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Neoadjuvant therapy in non-small cell lung cancer: Clinical, pathological and translational research

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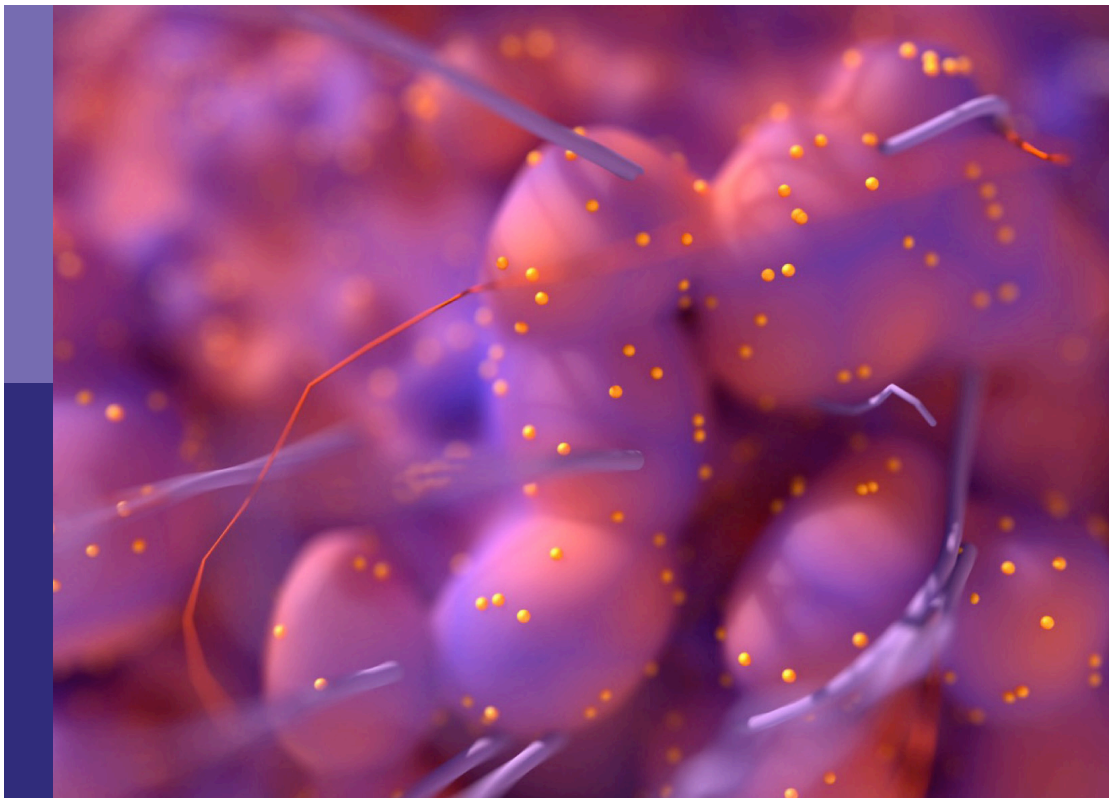

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Neoadjuvant therapy in non-small cell lung cancer: Clinical, pathological and translational research

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Robotic-assisted thoracic surgery following neoadjuvant chemoimmunotherapy in patients with stage III non-small cell lung cancer: A real-world prospective cohort study

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Objective: Stage III non-small cell lung cancer (NSCLC) is a heterogeneous group of diseases. For this subset of patients, clinical management is still under debate and prognosis remains poor so far. In the present study, we aimed to evaluate the feasibility and safety of robotic-assisted thoracic surgery after neoadjuvant chemoimmunotherapy in stage III NSCLC.

Methods: A real-world prospective cohort study was performed in a single-center setting from April 2021 to May 2022. Patients who were diagnosed with resectable or potentially resectable stage IIIA–B NSCLC and received neoadjuvant chemoimmunotherapy followed by robotic-assisted thoracic surgery were enrolled. Pathological response to neoadjuvant chemoimmunotherapy, treatment-related adverse events, and surgical outcomes of these patients were evaluated.

Results: A total of 44 patients who underwent robotic-assisted thoracic surgery after three doses of neoadjuvant chemoimmunotherapy were included in this study. Of these, 36 of 44 (81.8%) patients had a major pathological response, and 26 (59.1%) had a pathological complete response based on pathological examination of surgical specimen. Eight patients (18.2%) suffered grade 3

treatment-related adverse events, including neutropenia (n = 4), increased aminotransferases (n = 3), anemia (n = 1), and cutaneous capillary endothelial proliferation (n = 1). Robotic-assisted thoracic surgery was performed subsequently, and R0 resection was achieved in all patients. Only two (4.5%) patients required conversion to thoracotomy. Surgical complications occurred in five (11.4%) patients, including air leak (n = 3), chylothorax (n = 2), and surgical site infection (n = 1). There was no re-surgery or postoperative mortality within 90 days.

Conclusion: Robotic-assisted thoracic surgery following neoadjuvant chemoimmunotherapy showed good feasibility and safety in stage III NSCLC. It was not associated with unexpected perioperative morbidity or mortality and may be a promising therapeutic option in stage III NSCLC. These results need further confirmation by more large-scale clinical trials.

KEYWORDS

non-small cell lung cancer, neoadjuvant therapy, chemoimmunotherapy, robotic-assisted thoracic surgery, neoadjuvant immunotherapy

Introduction

NSCLC accounts for 80%–85% of all lung cancers worldwide and has become the top killer among cancers (1). Approximately 30% of patients with NSCLC are diagnosed with stage III disease, which represents a potentially curable disease (2). However, clinical prognosis of this subset of patients remains poor with a 5-year overall survival ranging from 13% to 36% (3).

Stage III NSCLC is a heterogeneous group of diseases with varying tumor and nodal statuses, treatment options, and prognosis. Multidisciplinary cooperation and multimodality treatments including radiotherapy, chemotherapy, immunotherapy, and surgical resection are required when dealing with patients with stage III NSCLC (4). Currently, surgical resection with adjuvant therapy is the first option for patients with resectable stage III NSCLC, and surgery plus neoadjuvant therapy is recommended in potentially resectable diseases, while radical concurrent chemoradiotherapy is recommended for those with unresectable diseases. Over the past decades, numerous studies have been conducted using chemotherapeutic agents, radiotherapy, and immune checkpoint inhibitors in stage III NSCLC. Despite survival advantages of neoadjuvant chemotherapy have been confirmed, the 5-year overall survival rate is slightly increased by 5% for patients with stage III NSCLC. In recent years, neoadjuvant immunotherapy with immune checkpoint inhibitors, combined with chemotherapy or not, has shed new light to this subpopulation (5). However, it also brings challenges including immune-related adverse events, surgical delay, increased surgical complexity, and conversion to thoracotomy. Therefore, there is an urgent need for exploring more effective multimodality therapeutic strategies to improve prognosis of patients with stage III NSCLC.

Robotic-assisted thoracic surgery (RATS) is an optional minimally invasive surgical approach for patients with NSCLC. Compared with thoracotomy, RATS offers numerous benefits, including reduced surgical trauma, milder postoperative pain, and less complications. Furthermore, RATS had several advantages over video-assisted thoracoscopic surgery (VATS). The robotic system provided improved three-dimensional vision and advanced instruments with more degrees of motion freedom, higher resolution, and better ergonomics (6). It has been reported that robotic-assisted surgeries were associated with reductions in mortality, length of stay, and complication rates when compared with thoracotomy and VATS (7, 8). However, it is unknown whether RATS might have any potential benefits in pulmonary resection of stage III NSCLC after neoadjuvant chemoimmunotherapy, which usually represents more complex thoracic surgical procedures.

Herein, we investigated the efficacy and safety of a therapeutic strategy combining neoadjuvant chemoimmunotherapy with RATS, through analyzing the real-world data of 44 patients with stage IIIA-B NSCLC who underwent RATS following neoadjuvant chemoimmunotherapy at Xiangya Hospital.

Methods

Study design and participants

This is a real-world prospective cohort study conducted at a tertiary hospital in China from 1 April 2021 to 31 May 2022. The

inclusion criteria of patients were listed as follows: (1) adult NSCLC patients, which was histologically confirmed in tissue; (2) stages IIIA/B eligible for surgery which were evaluated by comprehensive imaging examinations and lung function test; (3) no systemic cancer therapy was received; (4) ECOG performance status score ≤2. Patients who met any of the following criteria were excluded: (1) <18 years old; (2) EGFR or ALK aberrations positive; (3) immunodeficiency diseases, interstitial lung diseases, active hepatitis B, active tuberculosis, and current systemic immunosuppressive therapy with either corticosteroids (>10 mg daily prednisolone equivalent) or other immunosuppressive agents; (4) concurrent solid or hematological malignancies; (5) any previous medical treatment with immune checkpoint inhibitors. A total of 44 treatment-naive patients were diagnosed as resectable or potentially resectable stage III NSCLC by a multidisciplinary team at Xiangya Hospital, received neoadjuvant chemoimmunotherapy, and underwent RATS. This work has been reported in line with the STROCSS criteria (9). This study was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2200057840) and approved by the Institutional Review Board and Ethics Committee of Central South University (202104002).

Therapy procedures

Patients received three cycles of immune checkpoint inhibitors and platinum-based doublet chemotherapy as neoadjuvant treatment before surgical resection. All the drugs were administrated intravenously on day 1 of each 21-day treatment cycle. Before each treatment cycle, laboratory blood tests were routinely performed to monitor blood cell counts and biochemical parameters. After the completion of neoadjuvant chemoimmunotherapy, patients underwent a standard preoperative staging workup to assess the feasibility of surgical resection, including contrast-enhanced computed tomography (CT) scan of the chest, (18)F-fluorodeoxyglucose positron emission tomography/CT scan, brain imaging with magnetic resonance imaging or CT, and bronchoscopy examination before surgery. Subsequently, resection of the primary tumor and lymph nodes was completed by using the da Vinci surgical system (Intuitive Surgical, California, USA) according to standard institutional procedures.

Pathological response assessments

Pathological responses of patients were used to evaluate the efficacy of neoadjuvant chemoimmunotherapy. Surgical samples of primary tumor from lung and lymph nodes were examined in the Department of Pathology and staged according to the criteria of the American Joint Committee on Cancer (the eighth edition). Percentages of residual viable tumor cells were determined by routine hematoxylin and eosin staining. Major pathological response (MPR) was defined as no more than 10% viable tumor cells remaining in the primary tumor on postoperative pathologic review. Incomplete pathological response (IPR) was defined as the presence of more than 10% viable tumor cells in the primary tumor. Pathological complete response (pCR) was defined as no viable tumor cells remaining in the resected lung cancer specimen and all sampled regional lymph nodes (10–12).

Clinical data collection

Data of demographic information, clinical characteristics, histology subtypes, neoadjuvant treatment regimens, pathological responses, surgical details, and perioperative outcomes were extracted from medical records of patients. Postoperative 30- and 90-day mortality was obtained by routine monthly follow-up after surgery. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, V5.0). Surgical complications were defined according to the Society of Thoracic Surgeons database criteria. For all clinical data in this study, continuous variables were expressed as median and interquartile ranges. Categorical variables were expressed as numbers and percentages.

Results

Baseline characteristics of patients

As shown in Table 1, a total of 44 patients diagnosed as stage III NSCLC were included in this study. Their ages ranged from 35 to 70 years (median age: 61.5 years). Among these patients, 33 (75.0%) were men and 33 (75.0%) were current or former smokers. Forty-one of 44 (93.2%) patients had ECOG performance status score ≤1. Preoperative FEV1% predicted ranged from 60% to 100% (median FEV1% predicted: 85%). Overall, 61.4% of them were confirmed as stage IIIA and 38.6% as stage IIIB at baseline. A total of 33 (75.0%) patients were diagnosed as squamous cell carcinoma, while 10 (22.7%) were adenocarcinoma and one (2.3%) was adenosquamous carcinoma by preoperative tumor biopsy. There were six kinds of PD-1 inhibitors used for neoadjuvant therapy, including nivolumab (n = 20), camrelizumab (n = 8), toripalimab (n = 6), tislelizumab (n = 4), sintilimab (n = 4), and pembrolizumab (n = 2). Detailed baseline characteristics of each patient are shown in Supplementary Table 1.

TABLE 1 Baseline characteristics of patients and pathological responses to neoadjuvant chemoimmunotherapy.

Characteristics	Median (IQR) or n (%)
Age, years	61.5 (54-65)
Male	33 (75.0)
Smoking history	
Non-smoker	11 (25.0)
Former or current smoker	33 (75.0)
ECOG PS score	
0	27 (61.4)
1	14 (31.8)
2	3 (6.8)
FEV1% predicted	85% (75-90%)
Clinical stage	
IIIA	27 (61.4)
IIIB	17 (38.6)
Histologic subtype	
Squamous cell carcinoma	33 (75.0)
Adenocarcinoma	10 (22.7)
Others	1 (2.3)
Neoadjuvant chemoimmunotherapy	
ICI types	
Nivolumab	20 (45.5)
Camrelizumab	8 (18.2)
Toripalimab	6 (13.6)
Tislelizumab	4 (9.1)
Sintilimab	4 (9.1)
Pembrolizumab	2 (4.5)
Chemotherapy regimens	
TC	31 (70.5)
TP	6 (13.6)
PC	5 (11.4)
TL	2 (4.5)
Pathological response	
MPR	36 (81.8)
pCR	26 (59.1)

PS, performance status; Scc, squamous cell carcinoma; Ade, adenocarcinoma; ICI, immune checkpoint inhibitors; TC, paclitaxel plus carboplatin; TP, paclitaxel plus cisplatin; PC, pemetrexed plus carboplatin; TL, paclitaxel plus lobaplatin; pCR, pathological complete response; MPR, major pathological response; IQR, interquartile range which describes the middle 50% of values when ordered from lowest to highest; FEV1, forced expiratory volume in one second.

Pathological response to neoadjuvant chemoimmunotherapy and treatment-related adverse events

All patients received three cycles of neoadjuvant immunotherapy plus platinum-based doublet chemotherapy before surgery. In total, 36 (81.8%) of 44 patients who underwent surgery had an MPR and 26 (59.1%) had a pCR (Table 1). Representative radiological and histological images of case 7, who achieved pCR after neoadjuvant chemoimmunotherapy, are shown in Figure 1. Regression in the tumor area with viable tumor cells in surgical specimen of these patients is summarized in Figure 2. Overall, 83% of patients suffered treatment-related adverse events of any grade after neoadjuvant chemoimmunotherapy (Table 2). Only eight patients (18.2%) presented grade 3 adverse events, including neutropenia (n = 4), increased aminotransferases (n = 3), anemia (n = 1), and cutaneous capillary endothelial proliferation (n = 1). No grade 4 or 5 adverse events were observed. The most common treatment-related adverse events included neutropenia (29.6%), increased aminotransferases (20.4%), anemia (18.2%), neurotoxic effects (18.2%), rash (13.6%), fatigue (11.4%), and decreased appetite (11.4%).

Surgical outcomes of patients undergoing RATS after neoadjuvant chemoimmunotherapy

Surgical outcomes are summarized in Table 3. All 44 patients underwent RATS after neoadjuvant chemoimmunotherapy. R0 resection was performed in all patients, and neoadjuvant chemoimmunotherapy did not delay planned surgery. Lobectomy, bilobectomy, sleeve lobectomy, and pneumonectomy were performed in 39, two, two, and one patient, respectively. Adhesion, fibrosis, edema, and microbleeds in the chest were commonly observed during surgery (Figure 3). A surgical video for case 7 was attached as supplementary materials to show more details of RATS procedures. The median surgical time of these patients was 191 min (interquartile ranges: 150–235 min). The median estimated blood loss was 100 ml (interquartile ranges: 50–150 ml). Only two (4.5%) required conversion to thoracotomy. Surgical complications occurred in five (11.4%) patients, including air leak (n = 3), chylothorax (n = 2), and surgical site infection (n = 1). The median postoperative length of stay was 6.5 days. No patient died within 30 or 90 days after surgery. Detailed surgical outcomes of each patient are shown in Supplementary Table 2.

Discussion

In this study, we investigated the feasibility and safety of RATS after neoadjuvant chemoimmunotherapy in stage III NSCLC, which has not been well defined in previous studies. Our data support that neoadjuvant chemoimmunotherapy followed by RATS may be a promising therapeutic approach with a high pCR rate and low incidence of conversions and surgical complications for patients with stage III NSCLC.

Neoadjuvant therapy is an effective approach for patients with stage III NSCLC to increase resectability and extend survival (13). While meta-analyses of neoadjuvant chemotherapy revealed a significant survival advantage (HR = 0.87, P = 0.007) over surgery alone, only 22% of patients with stage I–IIIA NSCLC who received neoadjuvant chemotherapy achieved MPR, and 4% achieved pCR (10, 14). Encouragingly, neoadjuvant immunotherapy with immune checkpoint inhibitors has shed new light to resectable NSCLC, with an MPR rate ranging from 21% and 45%, acceptable toxicity, no delay in surgery, and no increase in operative mortality (15–17, 18). Recently, the efficacy and safety of neoadjuvant chemoimmunotherapy has been demonstrated by a series of clinical trials. In patients with resectable NSCLC in stages

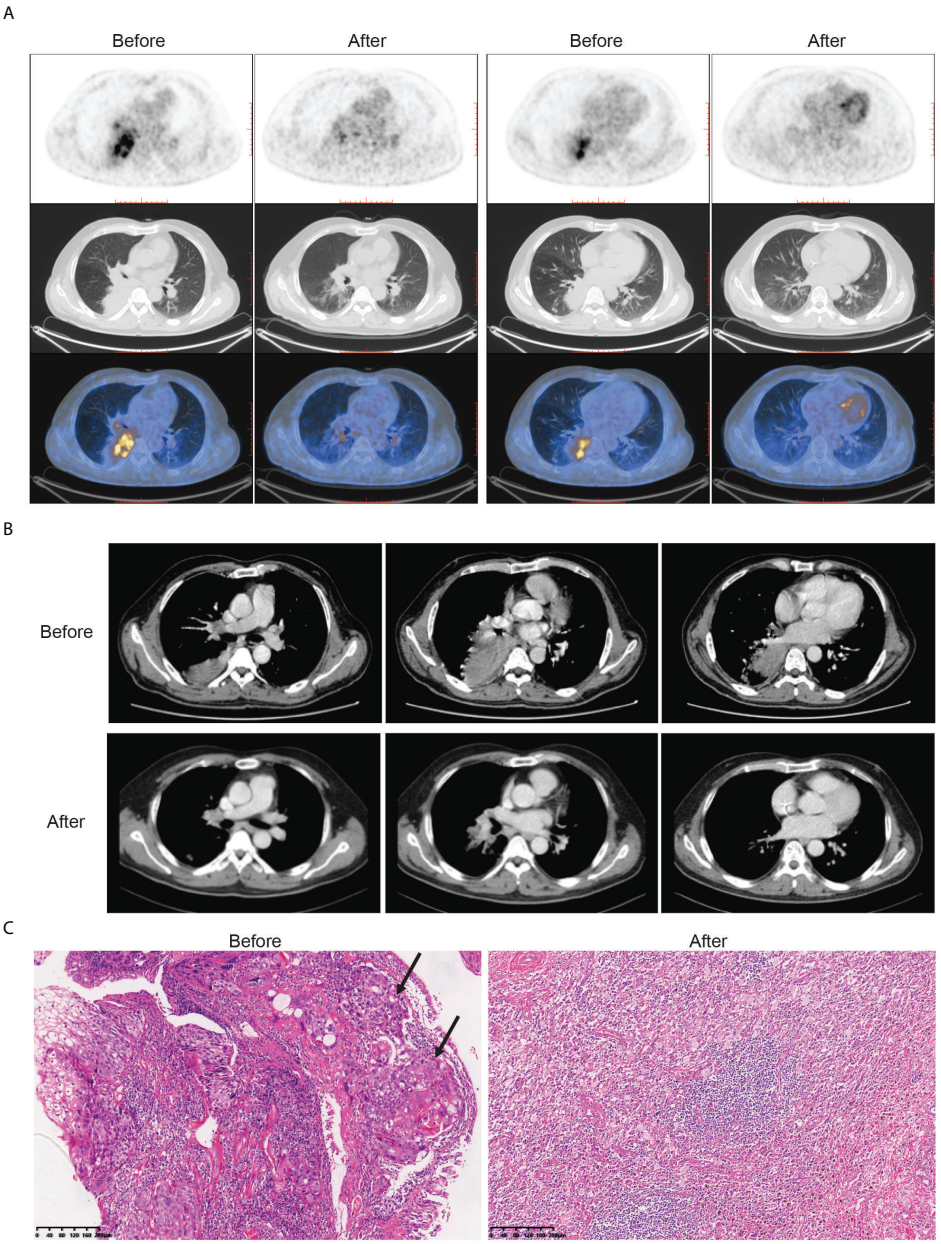

FIGURE 1
Radiological findings, and histological images in one patient (case 7) with stage III NSCLC who underwent robotic-assisted thoracic surgery following neoadjuvant chemoimmunotherapy. Case 7 had a pathological complete response to neoadjuvant chemoimmunotherapy. **(A)** Representative (18)F-fluorodeoxyglucose positron emission tomography/computed tomography before and after neoadjuvant chemoimmunotherapy. **(B)** Representative chest computed tomography imaging before and after neoadjuvant chemoimmunotherapy. **(C)** Histological examinations of pretreatment tumor biopsy and posttreatment resected tumor specimen by hematoxylin and eosin staining. Poorly differentiated tumor cells (black arrow) were observed before neoadjuvant chemoimmunotherapy, which was replaced by fibrotic, elastostatic, and necrotic tissue mixed with inflammatory cell infiltration afterward. Scale bar = 200 μm.

I–III, neoadjuvant atezolizumab plus chemotherapy led to an MPR rate of 50% and a pCR rate of 21.4% without surgical delay. Downstaging of nodal status was confirmed in 69% of patients with N2 at baseline after neoadjuvant therapy (19). In the NADIM trial (11), neoadjuvant nivolumab and chemotherapy were given to patients with stage IIIA resectable NSCLC. Remarkably, the results showed that 85% of patients had MPR, 71% had pCR, and 90% of patients achieved pathological downstaging of the clinical disease stage before surgery, with no surgical delay reported. The overall survival at 24 months was 100% in

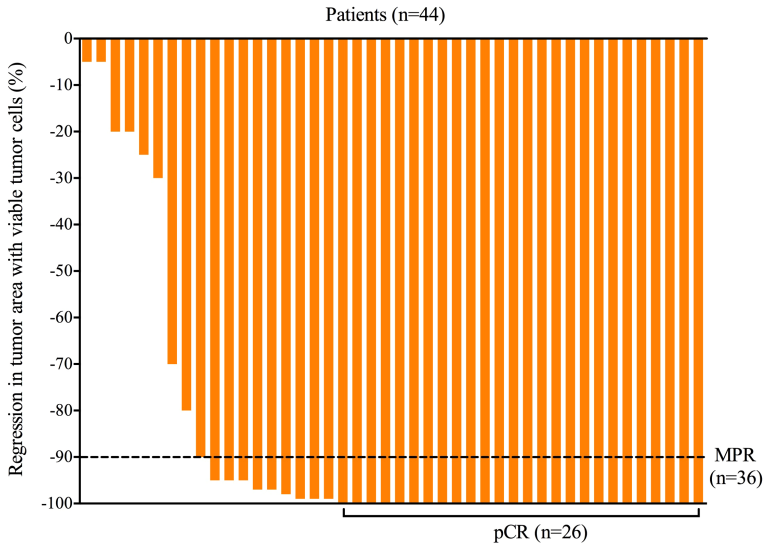

FIGURE 2
Regression in tumor area with viable tumor cells in surgical specimen of all patients after neoadjuvant chemoimmunotherapy. MPR, major pathological response; pCR, pathological complete response.

patients who achieved an MPR or pCR after neoadjuvant chemoimmunotherapy, and progression-free survival in patients with a pCR was significantly higher than that in patients with an IPR or MPR. Furthermore, updated research data from the CheckMate 816 trial (an ongoing phase 3 multicenter randomized controlled trial) strongly demonstrated the advantages of neoadjuvant chemoimmunotherapy over chemotherapy alone in NSCLC (20). Besides, several small-scale clinical studies also supported the efficacy and safety of neoadjuvant chemoimmunotherapy in a Chinese population with resectable NSCLC (21–23). Therefore, preoperative immunotherapy combined with chemotherapy is believed to represent a promising therapeutic option to increase resectability and improve the prognosis of NSCLC.

TABLE 2 Treatment-related adverse events of neoadjuvant chemoimmunotherapy.

Adverse events, n (%)	Grade 1-2	Grade 3
Neutropenia	9 (20.5)	4 (9.1)
Increased aminotransferases	6 (13.6)	3 (6.8)
Anemia	7 (15.9)	1(2.3)
Neurotoxic effects	8 (18.2)	0
Rash	6 (13.6)	0
Fatigue	5 (11.4)	0
Decreased appetite	5 (11.4)	0
Arthralgia	4 (9.1)	0
Thrombocytopenia	4 (9.1)	0
Alopecia	3 (6.8)	0
Hiccup	3 (6.8)	0
Constipation	3 (6.8)	0
Hyperthyroidism	3 (6.8)	0
Nausea	2 (4.5)	0
Oral ulcer	2 (4.5)	0
Hypothyroidism	1 (2.3)	0
Hyperglycemia	1 (2.3)	0
Headache	1 (2.3)	0
Cutaneous capillary endothelial proliferation	1 (2.3)	1 (2.3)

In this study, we concentrated on exploring an effective and safe therapeutic strategy for patients in stage III NSCLC, which encompasses a variety of local invasion and nodal involvement. Till today, clinical management of stage III NSCLC is still under debate. Our data consistently showed that neoadjuvant chemoimmunotherapy achieved a high MPR rate of 81.8% and a pCR rate of 59.1% in patients who were diagnosed with stage IIIA–B NSCLC and underwent surgery, with well-tolerable toxicity. Moreover, combination of immunotherapy and chemotherapy did not cause surgical delay despite increasing incidence of grade 1–2 treatment-related adverse events. Together with results from previous clinical trials, our data consistently support that neoadjuvant chemoimmunotherapy outperforms neoadjuvant chemotherapy or immunotherapy alone in pathological response without increasing surgical delay or severe adverse events, which may further improve the long-term prognosis of stage III NSCLC. It is noteworthy to mention that the pathological response to neoadjuvant chemoimmunotherapy in the NADIM trial (11) and our study, which focused on stage III NSCLC, was markedly better when compared with the NCT02716038 and CheckMate 816 trials which enrolled patients in stage I–III diseases [15, 16]. More large-scale clinical trials are required to confirm this phenomenon and investigate the potential mechanisms.

TABLE 3 Surgical outcomes of patients undergoing robotic-assisted resection after neoadjuvant chemoimmunotherapy.

Outcomes	Median (IQR) or n (%)
R0 resection	44 (100)
Incidence of surgical delay	0
Extent of resection	
Lobectomy	39 (88.6)
Sleeve lobectomy	2 (4.5)
Bilobectomy	2 (4.5)
Pneumonectomy	1 (2.3)
Surgical time (min)	191 (150-235)
Estimated blood loss (mL)	100 (50-150)
Conversion to thoracotomy	2 (4.5)
Intraoperative transfusion	3 (6.8)
Re-surgery	0
Surgical complications	5 (11.4)
Air leak	3 (6.8)
Chylothorax	2 (4.5)
Surgical site infection	1 (2.3)
Postoperative length of stay (days)	6.5 (5-8)
30-day mortality	0
90-day mortality	0

IQR, interquartile range which describes the middle 50% of values when ordered from lowest to highest.

As an option for minimally invasive thoracic surgery, RATS has shown at least comparable perioperative outcomes to those achieved by VATS in NSCLC (7, 8). Besides, a recent study further showed that robotic-assisted thoracic surgery was more cost-effective than open thoracotomy (24). Previously, the feasibility and safety of RATS in NSCLC have been demonstrated, especially for patients with a pathologic N2 disease (25). However, the safety and feasibility of RATS after neoadjuvant chemoimmunotherapy in stage III NSCLC remain unclear. Thus, RATS was attempted in this study for patients with stage III NSCLC after three doses of neoadjuvant chemoimmunotherapy in order to combine the advantages of these two therapeutics. R0 resection was achieved in all 44 patients, and the median surgical time of RATS (191 min) was similar to other surgical approaches (184 min) as reported in the CheckMate 816 trial (26). Only five (11.4%) patients had surgical complications, and no re-surgery or postoperative 90-day death event occurred. Our data support that RATS following neoadjuvant chemoimmunotherapy is safe and feasible in stage III NSCLC.

The risk of conversion to thoracotomy due to technical difficulties and serious intraoperative complications has been worrying for patients receiving neoadjuvant chemoimmunotherapy, especially for those with stage III NSCLC. In recent years, increasing amounts of studies have reported that neoadjuvant immunotherapy can cause significant adhesions, edema, and fibrosis in the chest that may increase surgical complexity and risk of conversion, which is particularly the case in patients with a significant treatment response (13). In 2017, Chaft and his colleagues (27) firstly described that dense fibrosis occurred after neoadjuvant T-cell checkpoint inhibitors in a series of NSCLC patients. In the TOP1201 trial, 12 patients with NSCLC were treated with preoperative chemotherapy and ipilimumab followed by VATS, and three of 12 (25%) converted VATS to open thoracotomy (28). Among 13 patients who attempted VATS or the robotic approach after three cycles of neoadjuvant nivolumab in the CheckMate159 trial (29), seven (54%) required conversion to thoracotomy, and the conversion rate was even higher (71%) in stage IIB/IIIA cases. Encouragingly, in the present study, only two out of 44 (4.5%) patients required conversion to thoracotomy due to massive bleeding during the process of RATS. It appeared to be lower than the conversion rate (11%) of patients receiving neoadjuvant chemoimmunotherapy in the CheckMate 816 trial. Therefore, RATS may be advantageous for reducing the conversion rate in stage III NSCLC based on our results.

There are several limitations in our study. First of all, this is a single-center real-world prospective cohort study, and the sample size is relatively small. Thus, the intrinsic heterogeneity of patients was unavoidable. Moreover, the single-arm design of this study does not allow us to compare the efficacy and safety of robotic and non-robotic surgical treatment stage III NSCLC, which presents an interesting line of inquiry for future studies. Second, long-term survival outcomes of these patients have not been evaluated yet.

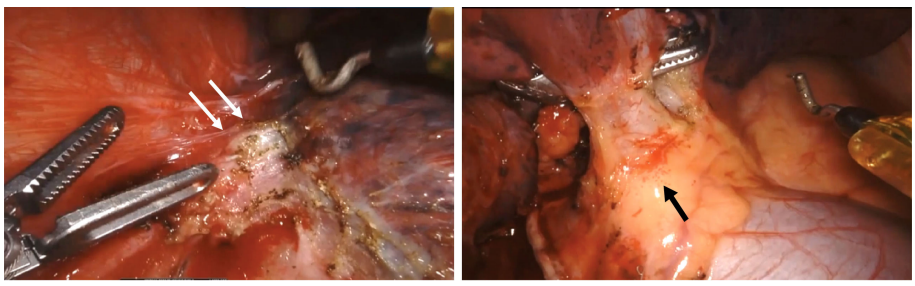

FIGURE 3
Representative intraoperative views of one patient (case 7) during robotic-assisted thoracic surgery. It showed adhesion and fibrosis (white arrow), edema, and microbleeds (black arrow) in the chest after neoadjuvant chemoimmunotherapy.

Third, we calculated the MPR and pCR rates in the total number patients who underwent surgery rather than the intention-to-treat population, which may affect the direct comparison of pathological response between other studies focusing on neoadjuvant chemoimmunotherapy and ours. However, we believe that RATS following neoadjuvant chemoimmunotherapy represents a promising therapeutic option for patients with stage III NSCLC, which requires confirmation in future randomized clinical trials.

Conclusions

RATS following neoadjuvant chemoimmunotherapy is an effective and feasible therapeutic approach in stage III NSCLC. Patients receiving neoadjuvant chemoimmunotherapy in this study had high pathological remission rates, which is superior to neoadjuvant chemotherapy or immunotherapy alone as reported in previous clinical trials. Subsequent RATS showed a low conversion rate and low incidence of perioperative complications. More large-scale randomized studies are needed to further confirm the advantages of this therapeutic approach in stage III NSCLC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by The Institutional Review Board and Ethics Committee of Central South University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: ZL, ML. Supervision, project administration, funding acquisition, and methodology: ZL, ML. Resources and investigation: YG, JJ, DX, YZ, HY, LW, BH, RH. Data collection: JJ, YG, YC, JZ. Data analysis: YG, JJ. Data interpretation: ML, ZL, YG, JJ; manuscript writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.969545/full#supplementary-material

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Case report: Major pathologic response induced by neoadjuvant treatment using BRAF and MEK inhibitors in a patient with stage IIIA lung adenocarcinoma harboring BRAF V600E-mutation

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Targeted therapy has achieved great success in advanced non-small lung cancer (NSCLC) with driver genes, and neoadjuvant-targeted therapy is increasingly being investigated. Although neoadjuvant-targeted therapy with EGFR-TKI and ALK-TKI showed good efficacy, there is no report of neoadjuvant-targeted therapy to BRAF V600E mutation on NSCLC so far. Here, we report the first case of a successful neoadjuvant-targeted therapy with BRAF and MEK inhibitors followed by radical surgical excision with major pathologic response (MPR) in a patient with stage IIIA lung adenocarcinoma (LUAD) harboring BRAF V600E mutation. The case informs us that targeted therapy with BRAF and MEK inhibitors could be administrated as a neoadjuvant strategy for selected cases of NSCLC harboring BRAF V600E mutation.

KEYWORDS

lung cancer, BRAF V600E mutation, neoadjuvant, targeted therapy, major pathologic response

Introduction

The emergence of targeted therapy and immunotherapy has brought about revolutionary changes in the treatment of non-small lung cancer (NSCLC). As for NSCLC with driver genes, the efficacy of immunotherapy is poor; targeted therapy is still the mainstream treatment option. The clinical success of targeted therapy in

patients with advanced NSCLC has also prompted an assessment of their efficacy in the neoadjuvant setting. BRAF mutation is recognized as driver mutation in NSCLC and has been reported in 1%–5% of NSCLC cases, with the BRAF V600E mutation present in 50% of these cases (1). Due to the rarity of this mutation, the neoadjuvant treatment to BRAF V600E mutation is less investigated compared with EGFR-TKI and ALK-TKI. Published data on the efficacy of neoadjuvant-targeted therapy to BRAF V600E mutation in the treatment of malignancy is limited, especially NSCLC. Herein, we report the first rare case of successful neoadjuvant-targeted therapy with BRAF and MEK inhibitors followed by radical surgical excision with major pathologic response in a patient with stage IIIA lung adenocarcinoma harboring a BRAF V600E-mutant.

Case report

A non-smoking 56-year-old man was presented with cough in September 2021; family history, physical examination, and laboratory studies have no positive findings. PET-CT revealed a nodule in the upper left lung (23 mm × 19 mm), accompanied by enlargement of multiple lymph nodes of the left lung hilum as well as mediastinum (4L, 5, 6) (Figure 1). Magnetic resonance imaging (MRI) of the brain was negative for metastatic disease. Computed tomography (CT)-guided percutaneous transthoracic needle biopsy of the nodule was performed, and pathological analysis and multiple-gene test (26 genes panel) showed lung adenocarcinoma with BRAF V600E (abundance 24.39%) and a TP53 mutation (abundance 21.16%); the sample was negative for oncogenic alterations in EGFR, ALK, ROS1, KRAS, MET, and RET. The PD-L1 tumor proportion score (TPS) was 90% (Dako 22C3). Therefore, the patient was diagnosed with an AJCC 8th stage IIIA (cT1cN2M0) primary left lung adenocarcinoma harboring BRAF V600E and PD-L1 TPS 90%+ after a complete initial evaluation.

After diagnosis, the patient initiated treatment with orally dabrafenib 150 mg twice daily in combination with orally trametinib 2 mg daily. Five days later, the patient experienced recurrent episodes of pyrexia which were due to community-acquired pneumonia and maybe therapy-related. The pyrexia was managed by the use of antibiotics and temporary drug dose interruption; the pyrexia resolved 10 days after the use of antibiotics and drug dose interruption. Chest CT demonstrated significant improvement of pneumonia; the patient restarted the bi-targeted therapy with the same dose 2 weeks after the interruption. The cough improved quickly and finally resolved. Two months later, at the first radiological assessment, his chest CT scan showed partial remission (PR) (Figure 2). The patient underwent robotic surgery of left upper lobectomy and systematic lymphatic dissection was performed, the surgery procedure was smooth, and the patient was discharged without complications 4 days after the operation. Postoperative pathological analysis showed major pathologic response for the tumor (Figure 3), and all 14 lymph nodes resected (station 4L, 5, 7, 10, 11, 12) (Figure 4) were negative. Postoperative adjuvant treatment with dabrafenib and trametinib was prescribed 1 month after surgery. The therapeutic process is shown in Figure 5. During the disease course, he only experienced aforementioned pyrexia, which lasted 10 days and resolved with use of antibiotics and the temporary interruption of bi-targeted therapy. No other toxic side effects were observed. The patient currently remains in good condition and complete remission at 3 months after surgery. The case presented here supports the use of neoadjuvant treatment with BRAF inhibitors in local advanced non-small lung cancer with BRAF V600E mutation. Our study received approval from the ethics committee of the second Xiangya Hospital, Central South University. The patient also provided written informed consent to publish this case report details.

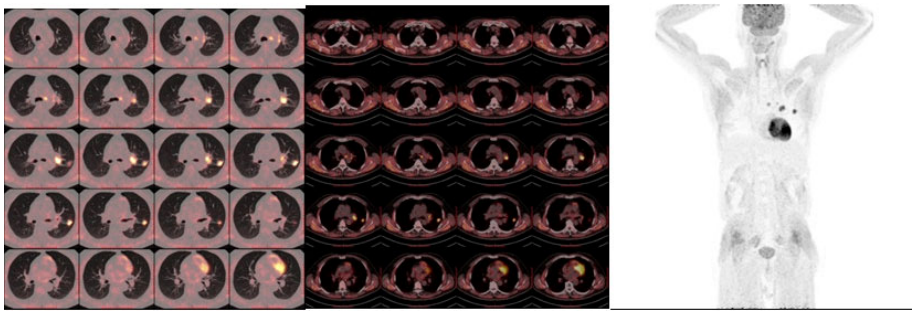

FIGURE 1
PET-CT at baseline 1 month before dabrafenib/trametinib treatment. PET-CT scan of the chest at baseline prior to dabrafenib plus trametinib therapy demonstrated a nodule in the upper left lung with elevated uptake of 18F-fluorodeoxyglucose (FDG), accompanied by enlargement of multiple lymph nodes of the left lung hilum as well as mediastinum (4L, 5, 6). No other lesions with elevated uptake of 18F-FDG were found.

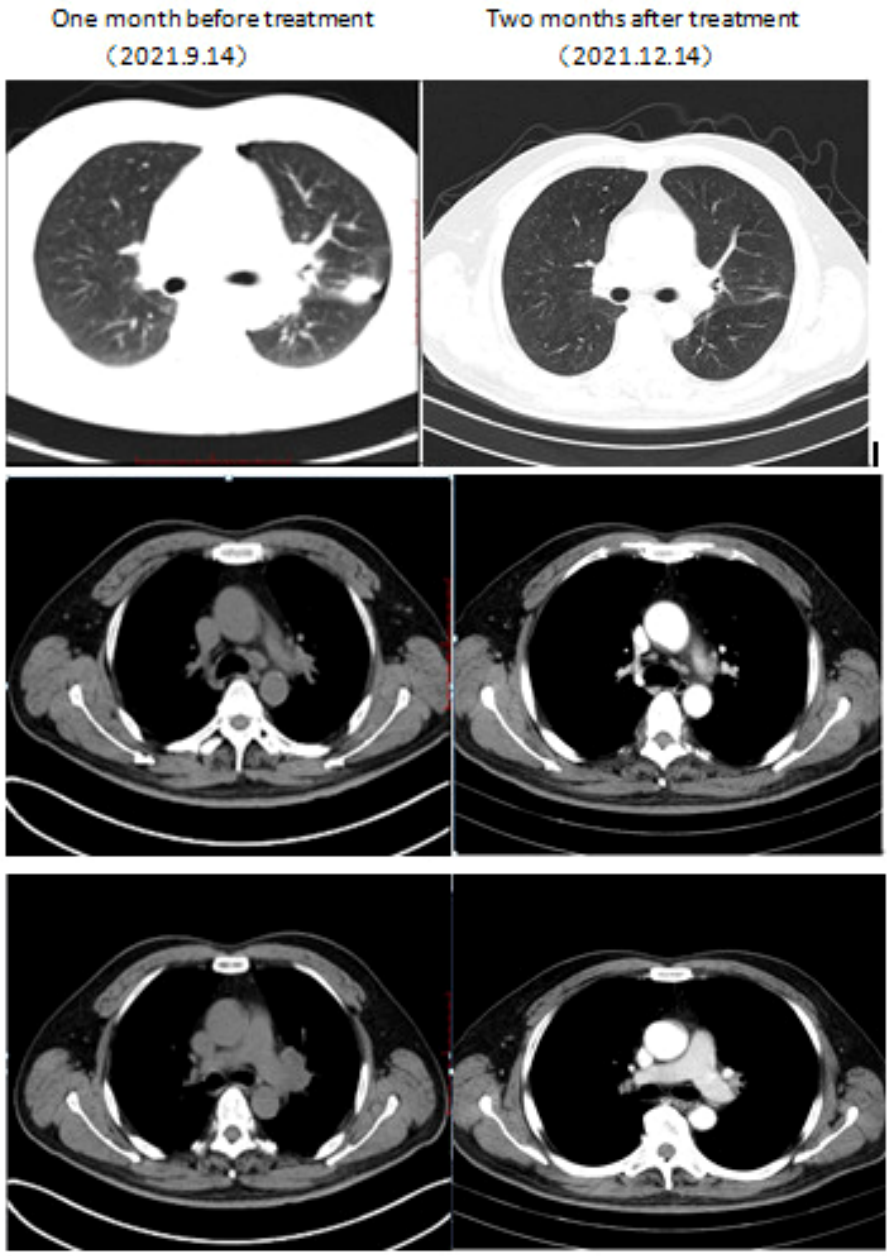

FIGURE 2
Computed tomography imaging showed initial response to combination of dabrafenib and trametinib. Left column: CT scan of the chest at baseline 1 month prior to dabrafenib plus trametinib therapy demonstrated a nodule in the upper left lung (lung window) accompanied by enlargement of multiple lymph nodes of the left lung hilum as well as mediastinum (mediastinal window). Right column: CT scan at 2 months after therapy demonstrated a marked response with a significant decrease in the nodule, left lung hilum, and mediastinum.

