IIIB NSCLC who received neoadjuvant immunotherapy combined with chemotherapy followed by surgery at the Department of Thoracic Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, and preliminarily examined the safety and effectiveness of combined chemotherapy with programmed cell death receptor 1 (PD-1) monoclonal antibody as a new adjuvant treatment for patients with stage-IIIB NSCLC. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-908/rc).

Highlight box

Key findings

- Neoadjuvant immunotherapy and chemotherapy combined with surgery in patients with stage-IIIB non-small cell lung cancer (NSCLC) is safe and effective.

What is known and what is new?

- In past decades, stage-IIIB NSCLC has been considered inoperable, and curative-intent radiotherapy and chemotherapy have been its standard treatment.
- Neoadjuvant immunotherapy and chemotherapy combined with surgery in patients with stage-IIIB NSCLC is safe and effective.

What is the implication, and what should change now?

- Patients with stage-IIIB NSCLC should also be considered for neoadjuvant chemoimmunotherapy followed by surgery.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Ethics Committee of the Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China (No. RA-2020-353). Individual consent for this retrospective analysis was waived. This study retrospectively analyzed the data of patients who were diagnosed with NSCLC at Renji Hospital, School of Medicine, Shanghai Jiao Tong University from January 2019 to September 2021 and received PD-1 monoclonal antibody combined with chemotherapy as a neoadjuvant treatment.

Inclusion criteria

Inclusion criteria for this study selected patients with NSCLC confirmed by histological examination, with preoperative stage-IIIB disease according to the 8th edition of lung cancer staging. (I) The patients should be judged as potentially resectable before treatment: stage T3/4N2 or T1/2 with single station of N3; (II) have a Karnofsky performance status score ≥80 points, and who were anticipated to be able to tolerate immunotherapy and chemotherapy; (III) had the feasibility of neoadjuvant therapy discussed by a multidisciplinary team (MDT); and (IV) had normal liver and renal functions and normal cardiopulmonary functions.

Exclusion criteria

Patients were excluded from the study if they met any of the following exclusion criteria: (I) were unable to tolerate immunotherapy or chemotherapy; (II) had a hepatorenal insufficiency; (III) had a history of a malignant tumor in other organs; and/or (IV) had cardiopulmonary insufficiency.

Treatment plan

PD-1 inhibitors were used for the immunotherapy, including pabolizumab, carrelizumab, tirelizumab, xindilizumab, and treprizumab. The chemotherapy regimen comprised albumin-binding paclitaxel (260 mg/m^2) + cisplatin (75 mg/m^2)/carboplatin (area under the curve: 5) or pemetrexed (500 mg/m^2) + cisplatin (75 mg/m^2). Immunotherapy and chemotherapy were both administered every 21 days until the achievement of partial response (PR) or up to a maximum of four cycles, and the efficacy was evaluated after every two cycles.

Evaluation method

All the patients underwent computed tomography (CT) examinations every two cycles, and the efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumor, version 1.1 (RECIST 1.1) (13). The preoperative imaging evaluation indexes included a complete response (CR), PR, stable disease (SD), progressive disease (PD), objective response rate (ORR), and disease control rate (DCR). The postoperative pathological evaluation indexes included the MPR and pathological complete response (pCR). The MPR was defined as a pathological residual tumor ≤10% after tumor regression induced by neoadjuvant therapy, and the pCR was defined as no residual tumor in pathology after tumor regression induced by neoadjuvant therapy (14,15). From the beginning of each patient's use of the observed drug in this study to the end of the treatment within 1 month, any adverse reaction, whether or not there was a causal relationship with the test drug, was considered an AE. AEs were evaluated according to the General Toxicity Standard of the National Cancer Institute, version 5.0.

Statistical method

We used Student's *t*-test to compare the continuous variables and used the χ^2 test to compare the categorical variables. A two-sided P value <0.05 was considered statistically significant, and all the data were analyzed using SPSS software version 22.0 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

According to the inclusion and exclusion criteria, 30 patients with stage-IIIB NSCLC who received preoperative neoadjuvant immunotherapy combined with chemotherapy were included in this study. The baseline characteristics of the patients are shown in *Table 1*. There were 29 males and one female in the cohort; 23 patients (77%) were aged ≥60 years and 7 patients (23%) were aged <60 years; 14 patients (47%) suffered from hypertension; 5 patients (17%) suffered from diabetes; 19 patients (63%) had a history of smoking; 10 patients (33%) had the adenocarcinoma subtype, and 20 patients (67%) had the squamous cell carcinoma subtype; 2 patients (7%) were diagnosed as stage T1N3, 4 patients (13%) as T2N3, 9 patients (30%) as T3N2, 15 patients (50%) as T4N2, and all the T stage were diagnosed by the tumor size; among these 30 patients, 9 patients (30%) undertook mediastinoscopy surgery to be diagnosed as N2 or N3, 11 patients (37%) undertook endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and other 10 patients (33%) were diagnosed as N2 or N3 just by positron emission tomography-CT (PET-CT); 2 patients (7%) received one cycle of treatment, 10 patients (33%) received two cycles of treatment, 16 patients (53%) received three cycles of treatment, and 2 patients (7%) received four cycles of treatment.

Imaging efficacy evaluation of neoadjuvant therapy

According to the RECIST 1.1, among the 30 patients, 21 patients (70%) had a PR (*Figure 1*), 4 patients (13%) had SD, 5 patients (17%) had PD. The ORR was 70.0%, and the DCR was 86.7%. In four patients with tumor progression after treatment, two patients had an enlargement of the primary tumor, one patient had a smaller primary tumor than before treatment but also a new bone metastasis, and one patient had lung metastasis.

Adverse reactions

The adverse reactions of the entire cohort were mainly

Table 1 Baseline characteristics of the patients

Baseline characteristics	Number (of 30 patients), n [%]
Age (years)	
≥60	23 [77]
<60	7 [23]
Gender	
Male	29 [97]
Female	1 [3]
Combined with hypertension	
Yes	14 [47]
No	16 [53]
Combined with diabetes mellitus	
Yes	5 [17]
No	25 [83]
Smoking	
Yes	19 [63]
No	11 [37]
Pathological type	
Adenocarcinoma	10 [33]
Squamous cell carcinoma	20 [67]
Stage	
T1N3	2 [7]
T2N3	4 [13]
T3N2	9 [30]
T4N2	15 [50]
Cycles of therapy	
1	2 [7]
2	10 [33]
3	16 [53]
4	2 [7]

grades 1–2. Only two patients had grade 3 anemia, and no grade 4 adverse reactions were observed (*Table 2*). Most of the adverse reactions were hematological adverse reactions, including three cases of a low leukocyte count, eight cases of a low neutrophil count, one case of a low platelet count, and 17 cases of anemia. Immune-related toxicity was observed in two cases of grade 2 immune pneumonia. The patients' symptoms improved after drug withdrawal and hormone treatment.

Operation details after treatment

Of the 30 patients, 2 patients (7%) were lost due to follow up, 5 patients (17%) showed progression and switched to curative-intent radiotherapy and chemotherapy, 3 patients (10%) had SD and chose non-surgical treatment, 1 patient (3%) experienced a decline in lung function after treatment. The other 19 patients (63%) underwent surgery after neoadjuvant treatment (*Table 3*) and all 19 patients achieved R0 resection. Among the 19 patients undergoing surgery, eight received two cycles of neoadjuvant treatment before surgery, 10 received three cycles of treatment, and one received four cycles of treatment. All the 19 patients had PR radiographically prior to surgery. There were 13 cases of three-port thoracoscopic surgery, three cases of single-port thoracoscopic surgery, and three cases of open surgery. Among the 19 cases, there were 10 cases of simple lobectomy, three cases of sleeve lobectomy, four cases of lobectomy with pulmonary artery lateral wall reconstruction, one case of double-sleeve resection, and one case of left pneumonectomy. The median operation time was 168 minutes (range, 75–295 minutes), and the average intraoperative bleeding was 215.3±258.4 mL. The median postoperative hospital stay was 8 days (range, 4–59 days). Three patients had a postoperative complication. Two patients developed bronchopleural fistulas which were from the staple line, and one patient died of postoperative pulmonary infection. There were no statistically significant differences between the duration of surgery or amount of blood loss of the patients who received two cycles of neoadjuvant therapy and those who received three or four cycles of neoadjuvant therapy (P>0.05).