Discussion

BRAF mutations are detected in 3%–8% of LUAD (2). The BRAF V600E mutation test is recommended for all patients with newly diagnosed advanced LUAD (3). Based on the results of a phase II clinical trial for patients with BRAF V600E–mutated NSCLC (NCT01336634), the U.S. Food and Drug Administration (FDA) has approved the combination therapy of BRAF inhibitor dabrafenib and the MEK1/2 inhibitor trametinib for treatment of advanced NSCLC patients with BRAF-V600E mutation, regardless of previous therapies (1, 4–6). In the trial, in cohorts for pretreated and

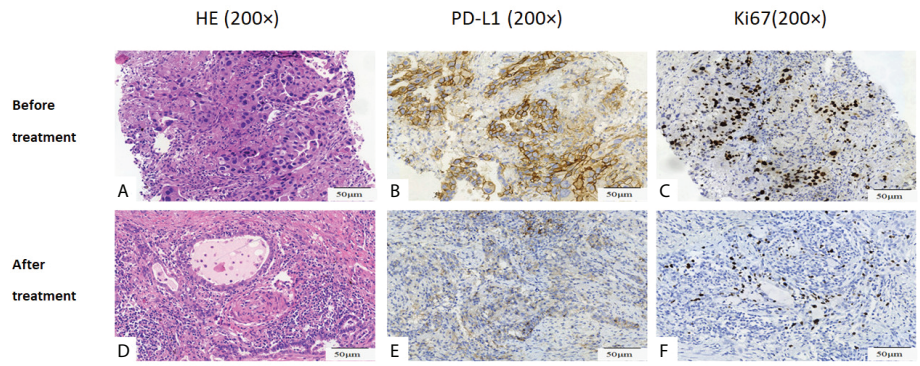

FIGURE 3
Histopathological assessment of tumor regression. **(A-C)** Pathological picture prior to dabrafenib plus trametinib therapy. **(D-F)** Pathological picture post dabrafenib plus trametinib therapy. **(A)** demonstrated moderately differentiated adenocarcinomas. **(D)** demonstrated marked necrosis and massive benign fibrous tissue proliferation with very few residual tumor cells in resected tumor. **(B)** and **(E)** showed PD-L1 90% **(B)** and 5% **(E)** before and after dabrafenib plus trametinib therapy. **(C)** and **(F)** showed Ki67 35%**(C)** and 1%**(F)** before and after dabrafenib plus trametinib therapy. Original magnification: **(A–F)**: ×200.

treatment-naive patients, the ORR of the combination therapy was 63% and 64% and the median PFS was 9.7 and 10.9 months; the recent updated 5-year overall survival rates were 19% and 22%, respectively.

Neoadjuvant-targeted therapy with EGFR-TKI and ALK-TKI has got promising preliminary results (7, 8). Like neoadjuvant EGFR-TKI and ALK-TKI therapy, the combination therapy of dabrafenib and trametinib also showed promising potential for neoadjuvant therapy in a series of malignancy, such as melanoma, anaplastic thyroid carcinoma, and papillary craniopharyngioma (9–12). However, no such case of successful neoadjuvant therapy with combination therapy of dabrafenib and trametinib has been reported in NSCLC so far.

Here we presented a case of stage IIIA (cT1cN2M0) primary left lung adenocarcinoma harboring BRAF V600E mutation. The patient had an excellent response to preoperative treatment with BRAF/MEK inhibitors and obtained MPR after surgery. To our knowledge, the MPR achieved with the use of BRAF/MEK inhibitors has not been previously reported in the literature of

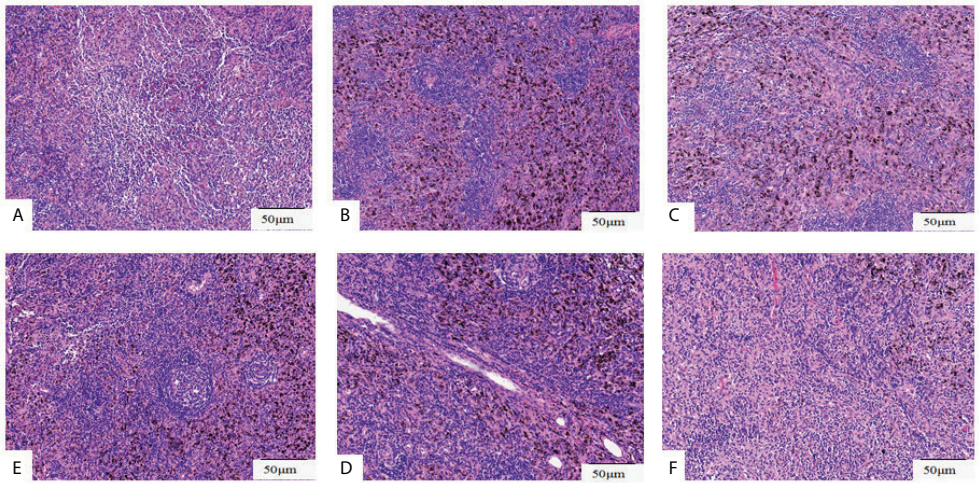

FIGURE 4
Histopathological assessment of lymph nodes resected. Pathological pictures of lymph nodes station 4L**(A)**, station 5**(B)**, station 7**(C)**, station10 **(D)**, station 11**(E)**, station 12**(F)**. Original magnification: **(A-F)**: ×200.

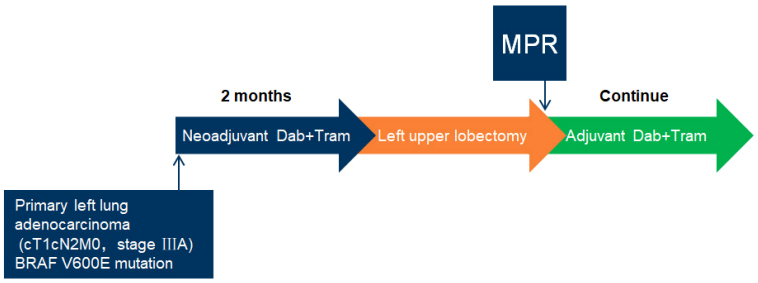

FIGURE 5
Brief summary of the therapeutic process.

NSCLC. The impressive response suggests that presurgical targeted therapy may be combined with surgery to achieve long-term survival in NSCLC with BRAF V600E mutation. Moreover, immunohistochemical results demonstrated that the expression of both PD-L1 and Ki67 decreased significantly after the use of BRAF/MEK inhibitors. Ki67 is a well-known cell proliferation mark for many tumor types including NSCLC; its decrease suggested that BRAF/MEK inhibitors harmed the proliferation capacity of NSCLC cells. A study showed that PD-L1 in some tumor cells would be downregulated at the beginning of BRAF/MEK inhibition and be upregulated after acquiring resistance to the treatment (13). Another study demonstrated in human colon cancer cell endogenous or exogenous BRAF V600E mutant vs. wild-type BRAF could increase PD-L1 messenger RNA (mRNA) and protein expression that was attenuated by MEK inhibition (14). The change of PD-L1 expression in the present case is consistent with these studies.

The role of immunotherapy in BRAF-mutated NSCLC patients is not established; clinical evidence of immunotherapy efficacy in such patients is only retrospective. In a study, BRAF-mutant NSCLC is associated with a high level of PD-L1 expression (15); the present patient who has a high expression of PD-L1 with TPS 90%+ is consistent with the study. Several retrospective studies demonstrated that the efficacy of immunotherapy in BRAF-mutated NSCLC patients is comparable to those observed in the unselected NSCLC population (15–17). A multinational retrospective study demonstrated that the objective response rate (ORR) of NSCLC harboring a BRAF mutation treated with immune checkpoint inhibitor (ICI) monotherapy is only 24%; median PFS was only 3.1 months (18). ICI monotherapy for NSCLC with driver genes including BRAF V600E mutation is unsatisfactory, so it is widely recommended that NSCLC with driver gene mutation should receive targeted therapies and chemotherapy before considering immunotherapy as a single agent (4, 18). The Checkmate 816 trial indicated a significantly higher pathological complete response rate of neoadjuvant immunochemotherapy than of neoadjuvant chemotherapy alone (odds ratio, 13.9). The trial included NSCLC with stage IB to IIIA and excluded EGFR or ALK mutation; it did not exclude BRAF V600E mutation, but there is no report about the efficacy of neoadjuvant immunochemotherapy to the BRAF V600E mutation subgroup in the trial. Although there was a NSCLC patient harboring BRAF V600E mutation who achieved pathological complete remission (PCR) after neoadjuvant combination of the PD-1 antibody and chemotherapy in our department, there is no comparative study of the combination with ICI and chemotherapy vs. combination of bi-targeted therapy in advanced/metastatic NSCLC harboring BRAF V600E mutation so far. Thus, which combination is the most effective strategy as neoadjuvant therapy needs further investigation. Regardless, the success of the neoadjuvant bi-targeted therapy for the present patient demonstrated that the combination of dabrafenib and trametinib may be used as neoadjuvant therapy for potential resectable NSCLC with BRAF V600E mutation.

Conclusion

Combination of BRAF and MEK inhibitors may be used as neoadjuvant therapy followed by surgical resection to improve the outcome of local advanced NSCLC patients harboring BRAF V600E mutation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by the ethics committee and institutional review board of the Second Xiangya Hospital, Central South University. The patient provided his written informed consent to publish his case report.

Author contributions

Main contribution: CL collected, analyzed, and interpreted the data and drafted the manuscript; ML and YY collected the materials and prepared the figures. XW performed the surgery and revised the final manuscript. FM and XL conceived and critically revised the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Neoadjuvant Savolitinib targeted therapy stage IIIA-N2 primary lung adenocarcinoma harboring *MET* Exon 14 skipping mutation: A case report

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MET exon 14 skipping mutation (*MET*ex14m) is rare and occurs in approximately 1-4% of all non-small cell lung cancer (NSCLC) patients and approximately 2.8% of resected stage I-III NSCLC patients. Savolitinib is an oral, potent and highly selective type Ib *MET* inhibitor, which has been shown to be promising activity and acceptable safety profile in patients with advanced NSCLC harboring *MET*ex14m. Most recently, many studies have been probing into the feasibility and efficacy of target therapy for perioperative application in NSCLC. Interestingly, there are very few recorded cases of such treatments. Here, we presented that systemic treatment with the *MET* inhibitor savolitinib before surgery could provide the potential to prolong overall survival (OS) of patients with locally advanced potentially resectable NSCLC. A 49-year-old woman was diagnosed with stage IIIA (T2bN2M0) primary lung adenocarcinoma exhibiting a *MET*ex14m by real-time quantitative polymerase chain reaction (RT-qPCR). Given that the tumor load and the size of lymph nodes experienced a significant downstaging after the neoadjuvant treatment of savolitinib with 600mg once a day for 5 weeks, left lower lobectomy and systemic lymphadenectomy were successfully performed. The pathological response was 50% and the final postoperative pathological staging was pT1cN0M0, IA3 (AJCC, 8th edition). The case provides empirical basis for the neoadjuvant treatment with savolitinib in *MET*ex14m-positive locally advanced primary lung adenocarcinoma, which will offer some innovative insights and clinical evidence for more effective clinical treatment of neoadjuvant targeted therapy for *MET*ex14m-positive NSCLC.

KEYWORDS

savolitinib, *MET* exon 14 skipping, neoadjuvant therapy, non-small cell lung cancer, targeted therapy

Introduction

The tyrosine-protein kinase Met (c-Met), also known as hepatocyte growth factor receptor (HGFR), is a heterodimer transmembrane tyrosine kinase receptor encoded by the *MET* proto-oncogene. *MET* is a novel therapeutic target for lung cancer and is closely related to the survival, prognosis and certain drug resistance of lung cancer patients (1). *MET* exon 14 skipping mutation (*MET*ex14m), *MET* kinase domain mutation, *MET* amplification and *MET* fusions are included in *MET* genomic alterations. *MET*ex14m is an independent oncogenic driver occurring in 1%-4% of non-small-cell lung cancer (NSCLC) patients. Patients with *MET*ex14m have a distinct clinicopathology and face-poor prognoses (2).

Several TKIs currently have been approved for advanced NCSLC patients with *MET*ex14m, such as savolitinib, capmatinib and tepotinib. Savolitinib is an oral, potent and highly selective type Ib *MET* inhibitor that has yielded promising activity and acceptable safety profile in patients with pulmonary sarcomatoid carcinoma and other NSCLCs harboring *MET*ex14m (2). Recently, a growing body of research has shown the feasibility of the neoadjuvant targeted therapy for early-stage resectable NSCLC patients with anaplastic lymphoma kinase (*ALK*) fusion gene, epidermal growth factor receptor (*EGFR*) mutations, RET rearrangements and ROS proto-oncogene 1 (*ROS1*) rearrangements (3–6). The fact suggests that the untargeted patients with *MET*ex14m had a shorter disease-free survival (DFS) (7). More importantly, since there have been presently no reported instances of savolitinib as a neoadjuvant treatment for NSCLC patients with *MET*ex14m. Here, we present the first case of stage IIIA-N2 primary lung adenocarcinoma patient harboring *MET*ex14m, who underwent left lower lobectomy and systemic lymphadenectomy resection treatment after receiving neoadjuvant savolitinib targeted therapy. Most encouraging of all, the patient received recovered well postoperatively and had no signs of recurrence during follow-up, which may predict better quality of life and prognosis. The case presented primary clinical evidence that supports the use of neoadjuvant treatment with savolitinib in *MET*ex14m-positive locally advanced primary lung adenocarcinoma.

Case report

A 49-year-old female patient visited a local municipal tertiary hospital with symptoms including dry cough, chest tightness and voice hoarseness for 1 month. The contrast-enhanced chest CT scan on July 1, 2021 demonstrated a 3.8 cm × 2.9 cm abnormal lung mass in the lobe of left lung. Enhanced signal was not detected inside the mass. Left hilar and subcarinal lymphadenopathy were also observed (Figure 1A). Fluorine-18 fluorodeoxyglucose (F18-FDG) positron emission tomography (PET)/CT was performed to evaluate the whole-body situation on July 6, 2021. The 18F-FDG PET/CT showed strong 18-FDG uptake in the left lung mass, as well as the left hilar and subcarinal lymph node, measuring up to 2.5 cm and 2.2 cm in short diameters, respectively, but there was no evidence of distant metastasis (Figure 2 and Supplementary Material). The patient had no history of smoking, no other concomitant diseases, and no family history of cancer.

After initial medical examination and assessment, the patient was admitted to our hospital on July 8, 2021. Stage IIIA (T2bN2M0) lung adenocarcinoma was confirmed on the basis of the 18F-FDG PET/CT results, CT guided lung puncture, and

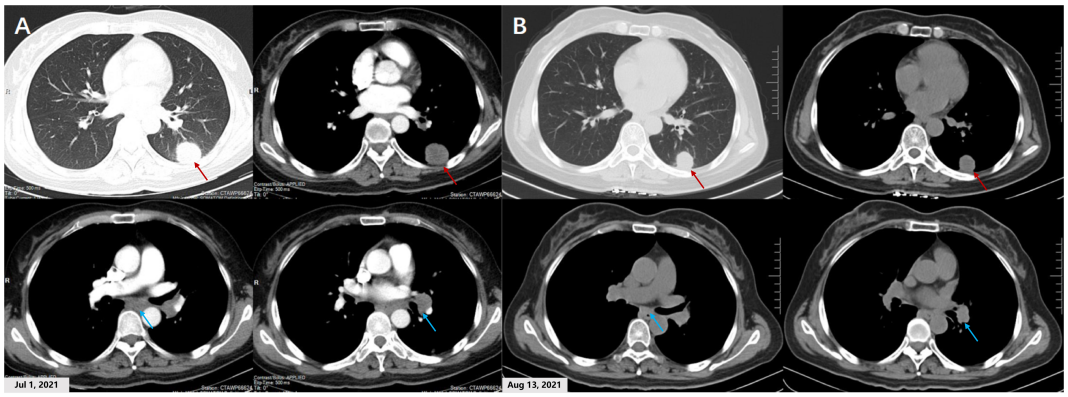

FIGURE 1
Chest CT scans of the patient before and after savolitinib treatment. **(A)** The chest contrast-enhanced CT scan on July 1, 2021 demonstrates a 3.8 cm × 2.9 cm abnormal lung mass (white arrows) in the lobe of left lung. Enhanced signal was not detected inside the mass. Left hilar and subcarinal lymphadenopathy (red arrows) also were observed. **(B)** After 21 days of savolitinib therapy, the chest CT scan on August 13, 2021 showed the mass (red arrows) had shrunk to 2.6 cm × 2.2 cm, achieving a partial response (PR). The Left hilar and subcarinal lymph node (blue arrows) also shrank significantly, and the short diameter did not exceed 7 mm.

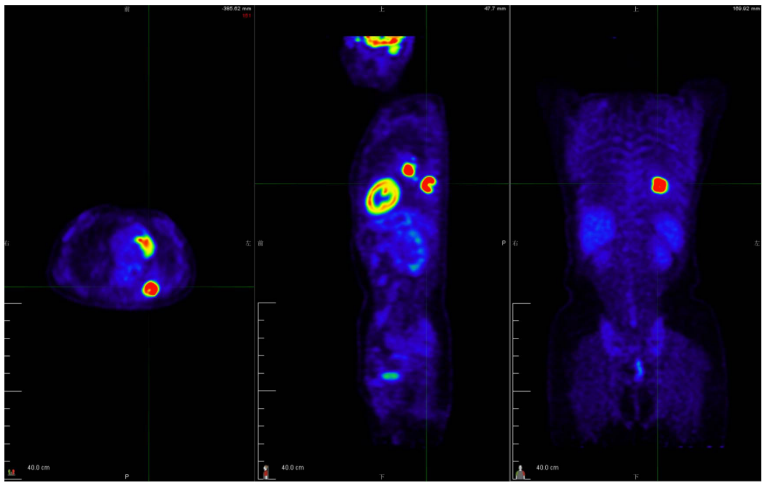

FIGURE 2
The 18F-FDG PET/CT examination was performed to evaluate the patient's tumor stage. The 18-FDG PET/CT revealed strong 18-FDG uptake in the left lung mass, as well as the left hilar and subcarinal lymph node, measuring up to 2.5 cm and 2.2 cm in short diameters, respectively, but there was no evidence of distant metastasis. See Supplementary Material for a dynamic 3D visualization.

subsequent pathological diagnosis. Genetic tests (real-time quantitative polymerase chain reaction, RT-qPCR) of the lung lesion biopsy revealed the results of *MET*ex14m, whereas other tested driver genes (*EGFR*, *ALK*, *ROS1*, *KRAS*, *BRAF*, *HER2*, *NRAS*, *PIK3CA*, and *RET*) were absent. After active discussions with the multiple disciplinary team (MDT) including respiratory physicians, thoracic surgeons, and radiologists, we all agreed that potentially resectable stage IIIA primary adenocarcinoma after adjuvant therapy would improve prognosis, prolong survival, and improve quality of life. Considering the N2 lymph node metastases involvement, we offered neoadjuvant chemotherapy followed by surgical resection. However, the patient preferred neoadjuvant target therapy rather than neoadjuvant chemotherapy. Given that there was no neoadjuvant indication for *MET* inhibitors, after adequate communication with the patient and her family and receiving written informed consent, we advised the patient to receive the target drug savolitinib as a neoadjuvant therapy based on the results of genomic testing.

On July 24, 2021, the patient received savolitinib, 600 mg orally, once daily as neoadjuvant therapy. Around three weeks later (August 13, 2021), the first evaluation of the therapeutic effect presented a partial response (PR) (target lesion shrank from 3.8 cm × 2.9 cm at baseline to 2.6 cm × 2.2 cm), on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Additionally, the left hilar and subcarinal lymph node obviously shrank, and the short diameter did not exceed 7 mm (Figure 1B). At the same time, we had also focused on evaluating the patient's drug tolerance state and adverse drug reactions. The patient experienced grade 2 impaired liver function (ALT 96 IU/L, AST 103 IU/L) during the first 4 weeks after the treatment. Liver enzyme levels in the patient were further increased (ALT 350 IU/L, AST 279 IU/L) after taking diammonium glycyrrhizin enteric-coated capsules for subsequent 5 days. Then, targeted therapy was temporarily discontinued on August 30, 2021 and the patient received glutathione in combination with magnesium isoglycyrrhizinate injection for 2 weeks. On September 14, 2021, the liver function tests returned to normal. There were no other adverse drug reactions such as fatigue, nausea and vomiting, appetite loss, rash, diarrhea, and edema. Considering that radiological downstaging was indicated after 5 weeks of savolitinib treatment, based on the re-discussion of the MDT team, surgical resection of the left lower lung lobe with dissection of the mediastinal lymph nodes was performed on September 24, 2021. The pathological diagnosis was poorly differentiated lung adenocarcinoma (solid type) with a size of 2.2 cm × 2.0 cm × 1.2 cm, and the visceral pleura was not involved. No infiltration of cancer cells was detected in the bronchus cutting edges, achieving R0 resection. The pulmonary hilar lymph node was negative (0/5) (Figure 3). The pathological response was 50% and the final postoperative pathological staging pT1cN0M0, IA3 (AJCC, 8th edition). The patient recovered well and the quality of life has been improved accordingly. For patients with completely resected IIIA-N2 stage NSCLC, adjuvant cisplatin-based chemotherapy for 4-6 cycles is recommended to prevent recurrence and improve survival by eradicating minimal residual disease (MRD). Therefore, the patient received following 5 cycles of pemetrexed plus carboplatin adjuvant chemotherapy. Up to now, the patient has been followed up postoperatively for 38 weeks with no sign of recurrence based on the last chest CT examination on June 3, 2022. The timeline for diagnosis and therapeutic interventions for the patient can be seen in Figure 4.

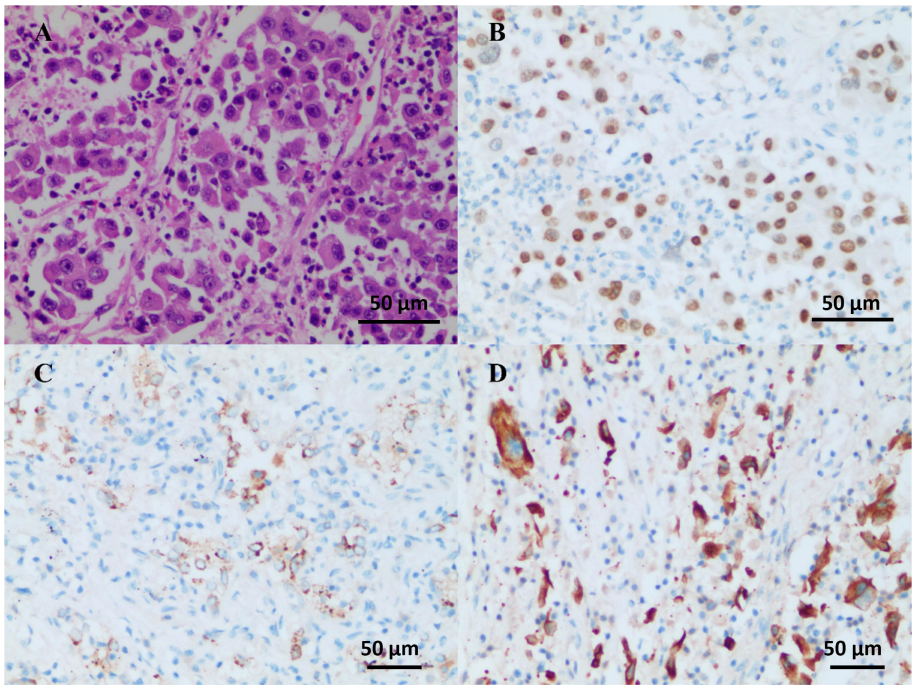

FIGURE 3
Operative and pathological findings. The pathological diagnosis was poorly differentiated lung adenocarcinoma (solid type) with the size of 2.2 cm × 2.0 cm × 1.2 cm, and the visceral pleura was not involved. No infiltration of cancer cells was detected in the bronchus cutting edges. Pulmonary hilar lymph node (-, 0/5). Immunohistochemistry outcomes were presented as: HE **(A)**, TTF-1 (+) **(B)**, NapsinA (+) **(C)**, CK7 (+) **(D)**, CK5/6 (-), CK (pan) (+), and Ki-67 (+, about 50%).

Discussion

Patients with stage I-II NSCLC are generally treated with curative-intent surgery if they are operable. However, some locally advanced (stage III) NSCLC cannot be operated due to factors such as tumor size and/or location. The prognosis of patients with unresectable stage III NSCLC is poor even after concurrent chemoradiotherapy (8). In unresectable stage III NSCLC, despite combination aggressive treatment with radiotherapy and chemotherapy, the 5-year relative survival rate is about 15%-20% (9). Stage III NSCLC is a highly heterogeneous disease and surgical resection with or without neoadjuvant therapy could be carried out in selected patients. Increasing the surgical resection rate is the key link to improving the overall prognosis and survival of patients. Neoadjuvant therapy may improve the overall resection rate and the R0 surgical resection rate of the primary tumor. The potential value of targeted therapy as neoadjuvant therapy for NSCLC patients with specific driver genes has been explored actively. NEOS study (ChiCTR1800016948) evaluated the efficacy and safety of osimertinib as a neoadjuvant treatment in resectable EGFR mutation-positive (EGFRm) lung adenocarcinoma. This study demonstrated the promising efficacy and good tolerability of neoadjuvant osimertinib (10). ESTERN was constructed to provide more insight into the effects on neoadjuvant erlotinib improving operability and survival in EGFRm NSCLC patients with stage IIIA-N2. Among the 19 patients who received erlotinib treatment, 14 patients underwent surgical treatment. The radical resection rate was 68.4% (13/19) with 21.1% (4/19) rate of pathological downstaging. The median progression-free survival (PFS) and overall survival (OS) were 11.2 and 51.6 months respectively in 19 patients with neoadjuvant therapy (11). CTONG 1103 was a randomized controlled phase II trial with erlotinib versus gemcitabine plus cisplatin as neoadjuvant/adjuvant therapy for stage IIIA-N2 EGFRm NSCLC patients. The study showed that neoadjuvant/adjuvant EGFR-TKI has potential and has a promising OS for resected N2 patients with EGFRm NSCLC (12). In a study involved 11 *ALK*-positive patients with pathologically confirmed N2 NSCLC, after received crizotinib at a starting dose of 250 mg twice daily, ten patients received an R0 resection and two patients achieved a pathological complete response to neoadjuvant crizotinib, which provided the evidence for neoadjuvant crizotinib in locally advanced NSCLC (4).

Previous clinical trials have already verified the availability of *EGFR* and *ALK* inhibitors neoadjuvant targeted therapy in the disease control and pathological downstaging for early-stage NSCLC patients harboring the corresponding mutation, and

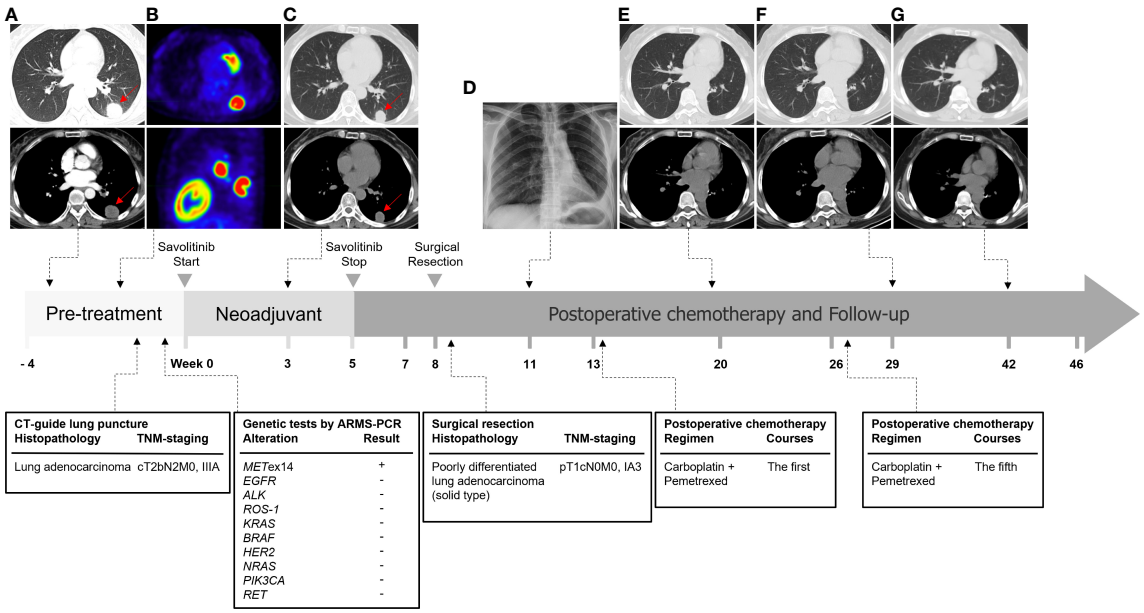

FIGURE 4
Timeline of diagnosis and treatment of this case. **(A)** The chest contrast-enhanced CT scan at the first visit to the hospital on July 1, 2021. **(B)** The 18-FDG PET/CT examination on July 6, 2021. **(C)** The chest CT scan after 21 days (August 13, 2021) savolitinib neoadjuvant therapy. **(D)** Postoperative chest x-ray on October 13, 2021 revealed good lung expansion of left lung. **(E–G)** The patients underwent re-examination of chest CT on December 20, 2021, March 2, 2022, and June 3, 2022 respectively, which showed postoperative changes and no signs of recurrence.

some case reports also observed that target therapy provided effective radiologic and pathologic response in *ALK*, RET and *ROS1*-positive resectable NSCLC patients (3, 6, 13–15). *MET*ex14m is an independent oncogenic driver occurring in 2.8% of resected stage I-III NSCLC patients (16). A previous case report on neoadjuvant treatment with crizotinib in a locally advanced, unresectable *MET*ex14m lung adenocarcinoma achieved pathologic complete response and led to the conversion to resectable disease (17). However, there is no evidence suggests that whether savolitinib can play a role in potentially resectable NSCLC patients. Savolitinib, an oral, highly selective ATP-competitive *MET* inhibitor for treating various cancers including NSCLC, gastric, renal cell carcinoma, esophageal carcinoma, and medulloblastoma, has been approved in China for treating metastatic NSCLC with *MET*ex14m alterations, particularly in patients who fail to tolerate platinum-based chemotherapy or has progress after chemotherapy (18). To date, this is the first case of stage IIIA-N2 *MET*ex14m primary lung adenocarcinoma treated with savolitinib neoadjuvant targeted therapy combined with surgery to reveal noteworthy clinical efficacy. Here, neoadjuvant savolitinib achieved tumor downstage, achieved R0 resection, and even complete the conversion to a potentially curable disease. We found that the patient achieved N0 disease the following 5 weeks of the neoadjuvant savolitinib, whereas 50% of the tumor cells in the postoperative tissues of the patient were still active, which implies the importance of radical resection after the induction of targeted therapy. It is worth noting that drug-induced liver injury (DILI) has been the most common adverse effect of savolitinib during clinical trials and post-market surveillance (19). In this case, the patient experienced grade 3 DILI that led to savolitinib discontinuation after 5 weeks neoadjuvant treatment. After savolitinib withdrawal and liver protection treatment for 2 weeks, the patient's liver function returned to normal. It is suggested that when using savolitinib, liver function should be monitored carefully.

Additionally, a phase II trial of neoadjuvant and adjuvant capmatinib in patients with stages IB-IIIA, N2, and selected IIIB (T3N2 or T4N2) NSCLC with *MET*ex14m or high *MET* amplification (Geometry-N) is ongoing (NCT04926831) (20). Given the prevalence of the *MET*ex14m in early-stage NSCLC and the preliminary findings from case reports of *MET* inhibitors as neoadjuvant therapies in early-stage NSCLC, clinical trials exploring the role of neoadjuvant *MET* targeted therapies in this population may be warranted.

Overall, the case presented primary clinical evidence that neoadjuvant savolitinib targeted therapy is an effective treatment for *MET*ex14m-positive locally advanced primary lung adenocarcinoma, which can provide a reference for clinical treatment of such patients. Neoadjuvant savolitinib targeted therapy in IIIA-N2 lung adenocarcinoma with *MET*ex14m

could achieve pathological downstaging and increase the possibility of radical surgery and R0 resection. Additionally, monitoring liver function is necessary during savolitinib treatment. Along with an acceptable side effect, neoadjuvant targeted therapy probably deserves to be recommended for these patients with lung cancers that harbor a targetable oncogene, which may have much more impressive therapeutic effects than the platinum-based chemotherapy typically used for neoadjuvant therapy. The findings of this case would provide some inspiring insights for prospective clinical studies to further explore the clinical value of neoadjuvant targeted therapy for *MET*ex14m-positive NSCLC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital) (Ethical Approval Number: 2022-RE-056). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

L-JC, J-QZ, and MF contributed to the conception and presentation of the case report. L-JC, J-QZ, and D-QX provided clinical expertise and interpretations. L-JC and J-QZ organized the MDT meeting. YF and WX recorded the detail of the MDT meeting. L-JC, J-QZ, H-LX, N-NH, Z-JL, MF, WX, and Z-MJ overall management and treat the patient. MF was responsible for the manuscript writing, literature review, and pictures production. C-MF contributed to manuscript revision, editing and proofreading. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.954886/full#supplementary-material

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Use of savolitinib as neoadjuvant therapy for non–small cell lung cancer patient with MET exon 14 skipping alterations: A case report

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Savolitinib is a tyrosine kinase inhibitor being developed for the treatment of metastatic non–small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) factor exon 14 skipping alterations. However, the role of savolitinib in neoadjuvant therapy for lung cancer remains unclear. Here, we present a case of a 65-year-old woman diagnosed with stage IIIA (cT2bN2M0, eighth TNM stage) upper right lung adenocarcinoma harboring MET exon 14 skipping alterations. After 4 weeks of therapy, a partial response was achieved with neoadjuvant savolitinib, and significant shrinkage in tumor and lymph nodes was observed. We also measured the immune microenvironment of the primary tumor pre- and posttreatment with savolitinib.

KEYWORDS

savolitinib, neoadjuvant, NSCLC, MET exon 14 skipping, targeted therapy

Introduction

Mesenchymal–epithelial transition (MET) exon 14 (METex14) skipping mutations occur in approximately 3% of lung adenocarcinoma patients and 1%–2% of patients with other lung cancer subtypes (1). This gene encodes a member of the receptor tyrosine kinase family of proteins which is the product of the proto-oncogene MET. In 2003 and 2005, Ma et al. reported a series of novel METex14 splicing variants (2, 3). In 2015, Paik et al. demonstrated that mutations of RNA splice acceptor and donor sites involving exon

14 of MET could lead to exon skipping, and the tumors with this mutation could respond to MET-targeted therapies (4).

Savolitinib, approved in June 2021 in China, was used for the treatment of NSCLC with METex14 skipping alterations in patients who are intolerant or whose disease had progressed after platinum-based chemotherapy (5). However, there are no reports regarding neoadjuvant treatment using savolitinib for NSCLC patients with METex14.

Case report

A 62-year-old female patient with no history of smoking presented with a non-productive cough and bloody sputum for 4 months. Enhanced computed tomography (CT) scan revealed a mass of 43-mm diameter in the right upper lung and enlarged mediastinal lymph nodes (stations 2, 3, and 4). Bronchoscopic biopsy confirmed the diagnosis of adenocarcinoma of clinical stage IIIA (cT2bN2M0) with a Ki-67 score of 40%. Further testing using a real-time PCR (including ALK, ROS1, RET, KRAS, BRAF, NRAS, HER2, PIK3C, MET, and EGFR) detected only METex14 skipping mutation. Multidisciplinary team (MDT) recommended neoadjuvant therapy followed by surgical resection. Savolitinib at a dosage of 250 mg twice daily was prescribed after obtaining informed consent from the patient.

After 4 weeks of treatment, a chest CT scan showed 60% tumor shrinkage and a partial decrease of mediastinal lymph nodes (Figures 1, 2). The patient developed mild dizziness and nausea during savolitinib treatment. After an MDT discussion, right upper lobectomy and systemic lymphadenectomy were performed without any severe in-hospital complications. The final histopathological staging diagnosed pT2aN2M0 with occult lymph node metastasis in stations 2 (2/8). Lymph nodes at levels 3, 4, 7, 11, and 12 were negative for tumor involvement. The pathological examination showed that the Ki-67 index had dropped to 30% (Figure 3). There is extensive lymphocytic infiltration in tumors. Cholesterol crystals were observed as well as necrosis and fibrosis. The patient has been receiving savolitinib treatment post-surgery without radiation or chemotherapy. At the final follow-up in June 2022 (6 months after surgery), no grade 3/4 adverse events or disease progression had occurred. To determine any changes in the tumor immune environment due to savolitinib neoadjuvant treatment, we performed multiplexed immunohistochemistry (mIHC) on the biopsy tissue and the surgical specimen. The immunohistochemistry analysis indicated that the number of M1 macrophages, $CD8^+$ tumor-infiltrating lymphocytes (TILs), and the level of PD-1 expression was increased significantly after neoadjuvant treatment, whereas PD-L1 amount remain unchanged. No $CD57^+$ lymphocytes were detected before and after neoadjuvant therapy.

Discussion

Neoadjuvant therapy is recommended to improve the survival rate of stage IIIA NSCLC patients. Previous reports

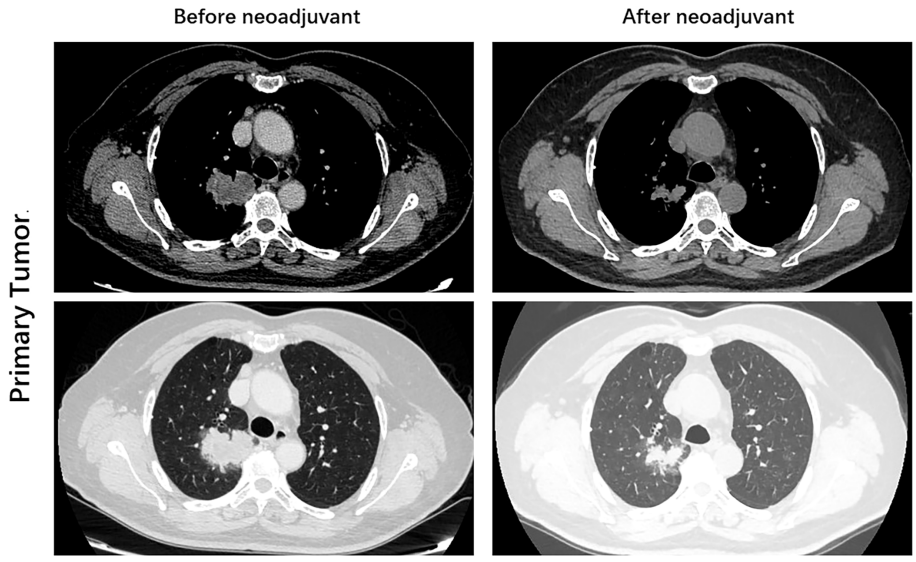

FIGURE 1
Images during neoadjuvant savolitinib treatment. Enhanced chest CT images of right lung adenocarcinoma before and after the neoadjuvant therapy.

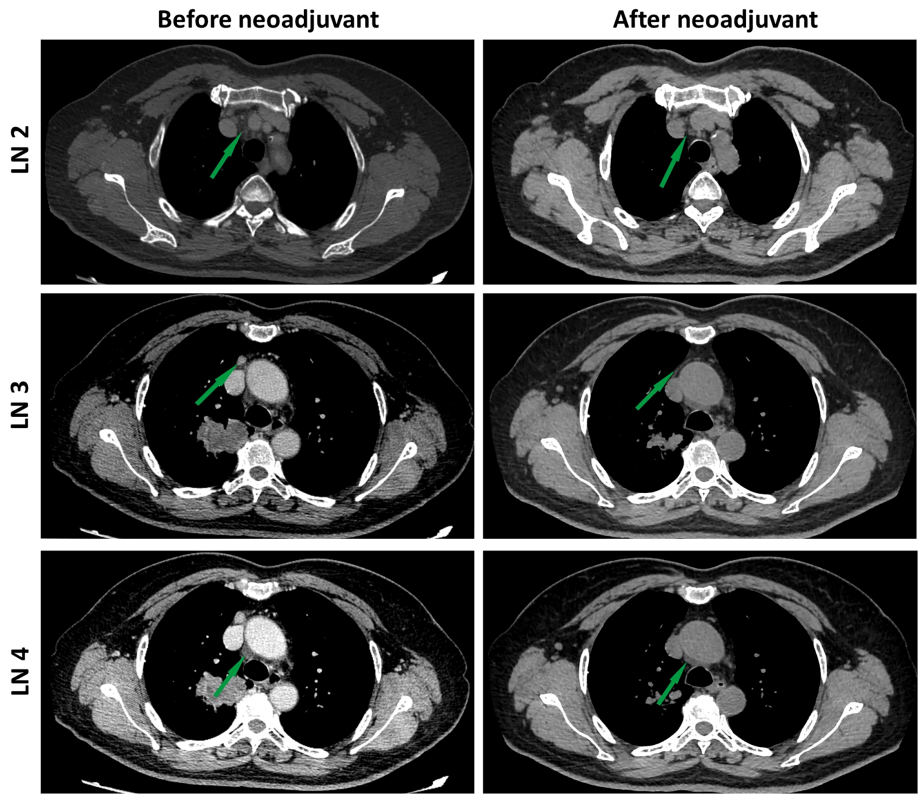

FIGURE 2
Images during neoadjuvant savolitinib treatment. Enhanced chest CT images of lymph nodes before and after the neoadjuvant therapy. The lymph nodes pointed by green arrows

have shown that neoadjuvant-targeted therapies are feasible for oncogene-positive NSCLC patients (6–8). We report the first case of neoadjuvant savolitinib treatment for NSCLC patients with METex14 skipping mutation.

In the present case, savolitinib exhibited a significant response in an NSCLC patient with METex14 skipping. The Ki-67 proliferation index decreased, and the tumor showed significant shrinkage after the savolitinib therapy, which was followed by successful lobectomy and systemic lymphadenectomy. Although radiological evaluation of most lymph nodes showed significant reduction after savolitinib neoadjuvant therapy, surgical pathology confirmed micrometastasis in lymph nodes [station 2 (2/8)]. Previous studies have reported that the response rate of CTONG 1103 (EMERGING) with a 42-day erlotinib neoadjuvant in EGFR-positive patients decreased, with a major pathologic response (MPR) of 9.7% and a lymph node downstaging rate of 10.8% (9). Thus, we assumed that savolitinib neoadjuvant treatment might achieve a longer median response than 4 weeks and better results if administered for a longer period before the operation.

Collectively in our case, neoadjuvant savolitinib may have converted the "cold" tumor to an immunologically "hot" tumor by recruiting $CD8^+$ TILs and M1 macrophages. A previous study has reported that $CD8^+$ TILs and NK cell populations decreased in patients with MET amplification, and it may be related to the MET signaling inducing the phosphorylation of UPF1 and downregulating the tumor cell STING expression (10). Thus, we proposed that the number of $CD8^+$ TILs may increase after savolitinib treatment in METex14 NSCLC. Therefore, anti–PD-1 immunotherapy may be a viable treatment option for patients who have acquired resistance to savolitinib TKI treatment.

However, the efficacy of immunotherapy for METex14 NSCLC remains controversial. Some studies showed that immunotherapy might be effective for METex14 NSCLC patients. Mayenga et al. reported that 6 of 13 patients with METex14-mutated NSCLCs, who received immune checkpoint inhibitors (ICIs) treatment, had prolonged responses (11). Chen et al. reported that a METex14 NSCLC patient who developed targeted therapy resistance had a significant response to immunotherapy, which showed that immunotherapy might be a promising candidate for treating NSCLC patients with METex14 harboring MET-TKI–resistant mutations (12). In contrast, Sabari et al. reported that the overall response rate of METex14-altered lung cancers to PD-1/PD-L1 immune checkpoint inhibition was low and the median PFS was short. Neither PD-L1 status nor tumor mutation burden was correlated

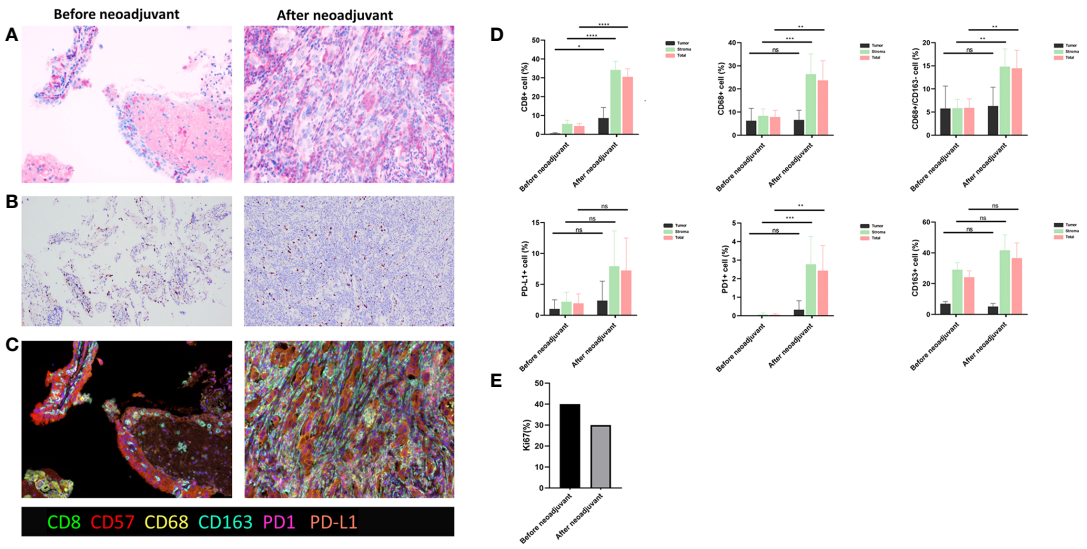

FIGURE 3
(A) Hematoxylin and eosin (HE) staining. **(B)** Ki67 staining. **(C)** Multiple immunohistochemistry staining, including CD8, CD57, CD68, CD163, PD-1, and PD-L1, before and after savolitinib neoadjuvant. **(D)** Quantitative analysis for staining data. ns, not significant. *p < 0.05; **p < 0.01; ***p < 0.001; ****p <0.0001; **(E)** Ki-67 index before and after savolitinib neoadjuvant.

with response to immunotherapy (13). The ICIs efficacy in MET-mutated NSCLC was comparable to that observed in patients with pretreated unselected NSCLC in a retrospective, multicenter study (14). A phase II trial of capmatinib and spartalizumab versus capmatinib and placebo as first-line treatment for advanced NSCLC patients with METex14 skipping mutation is undergoing to evaluate the benefit of MET-TKI with ICIs in METex14 NSCLC (NCT04323436). Further prospective studies are necessary to define the role of ICIs in lung cancer patients with METex14 mutation.

In conclusion, our study showed that savolitinib neoadjuvant therapy is feasible for NSCLC patients with METex14 skipping mutation. Currently, an ongoing phase II trial of neoadjuvant and adjuvant capmatinib in NSCLC with METex14 skipping mutation is underway (NCT04926831). For NSCLC patients with METex14 skipping mutation, savolitinib as neoadjuvant treatment might provide a better option to replace chemotherapy. Further clinical trials are needed to evaluate the outcome and long-term prognosis of savolitinib in neoadjuvant therapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HZ: Data curation, Formal analysis, Writing Original draft preparation. YZ: Formal analysis, Resources Writing Original draft preparation. HQ: Data curation, Writing-Original draft preparation. JT: Resources. BZ: Visualization. NZ: Formal analysis. LL: Resources. ZQ: Conceptualization, Methodology, Supervision, Writing- Reviewing and Editing. CL: Resources, Conceptualization, Supervision, Validation. SX: Conceptualization, Validation, Visualization. Writing-Reviewing and Editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Neoadjuvant immunotherapy combined with chemotherapy significantly improved patients' overall survival when compared with neoadjuvant chemotherapy in non-small cell lung cancer: A cohort study

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Background: Programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors displayed considerable advantages in neoadjuvant therapy of non-small cell lung cancer (NSCLC), but the specific application of neoadjuvant immunotherapy has not been well determined, and the long-term prognostic data of neoadjuvant immunochemotherapy combined with surgical resection of NSCLC remains limited. In this study, we intended to assess the efficacy of the neoadjuvant therapy of the PD-1 inhibitor and long-term prognosis in patients with resectable NSCLC.

Methods: We retrospectively analyzed NSCLC surgical patients treated with neoadjuvant therapy in our hospital, and divided them into a neoadjuvant chemotherapy group and a neoadjuvant immunotherapy combined with chemotherapy group. The propensity score matching method was used to evaluate the effectiveness of immunotherapy combined with chemotherapy in the treatment of resectable lung cancer, and the long-term prognosis of these two groups was compared.

Results: A total of 62 cases were enrolled, including 20 patients (20/62, 32.26%) in the immunotherapy group and 42 patients (42/62, 67.74%) in the chemotherapy group. The clinical baseline data of these two groups were balanced. In the immunotherapy group, all patients had tumor regression in imaging finding (tumor regression ratio: 11.88% - 75.00%). In the chemotherapy group, 30 patients had tumor regression (tumor regression ratio: 2.70% - 58.97%). The R0 removal rates of cancers were comparable between the immunotherapy group and chemotherapy group (19/20, 95.00% vs. 39/42, 92.86%, P=1.000). The two groups were balanced in complete minimally

invasive surgery, pneumonectomy, operative duration, blood loss, postoperative complications, and hospital stay. The immunotherapy group had more sleeve resection (36.84% vs. 10.26%, p=0.039) including bronchial sleeve and vascular sleeve, higher pathological complete response (pCR) rate (57.89% vs. 5.13%, P<0.001) and major pathologic response (MPR) rate (78.95% vs. 10.26%, P<0.001). There were no differences in survival curves for: smoker and non-smoker, squamous cell carcinoma and adenocarcinoma, or right lung cancer and left lung cancer. Moreover, patients who achieved MPR (including pCR) had significantly better overall survival (OS) and disease-free survival (DFS). Patients in immunotherapy group had significantly better OS and longer DFS than those in chemotherapy group.

Conclusions: In conclusion, neoadjuvant immunotherapy combined with chemotherapy can provide better OS and DFS and improving pCR and MPR rates by shrinking tumors.This study has been registered in the Chinese Clinical Trial Registry, number ChiCTR2200060433. http://www.chictr.org.cn/edit.aspx?pid=170157&htm=4.

KEYWORDS

neoadjuvant immunotherapy, lung resection, prognosis, non-small cell lung cancer, neoadjuvant chemotherapy

Introduction

Lung cancer is one of the most common cancers with extremely high morbidity and mortality rates worldwide (1, 2). Surgical resection is the main strategy for the treatment of early-stage non-small cell lung cancer (NSCLC), which has a high cure rate. However, patients with NSCLC have a poor prognosis after surgery with 5-year survival rates at approximately 50% for stage II and 20% for stage III, even if the tumor is completely removed (3). This poor prognosis may be a result of tumor metastasis or recurrence caused by residual tumor cells, tumor micro metastases, or circulating tumor cells (CTC) and circulating tumor DNA (ctDNA). Even neoadjuvant or adjuvant radiotherapy or chemotherapy can only improve the 5-year survival rate by 5%, which is relatively limited (4, 5). Therefore, novel neoadjuvant therapeutic strategies are urgently needed to reduce the risk of recurrence and further prolong the survival of patients with NSCLC.

Our understanding of the role of the immune system in the regulation of tumor development has significantly increased in recent years, which makes the promise of immunotherapy a revolution in the treatment of cancer. Immune checkpoints have been showed to regulate the immune response during tumor development (6, 7). Immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD-1) or its ligand (PD-L1) have achieved significant improvements in clinical adjuvant therapy for esophageal/esophagogastric junction carcinoma (8), bladder cancer (9), melanoma (10), and lung cancer (11). ICIs have become an important treatment for advanced non-small cell lung cancer, which can greatly improve the 5-year overall survival (OS) of patients (11, 12). In addition, ICIs also show considerable advantages in short-term results of NSCLC neoadjuvant therapy, such as safety, tolerability, and major pathological response (MPR), when compared with conventional neoadjuvant therapy (13–15). Neoadjuvant immunotherapy could adequately activate the immune response and may remove residual lesions or small metastases (16). However, the application of neoadjuvant immunotherapy has not been well established, and long-term prognostic data of neoadjuvant immunochemotherapy combined with surgical resection of NSCLC remains limited.

Therefore, in the current study, we retrospectively analyzed patients of NSCLC undergoing surgery after neoadjuvant therapy, which were then divided into a neoadjuvant chemotherapy group (Che. group) and a neoadjuvant immunotherapy combined chemotherapy group (Imm. group). The aims of this study were to evaluate the efficacy of neoadjuvant immunotherapy combined with chemotherapy in the treatment of resectable NSCLC, and to compare the long-term prognosis between the two groups. We present the following article in accordance with the STROBE reporting checklist.

Methods

Patients

The database of the Army Medical Center of Chinese People's Liberation Army (PLA) (Daping Hospital) was searched retrospectively from January 2017 to October 2021. This study was reviewed and approved by the ethics committee of the hospital (Ethics Committee of Army Medical Center of PLA, approval number: 2021-273). Individual consent for this retrospective analysis was waived. The study was performed in accordance with the Declaration of Helsinki. Patients who met the following criteria were included: (I) males or females aged 20-75 years; (II) initially diagnosed as NSCLC (clinical stage IB - IIIB) and treatment-naive; (III) resectable lung cancer at the first multidisciplinary diagnosis and treatment (MDT) assessment; (IV) Karnofsky performance status (KPS) ≥ 80, and tolerant to neoadjuvant therapy; (V) receiving neoadjuvant therapy prior to resection; (6) no targeted gene mutations in genetic testing and PD-L1 expression positive in immunohistochemical staining. Patients who met the following criteria were excluded: (I) poor cardiopulmonary function and intolerance of surgery due to cardiopulmonary or other organ dysfunction; (II) tumor progression to unresectable or distant metastasis after neoadjuvant therapy at the second MDT assessment; (III) patients with autoimmune diseases or using immunosuppressive drugs over a long-term; (IV) refusal to undergo follow-up. Data regarding age, sex, smoking status, predicted percentage of the forced expiratory volume (FEV1%), tumor size, tumor location, pathologic type of tumor, clinical stage of tumor, type of operation, operation time, blood loss during operation, postoperative complications, and hospital stay were collected and analyzed. The UICC/AJCC TNM Staging System Eighth Edition for NSCLC was used in this study to evaluate the tumor (17).

Treatment options

All treatment protocols of patients were conducted by MDT. There were 3 times MDTs: the first for the initial assessment, the second for the post-neoadjuvant therapy assessment, and the third for the adjuvant treatment and follow-up assessment (Figure 1).

Contrast-enhanced computed tomography (CT) of the chest, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET-CT), cardiopulmonary

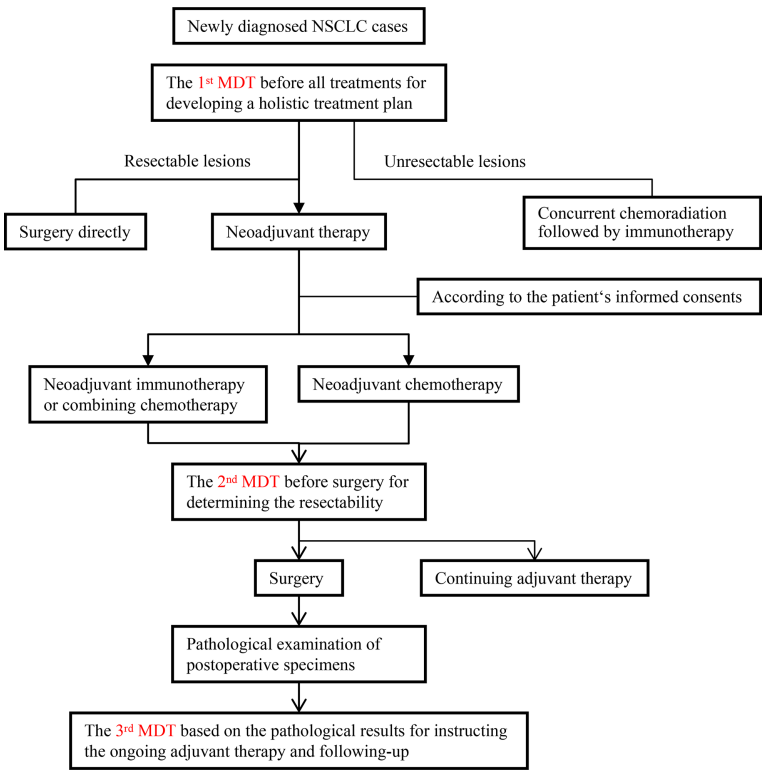

FIGURE 1
Flowchart summarizing the three multidisciplinary diagnosis and treatments (MDTs) and process of managing patients. NSCLC, non-small cell lung cancer.

function, blood test, and fiberoptic bronchoscopy or percutaneous lung puncture for obtaining pathological results were performed. Immunohistochemistry stains were conducted to detect the expression level of PD-L1 protein in tumor cells. The expression level of PD-L1 was indicated by the percentage of stained cells, which was <1% defined as negative expression and ≥1% defined as positive expression.

Two cycles of neoadjuvant chemotherapy or neoadjuvant immunotherapy combined with chemotherapy were performed. The neoadjuvant chemotherapy regimen was pemetrexed (500 mg/m^2, D1) + nedaplatin (75 mg/m^2, D1) for adenocarcinoma and paclitaxel liposome (175 mg/m^2, D1) + nedaplatin (75 mg/m^2, D1) for squamous carcinoma (the use of chemotherapy drugs was based on NCCN guidelines and Chinese Lung cancer Diagnosis and Treatment Guidelines (18)). The neoadjuvant immunotherapy was PD-1 inhibitors, including tislelizumab, nivolumab, pembrolizumab, sintilimab. In three to six weeks after completion of these treatments, chest CT and PET-CT are performed again to assess changes of the tumors.

Surgical procedures included video-assisted thoracoscopic surgery (VATS) or thoracotomy, lobectomy, bronchial or vascular sleeve resection, and mediastinal lymph node dissection. All patients were sent back to the thoracic surgery unit after surgery (after the operation, patients were required to stay for a short time in the recovery room until recovering from anesthesia). The patients were encouraged to cough and expectorate to promote drainage and pulmonary re-expansion and were instructed for early activities. Patients whose 24-hour chest drainage volume was less than 200 mL, had no pneumothorax or residual space on chest radiograph, and had no air leakage from the chest tube underwent chest tube removal.

The patients were admitted 1 month after surgery for the third MDT and further therapy according to the guidelines (12, 19) and our MDT recommendations. Patients in the neoadjuvant chemotherapy group received four cycles of adjuvant chemotherapy with the same regimen as before surgery. Patients in the neoadjuvant immunotherapy group received four cycles of adjuvant chemotherapy and six cycles of adjuvant immunotherapy with the same protocol as before surgery. During the follow-up, once tumor recurrence was found, the tolerance and tumor status of patients needed to be assessed by general examination, and the tissue of recurrent lesion should be obtained as far as possible for pathological and genetic testing. Through MDT assessment, individualized therapy plans were set out and implemented after patient's informed consent.

The postoperative overall survival (OS) was defined as the time from primary tumor resection (surgical date) to last follow-up or death. Disease-free survival (DFS) was defined as the time from the surgical date to the diagnosis of recurrence/metastasis or the last follow-up.

Tumor evaluation

The tumors were evaluated twice: imaging evaluation after 2 cycles of neoadjuvant therapy and postoperative pathological evaluation.

The imaging response of tumors to neoadjuvant therapy was reviewed centrally by two radiologists according to the Response Evaluation Criteria in Solid Tumor 1.1 (iRECIST Criteria 1.1) (20). To assess changes in primary tumor after neoadjuvant therapy, we recorded the tumor diameter.

We reextracted paraffin-embedded postoperative specimens previously processed by the pathology department and scored the percentage of residual tumor cells by two trained pathologists. Pathological complete response (pCR) was defined as the absence of viable tumor cells (ypT0N0M0) in the surgical resection specimen, and major pathologic response (MPR) was defined as less than 10% viable tumor remaining (21, 22). Additionally, the pathological response of the primary tumor was also assessed according to the College of American Pathologists (CAP) and National Comprehensive Cancer Network (NCCN) system (23) according to: tumor regression grade (TRG) 0 (no viable cancer cells), TRG 1 (single cells or rare small groups of cancer cells), TRG 2 (residual cancer with evident tumor regression), and TRG 3 (extensive residual cancer with no evident tumor regression). When there were disagreements between pathologists, a consensus would be reached through multi-head microscope review and discussion.

Propensity score matching

Propensity score (PS) matching was conducted using logistic regression to create a PS for individual patients using demographic and clinical variables. The variables used to estimate the PS were age, gender, smoking status, FEV1%, tumor size, tumor location, pathologic type of tumor, clinical stage of tumor, and type of operation. The PS was calculated using a logistic model. The nearest neighbor matching was adopted with common caliper <0.1 and 1:1 matching. Each patient who underwent neoadjuvant immunotherapy combined with chemotherapy was matched with a patient who underwent neoadjuvant chemotherapy and had the closest PS.

Statistical analysis

Data analysis was performed using SPSS 26.0 software (IBM SPSS Statistics, RRID: SCR_019096). Continuous data are presented as mean ± standard deviation (SD) and analyzed by the two-tailed t-test or rank sum test. Categorical data are presented as frequency and percentage (%) and were analyzed by either chi-square test or Fisher's exact test. Survival curves

were obtained using the Kaplan-Meier method, and the differences between survival curves were compared by the log-rank test. P<0.05 was considered significant. Multivariate Cox regression analysis was used to determine the risk factors for DFS, and to produce forest plot.

Results

Patients' clinical characteristics and PS matching

A total of 62 cases were enrolled, including 20 patients (20/62, 32.26%) in the immunotherapy group and 42 patients (42/62, 67.74%) in the chemotherapy group. Baseline characteristics of all cases are presented in Table 1. The two groups were similar in terms of age, gender, smoking status, FEV1%, tumor size, tumor location, pathologic type of tumor, and clinical stage of tumor. In these two groups, the majority were male (85.00% and 85.71%), smokers (85.00% and 66.67%), squamous cell carcinoma (85.00% and 64.29%), and advanced stage cancer (65.00% and 57.14%).

After excluding the patients with R1 or R2 resection and 1 to 1 propensity score matching, 19 pairs of patients were selected (Table 1). Also, the clinical characteristics including age, gender, smoking status, FEV1%, tumor size, tumor location, pathologic type of tumor, and clinical stage of tumor in the two groups were well balanced.

Preoperative treatment and response to neoadjuvant therapy

All candidates received 2 cycles of neoadjuvant therapy. At 3-6 weeks after neoadjuvant therapy, iRECIST criteria were used to evaluate the imaging response of the tumor. Of the 42 patients in chemotherapy group, 4 cases were not recorded due to inadequate archived CT data. In the immunotherapy group, all patients had tumor regression (tumor regression ratio: 11.88%-75.00%) (Figure 2A). In the chemotherapy group, 30 patients had tumor regression (tumor regression ratio: 2.70%-58.97%) (Figure 2B).

Surgical and postoperative results

The R0 removal rates for tumors were comparable between the immunotherapy group and chemotherapy group (19/20, 95.00% vs. 39/42, 92.86%, P=1.000) (Table 2). In the analysis of subsequent surgery and postoperative outcomes and propensity score matching, patients with R1 or R2 resection were excluded. The two groups were balanced in complete minimally invasive surgery,

TABLE 1 Patients' baseline and clinical characteristics.

Characteristics	Unmatched patients			Matched patients†		
	Immunotherapy	Chemotherapy	P	Immunotherapy	Chemotherapy	P
Patients(n)	20	42		19	19	
Age(years)	58.05 ± 7.05	56.45 ± 8.66	0.475	58.58 ± 7.14	56.84 ± 8.90	0.511
Gender (n [%])			1.000			1.000
Male	17 (85.00%)	36 (85.71%)		16 (84.21%)	15 (78.95%)	
Female	3 (15.00%)	6 (14.29%)		3 (15.79%)	4 (21.05%)	
Smoking status			0.130			0.693
Absent	3 (15.00%)	14 (33.33%)		3 (15.79%)	5 (26.32%)	
Present	17(85.00%)	28 (66.67%)		16 (84.21%)	14 (73.68%)	
FEV1 % predicted	85.60 ± 16.00	78.58 ± 15.04	0.097	84.42 ± 15.52	81.14 ± 16.08	0.526
Tumor size(cm)‡	4.97 ± 2.10	4.67 ± 1.67	0.544	5.10 ± 2.08	4.92 ± 1.82	0.773
Tumor location			0.713			1.000
Right lobe	9 (45.00%)	21 (50.00%)		8(42.11%)	9 (47.37%)	
Left lobe	11 (55.00%)	21 (50.00%)		11 (57.89%)	10 (52.63%)	
Tumor type			0.093			0.660
Squamous cell	17 (85.00%)	27 (64.29%)		17 (89.47%)	15 (78.95%)	
Adenocarcinoma	3 (15.00%)	15 (35.71%)		2 (10.53%)	4 (21.05%)	
Clinical stage§			0.555			1.000
I-II	7(35.00%)	18 (42.86%)		7 (36.84%)	6 (31.58%)	
III	13 (65.00%)	24 (57.14%)		12 (63.16%)	13 (68.42%)	

†Patients with R1 or R2 resection were excluded When we carried out propensity score matching. ‡Tumor size (cm) prior to immunotherapy. §Clinical stage prior to neoadjuvant therapy. Fisher's accurate test was adopted in Chi-square test after propensity score matching as the total number of samples was less than 40.

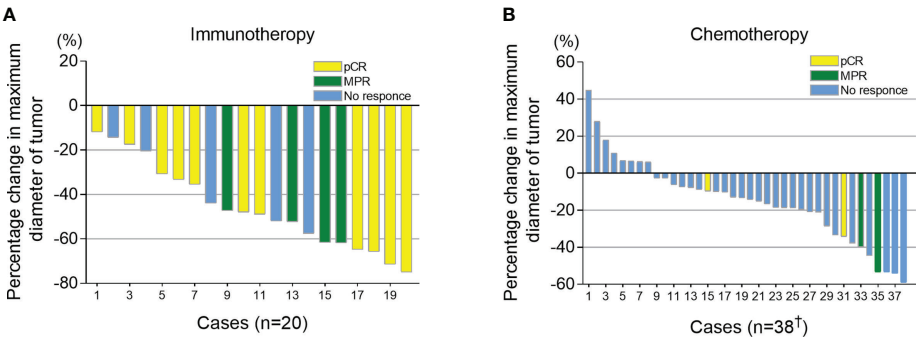

FIGURE 2
Imaging response (percentage change in maximum diameter of tumor) after neoadjuvant therapy. Combined with postoperative pathological results, patients who had a pathological complete response (pCR) were shown in yellow, major pathological response (MPR) shown in green and those with >10% viable tumor remaining are shown in blue. **(A)** Tumor size changes after neoadjuvant immunotherapy combined with chemotherapy. **(B)** Tumor size changes after neoadjuvant chemotherapy. †, Of the 42 patients in chemotherapy group, 4 cases were not recorded due to the inadequate archived CT data.

pneumonectomy, operative duration, blood loss, postoperative complications, and hospital stay.

The immunotherapy group had more sleeve resection (36.84% vs. 10.26%, p=0.039) including bronchial sleeve and vascular sleeve. The proportion of patients whose tumor reached pCR in the immunotherapy group was significantly higher than that in the chemotherapy group (57.89% vs. 5.13%, P<0.001) (Table 2). Additionally, the proportion of patients whose tumor reached MPR in immunotherapy group was significantly higher than that in chemotherapy group (78.95% vs. 10.26%, P<0.001). This difference persisted after propensity score matching (57.89% vs. 10.53%, P=0.002; 78.95% vs. 21.05%, P=0.001, respectively).

TRG scores of postoperative specimens were further analyzed (Figure 3). The results showed that the proportion of patients with a TRG score of "0" in the immunotherapy group was significantly higher than that in the chemotherapy group (57.89% vs. 5.13%, P<0.001), while the proportion with a TRG score of "3" was significantly lower than that in the chemotherapy group (5.26% vs. 51.28%, P<0.001).

TABLE 2 The comparison of the treatment results between the two groups.

Characteristics	Unmatched patients			Matched patients		
	Immunotherapy	Chemotherapy	P value	Immunotherapy	Chemotherapy	P value
Patients(n)	20	42		19	19	
R0 resection	19 (95.00%)†	39 (92.86%)†	1.000			
Sleeve resection	7 (36.84%)	4 (10.26%)	0.039	7 (36.84%)	3 (15.79%)	0.141
pCR	11 (57.89%)	2 (5.13%)	<0.001	11 (57.89%)	2 (10.53%)	0.002
MPR	15 (78.95%)	4 (10.26%)	<0.001	15 (78.95%)	4 (21.05%)	0.001
TRG			<0.001			0.001
0 - 1	15 (78.95%)	5 (12.82%)		15 (78.95%)	4 (21.05%)	
2 - 3	4 (21.05%)	34 (87.18%)		4 (21.05%)	15 (78.95%)	
Minimally invasive surgery‡	12 (63.16%)	16 (45.71%)	0.221	12 (63.16%)	9 (47.37%)	0.515
Pneumonectomy	2 (10.53%)	7 (20.00%)	0.610	2 (10.53%)	5 (26.32%)	0.405
Operative duration (min)	182.11 ± 67.19	170.31 ± 60.36	0.689	182.11 ± 67.19	179.63 ± 69.45	0.912
Blood loss (ml)§	120(20-1000)	150 (50-800)	0.403	120 (20-1000)	200 (50-800)	0.073
Overall complications	1 (5.26%)	6 (17.14%)	0.414	1 (5.26%)	3 (15.79%)	0.604
Hospital stay (days)	11.84 ± 4.17	14.36 ± 4.80	0.056	12.21 ± 4.37	14.89 ± 4.01	0.056

†Patients with R1 or R2 resection were excluded in the statistics of surgical outcomes in this table. ‡Minimally invasive surgery: Completely minimally invasive surgery. §The data of blood loss was described with the median (range) as they were not normally distributed, and Mann-Whitney U rank sum test was used. TRG, tumor regression grade. pCR, Pathological complete response. MPR, Major pathological response, indicated that there was more than 10% viable tumor remaining in postoperative specimen. Sleeve resection includes bronchial sleeve and vascular sleeve resection.

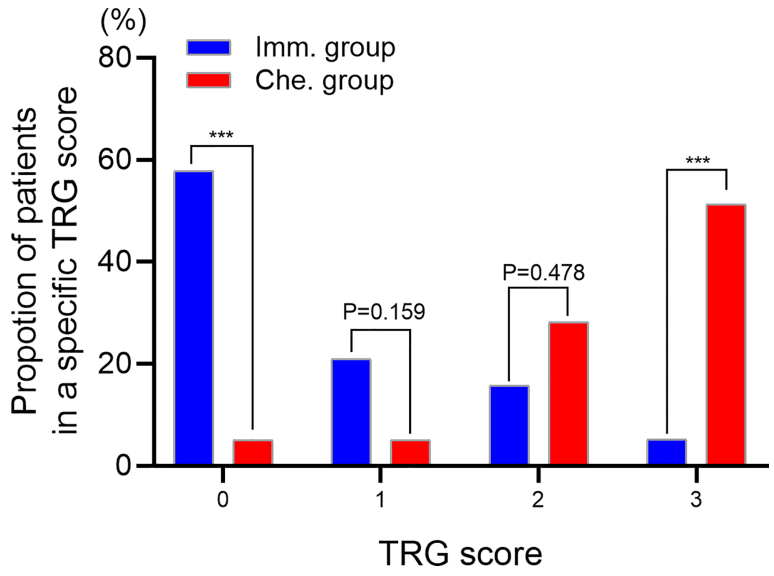

FIGURE 3
Evaluating the tumor regression grade (TRG) of postoperative specimens. TRG 0, no viable cancer cells. TRG 1, single cells or rare small groups of cancer cells. TRG 2, residual cancer with evident tumor regression. TRG 3, extensive residual cancer with no evident tumor regression. *** indicated P < 0.001. Imm., neoadjuvant immunotherapy combined chemotherapy. Che., neoadjuvant chemotherapy.

Survival analysis

All patients received CT and PET-CT evaluation on follow-up. The last follow-up was in June 2022. For all patients, the overall median follow-up period was 24 months (4 – 59 months). The 1-year OS was 93.1%, 2-year OS was 72.1%, and 3-year OS was 59.8%. There was no difference in survival curves between male and female, smoker and non-smoker, squamous cell carcinoma and adenocarcinoma, or right lung cancer and left lung cancer (Figures 4A-D). Moreover, patients who achieved MPR (including pCR) had significantly better OS (P=0.018) and DFS (P=0.016) (Figures 4E, F).

In the immunotherapy group, no death event occurred and 1 case experienced postoperative recurrence. The median follow-up period was 19 months (6 - 46 months), and the 3-year OS was 100%. In the chemotherapy group, the median follow-up period was 25 months (4 - 59 months). The 1-year OS was 77.3%, 2-year OS was 64.0%, and 3-year OS was 49.6%. Patients in the immunotherapy group had significantly better OS than those in the chemotherapy group (P = 0.014), and longer DFS (P = 0.006 (Figures 5A, B). After propensity score matching, we re-evaluated the impact of the two neoadjuvant therapies on the prognosis of patients. Neoadjuvant immunotherapy combined with chemotherapy was significantly associated with better OS (P=0.027) and better DFS (P < 0.042) (Figures 5C, D). Through COX regression analysis, female with hazard ratio 0.16 (95% CI, 0.03 to 0.95) and achieving MPR with hazard ratio 0.12 (95% CI, 0.01 to 0.93) were protective factors for DFS (Figure 6).

Discussion

We retrospectively analyzed the therapeutic outcomes and prognosis of neoadjuvant immunotherapy combined with chemotherapy for resectable NSCLC compared with neoadjuvant chemotherapy. Our results showed that neoadjuvant immunotherapy combined with chemotherapy can significantly improve the imagological regression of tumors, and patients had a significantly higher pCR rate, MPR rate, and better long-term prognosis with this combined therapy.

In our study, neoadjuvant immunotherapy combined with chemotherapy did not increase the risk of delayed surgery. It is well known that early diagnosis and timely operation can significantly improve the cure rate and survival of lung cancer (24). Tang et al. pointed out that when the time between diagnosis of lung cancer and surgery was greater than 50 days, patients' 1- and 5-year survival rates decreased (25). A study by Meyer et al. demonstrated that delaying surgery in favor of neoadjuvant therapy did not impair quality of life or result in additional tumors in cancer patients (26). In our study, we found that no patients in the neoadjuvant immunotherapy group experienced metastasis, recurrence, or death and that the neoadjuvant immunotherapy group experienced significantly improved DFS and OS compared with the neoadjuvant chemotherapy group.

Neoadjuvant immunotherapy combined with chemotherapy will not increase the unresectable rate. In this study, the R0 resection rate in the neoadjuvant immunotherapy group was

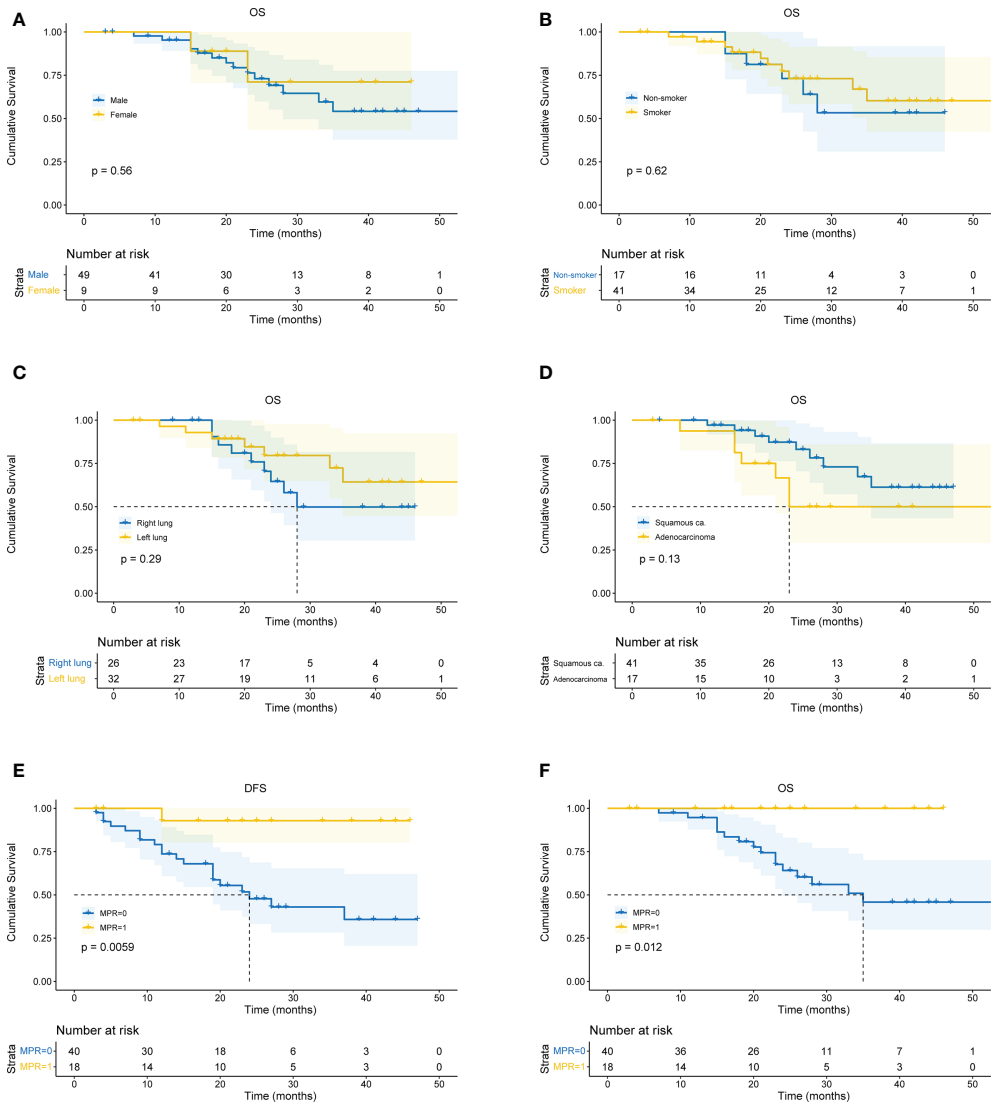

FIGURE 4
Kaplan-Meier curves for survival stratified by clinical parameters. **(A)** OS stratified by gender. **(B)** OS stratified by smoking status. **(C)** OS stratified by tumor location. **(D)** OS stratified by pathological type of cancer. **(E)** DFS stratified by MPR. **(F)** OS stratified by MPR. OS, overall survival. DFS, disease free survival. MPR, major pathological remissions. ca., carcinoma.

higher than in the neoadjuvant chemotherapy group (19/20, 95.00% vs 39/42, 92.86%, p=1.000). In CheckMate 816 trial, the R0 rate in neoadjuvant immunotherapy group was 83% (27). We adequately considered the integrated and radical resection of tumor. Not only did we ensure R0 resection rate, but the extent of resection was accorded to that before neoadjuvant therapy. This may also have something to do with our strict case selection. Additionally, no post-treatment tumor progression was observed in the neoadjuvant immunotherapy group (there were no increases in tumor diameter, no increases in tumor invasion, and no tumor metastasis). Of the patients in this group, there was 1 case of R2 resection, which was unresectable due to the invasion of the main bronchus by the seventh group of lymph nodes. After neoadjuvant therapy, the tumor diameter decreased by 44%, and the seventh group of lymph nodes decreased by 20%. In the neoadjuvant chemotherapy group, there were 4 cases without R0 resection. Therefore, the aim of neoadjuvant therapy in patients in more advanced stages is to shrink the tumor and convert tumors with unresectable margins into resectable lesions (28).

However, in some cases, the complexities of surgery could increase even after neoadjuvant chemoradiotherapy decreased the tumor stage (29, 30). This could be because neoadjuvant therapy can cause local tissue adhesions, which were observed in

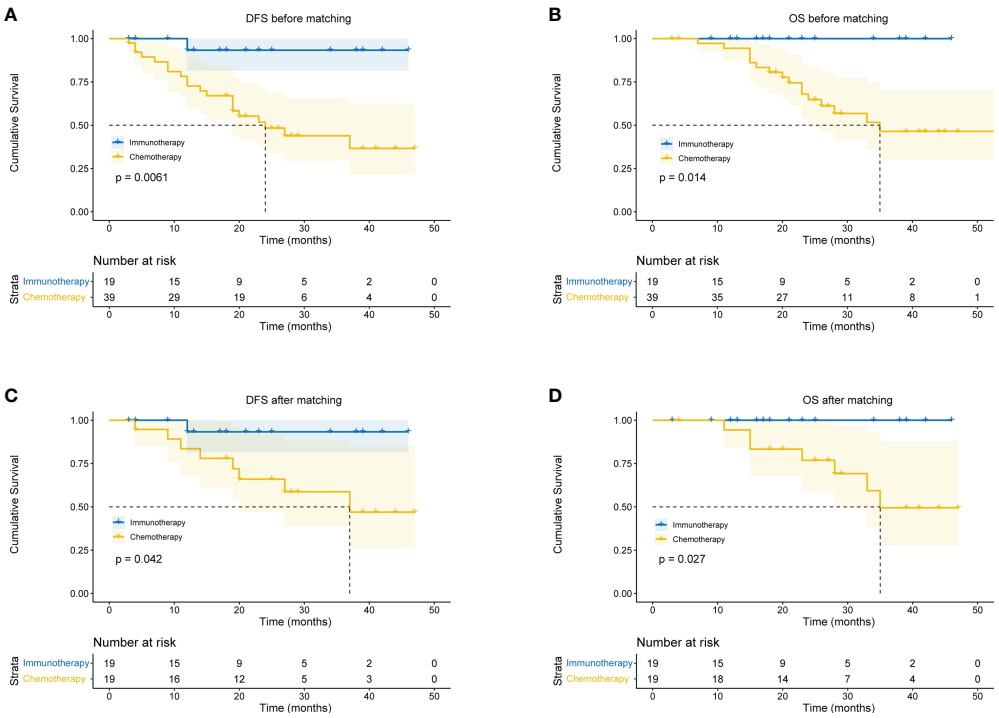

FIGURE 5
Kaplan-Meier curves for survival stratified by neoadjuvant therapy before or after propensity score matching. **(A)** DFS before PS matching. **(B)** OS before PS matching. **(C)** DFS after PS matching. **(D)** OS after PS matching. OS, overall survival; DFS, disease free survival; PS, propensity score.

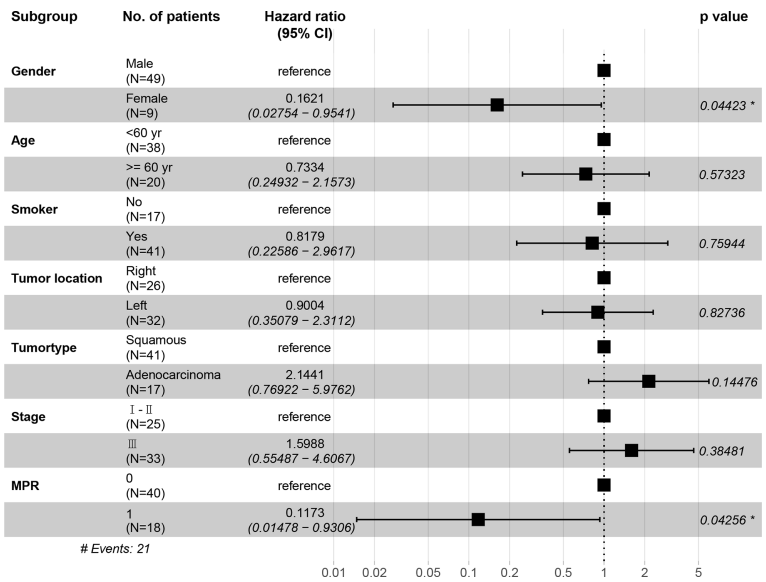

FIGURE 6
The hazard ratio of DFS among each subgroup shown in the forest plot. CI, confidence interval. *, indicates a significant difference. Stage, indicates the tumor stage at baseline.

patients experiencing significant responses to treatment. In this study, there was no significant difference observed in the surgery-related data between the two groups. The operation time for the neoadjuvant immunotherapy group was slightly longer than for the neoadjuvant chemotherapy group, which could be due to: 1) the small number of patients included in the study (which could create bias); and 2) killing tumor cells with PD-1/PD-L1 inhibitor requires antigen presentation by the tumor cells, which can then be recognized by the host T-cells. The activated T-cells can release cytokines after the blockade of the immunosuppressive PD1/PD-L1 interaction by inhibitory antibodies, which can kill the tumor cells (31). After killing the tumor cells, the local tumor bed and surrounding tissue are replaced by fibrous tissue, forming denser adhesions, which increases the difficulty of surgery and prolong the operation time.

The lack of a standardized approach for reporting the pathology of lung cancer patients resected after neoadjuvant therapy could indicate that pathologists are not involved in study designs (21, 32). We used the newer CAP/NCCN guidelines for tumor regression grading following neoadjuvant chemotherapy to evaluate postoperative pathological specimens in all cases, which increased the reliability of the study (33, 34). Our results demonstrate that the tumor regression grade of the neoadjuvant immunotherapy group was significantly better than that of the neoadjuvant chemotherapy group.

Neoadjuvant immunotherapy combined with chemotherapy significantly increased rates of pCR and MPR. One major limitation is MPR's lack of precision due to inherent inter-observer variability (13). However, it is well known that pCR or MPR is the primary endpoint of many neoadjuvant immunotherapy studies (22) and is associated with favorable tumor prognosis and improvements in overall survival (35, 36). MPR has been identified as a surrogate endpoint for survival in patients who received neoadjuvant therapy prior to lung cancer resection, while MPR improved the five-year overall survival rate from 40% to 85% (37, 38). Since MPR is associated with improved survival rates, it could provide a faster way to compare different neoadjuvant treatment options and reduce the time required to evaluate neoadjuvant therapies. Compared with patients who received only preoperative chemotherapy, the MPR rate was higher (16%) in patients with immunotherapy and chemotherapy (39) which was consistent with our results (40). However, it was difficult to obtain accurate postoperative pathological staging. Therefore, the comparison that based on the clinical TNM stage may be bias and we found that there were no significant differences between clinical stage I-II and stage III for DFS and OS respectively. Similarly, female seem to be a protective factor for DFS, possibly because of the small sample size and few events of DFS.To assess whether an increase in the pCR or MPR rate produced a survival benefit, we further analyzed OS and DFS. Survival rates were significantly higher in patients with pCR or MPR than in patients without pCR or MPR. Neoadjuvant immunotherapy significantly improved the survival rate of patients compared with the neoadjuvant chemotherapy group. Additionally, studies have demonstrated that neoadjuvant immunotherapy increased tumor-specific CD8+T cells in peripheral blood and organs. Therefore, neoadjuvant immunotherapy is better able to eradicate distant metastases and increase long-term survival rates after primary tumor resection than adjuvant immunotherapy (28). Currently, many clinical trials have analyzed the survival rates of lung cancer patients with neoadjuvant immunotherapy, and more attention is being paid to the safety and feasibility of neoadjuvant therapies. Most of the selected primary endpoints are either MPR or pCR (15, 41), or a short-term survival analysis (1-2 years) (42–44). In our study, the follow-up period was 24 months (6-53 months). There were no deaths and only 1 case of recurrence in the neoadjuvant immunotherapy group, which was an encouraging result.