Postoperative pathological evaluation

Of the 19 surgical patients, 14 achieved an MPR (73.7%), and 9 achieved a pCR (47.4%). In terms of the tumor stage, 17 patients achieved T stage downstaging, and 15 patients achieved N stage downstaging (*Figure 2*). Among the 19 patients who underwent surgery, there were nine patients with T4, of whom five had their tumors down staged to T0, two to T2, and one to T1; there were seven patients with T3, of whom three had their tumors down staged to T0, three to T2, and one to T1; there were two patients with T2, both of whom had their tumors down staged to T0; and there was one patient with T1 who did not have his/her tumor down

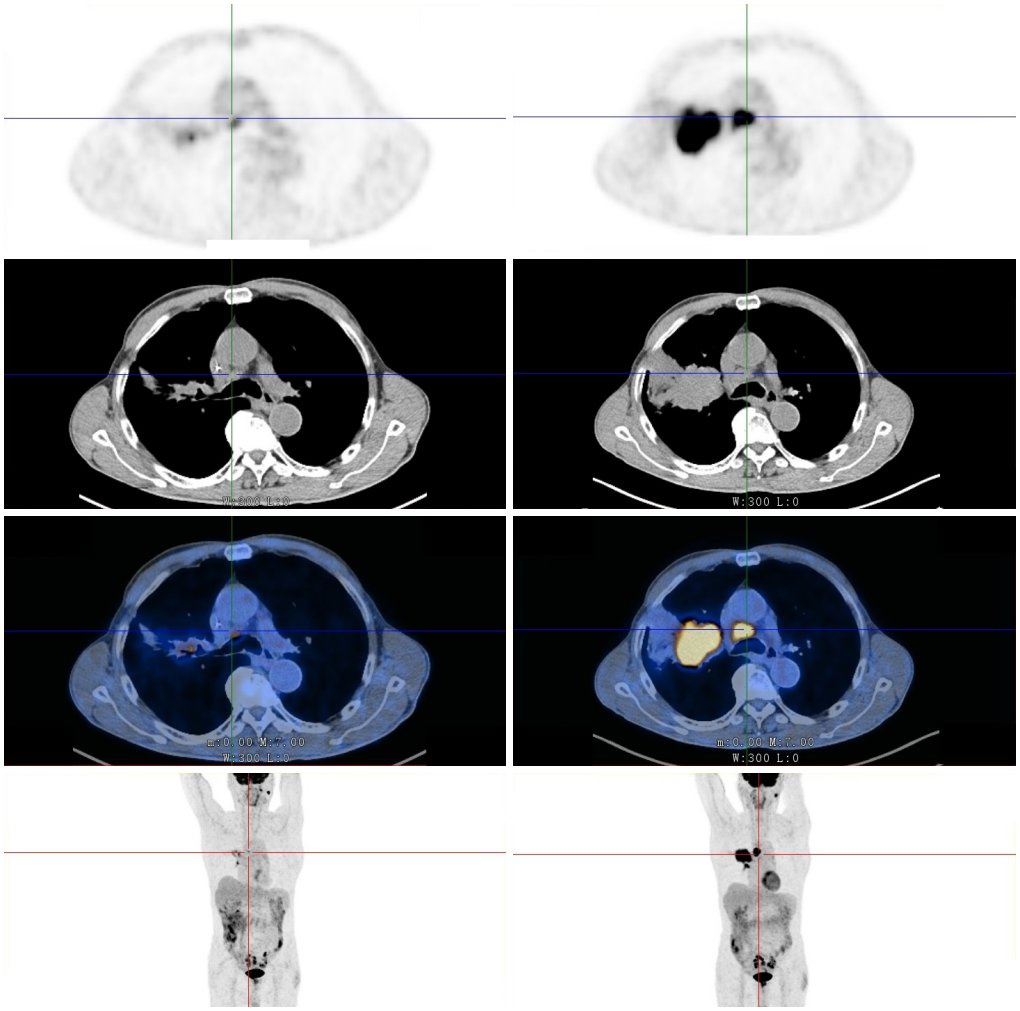

Figure 1 Comparison of PET-CT before and after neoadjuvant treatment in a patient: preoperative PET-CT on the right, showing central lung cancer with atelectasis in the right lung and mediastinal lymph node metastasis; PET-CT on the left after two cycles of neoadjuvant immunotherapy and chemotherapy, showing a significant reduction in the tumor and mediastinal lymph nodes, and a significant reduction in FDG metabolism. PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose.

staged. In terms of N stage, there were three N3 patients, all of whom had their disease down staged to N0; there were 16 patients with N2, of whom 6 patients were single station N2, 8 patients were bilevel N2 and 2 patients were Tri/higher level N2. Among these patients, 11 had their disease down staged to N0, and one to N1, and there were four patients who did not have their disease down staged.

Follow-up results

The median follow-up time of all the patients was 12.3 months. Among the 30 patients, there were 11 patients in the non-surgical group, of whom two patients were lost due to follow up, and five patients showed progression, including two patients with primary lesion progression, two patients with lung