Besides, our study provided clinical experiences in refining specific applications. Adjustments of clinical workflow and careful consideration for patient selection are undoubtedly necessary for neoadjuvant and adjuvant immunotherapy.

However, there were some limitations and shortcomings in our study. First, it was retrospective and lacked sufficient statistical analysis. Second, the sample size recruited was small and the follow-up time was short. We will continue this work with further follow-up and hope to obtain more accurate results in future studies.

Conclusions

The combination of neoadjuvant immunotherapy and chemotherapy can effectively shrink tumors, improve pCR and MPR rates of tumors, and help patients achieve better OS and DFS.

Author's note

Reporting Checklist: The authors have completed the STROBE reporting checklist.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Army Medical Center of PLA, approval number: 2021-273. The patients' individual consent for this retrospective analysis was waived.

Author contributions

Conception and design: WG. Administrative support: QT, RW. Provision of study materials or patients: CS, JZ, HN, QT, RW, WG. Collection and assembly of data: FD, XWa, YW, KL. Data analysis and interpretation: FD, XWu. Manuscript writing: All authors. Final approval of manuscript: All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Dramatic response to neoadjuvant savolitinib in marginally resectable lung adenocarcinoma with MET exon 14 skipping mutation: A case report and literature review

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Mesenchymal–epithelial transition (MET) exon 14 skipping mutation (METex14) is a low-frequency driver mutation in metastatic non-small cell lung cancer (NSCLC) (3%–4%) and is associated with a poor prognosis. With the advent of selective MET inhibitors such as capmatinib, tepotinib, and savolitinib, the outcome for these patients was significantly improved. Here, we report a 76-year-old male patient with marginally resectable stage IIIB lung adenocarcinoma harboring METex14 who was successfully treated with savolitinib for neoadjuvant therapy. An 82% shrinkage of the primary tumor was observed, and only 5% of the tumor was viable by pathology in the following radical surgery. A dozen of studies tested the efficiency of neoadjuvant immunotherapy or immunochemotherapy, but for NSCLC with driver mutations, neoadjuvant targeted therapy might be more appropriate. We advocated the neoadjuvant MET TKI treatment for NSCLC.

KEYWORDS

neoadjuvant therapy, savolitinib, MET exon 14 skipping mutation (METex14), NSCLC, case report, major pathological response

Introduction

The mesenchymal–epithelial transition (MET) factor, as a receptor for the hepatocyte growth factor (HGF), is encoded by the MET gene and plays a vital role in cancer progression. The major MET alterations were MET amplification and overexpression and MET exon 14 skipping mutation (METex14) (1). Specifically, METex14 occurs in approximately 3%–4% of non-small cell lung cancer (NSCLC) cases and is associated

with a worse prognosis, which has been a novel treatment target for NSCLC (2–5). In China, savolitinib was approved for the treatment of locally advanced or metastatic NSCLC with METex14 in patients who have progressed after or who are intolerant to platinum-based chemotherapy in 2021 (2).

To improve the prognosis of lung cancer, neoadjuvant strategies for NSCLC have aroused great interest. The significance of a molecular targeted agent as a preoperative treatment is currently unknown, whereas immunotherapy (IO) has shown promising results in phase 2 or 3 studies such as the LCMC3 (6), CheckMate-816 (7), and NADIM (8). It was observed that subjects with sensitive driver mutations usually were excluded from these trials. None of the patients harboring either EGFR mutations or ALK fusions (0/15) achieved a major pathological response (MPR) in the LCMC3 study (2). This strongly suggested that these patients with driver genes unlikely benefited from neoadjuvant immunotherapy. Neoadjuvant targeted therapy might be more appropriate.

Case presentation

A 76-year-old male patient with dyspnea, slight cough, weight loss (3 kg) in 2 months, and a history of smoking, without fever, chills, or syncope, visited our hospital on 7 September 2021. He had an Eastern Cooperative Oncology Group (ECOG) performance status of 2. A routine chest computed tomography (CT) scan showed a mass in the right lung, highly likely to be a tumor. A percutaneous pulmonary biopsy established the diagnosis of a poorly differentiated carcinoma (Figure 1A), with immunohistochemical (IHC) manifestation as CK (+), Ki-67 (~10%), TTF-1 (−), P63 (−), CgA (−), and Syn (−). A diagnostic workshop including enhanced CT scans of the chest and abdomen, MRI scan of the brain, and bone scintigraphy identified a soft tissue (5.8 × 4.9 cm) in the posterior segment of the right upper lobe, closely adjacent to the right superior lobe vein, compressing the bronchus, with right hilar and mediastinal lymph node enlargement (with a short diameter of 1.7 cm) (Figure 2A). Moreover, no distant metastasis was detected. His disease was evaluated as cT4N2M0, stage IIIB, which was considered a marginally resectable lesion through multidisciplinary team (MDT) discussion. Afterward, a next-generation sequencing (NGS) panel consisting of 56 driver genes (Burning Rock Biotech, China) was performed on his tumor sample and revealed MET exon 14 skipping mutation (METex14, 28.32%), point mutations in TP53, KDR, and KIT, and no EGFR/ALK alterations. PD-L1 expression and tumor mutation burden (TMB) were absent due to a limited biopsy sample. For unresectable locally advanced NSCLC, definitive chemoradiotherapy followed by durvalumab is the standard of care (SOC). Our patient was considered to have a marginally resectable disease through our MDT discussion, and then he was subjected to neoadjuvant therapy followed by surgical resection. The highly selective oral MET inhibitor savolitinib (HUTCHMED, AstraZeneca) was prescribed after getting the informed consent of the patient.

Oral savolitinib was commenced at a dose of 400 mg once daily. Six weeks later, a CT rescan identified dramatic regressions of the primary tumor (shrinkage of 69%, Figure 2B) and lymph nodes. The tumor response was assessed as a partial response (PR). The treatment was well tolerated with no adverse events. The symptoms of dyspnea and cough were relieved and the ECOG PS returned to 1. Another CT scan after an additional 1 month indicated an even smaller tumor (shrinkage of 82%, Figure 2C). After our MDT consultation, surgery was recommended. The patient underwent video-assisted thoracic surgery (VATS). Right upper lobectomy, wedge resection for the dorsal segment of the right lower lobe, and mediastinal lymph node dissection were performed. During the operation, mild pleural adhesion was observed without pleural effusion or pleural implants, blood loss was 30 ml, and the operative time was 60 min. In the postsurgical pathological examination, all dissected lymph nodes including stations 2R (3), 4R (4), and 7 (5) were free of tumor cells. The primary tumor was identified as a highly–moderately differentiated invasive adenocarcinoma (Figure 1B), confirmed by IHC [positive for TTF-1 (Figure 1E), Napsin A (Figure 1F), and CK7 (Figure 1G) and negative for CK5/6 (Figure 1H)], with 5% of the residual viable tumor and 95% of fibrosis and inflammation (Figures 1B–D). MPR was achieved. The patient was discharged and followed up for 8 months. Figure 3 demonstrates the timeline of the diagnosis, treatment, and follow-up of the patient.

Discussion

Our patient with marginally resectable lung adenocarcinoma harboring METex14 was successfully treated with savolitinib as neoadjuvant therapy. Recently, neoadjuvant strategies have aroused great interest. A dozen of studies tested the efficiency of neoadjuvant therapies, including targeted therapy, immunotherapy, or immunochemotherapy (Table 1). In the LCMC3 study, the largest neoadjuvant immunotherapy trial, two cycles of preoperative atezolizumab led to an MPR of 20.4% (30/181) and a pCR of 6.8% (6). Neoadjuvant immunochemotherapy has higher efficiency. The MPR was typically 36.9%–85% and the pCR was 18%–38% except for a higher pCR of 63% from the NADIM study (7–11). In the CheckMate-816 study, the immunotherapy combination achieved a pCR of 24.0% and an MPR of 36.9%, compared with 2.2% and 8.9% for chemotherapy. The median event-free survival was 31.6 and 20.8 months, respectively (7). Regarding toxicities, the rate of grade 3 or worse adverse events could be as low as 16.6% (LCMC3) (6) or as high as 88% (SAKK16/14) (9). Notably, none of the patients harboring either EGFR mutations

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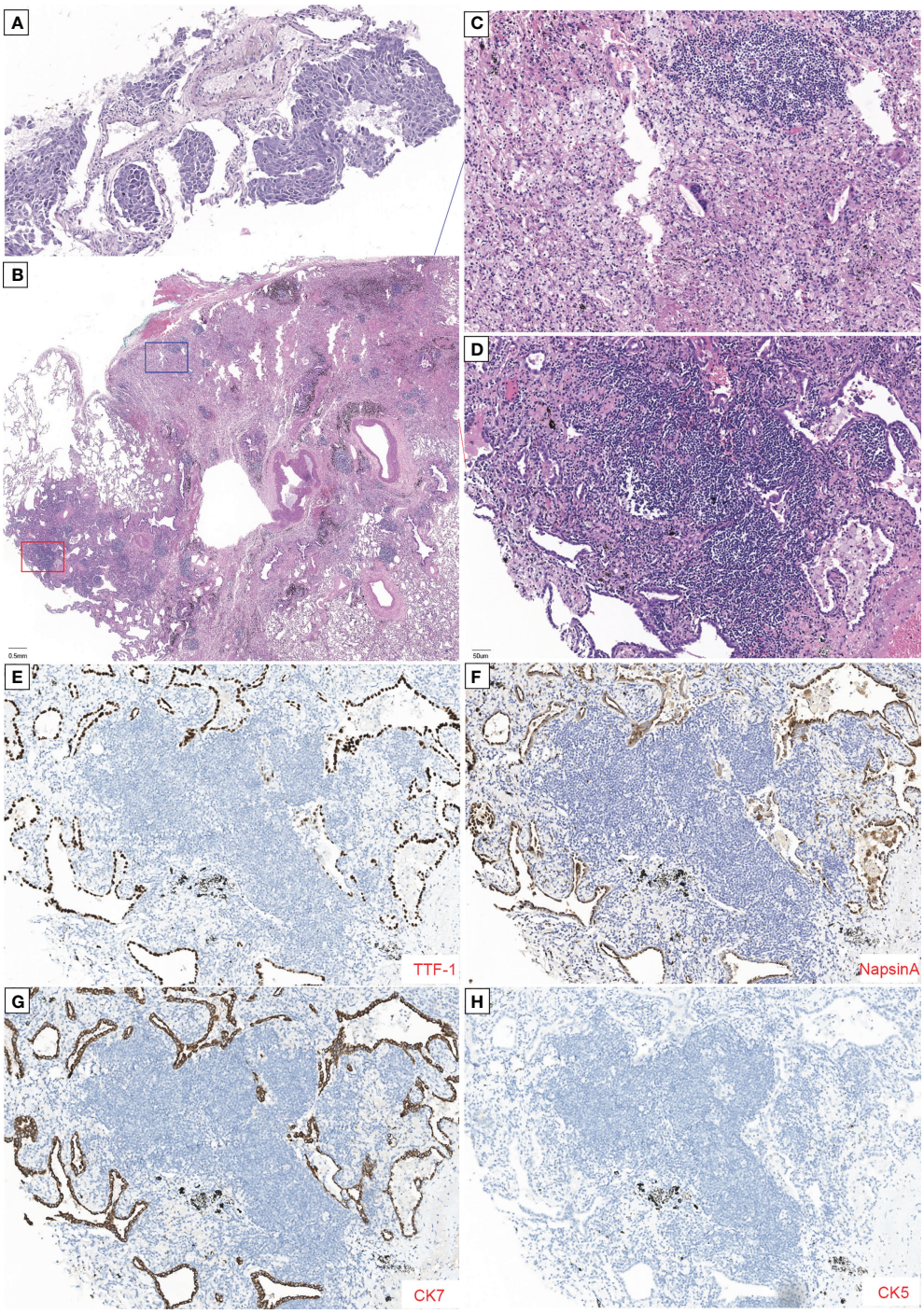

FIGURE 1
Histopathology of tumor with major pathological response (MPR) to neoadjuvant savolitinib. **(A)** High-power magnification (×200) shows tumor cell nests without inflammatory cell infiltration and initially diagnosed as a poorly differentiated carcinoma. **(B)** Low-power magnification (×20) shows that only 5% of this tumor was viable with 95% showing fibrosis and chronic inflammation without necrosis tissue in the pathology of postoperative samples by H&E staining. **(C, D)** Enlargement of the blue and red boxes in **(B)**. **(C)** H&E staining image shows numerous foam cells, multinucleated giant cells, and cholesterol crystals. No viable tumor was seen. **(D)** Higher power magnification shows the amount of inflammatory cell infiltration and the formation of lymphoid follicular, with the acinar type of tumor cells growing with adherence. Immunohistochemical (IHC) reveals that tumor cells were positive for TTF-1 **(E)**, Napsin A **(F)**, and CK7 **(G)** and negative for CK5 **(H)**. The scale length is 1 cm.

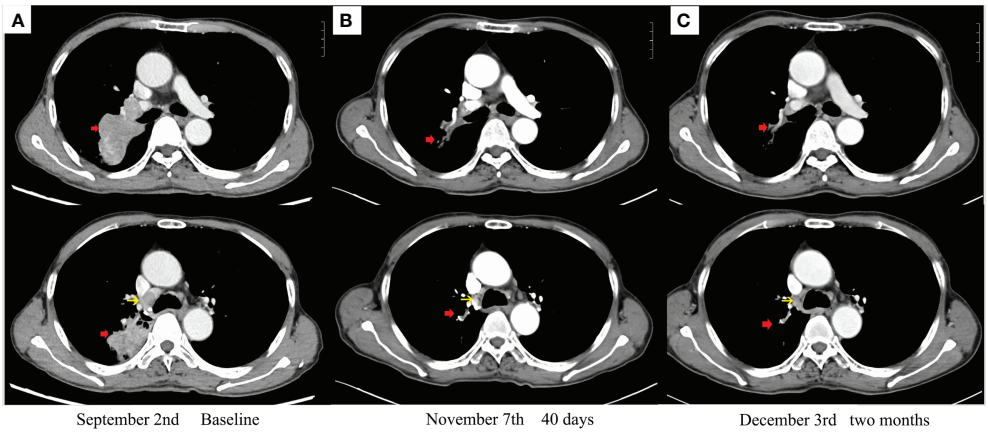

FIGURE 2
Enhanced chest CT scans during therapy: **(A)** baseline imaging. **(B)** After 40 days with savolitinib. **(C)** After 2 months with savolitinib. The red arrow indicates a primary tumor. The yellow arrow indicates metastatic lymph nodes.

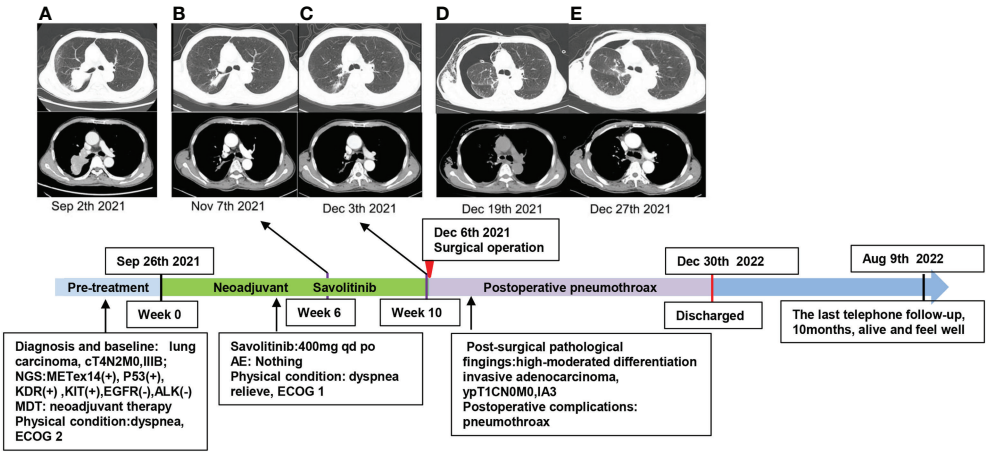

FIGURE 3
Timeline of the diagnosis and chest CT scans during the treatment and follow-up of this case. **(A)** Baseline imaging. **(B)** Treatment with savolitinib for 6 weeks. **(C)** Treatment with savolitinib for 10 weeks. **(D)** After 2 weeks of surgical operation, the patient had dyspnea, chest CT confirmed pneumothorax in the right lung, and closed thoracic drainage was performed on the patient. **(E)** Enhanced chest CT scans confirmed that the pneumothorax was improved 1 week later. The patient was alive and felt well at the last telephone follow-up on 9 August 2022.

or ALK rearrangement (0/15) achieved MPR in the LCMC3 study (6). This strongly suggested that these patients were unlikely to benefit from neoadjuvant immunotherapy.

For those with driver mutations, neoadjuvant targeted therapy might be more appropriate. In the EMERGING-CTONG1103 study, the only published RCT trial comparing neoadjuvant targeted therapy to platinum-based chemotherapy, neoadjuvant erlotinib achieved an MPR of 9.7% compared with 0% in the chemotherapy group. Moreover, the progression-free survival (PFS, 21.5 and 11.4 months) was significantly longer in the erlotinib group. Also, the overall survival (OS, 42.2 and 36.9 months) was numerically longer (18, 24). In another small-scale study, 11 patients with ALK rearrangement underwent surgery after neoadjuvant crizotinib therapy. Ten patients (91%) had R0 resection, including two cases of pCR (23). Furthermore, cases of successful neoadjuvant targeted therapy for ROS1, RET, or ALK rearrangement were reported (25–28). The prospective phase II ALNEO and NAUTIKA1 studies on neoadjuvant

TABLE 1 Summary of the published prospective neoadjuvant therapy trials.

	Pts	Neoadjuvant (ICI+CTH; ICI; target)	MPR (%)	pCR (%)	Survival		≥Grade3 TRAE (%)
					mDFS	mOS	
Forde 2022 (7)	358	Nivo+CTH vs. CTH	36.9 vs. 8.9	24 vs. 2.2	31.6 vs. 20.8 months	Not reached	34 vs. 37
Rothschild 2021 (9)	55	Durv+CTH	62	18	12 months: 73.3%	Not reached (28.6 months +)	88
Provencio 2022 (8)	41	Nivo+CTH	83	63	3 years: 81.1% 4 years: 81.1%	3 years: 91.0% 42 months: 87.3%	30.4
Shu 2020 (10)	30	Atez+CTH	57	33	17.9 m	Not reached (27.6 months +)	50
Zinner 2020 (11)	13	Nivo+CTH	85	38	NR	NR	15.4
Carbone 2021 (6)	181	Atez	20.4	6.8	1 year: 85%	1 year: 92%	16.6
Cascone 2021 (12)	44	Nivo; Nivo+ipil	22; 38	10; 38	Not reached	Not reached (22.2 months +)	13;10
Zhang 2022 (13)	40	Sint	40.5	8.1	3 years: 75%	3 years: 88.5%	10
Wislez 2021 (14)	46	Durv	NR	NR	18 months: 69.7%	Not reached	0
Besse 2020 (15)	30	Atez	14	0	NR	NR	10
Forde 2018 (16)	21	Nivo	45	15	18 months: 73%	Not reached	4.5
Chao 2022 (17)	40	Osim	10.7	3.6	NR	NR	7.5
Zhong 2021 (18)	72	Erlo vs. CTH	9.7 vs. 0	0 vs. 0	21.5 vs. 11.4 months	42.2 vs. 36.9 months	0 vs. 29.4
Xiong 2020 (19)	15	TKI	67	0	NR	51.0 months	NR
Zhang 2021 (20)	33	Gefi	24.2	NR	33.5 months	Not reached	0
Xiong 2019 (21)	19	Erlo	NR	NR	11.2 months	51.6 months	15.8
Tan 2019 (22)	13	Gefi	7.7	NR	20.2 months	NR	8
Zhang 2019 (23)	11	Criz	NR	18.2	NR	NR	9

CHT, doublet chemotherapy; DFS, disease-free survival; MPR, major pathological response; OS, overall survival; pCR, complete pathologic response; Nivo, nivolumab; Durv, durvalumab; Atez, atezolizumab; Ipil, ipilimumab; Sint, sintilimab; Osim, osimertinib; Erlo, erlotinib; Gefi, gefitinib; Criz, crizotinib; NR, not reported.

alectinib therapy finished enrolment, and preliminary results were reported (29, 30). For the completed resected patients harboring EGFR mutation, the phase III ADAURA study confirmed that osimertinib could achieve a longer DFS for stage IB to IIIA diseases. As a result, osimertinib is now recommended for these patients (31).

It should be noted that most, if not all, studies were performed on patients with resectable diseases. For those with marginally or potentially resectable lesions, preoperative therapy followed by surgery might also be possible. In an elegant pilot study, patients with initiative "unresectable" locally advanced lung cancer were successfully transformed into "resectable" disease by preoperative immunochemotherapy (32). This study highlighted the road to transformation of neoadjuvant treatment, given the high efficiency of the preoperative therapies.

METex14 is a low-frequency driver mutation in metastatic NSCLC (3%–4%) and is associated with a poor prognosis (1, 33). Patients with METex14 receiving chemotherapy had only an OS of 6.7 months (3). They also poorly responded to immune checkpoint inhibitors, with an objective response rate (ORR) of 17% and a PFS of 1.9 months (34). Non-specific inhibitors such as crizotinib brought an ORR of only 12% and a PFS of 2.6 months (35), which was far from satisfaction. Until now, three oral, highly selective, type Ib MET tyrosine kinase inhibitors (MET TKIs), namely savolitinib, tepotinib, and capmatinib, were approved for advanced NSCLC harboring METex14 (2, 4). Capmatinib and tepotinib were granted FDA approval, based on the results of the GEOMETRY mono-1 (capmatinib) and VISION (tepotinib) studies (4, 36, 37). In a crucial phase II trial conducted solely in a Chinese population (NCT02897479), savolitinib demonstrated an encouraging ORR of 49.2%, a disease control rate (DCR) of 93.4%, and a median overall survival (mOS) of 12.5 months (38). Savolitinib was approved for the treatment of advanced NSCLC patients with METex14 who progressed after or were intolerant to platinum-based chemotherapy (2). Savolitinib was the only one of this kind that got approval in China. Our patient was prescribed savolitinib.

Considering the high response rate of savolitinib, the neoadjuvant transformation strategy was explored in our patient. This treatment led to objective tumor regression, confirmed by the pathological response in the following

radical surgery. In our case, we advocated the neoadjuvant MET TKI treatment for NSCLC. In support of our proposal, a phase 2 trial (NCT04926831) of perioperative capmatinib in NSCLC with METex14 or MET amplification is being conducted. The results of this trial are warranted.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors conceived, directed, and supervised this paper. JT and ZL were responsible for data collection and manuscript writing. ZD revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy and safety evaluation of neoadjuvant immunotherapy plus chemotherapy for resectable non–small cell lung cancer in real world

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Objectives: The combination of immunotherapy and chemotherapy has shown great efficacy in stage IV non–small cell lung cancer (NSCLC) and is now widely used in clinical treatment strategy. This study retrospectively analyzed the efficacy and safety of neoadjuvant immunotherapy plus chemotherapy for resectable NSCLC in real world.

Methods: We retrospectively analyzed patients with NSCLC who received neoadjuvant immunotherapy plus chemotherapy and underwent complete tumor resection in Zhejiang Cancer Hospital between January 2019 and January 2021. Tumor staging was based on the eighth TNM classification system of the American Joint Committee on Cancer staging criteria. The safety and toxicity (including operative and postoperative complications) and the efficacy [including objective response rate (ORR), disease control rate (DCR), tumor major pathological remission (MPR), and pathological complete response (pCR)] were evaluated.

Results: In total, 368 patients with NSCLC were administered with neoadjuvant immunotherapy. Of them, 211 patients were included in this retrospective study. Most patients had stage II–III disease, with 75 (35.5%) and 88 (41.7%) patients diagnosed with clinical stages IIB and IIIA, respectively. A total of 206 patients (97.6%) received at least two doses of neoadjuvant immunotherapy plus chemotherapy. In addition, 121 patients (57.3%) have achieved MPR, and 80 patients (37.9%) have achieved pCR, with ORR at 69.2% and DCR at 97.7%. Treatment-related adverse events occurred in 46.4% of patients, and the incidence rate of grade 3 or 4 treatment-related adverse events was 13.3% (13/

98). Moreover, adverse events of any grade of surgical complication occurred in 15.6% of patients. One-year disease-free survival was 80.6% (170/211).

Conclusions: Neoadjuvant immunotherapy plus chemotherapy has significant efficacy with a high pCR and tolerable adverse effects for patients with resectable stage II–III NSCLC in real world.

KEYWORDS

NSCLC, neoadjuvant, immunotherapy, chemotherapy, surgery

Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide, and non–small cell lung cancer (NSCLC) accounts for 80%–85% of new cancer cases (1). Despite the combination of multimodal therapy treatment strategy including surgery, chemotherapy, and radiotherapy for patients with resectable NSCLC, 25%–70% of patients at different stages will relapse in 5 years (2). In the past decades, although many efforts have been made to develop the perioperative management of resectable NSCLC (3, 4), patients still have to face a high risk of recurrence and death. Therefore, it is still of urgent need to develop new treatment methods.

In past 5 years, immune checkpoint inhibitors (ICIs), especially programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, have significantly changed the treatment paradigm for patients with advanced NSCLC and provided long-term survival hope for patients with metastatic lung cancer. Now, PD-1 and PD-L1 inhibitors combined with chemotherapy have become the standard first-line treatment methods for advanced NSCLC (5–7). Given the profound impact of PD-1 and PD-L1 inhibitors on advanced NSCLC, many experts have paid great attention to investigating the potential role of ICIs in resectable NSCLC, and several undergoing clinical trials have reported promising results (8–11). The Checkmate 159 trial was the first study to use PD-1 inhibitor as neoadjuvant regimen for resectable NSCLC, and it showed that, after two doses of nivolumab preoperatively, 45% of resected tumors (9/20) had a major pathological remission (MPR), and 10% of patients (2/20) even achieved a pathological complete response (pCR) (12). The NADIM trial (NCT 03081689) applied three preoperative cylces of PD-1 inhibitor with chemotherapy on individuals with stage IIIA disease. The results showed that 41 patients had underwent tumor resection, 34 (83%) had achieved MPR, 26 (63%) had achieved pCR. Moreover, 37 patients (90%) achieved pathlogical downstaging, and 35 patients (85%) are alive and free of recurrence with a median follow-up of 24 months (9). Recently, the phase 3 Checkmate 816 trial showed that neoadjuvant with nivolumab and chemotherapy significantly improved the pCR (24.0%) compared with traditional chemotherapy (2.2%) for resectable NSCLC with a tolerable safety (13). All these data revealed that the neoadjuvant immunotherapy combined with chemotherapy may provide a new treatment strategy for resectable NSCLC.

In this study, we retrospectively collected data from 211 patients with resectable stage IB–IIIB NSCLC, who have received neoadjuvant immunotherapy plus chemotherapy and underwent complete tumor resection in our center to evaluate the efficacy and safety.

Methods

Patients and data collection

Patients with NSCLC who received neoadjuvant immunotherapy plus chemotherapy and underwent radical resection between January 2019 to January 2021 in Zhejiang Cancer Hospital were reviewed. A total of 211 patients with NSCLC identified from a screened population of 368 patients were enrolled in this study. The main inclusion criteria were as follows (1): histologically confirmed NSCLC (2), clinically stages I–III (3), no metastatic cervical lymph nodes or prior cancer therapy (4), negative driver mutation (5), received at least one dose of neoadjuvant immunotherapy plus chemotherapy, and (6) underwent radical surgery with curative intent. Tumor staging was based on the eighth TNM classification system of the American Joint Committee on Cancer staging criteria. All patients underwent routine baseline tumor diagnosis and staging, including chest computed tomography (CT), brain magnetic resonance imaging, and positron emission tomography–CT (PET-CT). The neoadjuvant regimen was PD-1 inhibitors combined with platinum-based chemotherapy, which was administered intravenously every 21 days. The PD-1 inhibitors include nivolumab, pembrolizumab, camrelizumab,

toripalimab, sintilimab, and tislelizumab. Preoperative chest CT scan was necessary to evaluate the efficacy of neoadjuvant regimen. Follow-up information was obtained through inpatient medical records and telephone inquiries. The last follow-up date was 1 March 2022. This retrospective study was approved by the Institutional Ethics Board of Cancer Hospital of the University of Chinese Academy (No. IRB-2022-48).

Study end points and assessment method

Radiological response of the tumor including objective response rate (ORR) and disease control rate (DCR) was assessed after neoadjuvant immunotherapy plus chemotherapy and before the operation according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Disease-free survival (DFS) was defined as the time from diagnosis to disease progression, relapse, or death, whichever came first.

Postoperative pathological remission including MPR and pCR was assessed by specilaized pathologist after neoadjuvant immunotherapy plus chemotherapy. MPR is defined as neoadjuvant therapy–induced tumor regression with less than 10% vital tumor tissue, and pCR is defined as neoadjuvant therapy–induced complete tumor regression without vital tumor tissue (14).

Neoadjuvant therapy adverse events were evaluated on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. From the beginning of neoadjuvant immunotherapy to the end of the treatment within 1 month, any adverse events that occurred, regardless of whether there is a relationship with the neoadjuvant immunotherapy, were judged as an adverse event. Time to surgery is defined as the time from the end of neoadjuvant therapy to the surgical operation. Postoperative complications occurred within 30 days after surgery were documented, including pain, anemia, subcutaneous emphysema, prolonged air leak, pneumonia, pleural effusion, and atrial fibrillation.

Statistical analysis

Patients were characterized by clinicopathological variables such as age, sex, histology, and stage. Categorical variables were presented as absolute and relative frequency, and numerical variables were presented as mean (SD) or median. The median length of follow-up was calculated using the Kaplan–Meier method. The Kaplan–Meier method was also used to calculate the DFS. All the statistical tests were two-sided with a significance level at $p<0.05$. Statistical analyses were performed with the SPSS 25.0.

Results

Patients and treatments

From January 2019 to January 2021, 211 patients who were diagnosed with primary NSCLC underwent radical R0 resection after neoadjuvant immunotherapy plus chemotherapy in our center. The major clinicopathological characteristics of 211 patients were shown in Table 1. The patients were predominately male patients (196, 92.9%) and pathologically confirmed squamous cell carcinoma (172, 82%). Most patients were in stages IIB (75, 35.5%) and IIIA (88, 41.7%). Most of them (206, 97.6%) received at least two doses of immunotherapy plus chemotherapy. A total of 139 patients (65.9%) received adjuvant immunotherapy after surgery.

Surgery summary

The median time to surgery was 4.1 (range, 0.9–17.4) weeks. The minimally invasive approach was more common, 154 patients (73.0%) underwent thoracoscopy surgery, 41 patients (19.4%) underwent thoracotomy, and 16 cases (7.6%) required conversion from thoracoscopy to thoracotomy. There are a total of 169 patients (80.1%) underwent lobectomy, 33 patients (15.6%) underwent sleeve lobectomy, and 9 patients (4.3%) underwent left pneumonectomy. The differences in surgical patterns of different cTNM stage were shown in Figure 1. The median length of hospitalization was 11 days (range, 5–31).

Pathological assessment and efficacy

According to the RECIST v1.1, four patients achieved CR, 142 patients achieved PR (partial response), 60 patients achieved SD (stable disease), and 1 patient were evaluated PD (progression disease). In addition, four patients were unknown due to the lack of imaging data after neoadjuvant immunotherapy plus chemotherapy. The ORR was 69.2%, and DCR was 97.7%. A total of 179 patients and 120 patients experienced T downstaged and N downstaged, respectively (Table 1). According to the postoperative pathological results, the percentage of pCR and MPR was 37.9% (80/211) and 57.3% (121/211), respectively. The depth of pathological regression in the primary tumor was shown in Figure 2A. Among patients achieved MPR, 50 patients (41.3%) were in stage II, of which ypN0, ypN1, and ypN2 were 84.0% (42/50), 8.0% (4/50), and 8.0% (4/50), respectively; and 71 patients (54.1%) were in stage III, of which ypN0, ypN1, and ypN2 were 85.9% (61/71), 8.5% (6/71), and 5.6% (4/71), respectively. Among patients who achieved pCR, 29 patients (36.3%) were in stage II and 51 patients (63.7%) were in stage III (Figure 2B). More patients

TABLE 1 Clinicopathological characteristics of 211 patients.

Characteristics	All patients (n, %)
Age, median (range), years	64 (38–77)
Sex Male Female	196 (92.9) 15 (7.1)
Smoking status Current/former Never	181 (85.8) 30 (14.2)
Histologic type of tumor Squamous Adenocarcinoma Other type/unknown	172 (81.5) 28 (13.3) 11 (5.2)
Disease stage at baseline	
IB	2 (0.9)
IIA	7 (3.3)
IIB	75 (35.5)
IIIA	88 (41.7)
IIIB	39 (18.5)
Doses of neoadjuvant immunotherapy 1 2 3 4	5 (2.4) 148 (70.1) 39 (18.5) 19 (9.0)
Adjuvant therapy*	
None	55 (6.1)
Chemotherapy	98 (46.4)
Immunotherapy	143 (67.8)
Radiotherapy	7(3.3)
T category downstaged	179 (84.8)
T category upstaged	13 (6.2)
N category downstaged	120 (56.9)
N category upstaged	17 (8.1)
*Eighty-nine patients received more than one adjuvant therapy.	

with squamous cell carcinoma could be observed in the MPR (χ^2 = 8.998, p = 0.003) and pCR group (χ^2 = 4.475, p = 0.034), with 71 patients (41.2%) who achieved pCR and 107 patients (62.2%) who achieved MPR (Figure 2C).

In addition, compared with the evaluation results of CT and postoperative pathology, the RECIST v1.1 evaluation based on preoperative CT imaging could not fully reflect the patient's final pathological remission status. In addition, 1 patient who has been evaluated PD by radiologic assessment was confirmed to have no disease progression after surgery. Among 80 patients who achieved pCR, only four patients showed CR according to the RECIST v1.1, whereas 63 patients showed PR and 10 patients showed SD. The conformity between radiologic assessment and pathological assessment was 48.3% (102/211). The difference between the preoperative CT imaging and pathological evaluation results of a representative patient was shown in Figure 3.

At a median follow-up of 17.0 months, 1-year DFS was 80.6% (170/211). Twenty-eight patients have relapsed, and the specific progression patterns were shown in Table 2. In addition, 14 patients died during postoperative follow-up. Among them, six patients were related with tumor progression, three patients were dead within 30 days after surgery, three patients died with immune-related adverse events during the postoperative adjuvant immunotherapy, and another two patients died with unknown cause.

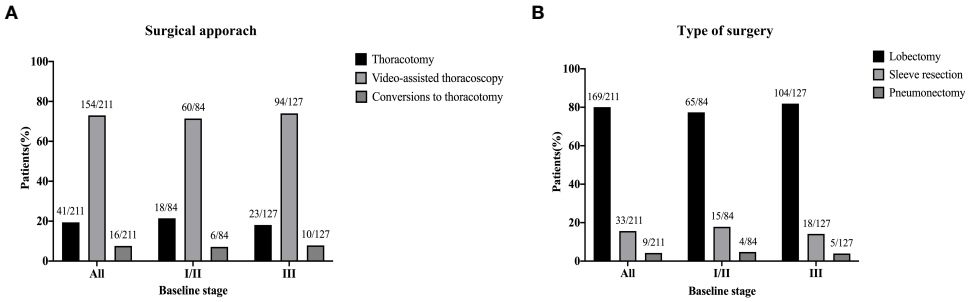

FIGURE 1
Surgical approach **(A)** and type of surgery **(B)** of patients by baseline stages of disease.

Safety and surgical complications

No previously unreported toxicities were observed in relation to the neoadjuvant immunotherapy plus chemotherapy. Overall, the incidence of treatment-related adverse events (TRAEs) was low, and most were grade 1 or 2. TRAE occurred in 46.4% of patients, and the incidence rate of grade 3 or 4 TRAE was 13.3% (13/98). The most common grade 3 or 4 TRAE was neutropenia (1.9%), immune-related hepatitis (1.4%), immune-related pneumonia (0.5%), thrombocytopenia (0.9%), and rash (0.9%) (Table 3). Among all these patients, 31 of them occurred more than two adverse events and six patients terminated the neoadjuvant immunotherapy due to the toxic effects.

Adverse events in any grade of surgical complication occurred in 15.6% of patients. The most common adverse events were prolonged air leak (7, 21.2%) and pleural effusion (7, 21.2%) (Table 4). In addition, one patient experienced reoperation due to postoperative bleeding, and two patients experienced pulmonary embolism.

Discussion

Neoadjuvant immunotherapy plus chemotherapy for resectable NSCLC is promising and attractive. This study is a retrospective real-world assessment of neoadjuvant PD-1

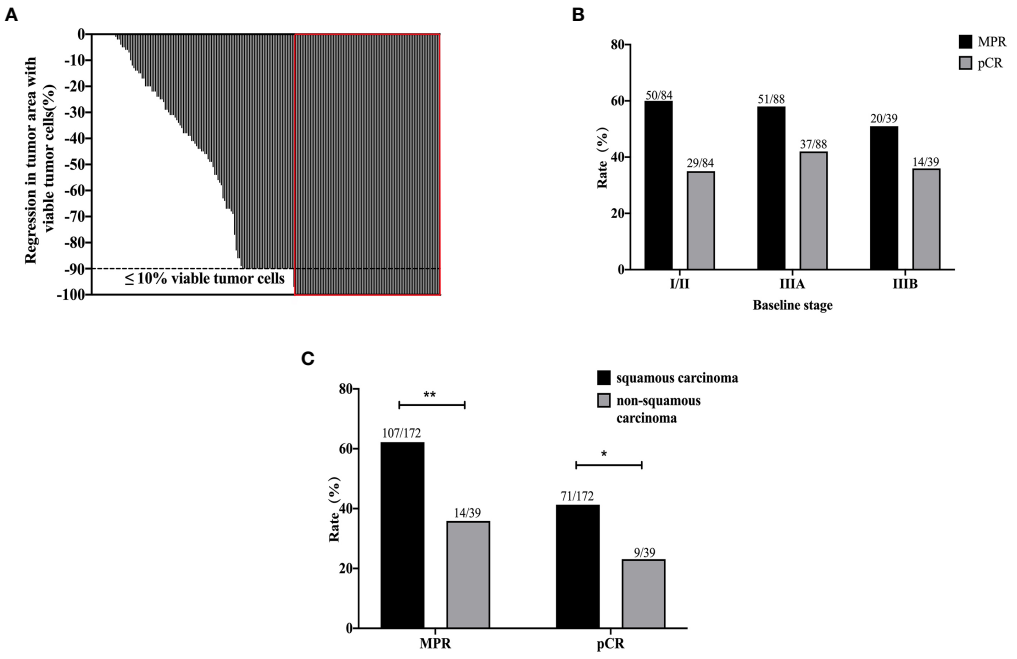

FIGURE 2
The pathological results of all 211 patients after neoadjuvant immunotherapy plus chemotherapy. The depth of pathological regression of all patients **(A)**. The MPR and pCR results by baseline stages of disease **(B)**. The MPR and pCR results of squamous carcinoma and non-squamous carcinoma **(C)**. **p < 0.01; *p < 0.05.

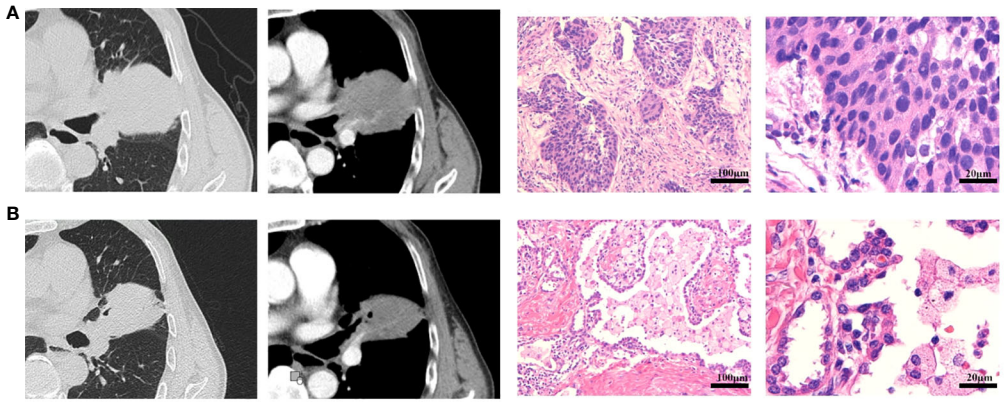

FIGURE 3
Radiological and pathological response of neoadjuvant immunotherapy plus chemotherapy. **(A)** The CT imaging and pathological diagnosis at baseline. **(B)** The CT imaging after two doses of neoadjuvant immunotherapy plus chemotherapy, and the pathological results after surgery. This was a 70-year-old male patient with smoking history, who was diagnosed as cT3N1M0 (stage IIIA) squamous cell carcinoma at baseline. After two doses of neoadjuvant immunotherapy plus chemotherapy, the patient achieved SD according to RECIST v1.1 with CT imaging assessment of 24% shrinkage of tumor. This patient underwent R0 resection with sleeve lobectomy and the pathological results with pCR. The regression bed is characterized by dense immune infiltrates with features of activation (tertiary lymphoid structure and dense tumor infiltrating lymphocytes infiltrates), along with features of cell death.

inhibitors plus platinum–based chemotherapy in patients with resectable stage I–III NSCLC. Neoadjuvant therapy given prior to radical surgery is usually conducted to downstage and improve the R0 resection rate in real world, and it had better compliance than adjuvant setting, with the biological effect that could be analyzed directly in the resected specimens (2). However, in the setting of neoadjuvant chemotherapy, the efficacy is relatively poor for NSCLC with pCR less than 4% (14). In addition, neoadjuvant chemotherapy just improved 5% of the 5-year survival rate on patients with resectable NSCLC with stage IB–IIIA (15). In our study, the combination treatment regimen with immunotherapy achieved significantly higher pathological response (MPR, 57.3%; pCR, 37.9%) compared with the historical neoadjuvant chemotherapy and tolerable adverse events. There are also several phase Ib/II clinical trials (9, 10, 12, 16–19), and a randomized phase III clinical trial (20) of neoadjuvant immunotherapy plus chemotherapy reported promising results. In the NADIM trial, the MPR rate was 83% (34/41). However, the initial results of the NEOMUN trial, which used pembrolizumab plus chemotherapy, reported that only four patients achieved MPR in 13 cases (17). Thus, the efficacy of neoadjuvant immunotherapy plus chemotherapy remained controversial based on the existing pilot studies, and more evidence is yet needed. The first reported phase III trial CheckMate 816 reported that neoadjuvant nivolumab plus chemotherapy significantly increased the MPR rates (36.9% vs. 8.9%, $p < 0.05$) and pCR rates (24.0% vs. 2.2%, $p < 0.001$) compared with neoadjuvant chemotherapy alone. Consistent with these clinical trials, higher percentage of pCR and MPR rate in squamous carcinoma group than that in non-squamous group was observed in our study with statistical significance (41.3% vs. 23.1% and 62.2% vs. 35.9%, respectively). In addition, patients with stage III NSCLC have the trend to benefit more from the combination treatment regimen than stage IB or II patients (pCR, 40.2% vs. 34.9%), which is consistent with previous reports of adjuvant chemotherapy (21).