metastasis, and one patient with bone metastasis. There were 19 patients in the operation group, of whom three patients showed progression, including one patient with lung metastasis, one patient with liver metastasis, and one patient who died of postoperative lung infection. The median progression-free survival (PFS) of the patients undergoing surgery was significantly better than that of the patients who did not (29 *vs.* 14 months, P=0.007).

Table 2 Adverse reactions in the entire cohort of patients

Adverse reactions	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematological adverse reactions					
Decrease of white blood cell count	27 [90]	3 [10]	0	0	0
Decrease of neutrophil count	22 [73]	8 [27]	0	0	0
Thrombocytopenia	29 [97]	1 [3]	0	0	0
Anemia	13 [43]	13 [43]	2 [7]	2 [7]	0
Other adverse reactions					
Vomiting	26 [87]	3 [10]	1 [3]	0	0
Erythra	24 [80]	6 [20]	0	0	0
Increased transaminase	23 [77]	7 [23]	0	0	0
Immune pneumonia	28 [93]	0	2 [7]	0	0

Data are presented as n [%].

Table 3 Perioperative data of the surgical patients

Variables	Total (n=19)	2 cycles (n=8)	3–4 cycles (n=11)	P
Surgical manner				0.85
Lobectomy	10	4	6	
Lobectomy + vascular sidewall reconstruction	4	1	3	
Sleeve lobectomy	3	2	1	
Double-sleeve resection	1	0	1	
Pneumonectomy	1	1	0	
Surgical approach				0.11
Single-port VATS	3	3	0	
Three-ports VATS	13	5	8	
Open	3	0	3	
Median operation time (min)	168 [75–295]	146 [75–197]	175 [82–295]	0.65
Mean intraoperative bleeding (mL)	215.3±258.4	135.0±77.5	273.6±327.2	0.20
MPR	14	6	8	0.91
pCR	9	3	6	0.46
Median postoperative hospitalization days (days)	8 [4–59]	7.5 [5–9]	13 [4–59]	0.17
Postoperative complications				0.11
BPF	2	0	2	
Pulmonary infection	1	0	1	

Data are presented as number, median [range], or mean ± standard deviation. VATS, video-assisted thoracoscopic surgery; MPR, major pathological response; pCR, pathological complete response; BPF, bronchopleural fistula.