National Comprehensive Cancer Network guidelines recommended four doses of adjuvant chemotherapy, whereas the dose of neoadjuvant immunotherapy plus chemotherapy is inconclusive. In general, most studies choose two to four doses, whereas CheckMate159 (12) and LCMC3 (19) trials chose two doses, NADIM (9) and CheckMate 816 trials were of three doses, and NCT02716038 trial (10) was of four doses. In addition, a meta-analysis showed that three doses of neoadjuvant chemotherapy could reduce the risk of death (15). In our study, more than two-thirds of patients received two doses of neoadjuvant of immunotherapy plus chemotherapy. In addition, 54.7% (81/148) of patients achieved MPR and 35.8% (53/148) achieved pCR. In the three or more doses subgroup, the percentage of MPR and pCR was 65.5% (38/58) and 44.8% (26/58), respectively. The results demonstrated that the increase of the neoadjuvant dose may have the trend to improve the pCR and MPR rate. In addition, preclinical studies suggested that there is a window between neoadjuvant immunotherapy and surgery, and shortening or delaying the interval between surgery and neoadjuvant immunotherapy could lead T cells to become inactivated or return to dysfunctional state, which will significantly affect survival (22). It is really challenging to determine the timing of surgery after neoadjuvant immunotherapy to ensure the strongest activity of T cells. In the NADIM trial, it is suggested to take operation 3 to 7 weeks after the end of neoadjuvant immunotherapy. In addition, the

TABLE 2 The specific progression patterns of 28 patients.

Patient No.	cTNM	ypTNM	MPR or pCR	Progression pattern
3	$cT_3N_2M_0$	$ypT_{1b}N_0M_0$	–	Regional
7	$cT_{2b}N_1M_0$	$ypT_0N_0M_0$	pCR	Regional+Distant
9	$cT_2N_2M_0$	$ypT_0N_2M_0$	MPR	Regional+Distant
33	$cT_{2a}N_1M_0$	$ypT_0N_2M_0$	MPR	Regional
48	$cT_3N_2M_0$	$ypT_{2b}N_0M_0$	–	Regional+Distant
52	$cT_3N_0M_0$	$ypT_{1a}N_1M_0$	MPR	Regional
61	$cT_3N_2M_0$	$ypT_{2a}N_1M_0$	–	Regional
64	$cT_3N_0M_0$	$ypT_3N_2M_0$	–	Distant
79	$cT_3N_2M_0$	$ypT_3N_1M_0$	–	Regional+Distant
84	$cT_{1b}N_2M_0$	$ypT_0N_0M_0$	pCR	Distant
88	$cT_3N_2M_0$	$ypT_0N_0M_0$	pCR	Regional+Distant
101	$cT_3N_0M_0$	$ypT_{2b}N_0M_0$	–	Regional
112	$cT_3N_2M_0$	$ypT_{1a}N_2M_0$	MPR	Regional+Distant
114	$cT_4N_0M_0$	$ypT_4N_0M_0$	–	Regional
115	$cT_3N_2M_0$	$ypT_{2a}N_0M_0$	–	Regional+Distant
117	$cT_3N_0M_0$	$ypT_{2a}N_0M_0$	–	Distant
145	$cT_3N_2M_0$	$ypT_{1a}N_0M_0$	MPR	Regional+Distant
174	$cT_{2a}N_2M_0$	$ypT_4N_2M_0$	–	Regional
176	$cT_{2a}N_2M_0$	$ypT_{2b}N_1M_0$	–	Distant
177	$cT_{1c}N_2M_0$	$ypT_{1b}N_2M_0$	–	Regional
178	$cT_4N_2M_0$	$ypT_4N_1M_0$	–	Regional
186	$cT_{2b}N_2M_0$	$ypT_2N_2M_0$	MPR	Distant
188	$cT_{2a}N_1M_0$	$ypT_{2b}N_2M_0$	–	Regional
34*	$cT_3N_1M_0$	$ypT_{2b}N_0M_0$	–	Regional
41*	$cT_4N_1M_0$	$ypT_0N_0M_0$	pCR	Distant
62*	$cT_4N_2M_0$	$ypT_{1c}N_0M_0$	–	Distant
162*	$cT_{1b}N_1M_0$	$ypT_4N_1M_0$	–	Regional+Distant
208*	$cT_{1c}N_1M_0$	$ypT_2N_2M_0$	–	Distant

*indicates that the patients were dead.

Checkmate 816 trial suggested to take operation within 6 weeks. An expert consensus for 2020 recommended to take operation 4 to 6 weeks after the last neoadjuvant immunotherapy (23). In this study, the median time between the end of neoadjuvant immunotherapy and surgery was 4.1 weeks. All patients underwent R0 resection, 73.7% of patients underwent minimally invasive surgery, and less than 10% patients received the conversion to thoracotomy. Moreover the addition of PD-1 inhibitors to neoadjuvant chemotherapy did not increase the incidence of surgery complications or impede the feasibility of surgery, as well as the length of hospitalization. These results indicated that the surgery timing in 4 to 6 weeks after the last neoadjuvant immunotherapy is practicable.

Notably, although studies have proposed MPR as a surrogate end point in neoadjuvant trials for resectable NSCLC (24–27), the relation between pCR and survival is still under debate in the setting of neoadjuvant immunotherapy. In the NADIM trial, the radiologic response according to CT scans and pCR was not significantly associated with survival (28). Unlike conventional chemotherapy, the response pattern of patients treated with

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TABLE 3 Treatment-related adverse events during neoadjuvant immunotherapy plus chemotherapy.

Adverse events, n (%)	Grade 1–2	Grade 3–4
Neutropenia	30 (14.2)	4 (1.9)
Decreased appetite	7 (3.3)	–
Fatigue	5 (2.4)	–
Nausea	4 (1.9)	–
Anemia	30 (14.2)	–
Rash	5 (2.4)	2 (0.9)
Increased aminotransferases	14 (6.6)	1 (0.5)
Thrombocytopenia	17(8.1)	2(0.9)
Pneumonia	2 (0.9)	1 (0.5)
Hepatitis	–	3 (1.4)
Fever	7 (3.3)	–
Arthralgia	5 (2.4)	–
Ninety-eight patients occurred treatment-related adverse events, of which 31 patients occurred more than two AEs (adverse events).		

immunotherapy may be different, with some patients developing pseudo-progression or hyperprogression (29). As in our study, the CT evaluation could not accurately reflect the efficacy of neoadjuvant immunotherapy, and recent studies showed that FDG PET-CT could better play the role in assessment of response to immunotherapy (30, 31). In addition, a recent study from the International Neoadjuvant Melanoma Consortium supports the role of pCR as an early surrogate end point for recurrence-free survival and overall survival (27). In our study, although we do not have the long-term survival data due to the short follow up, among the 28 patients who have progressed after surgery during follow up, only four patients were pCR, which may indicate that pCR may be related with better DFS. Thus, in this regard, it still need more trials and long follow-up to illustrate whether pCR is an appropriate surrogate end point. In addition, in the NADIM trial, PD-L1 expression could not predict survival (28), which was similar with the studies in metastatic NSCLC (5, 32). The SAKK 16/14 trial

TABLE 4 Surgery-related adverse events.

Postoperative complications	n (%)
Pain	3 (1.4)
pneumothorax	7 (3.3)
Subcutaneous emphysema	2 (0.9)
Atrial fibrillation	1 (0.5)
Pleural effusion	6 (2.8)
Hypokalemia	4 (1.9)
Hyperkalemia	1 (0.5)
Postoperative bleeding	2 (0.9)
Anemia	2 (0.9)
Pulmonary embolism	2 (0.9)
Pulmonary atelectasis	1 (0.5)
Hoarseness	2 (0.9)
Pneumonia	7 (3.3)
Thirty-three patients occurred surgical complications, of which 10 patients occurred more than two AEs.	

also demonstrated that there was no association between MPR and pretreatment PD-L1 expression (33). Thus, the PD-L1 expression was not mandatory in this study.

Overall, the preliminary results in this study showed the excellent efficacy of the neoadjuvant immunotherapy plus chemotherapy in resectable NSCLC. In addition, the addition of neoadjuvant of immunotherapy did not increase the difficulty of surgical procedure and surgery-related adverse events. However, there are some limitations in our study. It is a retrospective study from a single cancer center with short-term follow up, and there may be omissions in the records of immune-related and surgery-related adverse events. In addition, the PD-L1 expression status of patients at baseline and the patient reported outcomes were not recorded. This study only included patients who had undergone R0 resection after neoadjuvant immunotherapy, and the adjuvant therapy was not well controlled. Numerous questions still need to be investigated, such as the dose of neoadjuvant immunotherapy, the maintenance immunotherapy treatment after surgery, and the appropriate end point and biomarkers.

In conclusion, this study presented a promising efficacy of neoadjuvant PD-1 inhibitors plus chemotherapy for patients with resectable stage I–III NSCLC and tolerable toxicities. However, these findings still need prospective clinical trials to confirm.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Board of Cancer Hospital of the University of Chinese Academy (No. IRB-2022-48). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

(I) Conception and design: MF, JL, and XL. (II) Administrative support: JL and XL. (III) Provision of study materials or patients: JL and XL. (IV) Collection and assembly of data: MF, QH, LC, HJ, HY, QG, and XY. (V) Data analysis and interpretation: MF, QH, HJ, and JH. (VI) Manuscript writing: MF and QH. (VII) Final approval of manuscript: All authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Functional and postoperative outcomes after high-intensity interval training in lung cancer patients: A systematic review and meta-analysis

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Objective: The study evaluated the effects of high-intensity interval training (HIIT) on postoperative complications and lung function in patients with lung cancer compared to usual care.

Methods: We searched electronic databases in April 2022, including PubMed, Embase, the Cochrane Library, Web of Science, and the China National Knowledge Infrastructure (CNKI). Two authors independently applied the Cochrane Risk of Bias tool to assess the quality of RCTs. The postoperative complications, length of hospitalization, and cardiopulmonary functions from the studies were pooled for statistical analysis.

Results: A total of 12 randomized controlled trials were eligible for inclusion and were conducted in the meta-analysis. HIIT significantly increased VO_{2peak} (MD = 2.65; 95% CI = 1.70 to 3.60; I^2 = 40%; P <0.001) and FEV1 (MD = 0.12; 95% CI = 0.04 to 0.20; I^2 = 51%; P = 0.003) compared with usual care. A subgroup analysis of studies that applied HIIT perioperatively showed significant improvement of HIIT on FEV1 (MD = 0.14; 95% CI = 0.08 to 0.20; I^2 = 36%; P <0.0001). HIIT significantly reduced the incidence of postoperative atelectasis in lung cancer patients compared with usual care (RD = −0.16; 95% CI = −0.24 to −0.08; I^2 = 24%; P <0.0001). There was no statistically significant effect of HIIT on postoperative arrhythmias (RD = −0.05; 95% CI = −0.13 to 0.03; I^2 = 40%; P = 0.22), length of hospitalization (MD = −1.64; 95% CI = −3.29 to 0.01; P = 0.05), and the six-minute walk test (MD = 19.77; 95% CI = −15.25 to 54.80; P = 0.27) compared to usual care.

Conclusion: HIIT may enhance VO_{2peak} and FEV1 in lung cancer patients and reduce the incidence of postoperative atelectasis. However, HIIT may not reduce the incidence of postoperative arrhythmia, shorten the length of hospitalization, or improve the exercise performance of patients with lung cancer.

Systematic review registration: PROSPERO, CRD42022335441

KEYWORDS

HIIT, high-intensity interval training, lung cancer, postoperative outcome, lung function

1 Introduction

According to global cancer statistics, lung cancer is one of the most diagnosed cancers, with an estimated 2.2 million new cases and 1.8 million deaths in 2022 (1). Smoking is the major cause of lung cancer, with about 80% to 90% of lung cancer cases related to smoking (2, 3). Lung cancer is divided into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), and the prevalence of NSCLC is higher, accounting for about 85% (4). There are many treatments for lung cancer, such as surgical resection, chemotherapy, and radiotherapy (5). Surgical intervention is most applicable to early-stage lung cancer diagnoses and is considered the best curative option (6). Complications adversely affect survival after lung cancer surgery. Fernandez et al. showed that complications including delirium, blood transfusion, reintubation, and pneumonia are associated with worse survival in the early period (0–180 days) (7). Respiratory problems were found to be the most common cause of lung cancer readmission within 30 days after surgery, and postoperative pulmonary complications were strongly associated with mortality within 90 days after surgery (8). A prospective observational study found that patients who underwent a lung resection with postoperative pulmonary complications had a significantly prolonged length of hospital stay post-surgery and reduced overall survival in months compared with patients without postoperative pulmonary complications (9).

Exercise has been found to be effective in improving the health condition, quality of life, and exercise capacity of patients with lung cancer after surgery (10, 11). High-intensity interval training (HIIT) is a unique training method that consists of short (<45 s) to long (2–4 min) physical activity at submaximal to all-out intensity, interspersed with passive or active recovery sessions (12). HIIT was initially used as a physical training method for athletes to improve cardiopulmonary function and has been gradually applied in the field of disease prevention and rehabilitation recently (13). Previous meta-analyses focused on the effect of HIIT on cardiorespiratory fitness in lung cancer patients, especially on peak oxygen uptake (VO_{2peak}) (14, 15). There is a lack of studies on postoperative complications, length of hospitalization, and other cardiopulmonary function indicators in lung cancer patients (14). Therefore, in our meta-analysis, we evaluated the effects of HIIT on postoperative complications and lung function in patients with lung cancer compared to usual care.

2 Methods

This systematic review and meta-analysis strictly followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16). We registered a protocol for this systematic review and meta-analysis on PROSPERO (registration ID is CRD42022335441).

2.1 Search strategy and information source

We conducted a literature search on April 23, 2022. Five electronic databases were searched, including PubMed, Embase, Cochrane Library, Web of Science, and China National Knowledge Infrastructure (CNKI).

2.2 Inclusion and exclusion criteria

Identified studies were screened for eligibility if they met the following inclusion criteria: (1) patients who had been diagnosed with lung cancer; (2) the exercise protocol was defined as high-intensity interval training; (3) the HIIT group was compared with usual care or standard care; (4) only randomized controlled trials were included; and (5) all languages were available.

The exclusion criteria were as follows: (1) lack of usual care or standard care; (2) studies with missing data or outliers; (3) repeated publications; and (4) meeting abstracts.

2.3 Outcomes

Pulmonary function and postoperative complications were the primary outcomes of this study. Secondary outcomes included the length of hospitalization and the six-minute walk test.

2.4 Date extraction

Based on the inclusion and exclusion criteria, data were extracted independently by two authors. The data were extracted from each study using a standard form that included the first author, year, country, number of patients, sex percentage, age, TNM cancer stage, intervention (including HIIT protocol and the timing of HIIT), control, primary outcomes, and secondary outcomes. Any disagreements can be resolved through discussion or by having a third researcher reviewing.

2.5 Quality assessment

Two authors independently applied the Cochrane Risk of Bias tool to assess the quality of RCTs. It contains the following aspects to assess random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Any disagreement was solved by consensus or by asking another researcher to reassess.

2.6 Statistical analysis

Review Manager 5.4 software was used to analyze the extracted data. For continuous outcomes, we used the mean difference (MD) and their 95% confidence intervals for the study. The risk difference (RD) and their 95% confidence intervals were applied to dichotomous outcomes. The imported data were evaluated for statistical heterogeneity. Heterogeneity was tested using the I^2 statistic and the Cochrane Q statistic, as recommended by the Cochrane Handbook. I^2 and the p-value for Q statistics were applied to assess the heterogeneity across included trials, and I^2 >50.0% or P <0.10 was considered significant heterogeneity (17).

3 Results

3.1 Study selection and characteristic

A total of 4,141 articles were retrieved and identified after completing the search strategy, including one additional record identified through a manual search. The number was reduced to 3,793 after removing 348 duplicates. A total of 3,746 articles were excluded by two authors who independently read the title and abstract of each article. After assessing the remaining 47 articles, 32 articles were excluded by screening the full text; the excluded reasons were as follows: no RCT (n = 1), no HIIT intervention (n = 22), review (n = 8), repeated publication (n = 3), and non-lung cancer patient (n = 1). Finally, it resulted in the inclusion of 12 articles (Figure 1).

The main characteristics of the HIIT intervention studies included in this review are presented in Table 1. The studies originated in China (18–23), Denmark (24, 25), Spain (26), Norway (27), Australia (28), and Switzerland (29). The trial sample size ranged from 15 to 218. Clinical data were collected from 926 lung cancer-related patients in our meta-analysis. The gender of patients was predominantly male (95.5% to 28.6%). However, one study did not accurately report the age and gender characteristics of the patients (25). Two studies recruited patients with non-small-cell lung cancer (NSCLC) or small-cell lung cancer (SCLC) (21, 25). One study enrolled patients with both NSCLS and chronic obstructive pulmonary disease (COPD) (22). The rest of the studies enrolled patients in the early stages of non-small-cell lung cancer (18–20, 23, 24, 26–29).

Five studies conducted HIIT interventions preoperatively (18–20, 22, 29). In contrast, three studies conducted HIIT interventions postoperatively (21, 26, 27). One study applied HIIT during post-operation or post-chemotherapy (28). Three studies applied HIIT programs during targeted therapy (23), radiotherapy (24), and chemotherapy (25), respectively.

Most studies used high-intensity interval bicycling as the intervention method; a few studies used high-intensity interval walking; and a study used high-intensity interval respiratory muscle training (26). Seven studies applied high-intensity interval training solely (18–23, 29). Three studies combined HIIT with resistance training (25, 27, 28). One study combined HIIT with aerobic training (24). In particular, one study combined high-intensity interval respiratory muscle training, resistance training, and aerobic training together (26).

3.2 Risk of bias

(Figure 2) presents the risk of bias assessments for all 12 included studies. Four studies were deemed to have a low risk of bias (24–26, 28), and eight studies were considered to have a moderate risk of bias (18–23, 27, 29).

3.3 Outcomes

3.3.1 Pulmonary function

Seven studies supported the finding that HIIT increased VO_{2peak} in patients with lung cancer. The result of the meta-analysis was statistically significant and favored the HIIT intervention (MD = 2.65; 95% CI = 1.70 to 3.60; I^2 = 40%; P <0.001) (Figure 3). Five studies examined the effect of HIIT intervention on forced expiratory volume in 1 s (FEV1). The results showed statistical significance and favored the HIIT intervention (MD = 0.12; 95% CI = 0.04 to 0.20; I^2 = 51%; P = 0.003). We conducted a subgroup analysis to solve the heterogeneity. Only studies that conducted

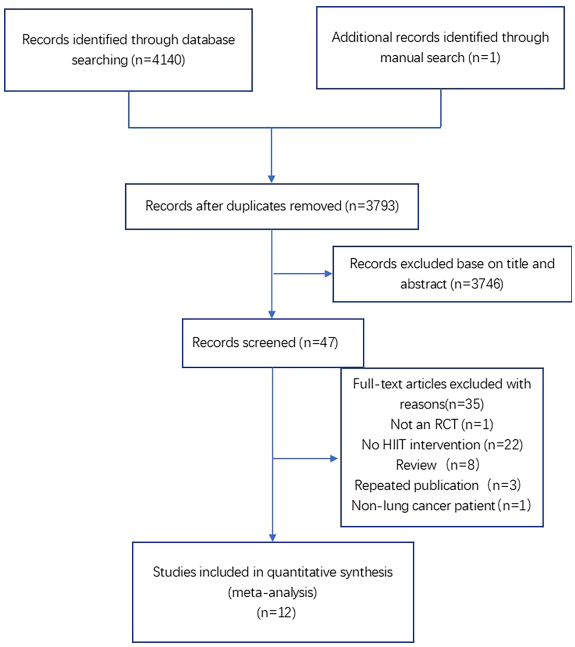

FIGURE 1
Flow diagram of the selection of studies.

TABLE 1 Characteristics of included randomized clinical trials.

Study	Country	Patients, total n	Male sex n (%)	Age, years	TNM cancer stage	Intervention	Control	Primary outcomes	Secondary outcomes
Gao (2022)	China	178 (89 vs 89)	56 (63) *vs* 46 (52)	54.36 (10.58) *vs* 52.93 (8.83)	I, II, III NSCLC/ SCLC	Post-operative, 3–5 times/day, 3–5 times/ week, 2 months Warm-up: no report HIIT: 15–30 s cycling all-out sprint and 15 s rest, total 5–10 min Cool down: no report	Usual care	FEV_1, FVC, MVV, 6MWT	SAS, FoP-Q-SF, SF-36, TNF-α, CRP, OS
Liu (2017)	China	68 (34 *vs* 34)	17 (50) *vs* 19 (56)	60.8 (4.3) *vs* 62.6 (5.1)	I, II, IIIa NSCLC	Pre-operative, 30 min/ times, two times/day, 7 days Warm-up: no report HIIT: 3 ∗(40%–100% HR_{max} climbing stairs and 3 min rest) Cool down: no report	Usual care	FVC, FEV_1, MVV, DLCO	Postoperative complications
Wang (2020)	China	56 (28 *vs* 28)	12 (42.86) *vs* 13 (46.43)	56.32 (5.48) *vs* 58.04 (8.27)	I, II, III NSCLC	Pre-operative, 1 time/ day, 3 months Warm-up: 10 min 70% HR_{max} cycling HIIT: 1 min high intensity (70%–100% HR_{max}) cycling + 1 min rest, total 35 min Cool down: 5 min rest	Usual care	6MWT	Dyspnea, anxiety, depression, exercise self-efficacy, self-care ability, Length of hospitalization
Wu (2015)	China	58 (29 *vs* 29)	19 (65.5) *vs* 20 (68.9)	61.4 (6.3) *vs* 61.6 (6.7)	Lung cancer	Pre-operative, five times/ week, 2 weeks Warm-up: 1 min 15 W cycling HIIT: 40 min cycling (60%–80% VO_{2peak}) and rest (1:1) Cool down: 5 min 15 W cycling	Usual care	Operation time, Intraoperative blood loss, Length of hospitalization	Postoperative complications
Fang (2013)	China	44 (22 *vs* 22)	21 (95.5) *vs* 21 (95.5	64.1 (7.16) *vs* 64.8 (6.82)	I, II, IIIa NSCLC with COPD	Pre-operative, five times/ week, 2 weeks Warm-up: 1 min 15 W cycling HIIT: 40 min cycling (60%–80% VO_{2peak}) and rest (1:1) Cool down: 5 min 15 W cycling	Usual care	FVC, FEV_1, MVV, DLCO	WR_{peak}, VO_{2peak}, AT, HR_{max}, VO_2/HR, VE_{max}, Postoperative complications, Length of hospitalization
Licker (2017)	Switzerland	151 (74 *vs* 77)	41 (55) *vs* 50 (65)	64 (13) *vs* 64 (10)	IIIa NSCLC or less	Pre-operative 8 HIIT sessions for 25 Days, three times a week Warm-up: 5 min cycling at 50% W_{peak} HIIT: 2 ∗ (15 s sprints at 100% W_{peak} and 15 s rest), total 20 min Cool down: 5 min cycling at 30% W_{peak}	Usual care	Postoperative complications	6MWT, VO_{2peak}, Length of hospitalization
Edvardse (2015)	Norway	61 (30 *vs* 31)	13 (43) *vs* 15 (48)	64.3 (9.3) *vs* 65.9 (8.5)	I–IV NSCLC	Post-resection, starting 5–7 weeks after surgery 60 min, three times/ week, 20 weeks HIIT: Walking uphill on a treadmill 80%–95% HR_{max} Resistance training: 3*6–	Standard postoperative care	VO_{2peak}	FEV_1, MVV, Tlco, Leg press (1 RM), Hand grip (1 RM), BMI, Total muscle mass, Chair stand, Stair run

(Continued)

TABLE 1 Continued

Study	Country	Patients, total n	Male sex n (%)	Age, years	TNM cancer stage	Intervention	Control	Primary outcomes	Secondary outcomes
						12 RM upper and lower limb, back strength			
Egegaard (2019)	Denmark	15 (8 *vs* 7)	3 (37.5) *vs* 2 (28.6)	64 (5.8) *vs* 65 (5.7)	IIIa, IIIb, IV NSCLC	During radiotherapy, 20 min/times, five times/week, 7 weeks Warm-up: 5 min light cycling HIIT: 5 ∗ 30 s 80%–95% iPPO cycling and 30 s rest, total 10 min Aerobic training: 5 min 80% iPPO cycling	Standard care	Feasibility	VO_{2peak}, 6MWT, FEV_1, FACT-L, HADS, reported daily, blood pressure
Cavalheri (2017)	Australia	17 (9 *vs* 8)	5 (29)	66 (10) *vs* 68 (9)	I, II, IIIa NSCLC	Post-resection 6–10 weeks or post-chemotherapy 4–8 weeks, 60 min/times, three times/week, 8 weeks Warm-up: no report HIIT: 20 min walking 70/80% 6MWT speed or 10 min cycling 80% WR_{peak} Resistance training: 3 ∗ 10 upper limb training Cool down: no report	Usual care	VO_{2peak}, 6MWT, AT	SF-36, FACT-L, EORTC QLQ-C30, muscle strength, respiratory function (spirometry)
Hwang (2012)	China	24 (13 *vs* 11)	5 (38.5) *vs* 7 (63.6)	61 (6.3) *vs* 58.5 (8.2)	IIIa, IIIb, IV NSCLC	During targeted therapy, 30–40 min, three times/week, 8 weeks Warm-up: 10 min running or cycling HIIT: treadmill or cycling ergometer 80% VO_{2peak}/RPE 15–17 and 60% VO_{2peak} active recovery, total 25 min Cool down: 5 min	Usual care	VO_{2peak}, RER	EORTC QLQ-C30
Messaggi-Sartor (2019)	Spain	37 (16 *vs* 21)	8 (50) *vs* 18 (85.7)	64.2 (8.1) *vs* 64.8 (8.9)	I or II NSCLC	Post-operative, 1 h/time, three times/week, 8 weeks Warm-up: 5 min HIIT: IEMT (5 ∗ 10 breathing) 50%PImax/PEmax (15 min) Aerobic training: cycling 60% W_{peak} (30 min) Resistance training: bicep curl, chest, and shoulder press Cool down: 5 min	Post-operative standard care	VO_{2peak}	Respiratory muscle strength, IGF-I, IGFBP-3, EORTC QLQ-C30, lung cancer recurrence, death Length of hospitalization
Quist (2020)	Denmark	218	No report	>18	IIIb–IV NSCLC and SCLC ED	During chemotherapy, 90 min/times, two times/week, 12 weeks Warm-up: 10 min 60%–90% HR_{max} cycling Strength training: 3 ∗ 5–8 70%–90% 1RM upper and lower training HIIT: interval training on stationary bikes, 85%–95% HR_{max}, 10–15 min	Usual care	VO_{2peak}	Muscle strength (1RM), 6MWT, FEV_1, HADS, FACT-L

(Continued)

TABLE 1 Continued

Study	Country	Patients, total n	Male sex n (%)	Age, years	TNM cancer stage	Intervention	Control	Primary outcomes	Secondary outcomes
						Cool down: 20–30 min stretching and progressive relaxation			

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MVV, maximal voluntary ventilation; 6MWT, six-minute walk test; SAS, Self-rating Anxiety Scale; FoP-Q-SF, Fear of Progression Questionnaire-Short Form; SF-36, the 36-Item Short Form Health Survey; TNF-α, Tumor necrosis factor-α; CRP, C-reactive protein; OS, Overall survival; DLCO, carbon monoxide diffusing capacity; $WR_{peak,}$ peak work rate; $VO_{2peak,}$ peak oxygen uptake; AT, anaerobic threshold; HR_{max}, maximal heart rate; VO_2/HR, oxygen pulse; VE_{max}, maximal minute ventilation; Tlco, carbon monoxide transfer factor; RM, repetition maximum; FACT-L, Functional Assessment of Cancer Therapy-Lung; HADS, the Hospital Anxiety and Depression Scale; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire Core 30; RER, respiratory exchange rate; IGF-I, levels of serum insulin growth factor I; IGFBP-3, IGF binding protein 3; HIIT, high-intensity interval training; IEMT, inspiratory and expiratory muscle training; iPPO, patient's peak Max power; HR_{max}, maximal heart rate; IEMT consisted of sets of repetitions followed by 1–2 min of unloaded recovery breathing (off the device), twice a day, 3 days per week, for 8 weeks; PImax, maximal inspiratory pressure; PEmax, maximal expiratory pressure; W_{peak}, peak workload.

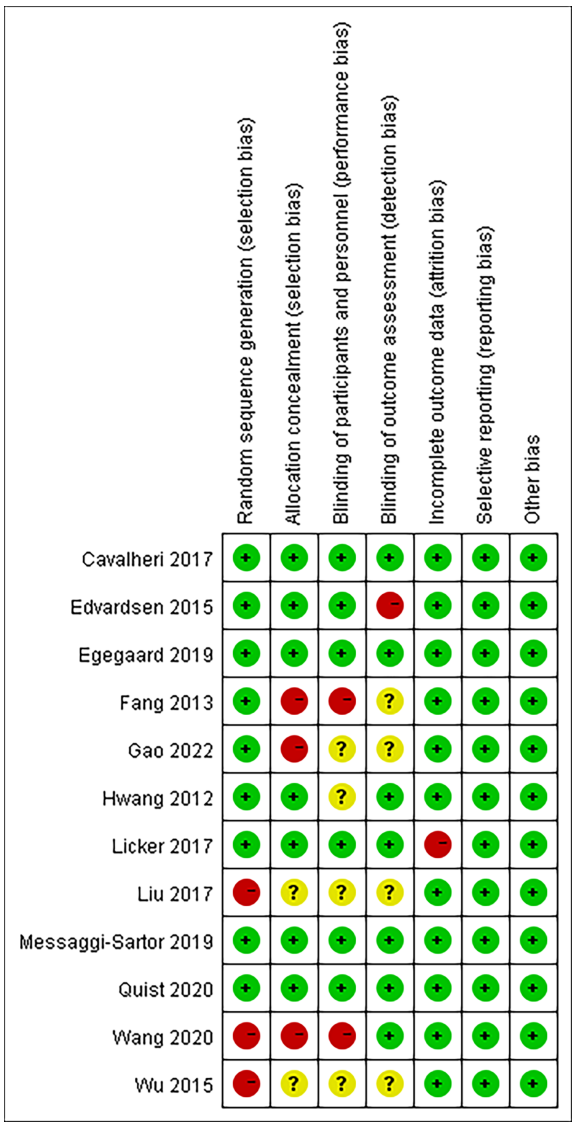

FIGURE 2
Risk of bias summary review authors' judgments about each risk of bias item for each included study.

HIIT perioperatively were included (20–22). The results still support that HIIT benefits FEV1 among patients with lung cancer compared with usual care (MD = 0.14; 95% CI = 0.08 to 0.20; I^2 = 36%; P <0.0001) (Figure 4).

3.3.2 Postoperative complications

A total of 59 patients in five studies reported atelectasis events, and the results showed that the HIIT intervention was beneficial to reduce postoperative atelectasis events in lung cancer patients compared with

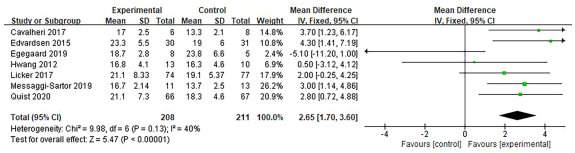

FIGURE 3
Meta-analysis of the effect of HIIT on VO_{2peak} (ml/kg/min) among lung cancer patients.

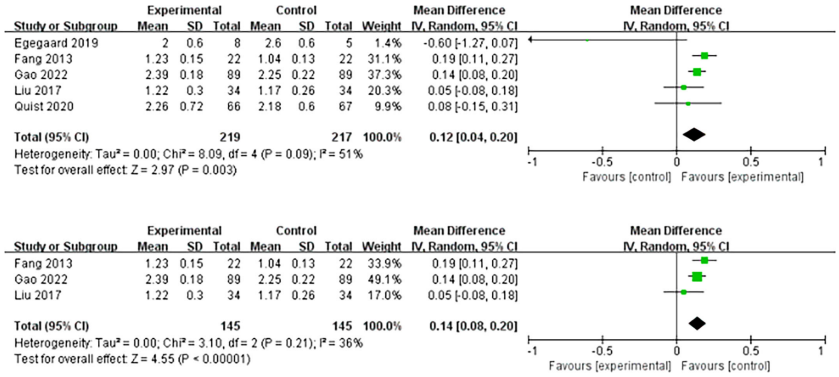

FIGURE 4
Meta-analysis of the effect of HIIT on FEV1 (L) and subgroup analysis among lung cancer patients.

usual care (RD = −0.16; 95% CI = −0.24 to −0.08; I^2 = 24%; P <0.0001) (Figure 5). Five studies reported arrhythmia events among 50 patients. There was no effect that HIIT had on postoperative arrhythmias in lung cancer patients compared to usual care (RD = −0.05; 95% CI = −0.13 to 0.03; I^2 = 40%; P = 0.22) (Figure 6).

3.3.3 Length of hospitalization

Five studies with 346 patients who reported length of hospitalization were included in our meta-analysis. The results showed no significant difference between the HIIT group and the usual care group (MD = −1.64; 95% CI = −3.29 to 0.01; P = 0.05). Heterogeneity was high (I^2 = 77%) (Figure 7).

3.3.4 The six-minute walk test

In our study, five studies presented 393 patients' 6MWT performance. The results proved no difference between the HIIT group and the usual group (MD = 19.77; 95% CI = −15.25 to 54.80; P = 0.27). Heterogeneity was high (I^2 = 76%) (Figure 8).

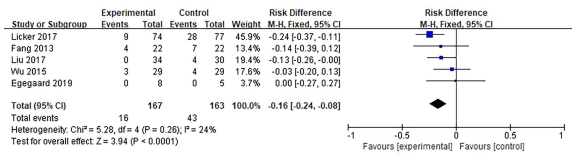

FIGURE 5
Meta-analysis of the effect of HIIT on atelectasis among lung cancer patients.

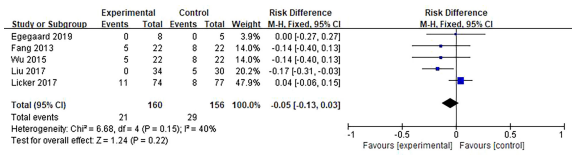

FIGURE 6
Meta-analysis of the effect of HIIT on arrhythmias among lung cancer patients.

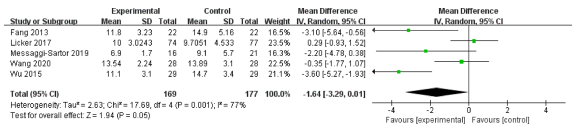

FIGURE 7
Meta-analysis of the effect of HIIT on length of hospitalization (days) among lung cancer patients.

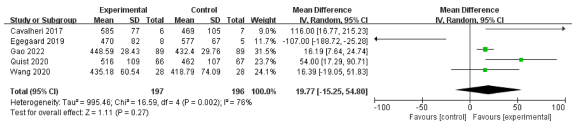

FIGURE 8
Meta-analysis of the effect of HIIT on 6MWT (meters) among lung cancer patients.

4 Discussion

This study examines the functional and postoperative outcomes of a high-intensity interval training intervention in lung cancer patients. With regard to pulmonary function, our results showed that both VO_{2peak} and FEV1 improved with the application of HIIT among lung cancer patients. With regard to postoperative outcomes, the postoperative incidence of atelectasis was significantly reduced. However, there is limited evidence that HIIT does not reduce the incidence of arrhythmias. Due to the high heterogeneity of the results, it is still unclear whether the length of hospitalization was shortened, and the six-minute walk performance increased in lung cancer patients.

Previous studies mentioned that VO_{2peak} played a key role in predicting surgical outcomes and survival in NSCLC patients (30, 31). It has been reported that HIIT induces VO_{2peak} enhancement (32). A meta-analysis that included 305 lung cancer patients from eight studies showed that VO_{2peak} was significantly increased by HIIT compared to usual care (14). Another study demonstrated that HIIT had a greater impact on VO_{2peak} than usual care (15). The same results were also observed in our meta-analysis. However, the difference is that our study focused not only on lung function in lung cancer patients after HIIT rehabilitation but also on postoperative outcomes. Our results showed that HIIT could also effectively improve FEV1 and reduce the postoperative incidence of atelectasis. Interestingly, our study showed that HIIT did not reduce the incidence of arrhythmia, possibly due to postoperative arrhythmia being associated with surgical inflammation, autonomic nerve injury, and cardiac overload (33). More research is still needed.

HIIT can effectively increase muscle metabolic capacity and promote increases in muscle strength and hypertrophy, thus improving lung respiratory function and mobility in lung cancer patients (27, 28). A study demonstrated that HIIT may increase skeletal muscle mitochondrial capacity, leading to improvements in whole-body metabolic homeostasis by improving several classical markers of mitochondrial biogenesis, including the maximal activity of citrate synthase (CS) and cytochrome c oxidase (COX) as well as the total protein content of CS and COX subunits II and IV (34). Another study found that six sessions of HIIT expanded skeletal muscle mitochondria, as assessed by cytochrome c oxidase activity (35). In terms of exercise capacity, cancer-induced cachexia causes muscle atrophy in cancer patients by inhibiting muscle protein synthesis and enhancing muscle catabolism (36). In two rat models, researchers found that HIIT could lead to muscle hypertrophy by improving the IGF-I/Akt/FoxO and myostatin/Smad signal transduction pathways (37), activating the mTOR pathway, altering the expression of MuRF-1 and MAFbx proteins, and improving autophagic flux (38).

The benefits of HIIT may be influenced by the timing of exercise. Perioperative exercise training included preoperative exercise, acute post-operative (in-hospital) exercise, and postoperative exercise (39). It has been indicated that lung cancer patients who have undergone resection can benefit from preoperative exercise, which includes the improvement of both pulmonary function and exercise capacity, a lower incidence rate of postoperative complications, a shorter length of hospital stay, and a lower degree of dyspnea (40–42). Acute post-operative exercise (in-hospital) involves sitting out of bed and walking around the hospital ward, with the aim of discharge from the hospital as soon as possible (43, 44). There is no consensus on whether acute post-operative exercise improved post-operative physical activity level, mobility, or lung function (45, 46). Cavalheri et al. found that postoperative exercise enhanced exercise performance but not HRQoL and FEV1 in patients with lung cancer (47). Interestingly, a randomized controlled trial showed that early rehabilitation avoided a temporary decline in HRQoL by comparing the effect of early rehabilitation (14 days after surgery) with the late rehabilitation group (14 weeks after surgery) (48). It can be inferred that preoperative HIIT is more beneficial for patients with lung cancer (10). However, there are few studies on preoperative HIIT, and further prospective studies with large samples are needed to explore the benefits of preoperative HIIT. Limited evidence has suggested that exercise training enhances mobility and physical fitness in lung cancer patients during chemotherapy (49). Larger randomized controlled trials are warranted to prove the effect of combining exercise with targeted therapy, chemotherapy, or radiotherapy.

The exercise type of HIIT may also influence the rehabilitation of lung cancer patients after surgery. Most studies included in this meta-analysis used cycling as a type of high-intensity training. Only one study used respiratory muscle training as a type of high-intensity training (26). Laurent et al. (50) showed that lung cancer patients who accepted resection surgery decreased pulmonary postoperative complications by applying respiratory muscle training. However, further studies are needed to determine which exercise type HIIT is more favorable for patients with lung cancer. Meanwhile, the stage, subtype, and smoking habits of patients with lung cancer may also affect postoperative rehabilitation and should be considered. Considering safety and practicality, it is possibly harmful to apply HIIT at all-out intensity for individuals with severe disease (34). Low-volume HIIT is safer and has a similar improvement effect as high-volume HIIT in improving individual cardiopulmonary function (51). Low-volume HIIT is defined as repetitions range from 1 to 10 times with an active interval time of fewer than 15 min, whereas high-volume HIIT requires active intervals and repetitions of more than 15 min and four times, respectively (52). Seven studies included in our meta-analysis used low-volume HIIT (20, 21, 23–26, 29). Therefore, we assume that low-volume HIIT may be a safer way to treat patients with lung cancer, and this needs to be confirmed. In this meta-analysis, three included studies combined HIIT with resistance training (25, 27, 28), and one combined HIIT with aerobic training (24). It is still unclear whether HIIT combined with other training will have a larger effect on lung cancer patients than using HIIT solely.

5 Conclusion

In conclusion, HIIT improved pulmonary function and reduced postoperative atelectasis in patients with lung cancer. However, the incidence of postoperative arrhythmias was not decreased by HIIT. Due to high heterogeneity, shortening the length of hospitalization and enhanced exercise capacity in lung cancer patients after HIIT intervention were not supported in this meta-analysis.

6 Future directions

As a timesaving, effective, and applicable rehabilitation method, high-intensity interval training could open a new perspective for treating lung cancer patients (14). However, the high-intensity interval training protocol remains unclear. It is necessary to determine the optimal types of exercise, the timing of using HIIT, intensity, and interval time in the future. Although some studies have obtained some results, future studies with large samples are still needed. At the same time, the different stages, subtypes, types of surgery, and smoking habits of lung cancer patients should be considered in HIIT rehabilitation, which significantly affects postoperative outcomes. Finally, the mechanism of HIIT for improving cardiopulmonary function and its effect on postoperative outcomes in patients with lung cancer should be more concentrated on by researchers.

7 Theoretical and practical implication

HIIT has great potential for clinical rehabilitation of patients with lung cancer. Because of its ease of operation and low economic cost, it can effectively improve the postoperative rehabilitation of lung cancer patients and reduce their economic burden. In clinical practice, clinicians and nurses can integrate HIIT into the treatment process as a beneficial measure to improve the health status of lung cancer patients. Personalized HIIT protocols should be developed based on the different treatment methods and health status of lung cancer patients.

8 Limitations

There are some limitations to our study, and further research is needed. First, most of the literature included in our study is a small sample, and the conclusions of these studies need to be treated with caution. Second, lung cancer patients are mainly male, and there may be differences between male and female patients. But we did not study them separately in our study. Third, although the included kinds of literature all adopted high-intensity interval training plans, the intensity and interval time of high-intensity training were different, which might affect the final results. Fourth, cycling was the main type of exercise in most of the included studies, while walking was also used. Bias can also be caused by different types of movement. Finally, warm-up and rest are equally important in HIIT planning, and some studies did not report warm-up and rest programs.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

ZC and JT conceived and planned the review, assessed the methodologic quality of the studies, verified the data, and drafted and revised the manuscript. JJ assessed the methodologic quality of the studies. DG extracted data. FL and JL conducted the literature search and selected studies. JT provided methodologic advice, content expertise, and revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Progress on neoadjuvant immunotherapy in resectable non-small cell lung cancer and potential biomarkers

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Immune checkpoint inhibitors (ICIs) are highly concerned in the treatment of non-small cell lung cancer (NSCLC), represented by inhibitors of programmed death protein 1 (PD-1) and its ligand (PD-L1), and inhibitors of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). The introduction of immunotherapy in the treatment of perioperative NSCLC has improved the prognosis to a great extent, as demonstrated by several phase II and III clinical trials. The target population for immunotherapy in early-stage NSCLC is still under discussion, and the biomarkers for neoadjuvant immunotherapy population selection are the next pending problem. The predictive efficacy of many potential makers is still being explored, including PD-L1 expression levels, tumor mutation burden, circulating tumor DNA, components of the tumor microenvironment, and several clinical factors. We summarize key findings on the utility of ICIs in clinical trials of preoperative NSCLC patients and conclude analyses of relevant biomarkers to provide a better understanding of potentially predictive biomarkers in neoadjuvant immunotherapy.

KEYWORDS

non-small cell lung cancer, neoadjuvant therapy, immune checkpoint inhibitors, PD-L1, circulating tumor DNA, tumor mutation burden

1 Introduction

Lung cancer is the leading lethal cause of malignant tumors worldwide. In recent decades, randomized trials worldwide have shown a 24-33% reduction in lung cancer mortality through low-dose CT screening in high-risk populations (1, 2). Notably, over 30% of NSCLC patients at diagnosis are considered resectable, including stage I-II and a selective portion of IIIA and IIIB (SEER database, Cancer statistics). For early-stage NSCLC, the best way to optimize patients' outcomes is radical resection together with proper maintenance treatment.

Especially for patients with stage IIB and stage III tumors, who could consider more than one treatment modality (surgery, radiation therapy, or chemotherapy), a multidisciplinary evaluation is usually recommended by The National Comprehensive Cancer Network (NCCN) clinical guidelines, including thoracic surgeons, physicians, radiation oncologists, and pathology oncologists. For patients who undergo successful surgical resection, a significant proportion may face difficult problems such as postoperative complications, local recurrence, and distant metastases, which reduce the quality of life and shorten survival after surgery. Therefore, for patients with stage IB (with high-risk factors) to stage IIIB (operable evaluated by surgeons) NSCLC, the primary issue is radical R0 resection with routine postoperative adjuvant therapy to reduce the probability of postoperative recurrence and prolong disease-free survival (DFS) and overall survival time (OS). Neoadjuvant therapy has shown its powerful ability to downstage and bring curative surgical opportunities to patients with early-stage and locally advanced NSCLC.

Chemotherapy has been the standard of care (SoC) in the adjuvant and neoadjuvant settings in rsectable NSCLC for a long period. Current data shows that neoadjuvant chemotherapy improved the OS by around 5% in OS and time to recurrence in patients with resectable NSCLC (3). The addition of radiation to neoadjuvant chemotherapy did not seem to further improve the survival benefit (4). Radiation gives help to control locoregional disease, but the PFS extension fails to translate into a long-term survival benefit (5–7). Therefore, New strategies aiming for a superior outcome are under exploration.

The rationale for immune neoadjuvant therapy could be concluded as the following points (Figure 1): Firstly, the excellent efficacy of immunotherapy in locally advanced and metastatic NSCLC has been confirmed by several clinical trials, and both FDA and NMPA have approved several PD-1/PD-L1/CTLA-4 inhibitors alone or in combination for the first-line treatment of advanced driver-negative NSCLC; secondly, pre-operation patients are more likely to better tolerate full-dose systemic therapy with a better performance status(PS) score and fewer complications. Another reason to support immune neoadjuvant therapy is that preoperative patients harbor a relatively high tumor burden and high neoantigen loads, besides, the immune system remains intact so the application of immunotherapy at this time can maximize the strength and activate the immune system to kill tumor cells and obliterate distant micro-metastases (8). This will provide the basis for tumor shrinkage, down-staging, and more complete radical surgery, to obtain longer survival benefits.

Currently, trials on neoadjuvant immunotherapy for resectable NSCLC patients are on the way. Combinations with chemotherapy and radiation, treatment cycles, and pre-and post-operative distribution, multiple issues are still under discussion. Despite the superior efficacy of neoadjuvant immunotherapy compared to standard chemotherapy, some patients do not benefit from the treatment, progress during treatment, or relapse after surgery. Thus, to monitor the dynamic of cancer disease, select optimized regimens for different populations, and predict response to neoadjuvant therapy, biomarkers involving tumor tissues and peripheral blood are discussed. Here we review the updated data from clinical trials and track the latest exploratory analysis on biomarkers, aiming to provide

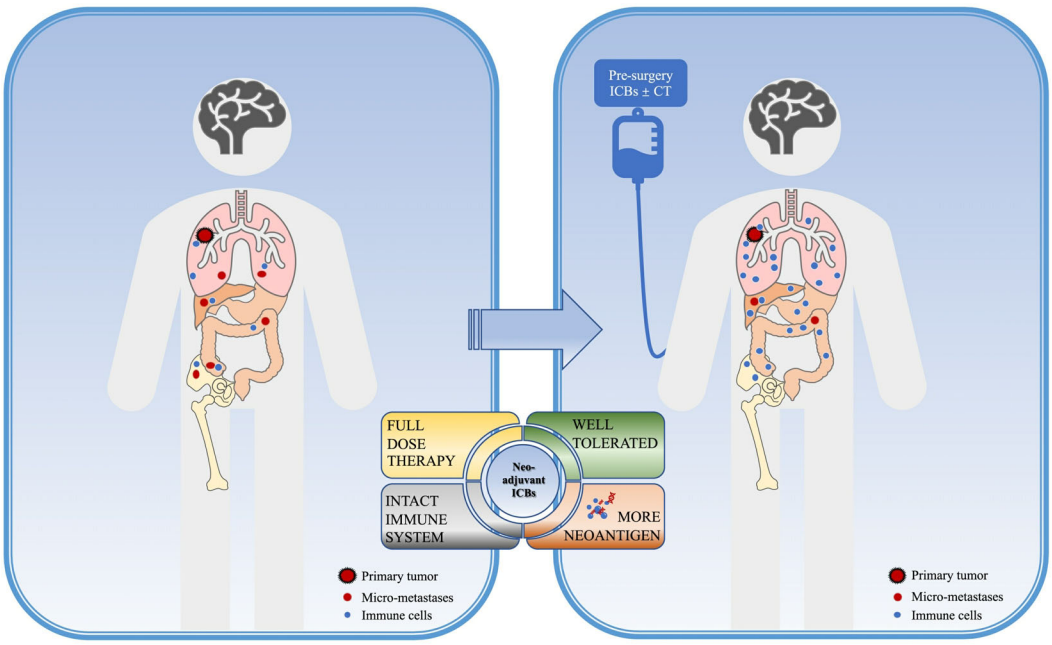

FIGURE 1
Rationale of neoadjuvant immunotherapy. Neoadjuvant immune checkpoint inhibitors (ICBs) in NSCLC might provide higher benefits for non-small cell lung cancer (NSCLC) patients due to the following points: before surgery, the primary tumor and distant micro-metastases providing a pleural of tumor-specific neoantigens, with the intact immune system, the immune response could be of the greatest work, which could obliterate micro-metastases in return. Also, better performance status before surgery could offer higher opportunities for patients to receive a full-dose systemic therapy with well tolerance. ICB, immune checkpoint inhibitors; CT, chemotherapy.

a better understanding of the routine use of biomarkers in clinical settings.

2 Evaluations of neoadjuvant therapy

To better evaluate the effect of tumor treatment, response evaluation criteria in solid tumors (RECIST) was proposed in 2000, and further updated by RECIST version 1.1 (9), which mainly evaluates the change of tumor size before and after treatment by radiological features, thus disease remission, stability or progression was judged. However, due to the limitations of the radiology characteristics, it is not clear whether the changes in images are disease progression or inflammatory response, and the effect of treatment may be underestimated. Along with the development of immunotherapy, immune response evaluation criteria in solid tumors (iRECIST) (10) were proposed to better suit the situation, but all these criteria were not quite fit in the neoadjuvant setting. Given the uniqueness of neoadjuvant therapy, as the primary lesion can be evaluated after surgical resection, pathological features can now be used as one of the approaches to assess the efficacy of neoadjuvant therapy for resectable NSCLC (11). The evaluation of pathological responses consists of a complicated evaluation (11), mainly including assessments of the percentages of (a) viable tumor, (b) necrosis, and (c) stroma (including inflammation and fibrosis) with a total adding up to 100%. It is now widely accepted that pathological response could be a surrogate endpoint of survival in studies of neoadjuvant therapy (12, 13). Previous studies have proved that major pathological response (MPR) defined as no more than 10% viable tumor in resected specimen could be a better predictor of overall survival than overall response rate (14, 15). Pathological complete response (pCR), is uniformly defined as no viable tumor cells after complete evaluation of a resected lung cancer specimen including all sampled regional lymph nodes, which is staged as ypT0N0 in the AJCC system (8^{th} edition). Pathological complete response(pCR) is another good measurement for efficacy, but due to its infrequency in the clinic, MPR is more widely used in both clinical evaluation and as an endpoint in clinical trials.

3 Clinical trials on neoadjuvant immunotherapy in potentially resectable NSCLC

3.1 Neoadjuvant immune monotherapy

MK3475-223 (16) is a Phase 1 study focused on the safety profile of Pembrolizumab in stage I/II NSCLC, only 6 patients were enrolled in this study, out of which 2 patients shown response. The overall results indicated that pembrolizumab is well tolerated. Another two phase 2 studies, TOP 1501 (17) and NEOMUN (18), further explored the utility of pembrolizumab as a neoadjuvant treatment in different settings of post-operative adjuvant study. Patients in TOP 1501 study received 2 cycles of neoadjuvant pembrolizumab and 4 cycles of adjuvant pembrolizumab with or without radiotherapy or chemotherapy as adjuvant maintenance therapy; while NEOMUN study required standard of care treatment as adjuvant therapy. All three studies suggested that pembrolizumab was safe and well tolerated with a higher pathological response rate compared to neoadjuvant chemotherapy, and not associated with excess surgical morbidity. Checkmate-159 (19) is a prospective phase 2 study, intended to evaluate the patients reached outcome and safety profile using nivolumab for 2 cycles as neoadjuvant monotherapy, followed by resection within 14 days. The outcome was encouraging, with 45% of patients reached MPR, of which 15% reached pCR. Though the population was relatively small (21 patients), it still demonstrated the potential of immunotherapy in pre-operation NSCLC patients. NEOSTAR study (20) enrolled 44 NSCLC patients, and explored mono-nivolumab or combined with ipilimumab followed by surgery. Thirty-nine out of 44 patients underwent surgery, and the R0 resection rate was 100%. No significant difference in pathological and radiological responses was observed between mono- and dual-immunotherapy. ChiCTR-OIC-17013726 (21) is a phase 1b study that evaluated the safety and outcome of sintilimab (a PD-1 inhibitor) in neoadjuvant setting. The study enrolled 40 patients with resectable NSCLC (stage IA–IIIB), including six patients with stage T3N2M0 and two patients with T4N2M0, all of whom received 2 cycles of sintilimab and 37 of whom underwent resection. The MPR rate reached 40.5%, demonstrating a reliable efficacy of neoadjuvant immune-monotherapy. So far, the LCMC3 study (22) recruited the largest population of patients with IB-IIIA(including selected IIIB)resectable NSCLC in the neoadjuvant immunotherapy setting. Patients were given two doses of pre-surgery atezolizumab and a post-operative atezolizumab as maintenance therapy for up to 12 months. A total of 181 patients were enrolled, 159 underwent surgery, out of which 30(20.4%) reached MPR, 10 (6.8%) reached pCR. Clinical trials of mono-drug neoadjuvant immunotherapy are summarized in Table 1.

3.2 Immunotherapy combinations

Immunotherapy combinations have shown better efficacy than monotherapy in neoadjuvant settings (Table 2). TOP 1201 (NCT01820754) (23) was the first study that demonstrate the safety and feasibility of neoadjuvant immunochemotherapy in resectable NSCLC. In this study, 2 to 3 cycles of ipilimumab combined with chemotherapy were used before surgery. Compared to historical data on neoadjuvant chemotherapy, the postoperative morbidity rate was not worse. NADIM study (24) confined the enrollment to stage IIIAN2 NSCLC patients. It is the earliest study that evaluated the safety, efficacy, and outcome of nivolumab combined with standard chemotherapy in the neoadjuvant setting of NSCLC. The combination of nivolumab and standard chemotherapy shown a high radical surgery rate (41/46, 89%) and a relatively long survival (3-year survival rate: 81.9%), confirming the feasibility of combined therapy in locally advanced NSCLC. Further, NADIM II(NCT03838159) study expanded the population to stage IIIA and IIIB(T3N2) patients, with a total count of 90 patients. Notably, the NADIM II study planned three cycles of nivolumab plus platinum-based doublet chemotherapy before surgery and postoperative maintenance immunotherapy using nivolumab (480mg Q4W) for six months, which is quite different from other adjuvant treatments (adjuvant immunotherapy for 1 year). In 2022 WCLC (25), researchers updated the results of this trial. The

TABLE 1 Clinical trials of neoadjuvant immunotherapy(mono-drug) in NSCLC.

Identifier	Acronym	phase	design	stage	Number of patients	Intervention	1 End Point	Biomarkers
NCT02938624	MK3475-223	1	Single arm	I-II	28	Pembrolizumab → Surgery	MPR; Toxicity	NG
NCT03030131	IONESCO	2	Single arm	IB-IIIA	46	Durvalumab → Surgery*	R0 resection	NG
NCT02818920	TOP 1501	2	Single arm	IB-IIIA	35	Pembrolizumab ×2→ Surgery → Pembrolizumab ×4	Surgical feasibility rate	NG
NCT03197467	NEOMUN	2	Single arm	II-IIIA	30	Pembrolizumab → Surgery	Feasibility; Safety; Clinical responses Pathological responses	NG
NCT02259621	CheckMate 159	2	Single arm	I-selected IIIB	21	Nivolumab → Surgery	Safety; Feasibility	PD-L1
NCT02927301	LCMC3	2	Single arm	IB-IIIB	180	Atezolizumab → Surgery → Atezolizumab	MPR	TMB; WES
NCT03158129	NEOSTAR	2	Parallel	I-IIIA	44	Nivolumab, Q2W×3→ Surgery → SoC	MPR	PD-L1; TIL quantification; Blood, tissue, and stool-based biomarkers
						Nivolumab, Q2W×3 + ipilimumab ×1 → Surgery → SoC		
ChiCTR-OIC-17013726	/	1b	Single arm	IA–llIB	49	Sintilimab ×2 → Surgery	Safety; Feasibility	PET-CT SUVmax
NCT02994576	PRICNEPS	2	Single arm	IA-IIIA (No N2)	60	Atezolizumab → Surgery	Toxicity	NG

* 27 patients received adjuvant therapy (chemotherapy or chemotherapy plus radiotherapy).
NSCLC, Non-small cell lung cancer; SoC, standard of care; NG, not given; MPR, major pathological response; TIL, tumor infiltrating lymphocytes.

surgery outcome favored the immunochemotherapy neoadjuvant strategy, with a R0 resection percentage of 92.5% in the combination group compared to that of chemotherapy group (65%). Also, the downstaging was markable in combination group, nearly 70% (37/53) patients reached a successful downstaging in combination group, where the number is 40% (8/20) in the chemo-group. The intention to treat population for nivo + chemo arm is 56 patients, out of which 21 reached pathological complete remission (pCR, 37.5%). Compared to that of chemo-group (2/28, 7.1%), the pCR rate is significantly higher while also comparable to the previous studies. Subgroup analysis suggested that PD-L1-positive patients and patients reached pCR shall benefit most from the immunochemotherapy neoadjuvant strategy. It is noteworthy that NADIM II study is the first trial that presented OS benefit in resectable stage IIIA-IIIB NSCLC patients. Several studies explored a new PD-1 inhibitor (Toripalimab) combined with chemotherapy as neoadjuvant therapy in stage IIB-IIIC NSCLC patients. In Renaissance Study (26) and ChiCTR1900024014 (27), patients that underwent surgical procedures reached a 100% R0 resection. The MPR and pCR rate was consistent with previous studies, ranging from 40.9% to 62.5% and 18% to 45%, respectively. Another study conducted in China neoSCORE (28) compared the possible difference between two cycles and three cycles of neoadjuvant immunochemotherapy. As the result suggested, there was a numerical but not statistical difference between the two arms, three cycles of neoadjuvant sintilimab plus doublet-chemotherapy shown a better MPR rate numerically. Also, the higher MPR rate benefit was shown in squamous NSCLC than in non-squamous NSCLC(p=0.003), consistent with a former study reported in 2020 by Shu CA. et al. (29), possibly because of a higher tumor necrosis rate in squamous cancer as observed in neoadjuvant chemotherapy cohorts (30).

Checkmate 816 is the first and only phase III study of neoadjuvant immunochemotherapy in early-stage NSCLC presenting the primary results so far. The trial included 358 patients with resectable NSCLC newly diagnosed as IB-IIIA stage with no known sensitive mutations of EGFR or ALK. Participants were randomly assigned to receive 3 cycles of nivolumab(360mg) plus platinum-based doublet chemotherapy once every three weeks, or chemotherapy alone. In the first analysis, the pCR benefits of adding nivolumab to chemotherapy were attained regardless of the patient's age or gender, disease stage, histology, PD-L1 expression, and tumor mutation burden. In the further analysis of the other primary endpoint (31), event-free survival (EFS, defined as the length of time from randomization to any disease progression precluding surgery, disease progression or recurrence after surgery, or death due to any cause), the superior efficacy of combined therapy was proved again. The median EFS of combined therapy reached 31.6 months (95%CI, 30.2-NR), which reflected a 10.8 months longer event-free survival as

TABLE 2 Clinical trials of neoadjuvant immunotherapy (combined therapy) in NSCLC.

Identifier	Acronym	phase	design	stage	Number of patients	Intervention	1 End Point	Biomarkers
NCT01820754	TOP 1201 IPI	2	Single arm	IB-IIIA	24	CT ×1 + (Ipilimumab + CT) ×2 → Surgery	Percentage of Subjects with Detectable Circulating T Cells After Treatment	NG
NCT03794544	NeoCOAST	2	Single arm	I (>2cm) -IIIA	27	Durva ×1 → Surgery	MPR rate	PD-L1; tumor and microbiome biomarkers; blood mRNA signatures
NCT05061550	NeoCOAST-2	2	Parallel	II-IIIA	140	Durvalumab + CT ×4+ Oleclumab → Surgery → Durvalumab + Oleclumab	pCR; Safety	PD-L1; ctDNA dynamics; immunogenicity
						Durvalumab + CT + Monalizumab → Surgery → Durvalumab + Monalizumab		
NCT03081689	NADIM	2	Single arm	IIIA (N2)	46	Nivolumab + CT, Q3W ×3 → Surgery → Nivolumab (240mg, Q2W×4m; 480mg, Q4W×8m)	24-month PFS	PD-L1; TMB; peripheral blood immune status; ctDNA
NCT03838159	NADIM II	2	Parallel	IIIA/ IIIB	90	Nivolumab + CT, Q3W ×3 → Surgery → Nivolumab (480mg, Q4W×6m)	pCR	ctDNA
						CT, Q3W ×3 → Surgery		
NCT04606303	Renaissance	2	Single arm	IIB-IIIB	53	Toripalimab + CT, Q3W ×2-4 → Surgery	MPR; pCR	NG
NCT04144608	TOGATHER	2	Single arm	IIIA-IIIB	40	Toripalimab + CT, Q3W ×2-4 → Surgery → Toripalimab + CT, Q3W ×2, Toripalimab Q3W ×13	R0 resection rate	IHC; RNA-seq; WES; TCR-seq
NCT04304248	NeoTAP01	2	Single arm	IIIA-IIIB (T3-4N2)	33	Toripalimab + CT, Q3W ×3 → Surgery	MPR	PD-L1
NCT04459611	neoSCORE	2	Parallel	IB-IIIA	60	Sintilimab + CT ×2 → Surgery → CT ×2 + Sintilimab(up to 1 year)	MPR rate	NG
						Sintilimab + CT ×3 → Surgery → CT ×1 + Sintilimab(up to 1 year)		

NSCLC, Non-small cell lung cancer; CT, chemotherapy; NG, not given; pCR, pathological complete response; MPR, major pathological response; EFS, event free survival; IHC, Immunohistochemistry; WES, Whole Exome Sequencing; TCR-seq, T-cell receptor sequencing; ctDNA, circulating tumor DNA; TMB, tumor mutation burden.

compared to the chemotherapy arm (20.8, 95%CI, 14.0-26.7; HR 0.63, 97.38%CI 0.43-0.91). What's more, the benefit of pCR was seen in all patients without regard to PD-L1 expression levels, and a significantly prolonged EFS was noticed in the PD-L1≥1% subgroup (HR 0.41, 95%CI 0.24-0.70), especially in PD-L1 ≥50% subgroup (HR 0.24, 95%CI 0.10-0.61). Significant improvement in EFS and pCR supports NIVO+ chemotherapy as a potential new treatment option for patients with resectable non-small cell lung cancer. According to the excellent results of Checkmate-816, nivolumab plus doublet chemotherapy has now been approved by FDA as a neoadjuvant treatment choice for resectable NSCLC in March 2022. This is so far the first neoadjuvant immunochemotherapy regimen approved by FDA.

In AACR 2022, Cascone, T., et al. reported results from the phase 2, randomized multidrug platform study of neoadjuvant durvalumab alone or combined with novel agents in patients with resectable NSCLC(NeoCOAST) (32). Patients with stage I-IIIA NSCLC were given durvalumab alone or combined with the anti-CD73 mAb oleclumab, the anti-NKG2A mAb monalizumab, or the anti-STAT3 antisense oligonucleotide danvatirsen as neoadjuvant therapy for one cycle followed by surgery. The combination has shown improvement in both MPR and pCR rates compared to durvalumab monotherapy with no new safety signals. Another study, NeoCOAST-2 (33), is an open-label, randomized parallel phase 2 study comparing four doses of neoadjuvant durvalumab combined with CT and either oleclumab

or monalizumab, followed by surgery and twelve doses of adjuvant durvalumab plus oleclumab or monalizumab, in patients with resectable, Stage IIA-IIIA NSCLC. These data warrant further investigation in resectable NSCLC.

Apart from the Checkmate-816 study mentioned above, there are more phase 3 studies ongoing currently (Table 3). The AEGEAN study (34) aimed to evaluate the efficacy and tolerability of Durvalumab plus standard chemotherapy for up to 4 cycles as preoperative treatment in resectable Stage IIA to select (N2) IIIB NSCLC. Study enrollment began in December 2018, with primary completion anticipated in April 2024. KEYNOTE-671 (NCT03425643) (35) is an international randomized, double-blind, placebo-controlled phase 3 study that evaluates standard neoadjuvant chemotherapy with perioperative pembrolizumab or placebo in early-stage NSCLC. An estimated 786 patients will be enrolled. IMpower030(NCT03456063) (36) is a Phase 3, double-blind, randomized study, 374 resectable stage II - select IIIB (T3N2) NSCLC patients will be enrolled, randomized to either 4 cycles of neoadjuvant atezolizumab (1200 mg Q3W, Arm A) or placebo (Arm B) in combination with an platinum-based chemotherapy regimen. Patients in Arm A will receive adjuvant atezolizumab treatment for up to 16 cycles, and patients in Arm B will receive best supportive care. RATIONALE-315 (37) is a dual-primary endpoint phase 3 study, evaluating the efficacy of neoadjuvant tislelizumab or placebo + platinum-based doublet chemotherapy for 3-4 cycles followed by adjuvant tislelizumab or placebo for up to 8 cycles. Results from these trials and more ongoing trials are anticipated for a better understanding of the efficacy and safety of immunotherapy in the neoadjuvant setting of NSCLC. Also, long-term follow-up data could provide more information on the selection of immune checkpoint inhibitors and the most beneficial population.

TABLE 3 Clinical trials of neoadjuvant immunotherapy (phase III randomized clinical trials) in NSCLC.

Identifier	Acronym	stage	Number of patients	Driver gene	Intervention	1 end point	biomarkers
NCT02998528	CheckMate-816	IB-IIIA	358	EGFR/ ALK WT	Nivolumab+ CT, Q3W → Surgery*	pCR(24%); EFS (31.6m)	ctDNA clearance
					CT, Q3W → Surgery*	pCR (2.2%); EFS (20.8m)	
NCT03425643	KEYNOTE-671	II-IIIB (T3-4N2)	786	EGFR/ ALK WT	Pembrolizumab + CT → Surgery → Pembrolizumab	EFS; OS	
					CT → Surgery → Placebo		
NCT03456063	IMpower-030	II-IIIB (T3N2)	374	EGFR/ ALK WT	Atezolizumab + CT, Q3W×4→ Surgery → Atezolizumab Q3W for up to 16 cycles	MPR → EFS	NG
					CT, Q3W×4 → Surgery → Supportive care		
NCT03800134	AEGEAN	IIA-IIIA (T3N2)	816	EGFR/ ALK WT	Durvalumab + CT, Q3W×3-4 → Surgery → Durvalumab, Q4W×12	pCR; EFS	NG
					CT Q3W×3-4 → Surgery → Placebo		
NCT04379635	RATIONALE-315	II-IIIA	380	EGFR/ ALK WT	Tislelizumab + CT, Q3W×3-4→ Surgery →Tislelizumab, Q6W×8	MPR; EFS	NG
					CT, Q3W×3-4 → Surgery → Placebo		
NCT04025879	CheckMate 77T	II-IIIB	452	EGFR/ ALK WT	Nivolumab + CT → Surgery → Nivolumab	EFS	NG
					CT → Surgery → Placebo		
NCT04158440	/	II-IIIB (N2)	406	EGFR/ ALK WT	Toripalimab + CT, Q3W ×4 → Surgery → Toripalimab + CT, Q3W ×13	MPR; EFS	PD-L1; TMB; WES; ctDNA dynamics
					CT, Q3W ×4 → Surgery → Placebo Q3W ×13		

*: followed by optional adjuvant chemotherapy with or without radiotherapy,
NSCLC, Non-small cell lung cancer; CT, chemotherapy; SoC, standard of care; NG, not given; pCR, pathological complete response; MPR, major pathological response; EFS, event free survival; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; WES, Whole Exome Sequencing; ctDNA, circulating tumor DNA; TMB, tumor mutation burden.

4 Potential predictive factors of neoadjuvant immunotherapy

4.1 PD-L1

PD-L1 is a co-regulatory molecule expressed on tumor cells that inhibits T-cell-mediated cell death. T cells express the negative regulator PD-1, which binds to ligands including PD-L1 (CD274) or PD-L2 (CD273). In the presence of PD-L1, T-cell activity is suppressed. The antibody inhibited the interaction between PD-1 and PD-L1, thus improving the anti-tumor activity of endogenous T cells. PD-L1 expression is an FDA-approved biomarker for predicting the efficacy of immunotherapy in advanced NSCLC. Several trials have found that high expression of PD-L1 indicates a longer existence in advanced NSCLC (38, 39). Whether PD-L1 status could be a predictive factor of neoadjuvant immunotherapy in NSCLC is still under discussion. Studies reported different results on this issue. In the study NEOSTAR (20), researchers came up with a conclusion that higher pretreatment PD-L1 level is associated with both radiological and pathologic antitumor activity. Higher pre-treatment tumor cell PD-L1 expression evaluated by immunohistochemistry (IHC) was associated with greater pathological responses and fewer residual tumor cells after treatment. However, it is of note that the pathological responses were also observed in PD-L1 negative patients, and the association was not found between post-therapy tumor PD-L1 expression and responses; thus this is still of doubt whether it could be a proper predictor. Checkmate-159 (15) indicated that major pathological response rate was not related to the PD-L1 expression level at diagnosis. Similar results were observed by Shu, CA. et al. (29), as PD-L1 expression did not appear to be predictive of a treatment benefit in neoadjuvant immunochemotherapy.

4.2 Tumor mutation burden

Tumor mutation burden refers to the number of somatic mutations per megabase of interrogated genomic sequence in tumor cells, which varies among malignancies. In metastatic NSCLC, the value of TMB as a predictive molecular marker is controversial (40). Theoretically, higher tumor mutation burden is an implication of higher neoantigens which could activate greater anti-tumor immune response (41), thus trigger a better response to immunotherapy. Some studies observed that patients with a high burden of tumor mutations (TMB-High) might respond better to immunotherapy treatments (42, 43), while in other scenarios the predictive value is doubted. Likewise, it is also under discussion whether TMB could be a predictor in the neoadjuvant setting for immunotherapy. In Checkmate-159 (15), of 20 patients who underwent surgical resection, 12 had provided pre-operative tissue for WES sequencing, and 11 underwent complete resections which are sufficient for evaluation. A higher mutation burden detected by whole-exome sequencing was found to be associated with MPR, and the residual tumor rate was found to be inversely related to the sequence alterations. However, this relation was not observed in other studies with more patients (LCMC3, Checkmate 816) (44).

4.3 Circulating tumor DNA

Circulating tumor DNA (ctDNA) proved to be a useful predictive biomarker of recurrence and outcome in the advanced NSCLC (45). In trials, researchers found that early clearance of ctDNA was predictive of a better response to treatment and a longer survival time in metastatic non-small cell lung cancer. As recommended by ESMO (46), different clinical scenarios may require different testing strategies. For example, driver-gene testing is required for disease diagnosis, minimal residual disease (MRD) testing after radical resection requires screening for patient-specific alterations, monitoring of patient-specific alterations also helps to identify early recurrence, and more extensive genetic analysis and genome-wide analysis is required at the stage of disease progression to identify mechanisms of drug resistance and select appropriate targeted agents.

In the neoadjuvant setting, the power of ctDNA as a biomarker of immunotherapy is explored in many studies. Current supporting proof comes from Checkmate-816, a phase 3 prospective study that assesses the efficacy of the nivo + chemo regimen in stage IIA-IIIB patients. As it is reported on 2021 ASCO data from the CheckMate-816 trial, investigators collected a portion of blood from the Nivolumab combination chemotherapy group and the chemotherapy group for 3 courses of ctDNA testing. The results shown that the ctDNA clearance rates were 56% and 34% in the Nivolumab combination and chemotherapy groups, respectively. The investigators further conducted a post-screening study on whether ctDNA was cleared and found that in the ctDNA clearance group, the pCR rates were 46% and 13% in the nivolumab combination and chemotherapy groups, respectively, which were significantly higher than the pCR rates of 24% and 2.2% in the unscreened group. The results of this study again suggest that ctDNA clearance rates are highly correlated with pCR and can be used for efficacy prediction of neoadjuvant immunotherapy efficacy. In the NADIM trial (47), lower pretreatment ctDNA levels were associated with improved PFS and OS, while undetectable ctDNA after neoadjuvant therapy was associated with better PFS and OS. Similar results were also found in NADIM II study (48). Another proof was reported by the LCMC3 study (49), indicating that ctDNA could be a predictor of better pathologic response and longer survival. After immunotherapy, greater ctDNA reduction was seen in patients with MPR than those with non-MPR (median log2 fold change −4.8 vs 0.3, $P<0.001$). Also, post-immunotherapy reduced ctDNA levels were associated with pathologic response ($P<0.001$, $r=0.38$) and regression in radiographic tumor size ($P<0.001$, $r=0.42$). What's more, patients that are ctDNA negative after surgery represented a higher 2-year DFS rate compared to those that are ctDNA positive (75% and 40%, respectively; HR, 3.6; 95% CI: 1.0, 13.1; $P=0.054$). The inclusion of ctDNA assessment in clinical trials may help identify patients who may be cured with surgery and short-term perioperative treatment, thus avoiding expensive and potentially toxic adjuvant therapy.

4.4 Tumor environment components

Multiple components in the tumor microenvironment (TME) surround the tumor cells (50). Differential of the components of the

TME might give rise to the proliferation of tumor cells or suppress the growth and metastases of the primary tumor. Cytotoxic immune cells recognize tumor cell antigen and kill the tumor cells; macrophages also give hand to this process. However, tumor cells could manipulate suppressive immune cells in the microenvironment to escape from immune surveillance and even transfer it to a tumor-genic environment. With neoadjuvant therapy, doctors are able to analyze the surgery specimen, where changes in TME could be spotted, and some of the dynamics might be associated with tumor regression and patients' survival.

Three subgroups from the NADIM study were explored for the potential relation between Peripheral Blood Mononuclear Cells (PBMCs) phenotype and the effect of neo-adjuvant chemo-immunotherapy treatment, especially with the degree of pathological response (51). 41 patients were enrolled in this analysis. The activation of CD4 T cells and NK cells and the expression of PD-1 receptor on immune cells were downregulated. A higher decrease in Platelet/Lymphocyte Ratio (PLR) post-neo-adjuvant treatment, a decrease of PD-1 expression in CD4, CD8, and NK cells, as well as a reduction of CD4 T cells and NK cells activation after neoadjuvant treatment, are associated with pCR. In LCMC3 (52), lower frequencies of $ILT2^+$ NK cells and $ILT2^+$ NK-like T cells in pretreatment peripheral blood were significantly associated with MPR. Immune profiling by flow cytometry has revealed changes after dual-agent ICI treatment in NEOSTAR study (20). Compared to nivolumab mono-agent arm, frequencies of tumor-infiltrating lymphocytes (TILs), tissue-resident memory (T_{RM}) T cells, $CD103^+$ effector T_{RM} cells, and $CD27^-CD28^+$ effector memory T cells in resected tumors were higher in dual-agent arm, indicating an enhanced T-cell infiltration. But the changes in TILs were not associated with the extent of pathological response.

T cell receptor (TCRs) clonality has been reported to be associated with acquired resistance to ICIs (53); greater TCR intratumor heterogeneity is associated with an elevated risk of recurrence after surgical procedure (54). In the advanced/metastatic NSCLC patients, studies have found that increased PD-1+ CD8+ TCR clonality after ICI treatment had longer PFS (7.3 months vs. 2.6 months, HR, 0.26; 95% CI, 0.08-0.86; P = 0.002) than those with decreased clonality (55). In the NEOSTAR study, peripheral and tumor TCR clonality was not associated with pathological tumor responses (20), though only one case of MPR was viable for analysis. In Checkmate-159, researchers examined the influence of treatment on T cell clone repertoire in the tumor and peripheral blood at the time of resection (56). Decreased residual tumor rate as well as MPR was associated with higher intratumoral TCR clonality. Further analysis suggests that peripheral T cells might serve as an originating compartment of effective antitumor immunity, and the exchange of T-cell clones between tumor and periphery might play a key role in pathological regression. Another cohort which enrolled 236 patients, suggested that higher TCR repertoire homology between the tumor and uninvolved tumor-adjacent lung indicated an inferior survival due to less tumor-specific T cell effect (57).

4.5 Clinical factors

The pivotal approach to measure tumor responses is radiology assessment in non-invasive evaluation methods. As aforementioned, criteria including RECIST, RECIST version1.1, and iRECIST are widely used as a uniform assessment. For most clinical trials ongoing, RECIST was used to assess imaging responses. In the NEOSTAR study (20), within patients who achieved MPR, the ratio of partial response (PR) plus complete response (CR) assessed by imaging according to RECIST was 60% in the dual-agent group. In NeoTAP01, RECIST radiological regression was not associated with pathological response. Reduction in SUVmax from baseline to post-neoadjuvant in ^{18}F-FDG PET-CT (58) has a significant relation with pathological tumor response. Due to the special effect of immunotherapy, the radiological response is not identical to that in chemotherapy (59). Studies have revealed that regression bed composed by immune-mediated tumor clearance presenting on radiology imaging after neoadjuvant immunotherapy could accounts for the discrepancy of tumor cells between CT-scan image and pathological assessment (59), thus the RECIST criteria are not always accurate in the evaluation of tumor responses, particularly in neoadjuvant immunotherapy. Currently, it is widely accepted that pathological response is more associated with survival than the radiological response in the neoadjuvant immunotherapy regimen.

Another interesting factor that might predict the outcome of neoadjuvant immune-combined therapy is immune-related adverse events (irAEs). In 2022 WCLC (60), an updated Renaissance trial reported the interesting relation between irAEs and outcome of neoadjuvant Toripalimab combined with platinum-based doublet chemotherapy. Five patients experienced grade 2-3 adverse event, out of which 3 patients underwent resection reached pCR with an interval of 8 weeks between surgery and the last dose of neoadjuvant immunochemotherapy, and the other two patients were not suitable for surgery or in the interval also reached clinical complete response or partial response. No extra surgery difficulties nor delays were spotted in these patients.

An ongoing trial initiated by researchers from Peking Union Medical College Hospital focused on the safety and potential biomarkers of Durvalumab in combination with albumin-paclitaxel plus cisplatin/carboplatin for stage IB-IIIA non-small cell lung cancer (NCT04646837). Whole exome sequencing (WES) and NanoString platform-based GEP (gene expression profiling) were implemented to find potential biomarkers. Another to investigate the impact of neoadjuvant immunotherapy on the tumor microenvironment at multiple levels, including genome, transcriptome, PD-1/PD-L1 protein transcription and expression, T cell TCR immunome library, and T cell subpopulation, aiming to provide comprehensive exploratory research evidence on immune mechanisms of neoadjuvant anti-PD-1/L1 therapy in lung cancer.

5 Discussion

Neoadjuvant therapy aims at improving the outcome of early-stage and locally advanced NSCLC. The utility of molecular markers in predicting efficacy has not been uniformly agreed upon, thus it is not necessary to select drugs based on molecular testing (61). A recent retrospective study claimed that the dynamics of circulating tumor DNA, defined as relative delta mean variant allele fraction, predicts neoadjuvant immunotherapy efficacy and recurrence-free survival in surgical non-small cell lung cancer patients, as ctDNA dynamics are

concordant with pathologic response, demonstrating 100% sensitivity (62). The circulating tumor DNA recurrence preceded radiographic relapse, with a median time of 6.83 months (62). Studies have supported that patient without minimal residue disease (MRD) after surgery have a much lower risk of recurrence, thus suggesting that MRD might be promising to contribute to the refinement of individualized adjuvant therapy and consolidation treatment (63). As it is reported by Zhang, et al. (64), the negative predictive value of longitudinal molecular residual disease is 96.8%, with only 6 patients reoccurred (3.2%). The findings suggested that MRD negative patients might not benefit from the adjuvant study, and longitudinal MRD negative populations are highly possible to be "cured" as indicated by long-term disease-free survival. Another prospective multicenter cohort study, LIBERTI, intending to evaluate the possible association between presence of circulating tumor DNA and the disease-free survival in completely resected phase II-III NSCLC, is now ongoing (65). Further evidence from prospective randomized clinical trials might help better illustrate the utility of ctDNA as a biomarker in NSCLC.

Till now, there has not been a unanimous biomarker for predicting outcomes of neoadjuvant immunotherapy. As a promising predictive biomarker in advanced NSCLC, PD-L1 expression and tumor mutation burden has been considered as highly potential biomarkers in the neoadjuvant setting predicting the outcome of neo-ICI therapy. However, results vary from different trials (15, 20, 29), no solid evidence till now support the predictive efficacy of these two factors. A recent meta-analysis indicated that PD-L1 expression and TMB could be predictive factors for pathological response (66), with higher expression of PD-L1 (≥1% vs <1%) correlated with higher MPR rate and pCR rate (OR = 2.62, P = 0.0006; OR = 2.94, P ≤0.0001, respectively). Previous studies have reported that PD-L1 status defining through three IHC scoring systems (Ventana SP263, Dako 22C3, and Dako 28-8) are highly agreeable with each other (67, 68), and the positive relation between higher PD-L1 expression and better MPR/pCR rate suggesting PD-L1 to be a potential stable predictive factor in neoadjuvant setting for clinical practice. Due to lack of clinical evidence and the technical problems in measuring TMB, it is removed from the recommended panel for metastatic NSCLC in the NCCN guideline (69). The predictive efficacy of TMB is also doubted in neoadjuvant setting with no more evidence than the Checkmate-159 study (15), in which a higher mean mutational burden number was suspected through sequencing in MPR population than in non-MPR population (311 ± 55 vs. 74 ± 60, P = 0.01). The utility of TMB as an ideal sole biomarker remains in doubt until more supportive evidence accumulated.

Novel technologies have given us more approaches to study the environment of tumor environments deeper. Studies revealed other molecular markers that could be predictive of the efficacy of immunotherapy in advanced NSCLC. For example, detected through next-generation sequencing, the apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like, also known as APOBEC, has been reported to predict the efficacy of immunotherapy (70), not only in NSCLC but also in pan-cancer analysis (71). Previous study (72) found that APOBEC signature in metastatic NSCLC is strongly associated with better immune responses, in terms of ORR and PFS. Tumor bulk RNA sequencing in NADIM trial recently revealed that certain tumor environmental gene expression could predict pCR with the AUC >0.9 (73). With innovational technique implying in this area, novel markers including mutational signature (74, 75), intestinal microbiota (76), radiomics (77, 78) are now under analysis in neoadjuvant setting of NSCLC, with the hope to provide us with a deeper understanding of the tumor environment and evolution. These new markers might perform well when combined with existing markers (TMB, PD-L1, Tumor neoantigen burden, etc.) or even reveal a better performance in predicting efficacy of ICIs in near future.

Pathologists' interpretation directly affects the interpretation accuracy of pathological response evaluation (79, 80). Consistent regulation of pathological interpretation of pathological response is essential in practice, and evaluations must be performed by experienced pathologists with adequate knowledge of pathological characteristics in post-immunotherapy specimens. As the pathological response to immune checkpoint inhibitors alters from that to chemotherapy, standardization of pathologic evaluation and reports on post-neoadjuvant specimens will give rise to an agreement amongst the pathologists, which will be key in accurately predicting outcomes for individual patients and facilitating comparisons in clinical practice (59). Another question on whether MPR rate or pCR rate could be translated into survival benefits is still under discussion, long-term follow-up of clinical trials and prospective real-world studies might give us more evidence on this issue. Currently, different designs of trials added difficulties to the direct comparison of results. So far, there is no agreement on adjuvant therapy after neoadjuvant immunotherapy, thus the designs vary among studies. Another factor that should be considered is the possible use of radiotherapy in the locally advanced NSCLC. The establishment of radiotherapy in the adjuvant setting of locally advanced NSCLC is still under discussion, but there is no doubt that radiation therapy should be discussed by a multidisciplinary team for the proper treatment of locally advanced patients.