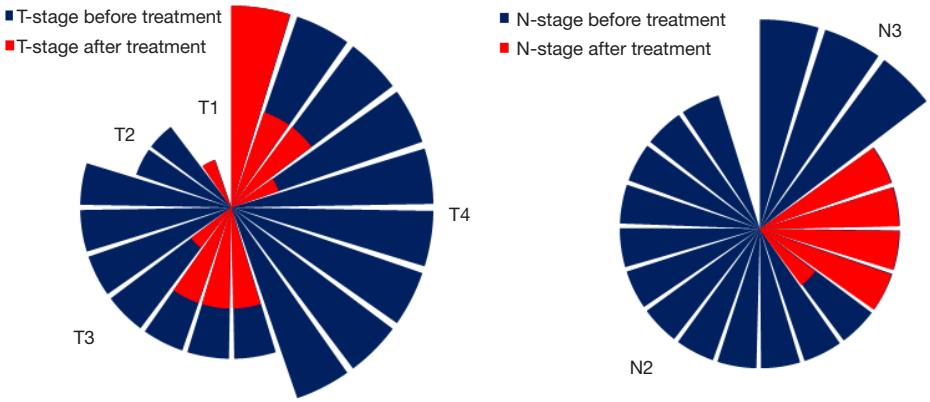

Figure 2 Nightingale rose diagram of the patients' downstaging.

Discussion

Stage-IIIB NSCLC is often considered inoperable due to large tumor size, invasion of adjacent vital organs, and/or distant lymph node metastasis (16). Radical radiotherapy and chemotherapy have been the gold standard for the treatment of stage-IIIB NSCLC. In recent years, the emergence of immunotherapy and the reporting of a large number of research data have brought new perspective regarding the treatment of advanced NSCLC. The PACIFIC research study showed that for stage-III unresectable NSCLC, consolidation therapy with duvalizumab after radical radiotherapy and chemotherapy significantly improved the overall 3-year survival rate of the patients (57.0% *vs.* 43.5%) (7). In terms of neoadjuvant therapy, Forde *et al.* (8) examined 21 patients with stage I–IIIa NSCLC who were treated with two-course nivolumab monotherapy. Among them, 20 patients achieved R0 resection (MPR rate: 45%), and two patients achieved a pCR. The NADIM study (16) was the first clinical trial to research the application of neoadjuvant immunotherapy combined with chemotherapy in the treatment of resectable NSCLC. This study used nivolumab + paclitaxel + carboplatin in the neoadjuvant treatment of patients with stage-IIIA NSCLC. The R0 surgical resection rate was 89%, the MPR rate was 83%, and the pCR rate was 59%, and these rates were significantly improved compared to those achieved by the single immunotherapy neoadjuvant treatment. However, there are little data from clinical studies on neoadjuvant therapy for unresectable stage-IIIB NSCLC patients.

Recently, the First Affiliated Hospital of Guangzhou Medical University conducted a retrospective study of 51 patients with unresectable stage-IIIB NSCLC who received neoadjuvant immunotherapy combined with chemotherapy at the hospital (4). Among them, 31 patients underwent surgical treatment, and had a postoperative MPR rate of 67.8% and a pCR rate of 35.5%. These results preliminarily confirmed the effectiveness and safety of radical surgical treatment after neoadjuvant immunotherapy combined with chemotherapy in patients with unresectable stage-IIIB NSCLC. However, there are still many issues that require further study.

The present study retrospectively analyzed the data of 30 patients with stage-IIIB NSCLC who underwent neoadjuvant immunotherapy combined with chemotherapy at the Department of Thoracic Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University from January 2019 to September 2021. All patients underwent imaging evaluation with PET CT after neoadjuvant treatment, and we observed 21 cases of PR (70.0%), 4 cases of SD (13%), 5 cases of PD (17%) with an ORR of 70.0%, and a DCR of 86.7%. Of the 30 patients, 19 underwent surgery, with a surgical resection rate of 63.3%, and all achieved R0 resection. The postoperative pathological evaluation showed an MPR rate of 73.7% (14/19) and a pCR rate of 47.4% (9/19). This is similar to the results of previous relevant clinical trials, and the effectiveness of neoadjuvant immunotherapy combined with chemotherapy has been verified through the pathological gold standard.

After the PACIFIC study, the improvement in the survival rate of NSCLC patients who undergo immunotherapy has been remarkable, and many oncologists have begun to question whether surgery after treatment is necessary (4). The follow-up results of the present study showed that among the patients who received neoadjuvant

immunotherapy combined with chemotherapy, the median PFS of the surgical patients was significantly better than that of the non-surgical patients (29 *vs.* 14 months, P=0.007). The baseline was different between the two groups of patients; however, the results also indicated that if complete resection is feasible after treatment, surgical treatment is still an effective treatment to improve the survival of patients with stage-IIIB NSCLC.

Current research is still inconclusive as to how many cycles of neoadjuvant immunotherapy combined with chemotherapy should be administered before surgery (17). Most research indicates two to four cycles (5). Of the 19 surgical patients in this study, eight received two cycles of treatment before surgery, 10 received three cycles of treatment before surgery, and one received four cycles of treatment before surgery. The patients who received two cycles of treatment before surgery were compared to those who received three or four cycles of treatment. No significant differences were observed between the two groups in the selection of the surgical methods (resection range, endoscopic, or open), the difficulty of the surgery (surgical time, and intraoperative bleeding volume), the number of days in hospital after surgery, and the incidence of complications. However, the increase in the preoperative application cycles did not improve the MPR or pCR of the patients.

The safety of neoadjuvant immunotherapy combined with chemotherapy is also a matter of concern. Serious immune-related adverse reactions may lead to delayed surgery or loss of surgical opportunity (18,19). In this study, no serious adverse reactions were observed during the treatment of the entire cohort. Only two patients had grade 3 anemia, and the other adverse reactions were grades 1–2. The incidence of adverse reactions related to the treatment was similar to that reported by other retrospective studies in China (5,6).

This study has a number of limitations. First, this study was a retrospective study with a small sample size, so the statistical results might have deviations and/or confounding variables. Prospective randomized controlled studies with larger sample sizes are needed for further validation. Second, there are only 67% of the 30 patients who undertook mediastinoscopy surgery or EBUS-TBNA to be diagnosed as N2 or N3. Over-diagnosis may be present in the other 10 patients. Third, in comparing the prognosis of patients in the surgical group and the non-surgical group, and comparing the perioperative data of patients with two cycles of treatment and three to four cycles of treatment, due to the small sample size, it was not possible to conduct propensity score matching; thus, differences in patients' individual situations or tumor infiltration might have affected the results of the comparison. Fourth, patients with a better response to neoadjuvant immunotherapy combined with chemotherapy had a greater chance of receiving surgery after treatment, which might have affected the comparison of the survival data between the two groups.

Conclusions

In summary, neoadjuvant immunotherapy combined with chemotherapy had significant efficacy in patients with stage-IIIB NSCLC with relatively few adverse reactions, and showed a reasonable safety and effectiveness. While the majority of patients in this study were able to undergo surgery, post neoadjuvant pulmonary resection was associated with a relatively high rate of morbidity and mortality. The long-term effects of patient treatment, optimal number of preoperative neoadjuvant treatment cycles, and postoperative adjuvant treatment options remain to be explored and validated in further large-sample prospective studies.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-908/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-908/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study was approved by the Ethics Committee of the Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China (No. RA-2020-353). Individual consent for this retrospective analysis was waived.

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