6 Conclusion

Up to this date, no molecular marker has been unanimously agreed on as a powerful predictor in neoadjuvant setting. We are expecting a wide range of immunotherapy and combined regimens as well as a more profound genre of predictive and prognostic biomarkers in neoadjuvant setting of NSCLC in the coming future. Dynamic change of circulating tumor DNA is currently the most likely predictive biomarker of neo-immunotherapy. The predicting power of PD-L1 expression warrants further validation, while TMB is not recommended yet. Further exploration on biomarkers focusing on immune-related adverse events is of great importance as well for the underlying population that might not benefit from neoadjuvant immunotherapy.

Author contributions

XW: Data curation, Writing- Original draft preparation, Visualization. YC: Data curation, Validation. HB: Validation, Supervision. XZ: Reviewing the Final draft. JW: Supervision, Reviewing the Final draft. JD: Conceptualization, Supervision, Reviewing and Editing the Original and Final draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The efficacy of neoadjuvant *EGFR*-TKI therapy combined with radical surgery for stage IIIB lung adenocarcinoma harboring *EGFR* mutations: A retrospective analysis based on single center

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (*EGFR*-TKIs) could provide survival benefits for locally advanced *EGFR*-mutant (*EGFR*m) non-small cell lung cancer (NSCLC). However, the role of radical surgery for *EGFR*-TKI treated stage IIIB *EGFR*m NSCLC remains controversial. This study attempted to assess the feasibility of neoadjuvant *EGFR*-TKI followed by radical surgery for stage IIIB *EGFR*m NSCLC.

Patients and Methods: Between 2013 and 2020, *EGFR*m lung adenocarcinoma (LUAD) patients in clinical stage IIIB undergoing neoadjuvant *EGFR*-TKI followed by surgery (T-S-Arm) and *EGFR*-TKI alone (T-Arm) were reviewed retrospectively in Shanghai Pulmonary Hospital (SPH). The chi-square test, Student's *t*-test or Fisher's exact test was performed for analysis of baseline characteristics. Progression-free survival (PFS) was estimated using the Kaplan-Meier analysis. Multivariate Cox regression analysis was used to identify independent predictors of progression.

Results: A total of 43 patients were divided into T-S-Arm (n = 21) and T-Arm (n = 22). Patients were well-balanced between the two arms. The majority of patients were female (n = 25, 58.1%), non-smokers (n = 35, 81.4%), first-generation of *EGFR*-TKI treatment (n = 39, 90.7%), and exon 19 deletions (19-DEL) (n = 26, 60.5%). The median diagnostic age was 63.0 years [interquartile range (IQR), 54.0-67.5 years). At the cut-off date with June 30th 2022, median follow-up time was 28 months (IQR, 20-39 months). Neoadjuvant *EGFR*-TKI treatment followed by radical surgery could significantly improve the median PFS compared with patients underwent *EGFR*-TKI alone (23.0 months vs 14.5 months, P = 0.002). Multivariate Cox regression analysis demonstrated that radical surgery (T-S-Arm vs. T-Arm, HR: 0.406; 95% CI: 0.207-0.793, P = 0.027) was the only independent predictor for disease progression. The stratified analysis demonstrated patients with N2 disease could benefit from radical surgery (HR, 0.258; 95% CI, 0.107-

0.618), especially for patients harboring L858R mutation (HR, 0.188; 95% CI, 0.059-0.604).

Conclusions: For stage IIIB *EGFR*m NSCLC patients, the prognosis might be improved by neoadjuvant *EGFR*-TKI followed by radical surgery versus *EGFR*-TKI alone, especially for those with N2 disease and harboring L858R mutation.

KEYWORDS

non-small cell lung cancer, adenocarcinoma, neoadjuvant targeted therapy, epidermal growth factor receptor, stage IIIB

Introduction

Non-small cell lung cancer (NSCLC) represents approximately 85% of lung cancer worldwide (1), and 22% of NSCLC patients were diagnosed with locally advanced (stage III) disease (2). NSCLC in stage III is divided into IIIA to C (3). NSCLC patients with stage IIIB disease, considering unresectable disease, have limited benefits from surgery followed by adjuvant treatment (4). In 2014, the multicenter phase II study (TAX-AT 1.20 trial) demonstrated neoadjuvant chemotherapy with docetacxel/cisplatin followed by complete resection could improve prognosis of NSCLC patients in stage II, IIIA and IIIB (5). ASCO guideline has recommended that patients with unresectable stage III disease may be offered induction therapy followed by complete resection (6).

The percentage of Asian NSCLC patients with epidermal growth factor receptor (*EGFR*) mutations is 30%, and the most common mutations are deletions in exon 19 (19-DEL) and the exon 21 codon p.Leu858Arg point (L858R) mutation (7). In patients with *EGFR* mutations, *EGFR*-TKI therapy has shown good efficacy and well-tolerance compared with chemotherapy (8). In recent years, studies showed neoadjuvant *EGFR*-TKI therapy could downstage the tumor and improve the rate of radical surgery in patients with locally advanced NSCLC. Xiong et al. demonstrated that neoadjuvant erlotinib therapy could improve the rate of radical surgery (13/19, 69.4%) of *EGFR*m NSCLC patients in stage IIIA-N2, achieving a median progression-free survival (PFS) of 12.1 months (95% CI, 9.4-31.8) (9). Zhang et al. demonstrated the feasibility of neoadjuvant gefitinib therapy followed by radical surgery for *EGFR*m NSCLC patients in stage II-IIIA [disease-free survival (DFS), 33.5 months, 95% CI, 19.7-47.3], and patients with major pathologic response (MPR, proportion of patients with no more than 10% residual viable tumor cells) had a better prognosis (DFS, $P = 0.019$) (10).

The safety and efficacy of neoadjuvant *EGFR*-TKI therapy for locally advanced *EGFR*m NSCLC have been confirmed by clinical trials above mentioned. However, no clinical trial focused on the efficacy of neoadjuvant targeted therapy combined with radical surgery for stage IIIB NSCLC harboring *EGFR* mutations. The efficacy of complete resection based on tumor downstaging after treated with neoadjuvant *EGFR*-TKI therapy remains controversial for *EGFR*m NSCLC patients diagnosed as stage IIIB disease. In this study, we attempted to assess the clinical efficacy of radical surgery after induction targeted therapy for *EGFR*m lung adenocarcinoma (LUAD) patients with stage IIIB disease.

Methods

Patient selection

We retrospectively included the NSCLC patients between January 2013 and December 2020 in Shanghai Pulmonary Hospital (SPH). The approval of the study was granted by Ethical Committee of Shanghai Pulmonary Hospital, and informed consent was obtained by all patients. The inclusion criteria were as followed: (I) patients harboring L858R mutation or 19-DEL confirmed by molecular biological detection; (II) patients diagnosed as NSCLC with clinical stage IIIB disease; (III) the diagnostic age of patients elder than 18 years; (IV) Eastern Cooperative Oncology Group (ECOG) performance status was 0 to 1; (V) radical surgery could not be completed at the time of diagnosis. The exclusion criteria were as followed: (I) history of cancer within 5 years; (II) primary resistance to *EGFR*-TKIs; (III) other systemic neoadjuvant antitumor therapy before preoperative evaluation. These patients underwent neoadjuvant *EGFR*-TKI followed by surgery (T-S-Arm) and *EGFR*-TKI alone (T-Arm) respectively. The pathological diagnosis of NSCLC was established on the basis of needle biopsy or endobronchial ultrasound (EBUS). All patients were pathologically diagnosed as LUAD. The type of *EGFR* mutations was confirmed by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). The NSCLC stage of all patients was evaluated by pathological detection and/or standardized uptake value (SUV) in positron emission tomography/CT (PET/CT). The stage of the primary tumor (T), lymph node (N), and metastasis (M) were evaluated based on the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system for NSCLC (3). Patients with pre-induction N3 disease in T-S-Arm had downstaging and their N3 lymph nodes were negative after *EGFR*-TKI therapy, which was confirmed by PET/CT and ultrasound-guided fine-needle aspiration. In T-S-Arm, all patients should be performed surgery within 3 weeks after *EGFR*-TKI discontinuation. For patients received the first-generation *EGFR*-TKI, at least three days interval from *EGFR*-TKI

discontinuation to surgery, and for patients received the second-generation *EGFR*-TKI treatment, the interval should be extended to 7 days. All patients in T-S-Arm were strongly required to undergo complete resection for LUAD after neoadjuvant treatment.

Efficacy assessment

To evaluate the treatment response after *EGFR*-TKI treatment, chest CT images of all patients were reviewed and evaluated by radiologists based on the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) (11). The tumor responses were classified as progressive disease (PD, ≥20% increased in size or the occurrence of now lesions), stable disease (SD, change in size between -30% to +20%), partial response (PR, ≥30% reduced in size) and complete remission (CR, no resident lesion). Chest CT and EBUS were performed to evaluate the lymph node response after *EGFR*-TKI treatment and to assess the surgical feasibility. Brain magnetic resonance imaging (MRI) and PET/CT or bone emission computed tomography (ECT) scan were performed to confirm the absence of distant metastasis.

Follow-up strategy

Follow up was conducted by outpatient visits or telephone calls. For postoperative patients, physical examinations and chest CT were performed every 3 months for the first year, every 6 months for 2 to 5 years, and annually from then on. Brain MRI, ultrasonography of abdominal and bone ECT were performed annually or physicians considered necessary. For patients without surgery, physical examinations and chest CT were performed every 2 months. The cutoff date was June 30th 2022. PFS was defined as the interval of time from the beginning of treatment to the first progression or last follow-up. OS was defined as the interval of time from the beginning of treatment to death or last follow-up. Data was censored at the last follow-up for patients without recurrence or death.

Statistical analysis

The statistical analysis used R software (R v.4.1.3). The chi-square test or fisher's exact test and Student's *t*-test were used for comparing the differences of categorical and continuous variables between T-S-Arm and T-Arm. PFS was analyzed by Kaplan-Meier method and was compared using the log-rank test. The stratified analyses of PFS were performed with the Cox proportional hazards model according to clinical characteristics. Multivariate Cox regression was used to evaluate independent survival predictors of progression, and factors with $P < 0.1$ from the univariate Cox regression was included in the multivariate Cox regression. $P < 0.05$ indicated statistical significance.

Results

Patient characteristics

A total of 43 *EGFR*m LUAD patients with clinical stage IIIB were included in this study retrospectively (21 in T-S-Arm and 22 in T-Arm respectively) (Figure 1). The characteristics of patients were summarized in Table 1. The median age was 63 years [interquartile range (IQR), 54.0-67.5]. The majority of patients were female (n = 25, 58.1%), non-smokers (n = 35, 81.4%), the first-generation *EGFR*-TKIs treated (n = 39, 90.7%), and harboring 19-DEL (n = 26, 60.5%). No significant difference was observed in the distribution of age, gender, smoking history and mutation subtypes between T-S-Arm and T-Arm. While, compared with patients in T-Arm, T-S-Arm patients had larger target lesions (57.0mm vs 37.9mm, $P = 0.007$). There were two (9.5%) patients with single N2 disease in T-S-Arm. There were 15 (15/21, 71.4%) patients in T-S-Arm receiving neoadjuvant therapy for up to 2 months (range, 1-2 months), and 6 (6/21, 28.6%) for more than 2 months (range, 3-6 months).

Treatment feasibility

As Table 2 demonstrated that the efficacy of neoadjuvant *EGFR*-TKI therapy was assessed by RECIST (version 1.1). PR was observed in 26 patients, and SD was observed in 16 patients. Only one patient refused to evaluation in our center after neoadjuvant treatment. The objective response rate (ORR) in this study was 61.9% (26/42). There was no CR radiologically. The distribution of tumor response was similar between T-S-Arm and T-Arm. After *EGFR*-TKI treatment, the rate of patients occurred radiologically CR in lymph nodes (N0) was higher in T-S-Arm (52.4% vs 27.3%, $P = 0.148$). Only one patient discontinued *EGFR*-TKI therapy for serious adverse event (interstitial pneumonia).

Patients in T-S-Arm all received neoadjuvant treatment followed by complete resection. There were 19 (19/21, 90.5%) patients receiving lobectomy, and 1 (1/21, 4.8%) receiving sleeve resection in T-S-Arm. There was one (1/21, 4.8%) patient receiving segmentectomy for poor pulmonary function. The median operation time was 2.25 hours (IQR, 2.00-3.00), and the median blood loss was 50.0 mL (IQR, 50.0-150.0) (Table 3). Perioperative complications included one (1/21, 4.8%) patient with pulmonary embolism (PE) and one (1/21, 4.8%) patient with pleural effusion. No surgical related death was observed within 90 days postoperatively.

There were 17 (17/21, 81.0%) patients in T-S-Arm receiving *EGFR*-TKI for at least 2 years or until disease progression postoperatively. And four (4/21, 19.0%) patients received adjuvant

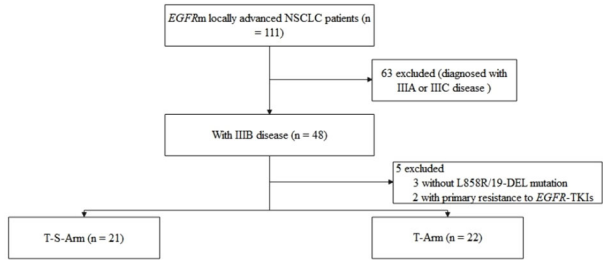

FIGURE 1
Study flow diagram. *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; *EGFR*-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

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TABLE 1 Baseline information of patients receiving *EGFR*-TKIs.

	Total (N=43)	T-S-Arm (N=21)	T-Arm (N=22)	
Median age, years (IQR)	63 [54.0, 67.5]	61.0 [53.0, 67.0]	64.0 [59.0, 68.5]	0.225
Gender				0.223
Male	18 (41.9%)	11 (52.4%)	7 (31.8%)	
Female	25 (58.1%)	10 (47.6%)	15 (68.2%)	
Smoking history				0.457
Current or ever	8 (18.6%)	5 (23.8%)	3 (13.6%)	
Never	35 (81.4%)	16 (76.2%)	19 (86.4%)	
The Generation of TKI				-
I	39 (90.7%)	17 (81.0%)	22 (100%)	
II	4 (9.3%)	4 (19.0%)	0 (0%)	
Mutation Subtype				0.124
L858R	17 (39.5%)	11 (52.4%)	6 (27.3%)	
19-DEL	26 (60.5%)	10 (47.6%)	16 (72.7%)	
Mean target lesions, mm (IQR)	46.5 [30.3-60.5]	57.0 [36.0-72.0]	37.9 [22.0-50.0]	0.007
T stage				0.588
T1	8 (18.6%)	3 (14.3%)	5 (22.7%)	
T2	13 (30.2%)	5 (23.8%)	8 (36.4%)	
T3	9 (20.9%)	5 (23.8%)	4 (18.2%)	
T4	13 (30.2%)	8 (38.1%)	5 (22.7%)	
N stage				0.227
N2	22 (51.2%)	13 (61.9%)	9 (40.9%)	
N3	21 (48.8%)	8 (38.1%)	13 (59.1%)	
LN station				0.277
Single station N2	2 (4.7%)	2 (9.5%)	0 (0%)	
Multiple station N2	21 (48.8%)	11 (52.4%)	10 (45.5%)	
N3	20 (46.5%)	8 (38.1%)	12 (54.5%)	

IQR, interquartile range; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; LN, lymph nodes.

chemotherapy every 3 weeks for 4 cycles. No patient received the third-generation *EGFR*-TKI as an adjuvant therapeutic regimen.

Survival analysis

The median follow-up time was 28 months (IQR, 20-39). In T-S-Arm, there were 10 (10/21, 47.6%) patients occurring tumor recurrence, including one (1/10, 10%) local recurrence and nine (9/10, 90%) distant recurrence. As Figure 2A illustrated that the median PFS of patients in T-S-Arm was significantly better than those in T-Arm (23.0 months vs 14.5 months, $P = 0.002$). Improvement of PFS at 1-year (85.7% vs 50.0%, $P = 0.021$) was also observed in T-S-Arm. PFS at 2-year (42.9% vs 10.9%, $P = 0.103$) was similar between T-S-Arm and T-Arm. As of the final follow-up date, 32 (32/43, 74.4%) patients survived, 6 (6/43, 14%) were lost to follow-up after recurrence or progression and 5 (5/43, 11.6%) died of distant metastasis (3 in T-S-Arm and 2 in T-Arm). The median OS did not reach in both groups (Figure 2B).

Multivariate Cox regression analysis showed that radical surgery (HR, 0.406; 95% CI, 0.207-0.793; $P = 0.027$) was the only independent predictive factor for disease progression (Table 4). In the stratified analysis, PFS favored radical surgery in younger patients (HR, 0.165; 95% CI, 0.052-0.523; $P = 0.010$), non-smokers (HR, 0.316; 95% CI, 0.137-0.971; $P = 0.010$), harboring L858R mutation (HR, 0.188; 95% CI, 0.059-0.604; $P = 0.019$), with stage N2 disease (HR, 0.258; 95% CI, 0.107-0.618; $P = 0.011$), radiological PR (HR, 0.291; 95% CI, 0.128-0.659; $P = 0.013$) and without lymph node CR (HR, 0.329; 95% CI, 0.139-0.776; $P = 0.033$). There was no significant difference in other subgroups (Figure 3).

Discussion

The radical surgery remains uncertain in stage IIIB NSCLC patients harboring *EGFR* mutations occurring downstaging after neoadjuvant *EGFR*-TKI therapy. Recent studies have reported a small sample of *EGFR*m NSCLC patients in stage IIIB receiving

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TABLE 2 Efficacy of patients receiving neoadjuvant *EGFR*-TKI plus complete resection or *EGFR*-TKI alone.

	Total (N=43)	T-S-Arm (N=21)	T-Arm (N=22)	*P* value
Tumor response				1.000
PR	26 (60.5%)	13 (61.9%)	13 (59.1%)	
SD	16 (37.2%)	8 (38.1%)	8 (36.4%)	
Missing	1 (2.3%)	0 (0%)	1 (4.5%)	
Clinical T stage after treatment				0.871
T1	24 (55.8%)	13 (61.9%)	11 (50.0%)	
T2	15 (34.9%)	7 (33.3%)	8 (36.4%)	
T3	1 (2.3%)	0 (0%)	1 (4.5%)	
T4	2 (4.7%)	1 (4.8%)	1 (4.5%)	
Missing	1 (2.3%)	0 (0%)	1 (4.5%)	
Pathological T stage after treatment				-
T1	11 (25.6%)	11 (52.4%)	0 (0%)	
T2	9 (20.9%)	9 (42.9%)	0 (0%)	
T3	0 (0%)	0 (0%)	0 (0%)	
T4	1 (2.3%)	1 (4.8%)	0 (0%)	
Missing	22 (51.2%)	0 (0%)	22 (100%)	
Pathological N stage after treatment				-
N0	11 (25.6%)	11 (52.4%)	0 (0%)	
N1	2 (4.7%)	2 (9.5%)	0 (0%)	
N2	8 (18.6%)	8 (38.1%)	0 (0%)	
Missing	22 (51.2%)	0 (0%)	22 (100%)	
LN response				0.148
Downstaging to N0	17 (39.5%)	11 (52.4%)	6 (27.3%)	
Downstaging to N1 or N2	9 (20.9%)	5 (23.8%)	4 (18.2%)	
Unchanged	16 (37.2%)	5 (23.8%)	11 (50.0%)	
Missing	1 (2.3%)	0 (0%)	1 (4.5%)	
Recurrence or progression				<0.001
Yes	31 (72.1%)	10 (47.6%)	21 (95.5%)	
No	12 (27.9%)	11 (52.4%)	1 (4.5%)	
Recurrence or progression position				<0.001
Local	19 (44.2%)	1 (4.8%)	18 (81.8%)	
Distance	12 (27.9%)	9 (42.9%)	3 (13.6%)	
None	12 (27.9%)	11 (52.4%)	1 (4.5%)	
Status				0.660
Alive	32 (74.4%)	15 (71.4%)	17 (77.3%)	
Dead	5 (11.6%)	3 (14.3%)	2 (9.1%)	
Censored	6 (14.0%)	3 (14.3%)	3 (13.6%)	

EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; LN, lymph nodes; PR, partial response; SD, stable disease.

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TABLE 3 Surgical information and adjuvant therapy of patients in T-S-Arm.

	T-S-Arm (N=21)
Operative procedure	
Lobectomy	19 (90.5%)
Segmentectomy	1 (4.8%)
Sleeve resection	1 (4.8%)
Surgical approach	
VATS	14 (66.7%)
Open	7 (33.3%)
Median operation time, h (IQR)	2.25 [2.00, 3.00]
Median blood loss, mL (IQR)	50.0 [50.0, 150.0]
Perioperative complications	
Pulmonary embolism	1 (4.8%)
Pleural effusion	1 (4.8%)
None	19 (90.5%)
Adjuvant therapy	
EGFR-TKI	17 (81.0%)
Chemotherapy	4 (19.0%)

VATS, video-assisted thoracic surgery; IQR, interquartile range; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

salvage surgery following *EGFR*-TKI treatment and demonstrated the feasibility of neoadjuvant *EGFR*-TKI therapy for *EGFR*m NSCLC in stage IIIB (12, 13). The results suggested that neoadjuvant *EGFR*-TKI therapy in combination with radical surgery could provide significantly better median PFS with *EGFR*m LUAD patients in stage IIIB compared with these patients receiving *EGFR*-TKI alone (23.0 months vs 14.5 months, $P = 0.002$).

The randomized phase II study (EMERGING-CTONG1103) reported the median PFS of 21.5 months (95% CI, 16.7-26.3) of NSCLC patients with stage IIIA-N2 disease receiving neoadjuvant erlotinib therapy combined with radical surgery and the ORR was 54.1% (20/37) (14). The open label phase III study (WJTOG3405) showed that median PFS of *EGFR*m NSCLC patients in stage IIIB (6th edition TNM classification, including T3N3 and T4N3 disease) receiving gefitinib was 13.7 months (95% CI, 7.2-20.5), and the ORR was 62.1% (36/58) (15). The median PFS and ORR of patients in T-Arm were consistent with those in WJTOG3405. However, the median PFS and ORR of patients in T-S-Arm were slightly higher than those in EMERGING-CTONG1103. One possible reason is that we excluded patients with primary resistance to *EGFR*-TKIs who had worse PFS, while there were 3 patients with PD in EMERGING-CTONG1103. Another reason is that the longer period of neoadjuvant *EGFR*-TKI might provide enough time for tumor to decrease. In our study, the duration of neoadjuvant *EGFR*-TKI varied 1 to 6 months, while patients in EMERGING-CTONG1103 received preoperative *EGFR*-TKI for 42 days.

The preferred treatment for NSCLC patients with N3 disease is systemic therapy instead of surgery. In 2018, Ning et al. reported 2 *EGFR*m NSCLC patients in stage IIIB receiving complete resection after *EGFR*-TKI treatment. Both of them were in stage N2 and downstaged to N0 preoperatively (16). In 2021, Li et al. collected 91 NSCLC patients with unresectable disease before receiving *EGFR*-TKI treatment, and 18 of them downstaged and received salvage resection after *EGFR*-TKI treatment. There were 3 patients with N3 disease undergoing surgery, achieving a mean PFS of 15.8 months (range, 8.5-26 months) (13). In our study, patients with stage N3 disease in T-S-Arm were carefully assessed as downstaging to make sure that all of them could receive radical surgery. However, subgroup analysis showed that there was no significant difference between T-S-Arm and T-Arm in patients with N3 disease. Therefore, radical surgery might be unsuitable for patients with N3 disease. It was also reported that surgery might improve long-term survival compared with chemoradiation in patients with N3 disease (17). Unfortunately, it could not be demonstrated in our study for the follow-up time was too short. Large-scale clinical trial and longer period of follow-up are needed to confirm the feasibility of treatment strategies aiming at complete resection in *EGFR*m NSCLC patients with N3 disease.

In previous studies, patients with 19-DEL were generally more sensitive to *EGFR*-TKIs than those with L858R mutation (18, 19). Kuan et al. demonstrated that *EGFR*-TKIs could improve PFS of patients with 19-DEL (HR, 0.27; 95% CI, 0.21-0.35) and L858R mutation (HR, 0.45; 95% CI, 0.35-0.58), but there was no benefit for OS of patients with L858R mutation (20). In EMERGING-CTONG1103, there was no significant difference in DFS between patients with L858R mutation and 19-DEL receiving neoadjuvant *EGFR*-TKI therapy combined with radical surgery (21.9 months vs 21.7 months) (14), and this conclusion was confirmed in this study. However, PFS of patients with L858R mutation receiving radical surgery was significantly improved compared with *EGFR*-TKI alone (HR, 0.188; 95% CI, 0.059-0.604), indicating that patients with L858R mutation could benefit more from radical surgery than those with 19-DEL. In previous studies, it was observed that T790M, which was sensitive to the third-generation of *EGFR*-TKIs, was more frequent in patients with resistance to *EGFR*-TKIs harboring 19-DEL than those harboring L858R mutation (21). Therefore, there are more options of second-line therapies for patients with 19-DEL than those with L858R mutation. In this study, we found that radical surgery could provide the alternative for patients with L858R mutation. Future clinical trials should take 19-DEL and L858R mutation as distinct factors and individualize treatment plans.

Lymph nodes clearance after neoadjuvant therapy was proved to be a prognostic of survival for NSCLC patients with stage III disease (22, 23). However, Andrews et al. showed that there was no significant difference in survival between patients with persistent N2 disease and with mediastinal downstaging undergoing complete resection (24), which was also observed in this study. For pre-induction N2 disease, radical surgery is recommended after *EGFR*-TKI therapy even if there is persistent N2 disease preoperatively.

Our study had limitations: (I) As this study was retrospective, selection bias was inevitable and could affect the results of this study. Randomized controlled clinical trials were needed for further

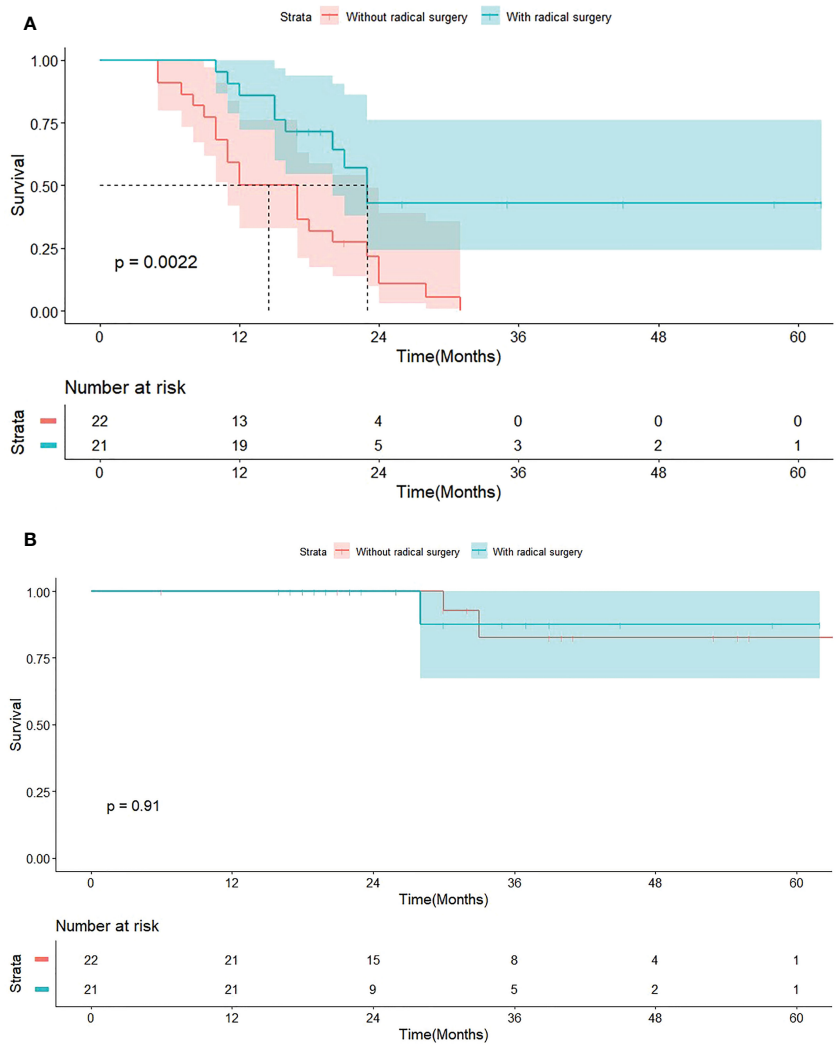

FIGURE 2
Survive curves for 43 patients with *EGFR*-TKI treatment. **(A)** Progression-free survival (PFS) grouped by patients with or without radical surgery. **(B)** Overall survival (OS) grouped by patients with or without radical surgery.

TABLE 4 Univariate and multivariate Cox regression analysis for PFS in patients with receiving *EGFR*-TKIs.

	Univariable		Multivariable	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age		0.403		
<60	1.000			
≥60	1.380 (0.732-2.599)			
Gender		0.686		
Female	1.000			
Male	1.162 (0.631-2.139)			
Smoking history		0.547		
Never	1.000			
Current or ever	1.318 (0.621-2.798)			

(Continued)

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TABLE 4 Continued

	Univariable		Multivariable	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Mutation type		0.060		0.293
L858R	1.000		1.000	
19-del	2.125 (1.100-4.103)		1.554 (0.780-3.097)	
Target lesions	0.996 (0.982-1.010)	0.637		
Stage N		0.235		
II	1.000			
III	1.555 (0.844-2.867)			
Tumor response		0.802		
PR				
SD	0.909 (0.486-1.700)			
LN response		0.083		0.175
To N0	1.000		1.000	
To N1 or unchanged	1.977 (1.035-3.776)		1.721 (0.891-3.323)	
Therapy		0.004		0.027
Without radical surgery	1.000		1.000	
With radical surgery	0.325 (0.172-0.615)		0.406 (0.207-0.793)	

LN, lymph nodes; HR, hazard ratio; CI, confidence interval; PR, partial response; SD, stable disease; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

confirmation. (II) The sample size was too small to define the difference of patients in stage N3 with downstaging after *EGFR*-TKI treatment between T-S-Arm and T-Arm, for radical surgery was not the routine treatment for these patients according to clinical guidelines. (III) The follow-up duration was relatively short. (IV) The information of survival status and therapeutic regimens after disease progression or recurrence was missing for some patients during follow-up. Thus, the OS was not discussed in this study profoundly. Further studies would extend the follow-up duration and analyze the treatment strategies for post-recurrence. (IV) The clinical N stage before treatment was evaluated according to the SUV in PET/CT, for the information of pathological lymph nodes involvement before treatment of a part of patients was missing. (V) Information about adverse events in grade 1 to 2 was missing for the majority of patients. However, it is highlighted that *EGFR*-TKIs were well-tolerated and the treatment protocols were well-established according to previous clinical trials.

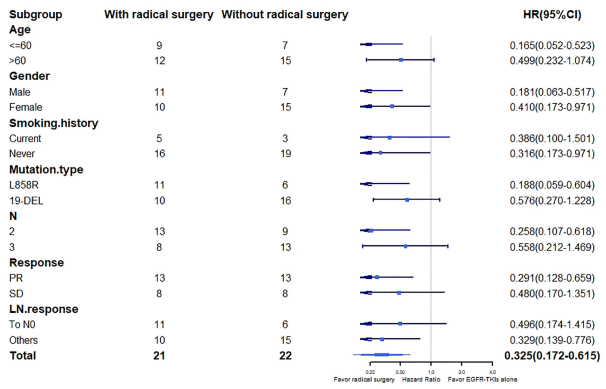

FIGURE 3
PFS in patient's subgroups. PFS, progression-free survival; *EGFR*-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; PR, partial response; SD, stable disease; LN, lymph nodes; HR, hazard ratio; CI, confidence interval.

In conclusion, neoadjuvant *EGFR*-TKI in combination to radical surgery could improve the prognosis of *EGFR*m LUAD patients in stage IIIB, especially for patients with N2 disease and harboring L858R mutation. Radical surgery should be carefully selected for patients with N3 disease after *EGFR*-TKI treatment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding authors.

Author contributions

YX and DB conceived and designed the analysis. Data collection was performed by YX and ZH. Analysis and interpretation of the data were supported by YX, DB, HY, and JH. PZ, WH, and HL revised the manuscript critically for important intellectual content. All authors participated in manuscript writing and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neoadjuvant osimertinib and chemotherapy for stage IIIA primary pulmonary carcinosarcoma with EGFR 19DEL mutation: A case report

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Epidermal growth factor receptor (EGFR) mutations have been frequently detected in patients with pulmonary adenocarcinoma. EGFR Exon 19Del and 21L858R mutations are the two most common EGFR mutations. EGFR-tyrosine kinase inhibitors (TKIs) are widely employed to treat patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations. Recently, there has been rapid growth in clinical trials assessing neoadjuvant targeted therapy, indicating good application prospects owing to high efficiency and low toxicity. Herein, we discuss the case of a 56-year-old male patient who was initially diagnosed with stage IIIA pulmonary adenocarcinoma (AJCC,8th edition) of the left lower lung with an EGFR Exon 19Del mutation. The patient was treated with osimertinib but failed to undergo timely review and surgery. Subsequently, the patient underwent two cycles of neoadjuvant chemotherapy (NAC) combined with neoadjuvant targeted therapy. After the tumor load and size had significantly decreased, radical surgery was successfully performed under thoracoscopy. However, postoperative pathology revealed carcinosarcoma, pT2aN0M0, stage IB, and the pathological response was 50%. The present case report provides practical clinical evidence for the application of neoadjuvant targeted therapy combined with chemotherapy for locally advanced primary pulmonary carcinosarcoma with EGFR mutation.

KEYWORDS

osimertinib, chemotherapy, neoadjuvant, pulmonary carcinosarcoma, EGFR

1 Introduction

Osimertinib, the first approved third-generation irreversible selective inhibitor of epidermal growth factor receptor (EGFR) mutations, has been widely used in patients with advanced NSCLC harboring Exon 19Del/21L858R mutations. Osimertinib reportedly exhibits marked efficacy in untreated patients with EGFR mutations, especially those with the EGFR Exon 19Del mutation, thereby affording a longer progression-free survival than first-generation EGFR-TKIs with a similar safety profile (1). On April 14, 2021, the China National Medical Products Administration officially approved the application of osimertinib for the adjuvant treatment of patients with stage IB-IIIA NSCLC harboring EGFR Exon 19Del/21L858R mutations. Considering a prospective clinical trial assessing neoadjuvant targeted therapy, preliminary results have revealed that osimertinib affords substantial clinical effects and good safety, reducing the complexity and scope of surgical resection and improving surgical efficacy (2).

According to the World Health Organization (WHO) classification of thoracic tumors (2021), pulmonary carcinosarcoma (PCS) is a rare type of pulmonary sarcomatoid carcinoma (PSC), accounting for only 4% of PSCs and approximately 0.27% of malignant lung tumors, associated with poor prognosis (3). PCS is more common in middle-aged and elderly male patients than that in female patients, and most patients typically have a prolonged history of heavy smoking. PCS is a special category of lung malignancy with malignant epithelial and mesenchymal components, either clearly demarcated or mixed. Malignant epithelial components mainly include squamous cell carcinoma and adenocarcinoma, whereas malignant mesenchymal components primarily include rhabdomyosarcoma, chondroid sarcoma, and osteosarcoma. Undifferentiated pleomorphic sarcomas are rare. Clinical manifestations are nonspecific, including cough, bloody sputum, chest pain, low fever, emaciation, fatigue, and other discomforts. Chest computed tomography (CT) scans frequently exhibit large lobulated masses prone to bleeding and necrosis. PCS is likely to be misdiagnosed as simple pulmonary carcinoma or sarcoma upon both bronchoscopic biopsy and peripheral puncture biopsy owing to the limited sample size; thus, pathological examination with complete excision is needed to further confirm the diagnosis.

2 Case report

A 56-year-old male patient with dry cough, weight loss (2 kg) over 2 months, and a history of smoking (> 35 years), without expectoration, hemoptysis, fever, chills, or dyspnea, was admitted to the Department of Respiratory Medicine at our hospital on December 2, 2021. Family history and physical examination revealed no positive findings. He had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Enhanced chest CT showed occupation of the left lower lung (approximately 93 mm × 70 mm), with no obvious enlargement of the mediastinal lymph nodes (Figure 1A). Electronic bronchoscopy revealed an external pressure stenosis of the basal branch of the lower lobe of the left lung. Ultrasound-guided puncture biopsy of the left lower lung mass revealed moderately differentiated adenocarcinoma (Figures 2A, B). No signs of metastasis were detected on upper abdominal enhanced CT,

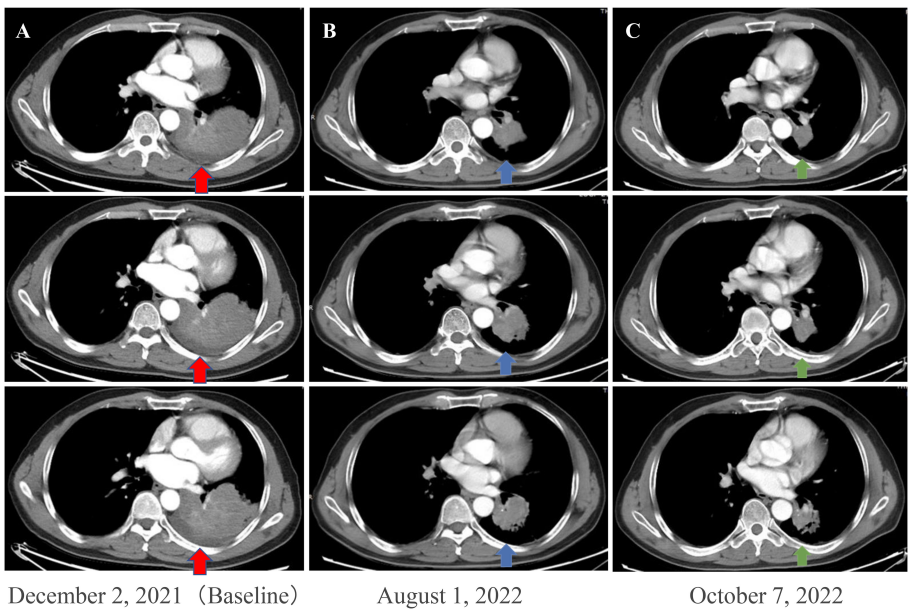

FIGURE 1
Enhanced chest CT scans of the patient during neoadjuvant therapy. **(A)** Baseline imaging demonstrating a 93 mm × 70 mm abnormal lung mass (red arrows) in the lower lobe of the left lung. **(B)** After 210 days of osimertinib therapy, the chest CT scan shows mass shrinkage (blue arrows) to 48 × 44 mm, achieving a partial response (PR). **(C)** After two cycles (42 days) of osimertinib and chemotherapy, the chest CT scan shows mass shrinkage (green arrows) to 40 mm × 37 mm, achieving a sustained partial response (sPR). CT, computed tomography.

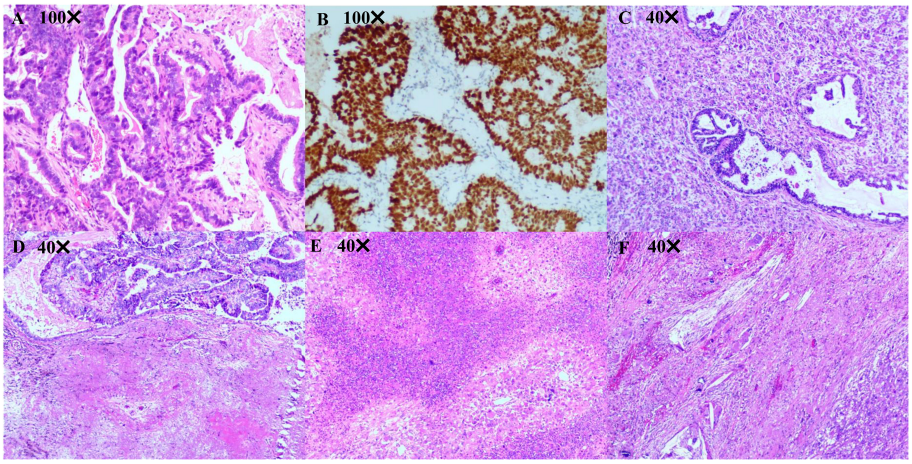

FIGURE 2
Pathological diagnosis. **(A, B)** Pathological diagnosis of the lung biopsy revealing a moderately differentiated lung adenocarcinoma. Immunohistochemistry results are presented as follows: TTF-1(+), Napsin A (+), CK7 (+), CK5/6 (-), P40 (-), Ki67 (50%+), Syn (-), and CgA (-). **(C-F)** Pathological diagnosis of lung surgery is carcinosarcoma (adenocarcinoma accounts for approximately 40% and undifferentiated pleomorphic sarcoma accounts for approximately 60%) with a size of 40 mm × 33 mm × 26 mm, and the visceral pleura appears uninvolved. No tumor involvement can be observed in the bronchial stump, with no tumor metastasis in the lymph nodes of each group (–, 0/14). Immunohistochemistry outcomes were presented as follows: CK(pan)(partial+), Vimentin (partial+), TTF-1(partial+), CK7 (partial+), NapsinA (partial+), P40 (-), CK5/6 (-), Syn (-), CD56 (few+), S100 (-), SMA (-), Desmin (-), Calponin (-), MyoD1 (-), Myogenin (-), P53 (90%+), Ki67 (60%+), CD31 (partial +), ERG (Vascular +).

whole-body bone imaging, or brain magnetic resonance imaging (MRI). The tumor was classified as stage IIIA (cT4N0M0). Next-generation sequencing (NGS) analysis (including EGFR, ALK, ROS1, MET, RET, KRAS, BRAF, NRAS, HER2, PIK3CA, and TP53) indicated EGFR Exon 19Del and TP53 mutations (Supplementary Material). Following a discussion with the multidisciplinary team at our hospital (including respiratory physicians, oncologists, thoracic surgeons, pathologists, and radiologists), surgical resection combined with adjuvant or neoadjuvant targeted therapy (osimertinib) was recommended. The patient received immediate neoadjuvant targeted therapy (osimertinib 80 mg orally once daily with or without food). However, regular re-examinations and surgery were not performed as required.

On August 1, 2022 (210 days after osimertinib therapy), the patient visited the hospital for a re-examination. Based on enhanced chest CT, the tumor in the left lower lung was significantly reduced (Figure 1B). Radiographic assessment was partial response (PR) based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Subsequent positron emission tomography (PET)-CT displayed a tumor in the left lower lung accompanied by increased glucose metabolism (SUVmax:27.998) and no other signs of metastasis (Figure 3). There was no obvious abnormality on the enhanced brain MRI. Moreover, no notable adverse reactions were observed during osimertinib treatment. Surgery was recommended, and the patient and his family requested consultation before the final determination. From August 25, 2022, to September 16, 2022, the patient received neoadjuvant osimertinib, combined with neoadjuvant chemotherapy, a two-cycle PC regimen (pemetrexed + carboplatin). After chemotherapy, the patient developed moderate gastrointestinal reactions with no obvious myelosuppression. On October 7, 2022, an enhanced chest CT scan showed progressive tumor shrinkage in the left lower lung, exhibiting a size of approximately 40 mm × 37 mm (Figure 1C). Radiographic assessment revealed sustained PR (sPR). The urgency of surgery was well-communicated with the patient and his family, and thoracoscopic left lower lobectomy, mediastinal lymph node dissection, and bronchoplasty were successfully completed on October 14, 2022. Postoperative pathological diagnosis was carcinosarcoma with marked necrosis, interstitial degeneration, inflammatory cell infiltration, cholesterol crystals, and small vascular hyperplasia (Figures 2C-F). Complete resection was performed, and the pathological response was 50%. The final postoperative pathological stage was pT2aN0M0, stage IB. The patient recovered well post-surgery. Considering the diagnosis of rare primary PCS post-surgery, NGS analysis was re-performed on November 05, 2022, which revealed EGFR Exon 19Del and TP53 mutations (Supplementary Material). The patient requested continued adjuvant targeted therapy with osimertinib and regular review. Owing to the impact of the coronavirus disease 2019 (COVID-19) pandemic, the patient was telephonically followed up for three months, exhibiting good health to date (January 14, 2023). The process of clinical diagnosis and treatment for this patient is shown in Figure 4.

3 Discussion

Although stage IIIA NSCLC is potentially resectable, traditional treatment options, including preoperative or postoperative chemotherapy, offer similar effects (4). Considering patients with resectable NSCLC without known ALK translocations or EGFR mutations, the emergence of neoadjuvant immunotherapy combined with chemotherapy could markedly prolong the event-

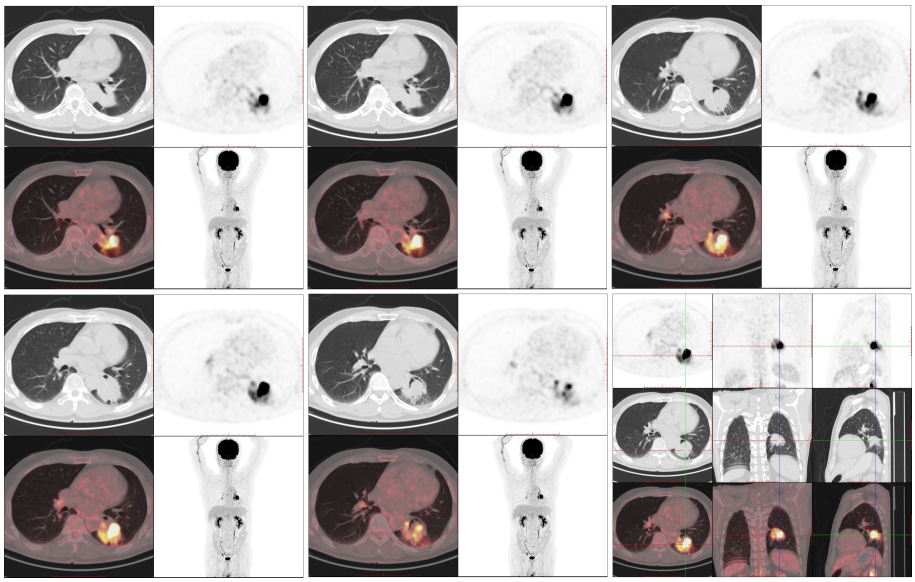

FIGURE 3
The 18F-FDG PET/CT examination (August 3, 2022). 18-FDG PET/CT shows robust 18-FDG uptake in the left lung mass (SUVmax: 27.998) with a size of 45 × 41 mm; no distant metastasis can be observed.

free survival of patients and improve the pathological complete response (pCR) rate, with no increase in the incidence of adverse events, thereby suggesting survival benefits in patients (5). In the present case report, we recommended neoadjuvant EGFR-TKI treatment for NSCLC owing to the high response rate to osimertinib. However, neoadjuvant targeted therapy for resectable NSCLC with EGFR mutations is currently in its infancy. Based on preliminary studies, EGFR-TKIs have good application prospects in neoadjuvant therapy (2, 6). A phase III, randomized, controlled, multicenter, three-arm study assessing neoadjuvant targeted therapy with EGFR-TKI is ongoing (NeoADAURA) (7). The duration of neoadjuvant targeted therapy was found to vary across different clinical studies and was frequently less than 90 days; the optimal neoadjuvant duration remains uncertain (8, 9).

Considering the present patient, the need for prolonged neoadjuvant targeted therapy could be attributed to poor compliance. However, surgery was not performed despite successful downgrading on the first radiographic assessment of PR after 210 days of osimertinib therapy. In patients with advanced NSCLC harboring EGFR mutations, osimertinib combined with chemotherapy remains safe and tolerable despite increased toxicity (10). Currently, the NeoADAURA study is recruiting patients to evaluate neoadjuvant osimertinib with or without chemotherapy versus chemotherapy alone prior to surgery in patients with operable stage II-IIIB N2 EGFR mutation NSCLC (7). The findings of the NeoADAURA study will likely clarify the most effective combination strategy for neoadjuvant therapy.

TP53 is the most common co-mutant gene in patients with NSCLC carrying EGFR mutations. In addition, TP53/EGFR co-mutations have been associated with poor prognosis (11). Targeted therapy combined with chemotherapy can afford considerable survival benefits in patients with TP53 mutations and a poor prognosis. Moreover, TP53 mutations can shorten the relapse time in postoperative patients who are more likely to benefit from targeted therapy combined with chemotherapy (12). Herein, the postoperative pathology of the patient indicated carcinosarcoma. Establishing whether sarcoma components carry EGFR and TP53 mutations could help further elucidate the pathogenesis of carcinosarcoma and guide postoperative adjuvant therapy. Reportedly, both EGFR

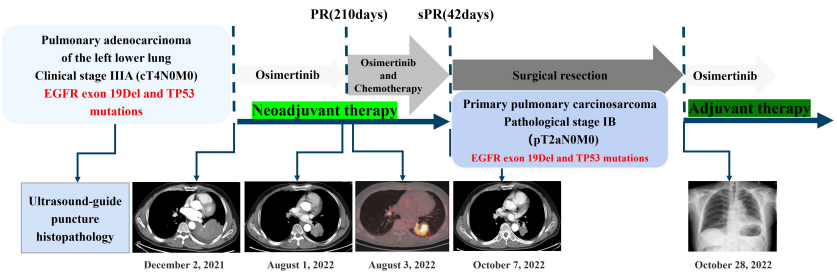

FIGURE 4
A summary of the treatment strategy employed in this patient.

and TP53 mutations exhibit a certain mutation frequency in patients with PCS; however, limited patients carry the same gene mutations in both components (13). Related cases have reported that both pulmonary adenocarcinoma and sarcoma components can simultaneously carry EGFR Exon 19Del mutation (14, 15), corroborating the theory of monoclonal histogenesis (13). In the present case report, we successfully separated the carcinoma and sarcoma components using microdissection technology, revealing that both components harbored TP53 and EGFR mutations using NGS (Supplementary Material).

In the ADAURA study (16), disease-free survival (DFS) was documented in patients who received adjuvant chemotherapy (hazard ratio [HR] = 0.16, 95% confidence interval [CI]: 0.10–0.26), as well as in those who did not receive adjuvant chemotherapy (HR = 0.23, 95% CI: 0.13–0.40). The authors found that the DFS of the osimertinib group was superior to that of the placebo group regardless of disease stage (stage IB-IIIA). However, the ADAURA study failed to clarify whether the combination adjuvant chemotherapy should be undertaken. The Lung Adjuvant Cisplatin Evaluation (LACE) study (17) revealed that cisplatin-based chemotherapy could significantly improve overall survival (OS) and DFS of the overall population, and the absolute OS rate could be significantly increased by 5.4% in 5 years. However, the OS of stage IB patients was not significantly improved (HR = 0.92, 95% CI: 0.78-1.10). According to the CALGB9633 study (18), some patients with stage IB NSCLC (with high-risk factors) could benefit from postoperative adjuvant chemotherapy. Therefore, adjuvant chemotherapy should not be recommended for stage IB NSCLC except in the presence of pathological risk factors for relapse. In addition, studies have evaluated and demonstrated the potential of circulating tumor DNA-minimal residual disease in predicting the risk of disease recurrence and the benefit of adjuvant chemotherapy post-surgery; however, these results need to be further confirmed in future investigations (19, 20). Moreover, adjuvant immunotherapy may afford limited or uncertain benefits in patients with lung cancer harboring EGFR mutations (21), and related phase II clinical studies are being conducted (22). Large-scale, prospective, phase III, randomized controlled clinical studies are urgently needed for further validation.

In conclusion, this is a successful case of radical surgery after neoadjuvant therapy for stage IIIA PCS with EGFR 19DEL mutation, which also provides specific clinical experience and guidance for perioperative therapy for oncogene-driven NSCLC.

Data availability statement

The datasets presented in this article are not readily available because of ethical/privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Author contributions

HW and ZW collected and analyzed the clinical material and drafted the manuscript. HW, YD, TW, JQ, and WT prepared the figures and Supplementary Material. WX performed the surgery. HW, ZW, WD, JC, JZ, SL, and YZ contributed to management and treatment of the patient. ZX revised the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1145021/full#supplementary-material

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Effectiveness of neoadjuvant immunochemotherapy compared to neoadjuvant chemotherapy in non-small cell lung cancer patients: Real-world data of a retrospective, dual-center study

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Background: Studying the application of neoadjuvant immunochemotherapy (NICT) in the real world and evaluating its effectiveness and safety in comparison with neoadjuvant chemotherapy (NCT) are critically important.

Methods: This study included the II-IIIB stage non-small cell lung cancer (NSCLC) patients receiving NCT with or without PD-1 inhibitors and undergoing surgery after neoadjuvant treatments between January 2019 to August 2022. The clinical characteristics and treatment outcomes were retrospectively reviewed and analyzed.

Results: A total of 66 patients receiving NICT and 101 patients receiving NCT were included in this study. As compared to NCT, NICT showed similar safety while not increasing the surgical difficulty. The ORR in the NICT and NCT groups was 74.2% and 53.5%, respectively, $P = 0.009$. A total of 44 patients (66.7%) in the NICT group and 21 patients (20.8%) in the NCT group showed major pathology response (MPR) ($P < 0.001$). The pathology complete response (pCR) rate was

also significantly higher in NICT group than that in NCT group (45.5% vs. 10.9%, *P* <0.001). After Propensity Score Matching (PSM), 42 pairs of patients were included in the analysis. The results showed no significant difference in the ORR between the two groups (52.3% vs. 43.2%, *P* = 0.118), and the proportions of MPR (76.2%) and pCR (50.0%) in NICT group were significantly higher than those of MPR (11.9%) and pCR (4.7%) in the NCT group (*P* <0.001). The patients with driver mutations might also benefit from NICT.

Conclusions: As compared to NCT, the NICT could significantly increase the proportions of patients with pCR and MPR without increasing the operation-related bleeding and operation time.

KEYWORDS

non-small cell lung cancer, neoadjuvant immunochemotherapy, neoadjuvant chemotherapy, pathological response, real world study

Introduction

Non-small cell lung cancer (NSCLC) is a highly invasive cancer type. Some patients show recurrence even after surgery. Among the locally advanced NSCLC patients, a recurrence rate of 70% and a long-term survival rate of less than 30% are observed even after radical surgery (1, 2). The five-year event-free survival (EFS) rate of NSCLC patients ranges from 68% for those with stage IB to 36% for those with stage IIIA (2). By inducing the downstaging of a tumor, preoperative chemotherapy might increase the R0 resection rate for patients with stage IB-IIIA NSCLC. Although preoperative chemotherapy has shown marginal improvements, the survival rate is only 5.4% higher than that of surgery alone (3). For neoadjuvant chemotherapy (NCT), only a few patients have shown pathological complete response (pCR) (median: 4%, range: 0 to 16%) and major pathological response (MPR) (4–8). Numerous studies have confirmed that pCR and MPR are closely correlated with local control, disease free survival (DFS), and overall survival (OS). Moreover, pCR and MPR are used as potential early predictors of survival (9).

The anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) immunotherapies have revolutionized the treatment of metastatic and advanced-stage NSCLC (10, 11). The NADIM and LCMC-3 studies demonstrated the potential of neoadjuvant immunotherapy for NSCLC patients (12, 13). The CHECKMATE-816 study, a phase III clinical trial, confirmed that as compared to chemotherapy, neoadjuvant immunochemotherapy (NICT) could significantly increase the number of patients with pCR (24.0% vs. 2.2%) among the patients with stage IB-IIIA NSCLC, while the combination of neoadjuvant immunotherapy with chemotherapy remarkably prolonged the EFS (31.6 months vs. 20.8 months) (14). The NADIM II study highlighted that as compared to NCT, the NICT improved the MPR rate of patients with stage IIIA-B NSCLC (52.6% vs. 13.8%), enabling more patients to receive surgical treatment (93% vs. 69%) (15). However, whether the application of neoadjuvant therapy will increase the difficulty of surgery is an important concern. The previous studies suggested that neoadjuvant immunotherapy could slightly increase drug-related adverse reactions but did not significantly increase the risk of surgery.

These studies supported the application of immunochemotherapy for neoadjuvant treatment. However, the patients in clinical settings are highly selected, and the efficacy of NICT in the real-world environment requires further investigation. Based on this, the current study retrospectively analyzed the real-world data of NICT in Cancer Hospital, Chinese Academy of Medical Sciences and Shanxi Provincial Cancer Hospital to explore its effectiveness and safety.

Patients and methods

Patients

In this study, the resectable NSCLC patients treated with NCT with or without PD-1 inhibitors at two centers, including the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, and Shanxi Provincial Cancer Hospital of Chinese Academy of Medical Sciences, Shanxi, from January 2019 to August 2022. The inclusion criteria were as follows: 1) the patients with stage II-IIIB NSCLC confirmed using imaging and histological examination before surgery; 2) the patients, who received feasible neoadjuvant therapy after an assessment; 3) the patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1; and 4) the patients, who underwent surgery after neoadjuvant treatment. Two researchers reviewed the clinical data of the patients from both centers, screened the neoadjuvant patients, which met the requirements, and collected the clinical baseline information, treatment response, and follow-up data. The baseline data included age, gender, and smoking history, and clinical features included comorbidities, primary lesion size, and location, while

efficacy evaluation included imaging evaluation, pathological evaluation, and adverse reactions.

Treatment methods

A total of 167 patients were divided into the NICT group (n = 66, treated with neoadjuvant PD-1 inhibitors in combination with chemotherapy) and the NCT group (n = 101, treated with chemotherapy only). All patients received conventional platinum-based doublets chemotherapy (cisplatin/carboplatin/nedaplatin/lobaplatin) (21 days per cycle). For the NICT group patients, Tislelizumab (26 cases, 39.4%), Camrelizumab (12 cases, 18.2%), Nivoliumab (10 cases, 15.2%), Pembrolizumab (9 cases, 13.6%), Sintilizumab (8 cases, 12.1%), and Toripalimab (1 case, 1.5%) were used. All the patients received video-assisted thoracic surgery (VATS) or traditional open thoracotomy.

Evaluation

The image evaluation was performed by the researchers based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Imaging was performed every two cycles or before the operation, and the treatment effects were evaluated by comparing preoperative images with baseline images. Objective response rate (ORR) was defined as the proportion of patients, who have a complete response (CR) or partial response (PR) to the treatments; it was evaluated based on RECIST v1.1. The pathological assessment was performed after surgery by professional pathologists based on the proportion of remaining tumor cells. If the proportion of residual tumor cells was less than 10%, it was defined as an MPR, and if no tumor cells were remaining, it was defined as pCR (16, 17). The treatment-related adverse events were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 published by the US Department of Health and Human Services (18).

Follow up

During follow-up, the data of time to recurrence, site of recurrence, and survival date were collected. The patients were followed up once every three months for two year and every six months till November, 2022 (endpoint of study). At the endpoint of the study, the patients, who had not yet relapsed and those, who were still alive were analyzed for disease-free and overall survival. DFS was defined as the time from the patient's surgery until the first discovery of disease recurrence or death, and OS was defined as the time from the discovery of the disease to the last follow-up or death of the patient.

Statistical analyses

The continuous variables were expressed as means, medians, standard deviations, and ranges and analyzed using the Mann-Whitney U test and Kruskal-Wallis test to measure the best response outcome. The categorical variables were expressed as frequency and relative frequency and analyzed using Fisher's exact test. The DFS of patients was identified using the Kaplan–Meier (KM) survival curve analysis and log-rank test. The clinical characteristics, including age, gender, smoking habits, comorbidity, ECOG score, cT stage, cN stage, and cTNM, histology, differentiation, and neoadjuvant treatment choice, were balanced using the PSM method in both the groups and analyzed using the nearest-neighbor method with a ratio of 1:1 without replacement and a 0.02-caliper width.

Results

Baseline characteristics of the patients

A total of 167 patients with resectable NSCLC, including 66 patients receiving NICT and 101 patients receiving NCT, were enrolled in this study. There were no significant differences in the clinical characteristics and baseline demographic characteristics between the two groups (Table 1). The majority of the enrolled patients were males, accounting for 89.4% and 80.2% of the NICT and NCT groups, respectively (P = 0.136), while the patients with ages above 60 years accounted for 40.9% and 50.5% in the two groups, respectively (P = 0.268). There were no significant differences in smoking and drinking habits and comorbidities of the patients between the two groups. Most patients showed excellent PS before neoadjuvant treatment in both groups (ECOG = 0, 45.5% and 1, 54.5%). The cT staging, cN staging, and cTNM grading before neoadjuvant therapy were similar between the two groups, showing no significant difference. Lung squamous cell carcinoma was the main pathological type among the NSCLC patients in both groups (78.8% and 64.4%, P = 0.057). Additionally, there were cases of squamous cell carcinoma with neuroendocrine differentiation in the NICT (4 cases, 6.1%) and NCT (2 cases, 2.0%) groups. Moreover, there was also one patient with adeno-squamous carcinoma in the NICT group. The pathological differentiation degree of patients mainly included low differentiation, accounting for 62.1% and 72.3% in the NICT and NCT groups, respectively (P = 0.374). Imaging showed that the tumor maximum tumor diameter (MTDs) in both groups were 5.383 cm and 4.500 cm respectively (P = 0.049). Both the groups received 1-4 cycles of neoadjuvant therapy before surgery, and most patients (75.8% and 76.2% in the NICT and NCT groups, respectively) underwent radical surgical resection of NSCLC after two cycles of neoadjuvant therapy. In this study, the number of patients receiving cisplatin chemotherapy was significantly more in the NCT group (51.5%) as compared to those in the NICT group (15.2%, P <0.001).

PSM analysis was used to more accurately evaluate and compared the effectiveness and safety of NICT and NCT. PSM analysis included twelve baseline factors, including age, gender, smoking habits, comorbidity, ECOG score, cT stage, cN stage, cTNM, histology, differentiation, cycles of neoadjuvant treatment, and balance of cisplatin usage between the two groups (Table 2). A

TABLE 1 Baseline clinical and sociodemographic characteristics of patients.

	Total n=167 (%)	Type of neoadjuvant treatment		*p*-value
		NICT n=66 (%)	NCT n=101(%)	
Sex				
Male, n (%)	140 (83.8%)	59 (89.4%)	81 (80.2%)	0.136
Female, n (%)	27 (16.2%)	7 (10.6%)	20 (19.8%)	
Age				
≥60 years, n (%)	78 (46.7%)	27 (40.9%)	51 (50.5%)	0.268
<60 years, n (%)	89 (53.3%)	39 (59.1%)	50 (49.5%)	
Smoking history				
Yes, n (%)	122 (73.1%)	51 (77.3%)	71 (70.3%)	0.374
No, n (%)	45 (26.9%)	15 (22.7%)	30 (29.7%)	
Drinking history				
Yes, n (%)	60 (35.9%)	25 (37.9%)	35 (34.7%)	0.742
No, n (%)	107 (64.1%)	41 (62.1%)	66 (65.3%)	
Comorbidity				
Yes, n (%)	61 (18,3%)	25 (18.9%)	36 (17.8%)	0.885
No, n (%)	273 (81.7%)	107 (81.1%)	166 (82.2%)	
ECOG				
0, n (%)	76 (45.5%)	30 (45.5%)	46 (45.5%)	1.000
1, n (%)	91 (54,5%)	36 (54,5%)	55 (54,5%)	
MTD in imaging (cm)		5.383 ± 1.871	4.500 ± 1.997	0.049
Clinical T stage				
cTl, n (%)	18 (10.1%)	6 (7.8%)	12 (11.9%)	0.509
cT2, n (%)	60 (33.7%)	23 (29.9%)	37 (36.6%)	
cT3, n (%)	56 (31.5%)	26 (33.8%)	30 (29.7%)	
cT4, n (%)	44 (24.7%)	22 (28.6%)	22 (21.8%)	
Clinical N stage				
N0,n (%)	14 (8.4%)	8 (12.1%)	6 (5.9%)	0.194
N1,n (%)	49 (29.3%)	22 (33.3%)	27 (26.7%)	
N2,n (%)	104 (62.3%)	36 (54.5%)	68 (67.3%)	
Clinical TNM stage				
IIA, n (%)	2 (1.2%)	1 (1.5%)	1 (1.0%)	0.253
IIB, n (%)	21 (12.6%)	12 (18.2%)	9 (8.9%)	
IIIA, n (%)	102 (61.1%)	36 (54.5%)	66 (65.3%)	
IIIB, n (%)	42 (25.1%)	17 (25.8%)	25 (24.8%)	
Histology type				
Squamous	117 (70.1%)	52 (78.8%)	65 (64.4%)	0.057
Non-squamous	50 (29.9%)	14 (21.2%)	36 (35.6%)	
Pathological differentiation				

(Continued)

TABLE 1 Continued

	Total n=167 (%)	Type of neoadjuvant treatment		*p*-value
		NICT n=66 (%)	NCT n=101(%)	
High	2 (1.2%)	1 (1.5%)	1 (1.0%)	0.374
Medium	51 (30.5%)	24 (36.4%)	27 (26.7%)	
Low	114 (68.3%)	41 (62.1%)	73 (72.3%)	
Treatment cycles				
1 cycles	11 (6.6%)	3 (4.5%)	8 (7.9%)	0.807
2 cycles	127 (76.0%)	50 (75.8%)	77 (76.2%)	
3 cycles	22 (13.2%)	10 (15.2%)	12 (11.9%)	
4 cycles	7 (4.2%)	3 (4.5%)	4 (4.0%)	
Median (IQR)		2 (± 0)	2 (± 0)	
Cisplatin				
Yes, n (%)	62 (37.1%)	10 (15.2%)	52 (51.5%)	<0.001
No, n (%)	105 (62.9%)	56 (84.8%)	49 (48.5%)	

NCT, neoadjuvant chemotherapy; NICT, neoadjuvant immunochemotherapy; MTD, maximum tumor diameter; IQR, interquartile range.

total of 42 patients receiving NICT and 42 patients receiving NCT were matched.

Perioperative-related indicators

All the patients underwent radical tumor surgery within 16 to 42 days of the last cycle of neoadjuvant therapy with no surgical delay (with intervals exceeding the prescribed 42 days). Most patients in the NICT and NCT groups, accounting for 81.8% and 67.3% (P = 0.050), respectively, were mainly assisted by VATS. It could not be determined that the NICT group patients were more conducive to using VATS surgery (Table 3). Unilateral lobectomy was the main choice for the patients in the NICT and NCT groups (56.1% and 49.5%, respectively). Extensive resection was mainly unilateral lobectomy or unilateral combined lobectomy (18.2% or 13.6% in the NICT group and 15.8% or 23.8% in the NCT group, respectively). Wedge resection and sleeve resection were used for

TABLE 2 Baseline clinical and sociodemographic characteristics of patients after PSM.

	Total n=84 (%)	Type of neoadjuvant treatment		*p*-value
		NICT n=42 (%)	NCT n=42 (%)	
Sex				
Male, n (%)	73 (86.9%)	37 (88.1%)	36 (85.6%)	0.748
Female, n (%)	11 (13.1%)	5 (11.9%)	6 (14.4%)	
Age				
≥60 years, n (%)	43 (51.2%)	23 (54.8%)	20 (47.6%)	0.513
<60 years, n (%)	41 (48.8%)	19 (45.2%)	22 (52.4%)	
Smoking history				
Yes, n (%)	59 (70.2%)	32 (76.2%)	27 (64.3%)	0.233
No, n (%)	25 (29.8%)	10 (23.8%)	15 (35.7%)	
Comorbidity				
Yes, n (%)	34 (40.5%)	18 (42.9%)	16 (38.1%)	0.657
No, n (%)	50 (59.5%)	24 (57.1%)	26 (61.9%)	
ECOG				

(Continued)

TABLE 2 Continued

	Total n=84 (%)	Type of neoadjuvant treatment		*p*-value
		NICT n=42 (%)	NCT n=42 (%)	
0, n (%)	13 (15.5%)	6 (14.3%)	7 (16.7%)	0.763
1, n (%)	71 (84.5%)	36 (85.7%)	35 (83.3%)	
Clinical T stage				
cTl, n (%)	11 (13.1%)	4 (9.6%)	7 (16.7%)	0.363
cT2, n (%)	33 (39.3%)	14 (33.3%)	19 (45.2%)	
cT3, n (%)	23 (27.4%)	14 (33.3%)	9 (21.4%)	
cT4, n (%)	17 (20.2%)	10 (28.6%)	7 (16.7%)	
Clinical N stage				
N0,n (%)	8 (9.5%)	5 (11.9%)	3 (3.6%)	0.696
N1,n (%)	27 (32.1%)	14 (33.3%)	13 (31.0%)	
N2,n (%)	49 (58.3%)	23 (54.8%)	26 (61.9%)	
Clinical TNM stage				
IIA, n (%)	3 (3.6%)	1 (2.4%)	2 (4.8%)	0.544
IIB, n (%)	12 (14.3%)	6 (14.3%)	6 (14.3%)	
IIIA, n (%)	59 (70.2%)	28 (66.7%)	31 (73.8%)	
IIIB, n (%)	10 (11.9%)	7 (16.7%)	3 (7.1%)	
Pathological type				
Squamous	60 (70.1%)	30 (78.8%)	30 (64.4%)	1.000
Non-squamous	24 (29.9%)	12 (21.2%)	12 (35.6%)	
Pathological differentiation				
Medium	40 (47.6%)	24 (57.1%)	16 (38.1%)	0.081
Low	44 (52.4%)	18 (42.9%)	26 (61.9%)	
Treatment cycles				
1 cycles	7 (8.3%)	2 (4.8%)	5 (11.9%)	0.689
2 cycles	63 (75.0%)	33 (78.6%)	30 (71.4%)	
3 cycles	8 (9.5%)	4 (9.5%)	4 (9.5%)	
4 cycles	6 (7.1%)	3 (7.1%)	3 (7.1%)	
Median (IQR)		2 (± 0)	2 (± 0)	
Cisplatin				
Yes, n (%)	40 (47.6%)	21 (50.0%)	19 (45.2%)	0.662
No, n (%)	44 (52.4%)	21 (50.0%)	23 (54.8%)	

NCT, neoadjuvant chemotherapy; NICT, neoadjuvant immunochemotherapy; IQR, interquartile range.

1.5% and 10.6% of the NICT group patients and 1.0% and 9.9% of the NCT group patients, respectively. There were no significant differences in tumor resection (P = 0.581) and operation time (150 min and 170 min, respectively, for the NICT and NCT groups) (P = 0.108). The amount of blood loss from the patients in the NICT group (50.0 ± 227.2 mL) was significantly lower than that in the NCT group (170.000 ± 142.663 mL, P <0.001). There were no perioperative-related deaths or re-hospitalization due to surgical complications in both groups.

The post-PSM analysis (Table 4) showed that the incidence of drug-related adverse reactions in both groups was slightly 47.6%, and none of them were above grade 3 in both groups. There were no significant differences between the two groups in terms of surgical approach, resection range, operation time, and the number of

TABLE 3 Comparison of treatment modality and surgical outcomes for NSCLC patients.

	Total n=167 (%)	Type of neoadjuvant treatment		*p*-value
		NICT n=66 (%)	NCT n=101(%)	
Extent of resection				
Pneumonectomy	28(16.8%)	12(18.2%)	16(15.8%)	0.581
Lobectomy	87(52.1%)	37(56.1%)	50(49.5%)	
Bilobectomy	33(19.8%)	9(13.6%)	24(23.8%)	
Local resection	2(1.2%)	1(1.5%)	1(1.0%)	
Sleeve	17(10.2%)	7(10.6%)	10(9.9%)	
Operation time (min)		150.000 ± 50.439	170.000 ± 59.186	0.108
Intraoperative blood loss (ml)		50.000 ± 227.182	170.000 ± 142.663	<0.001
Total lymph nodes resected		19.32 ± 9.46	16.31 ± 5.43	0.198

VATS, video-assisted thoracic surgery; Mann-Whitney U test and Fisher's exact test were used.

lymph node dissections. The blood loss from the patients in the NICT group was still lower than that from the patients in the NCT group (176.13 ± 264.93 mL vs. 182.42 ± 162.37 mL, $P = 0.025$).

pCR and MPR

As listed in Table 5, radiographic response evaluation was performed in all the patients before surgery, showing the ORR of 74.2% and 53.5% in the NICT and NCT groups, respectively ($P = 0.009$). The pathological analysis after surgery showed significantly higher MPR in 44 patients (66.7%) in the NICT group as compared to that in 21 patients (20.8%) in the NCT group ($P <0.001$). The pCR rate was also significantly higher in the NICT group than that in the NCT group. (45.5% vs. 10.9%, $P <0.001$). After PSM, there was no significant difference in ORR between the NICT and NCT groups (52.3% vs. 43.2%, $P = 0.118$), and the proportions of MPR (76.2%) and pCR (50.0%) were significantly higher in the NICT

TABLE 4 Comparison of treatment modality and surgical outcomes for NSCLC patients after PSM.

	Total n=84 (%)	Type of neoadjuvant treatment		*p*-value
		NICT n=42 (%)	NCT n=42(%)	
TRAEs related to drugs				
Yes	40 (47.6%)	20 (47.6%)	20 (47.6%)	1.000
No	44 (52.4%)	22 (52.4%)	22 (52.4%)	
Surgical approach				
Thoracotomy	23 (27.4%)	8(19.0%)	15 (35.7%)	0.087
VATS	61 (72.6%)	34 (81.0%)	27 (64.3%)	
Extent of resection				
Pneumonectomy	11 (13.1%)	4 (9.5%)	7 (16.7%)	0.632
Lobectomy	41 (48.8%)	22 (52.4%)	19 (45.2%)	
Bilobectomy	24 (28.6%)	11 (26.2%)	13 (31.0%)	
Sleeve	8 (9.5%)	5 (11.9%)	3 (7.1%)	
Operation time (min)		166.22 ± 50.55	169.10 ± 52.11	0.763
Intraoperative blood loss (ml)		176.13 ± 264.93	182.42 ± 162.37	0.025
R0 resection				
Yes, n(%)	80 (95.2%)	41 (15.2%)	39 (51.5%)	0.608
No, n (%)	4 (4.8%)	1 (84.8%)	3 (48.5%)	
Total lymph nodes resected		18.54 ± 10.46	15.31 ± 6.43	0.208

VATS, video-assisted thoracic surgery; Mann-Whitney U test and Fisher's exact test were used.

TABLE 5 Comparison of treatment effectiveness in NSCLC patients.

	Before PSM		p-value	After PSM		*p*-value
	NICT n=66 (%)	NCT n=101(%)		NICT n=44 (%)	NCT n=44(%)	
ORR(PR+CR)						
Yes, n (%)	49 (74.2%)	54 (53.5%)	0.009	22 (52.3%)	19 (43.2%)	0.118
No, n (%)	17 (25.8%)	47 (46.5%)		20 (47.7%)	23 (56.8%)	
pCR						
Yes, n(%)	30 (45.5%)	11 (10.9%)	<0.001	21 (50.0%)	2 (4.7%)	<0.001
No, n (%)	36 (54.5%)	90 (89.1%)		21 (50.0%)	40 (95.3%)	
MPR						
Yes, n(%)	44 (66.7%)	21 (20.8%)	<0.001	32 (76.2%)	5 (11.9%)	<0.001
No, n (%)	22 (33.3%)	80 (79.2%)		10 (23.8%)	37 (88.1%)	

ORR, Objective response rate, the proportion of patients who typically achieved a 30% reduction in tumor volume and maintained it for more than 4 weeks; total response (CR) and partial response (PR).

group than those (11.9% and 4.7%, respectively) in the NCT group (P <0.001).

Outcomes of DFS

At the endpoint of this study (November 15, 2022), the median follow-up of patients in the NICT group was 9.7 months (range: 2.5-28.7 months), while that of patients in the NCT group was 23.0 months (range: 2.6-44.5 months). Only 4 (6.1%) and 23 (22.8%) patients in NICT and NCT groups, respectively, showed disease recurrence, which might be due to the limited follow-up time. After PSM, as compared to the NCT group, the NICT group showed a decreasing trend in the disease progression risk; however, the difference was not statistically significant (HR 0.46, 95% CI, 0.17-1.25, P = 0.171) (Figure 1).

Efficacy in patients with driver mutations

In the NICT and NCT groups, a total of 19 and 39 patients underwent genetic screening after surgery, respectively. The results identified 5 and 13 patients with driver mutations in the NICT and NCT groups, respectively. The specific mutation information of the patients is listed in Supplementary Table S1. Due to the limited number of cases, statistical analysis was not conducted. In the NICT group, 3 (60%) patients with positive driver mutation showed MPR (one patient showed pCR), and 3 (23.1%) patients showed MPR (one patient showed pCR) in the NCT group (Table 6).

Discussion

In this study, the efficacy and safety of NICT and NCT were compared using dual-center real-world data. The results showed that NICT resulted in a significantly higher pCR ratio (45.5% vs. 10.9%, P <0.001) and MPR ratio (66.7% vs. 20.8%, P <0.001) as compared to those of the NCT group, which might reduce the risk of disease recurrence. Furthermore, the baseline and neoadjuvant treatment characteristics of the two groups were balanced using the PSM method, which verified that NICT significantly improved the pCR and MPR without increasing the surgical risk.

The CHECKMATE-816 study confirmed that the application of NICT in NSCLC patients could improve the EFS of patients as compared with that of NCT. However, the real-world data comparing NICT with NCT is still relatively limited (19, 20). Therefore, the current study compared the data of dual-center

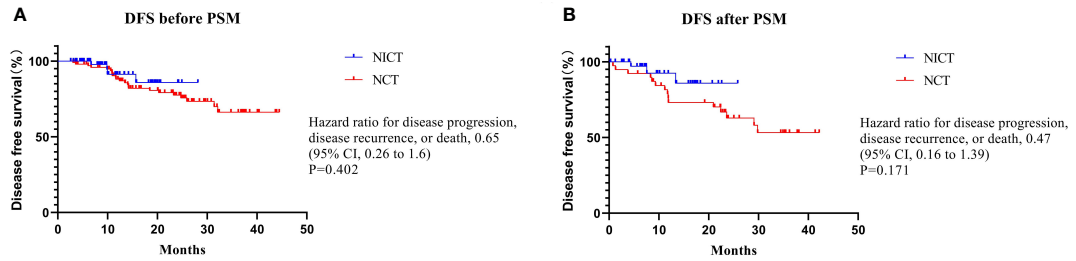

FIGURE 1
Disease free survival Summary. There was no statistically significant difference in DFS before or after PSM.

TABLE 6 Pathological response of patients with driver mutations and wild-type.

	Driver mutation		Wild-type	
	NICT n=5 (%)	NCT n=13 (%)	NICT n=61 (%)	NCT n=88 (%)
pCR				
Yes, n (%)	1 (20.0%)	1 (7.7%)	29 (47.5%)	10 (11.4%)
No, n (%)	4 (80.0%)	12 (92.3%)	32 (52.5%)	78 (88.6%)
MPR				
Yes, n (%)	3 (60.0%)	3 (23.1%)	41 (67.2%)	18 (20.5%)
No, n (%)	2 (40.0%)	10 (76.9%)	20 (32.8%)	67 (79.5%)

Due to the limited numbers of cases, statistical analysis was not conducted.

NICT with NCT. The results suggested that NICT might improve the pCR and MPR of patients.

Several phase III studies and meta-analyses suggested that as compared to surgery alone, NCT could reduce the death risk of NSCLC patients by 13% to 16% and show a 5% benefit in their five-year survival (3, 7, 21). A PSM study analyzed 92 pairs of patients with cT2-4N0-1M0 NSCLC receiving adjuvant chemotherapy or NCT. The results showed no significant difference in the prognosis of patients between the two groups. Compared with surgery alone, neoadjuvant chemotherapy and adjuvant chemotherapy can improve the 5-year survival rate by about 5% (22). NCT could significantly improve the prognosis of patients as compared to surgery alone, but about 5% of the patients receiving NCT could not accept surgery due to disease progression, adverse reactions, and other factors (6, 7); therefore, NCT is mostly used for the patients, who are initially at risk of failing to achieve R0 resection. Compared with NCT, NCT combined with radiotherapy can further improve the R0 resection rate and prognosis of patients, but neoadjuvant radiotherapy improves the incidence of postoperative complications, so it is not widely used. The CHECKMATE-816 study included patients with stage IB to IIIA [according to 7th edition American Joint Committee on Cancer (AJCC)] NSCLC. The subgroup analysis revealed that stage IIIA or IB-II NSCLC patients treated with NICT could obtain higher pCR and MPR rates. However, the NICT could significantly improve the EFS of patients with stage IIIA disease only. For patients with IB-II NSCLC, whether the improvement of pCR and MPR rates can translate into EFS and OS benefits remains to be further studied. For patients with stage IIIA-B, whether NICT can replace neoadjuvant radiotherapy and chemotherapy remains to be further explored. For stage IIIA-B patients, NICT can improve MPR rate and EFS, and has the potential to replace NCT combined with radiotherapy.

The 7th edition of the AJCC staging manual classified T3N2M0 patients as stage IIIA patients, while the 8th edition classified them as stage IIIB patients (2). The patients with stage IIIB NSCLC in this study were initially resectable patients, excluding patients with N3 lymph node-positive. For the N2-positive patients, due to the risk of failing to achieve R0 resection, other treatment options, including concurrent chemoradiotherapy, surgery after neoadjuvant chemoradiotherapy, and surgery after induced chemotherapy are available (23–25). For operatable patients, surgery can improve the OS. As compared to NCT, NICT can improve the prognosis; however, it might cause difficulty in surgery, thereby limiting its application. Based on this study and previous studies, as compared with NCT, NICT did not lead to longer operation time, more bleeding, and higher perioperative complication rates (19, 26). Therefore, NICT might become one of the best treatment options for N2-positive patients.

Unlike the previous studies, which did not include patients with driver mutations or did not involve relevant gene screening, this study included some patients with driver mutations, the details of which are provided in Supplementary Table 1. In this study, the NICT group included 3 patients with epidermal growth factor receptor (EGFR) mutations, one patient with anaplastic lymphoma tyrosine kinase gene (ALK) fusion, and one patient with ROS proto-oncogene 1 (ROS1) fusion. Among these, 3 patients showed MPR (including one pCR). The NCT group included 9 patients with EGFR mutations, 3 patients with ALK fusion, and one patient with ROS1 fusion. Among these, only 3 patients showed MPR (including one pCR). This proportion was significantly lower than that in the NICT treatment group. All patients with EGFR mutation received EGFR-TKIs adjuvant treatment after surgery, while patients with ALK and ROS1 fusion did not receive targeted drug treatment after surgery, and none of the above patients had disease recurrence. Previous studies suggested that the MPR rate of patients with EGFR mutations, receiving neoadjuvant targeted therapy, was low (5% to 24.2%) (27–30). A multicenter study suggested that the patients with positive driver genes might still benefit from NICT treatment (31); these results were consistent with those observed in the our study. The selection of perioperative treatment and improvement the survival of these patients by NICT require further exploration.

As a retrospective study, this study was limited by the sample size and included only 42 patients in the analysis after PSM. This limitation made the subgroup analysis of patients, benefiting from NICT, impossible. Due to the short follow-up time and the difference of median follow-up time between the two groups, the data on DFS and OS in this study were not mature yet; therefore, the validity of NICT was evaluated using pCR and MPR as potential alternative endpoints. Therefore, for many problems, including the best applicable population of NICT and the best perioperative treatment strategy for patients with driver

gene mutations, further prospective randomized controlled study is needed to explore.

In conclusion, using the dual-center real-world data, this study suggested that in clinical practices, the selection of patients with new adjuvant therapy could be based on the resectable patients with II-IIIB stage NSCLC. As compared with NCT, NICT could significantly increase the proportion of pCR and MPR in the patients without increasing the operation-related bleeding and operation time.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Chinese Academy of Medical Sciences and Peking Union Medical College. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, JD and XZ; validation, JD and FT; data collection, KF, GG, ZW YW, JZ, XH, WG, and WS; statistical analysis, KF and GG; writing original draft preparation, KF and GG; writing-editing, JD and JX; supervision, YW, JW, ZW, QG, and LZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1145303/full#supplementary-material

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Association of early immune-related adverse events with treatment efficacy of neoadjuvant Toripalimab in resectable advanced non-small cell lung cancer

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Background: Neoadjuvant immunotherapy with anti-PD-1 was proved promising in resectable non-small cell lung cancer (NSCLC). Immune-related adverse events (irAEs) have been preliminarily implicated their association with treatment efficacy. Here we elucidated the early onset of irAEs associated with better clinical outcomes in a prospective study (Renaissance study).

Methods: We conducted the prospective study of NSCLC patients treated by neoadjuvant Toripalimab (240mg, every 3 weeks) plus double platinum-based chemotherapy from December 2020 to March 2022 at Peking University Cancer Hospital. Patients were enrolled if they have resectable IIB-IIIB NSCLC without EGFR/ALK mutation. Data were analyzed to explore the relationship between clinical outcome and irAEs after neoadjuvant treatment. A multidisciplinary team including physicians, surgeons, and radiologists, confirmed the irAEs according to the clinical manifestation. The relationship between irAEs and pathological outcomes was analyzed. The Renaissance study was approved by the Peking University Ethic board (2020YJZ58) and registered at https://clinicaltrials.gov/ as NCT04606303.

Results: Fifty-five consecutive patients were enrolled with a male-to-female ratio of 10:1, the median age was 62 years old (IQR: 45-76), of which 44 patients (80%) were diagnosed with squamous cell carcinoma. Forty-eight of 55 patients finally received thoracic surgery with a median preoperative waiting time of 67 days (IQR 39-113 days). Pathological results demonstrated that 31 (64.6%) patients achieved major pathological response (MPR) and 24 (50.0%) achieved complete pathological response (pCR). Among 48 patients who received R0 resection, immunotherapy-related thyroid dysfunction, rash/pruritus and enteritis occurred in 11 patients (22.9%), 7 patients (14.6%), and 1 patient (2.1%), respectively. Six patients (54.5%) with thyroid dysfunction achieved MPR with 5 (45.5%) achieved pCR, and a median time to onset was 45 days (IQR 21-91 days). Six patients (85.7%) with rash or pruritus achieved MPR and 5 patients (71.4%) achieved pCR, with median time to onset being 8 days (IQR 6-29 days). Furthermore, irAEs had no significant influence on operation time (170.6 min vs 165.7 min, P=0.775), intraoperative blood loss (67.4 mL vs 64.3 mL,

P=0.831) and preoperative waiting time (93 days vs 97 days, P=0.630) when comparing with patients without irAEs (Figure 1).

Conclusion: The immunotherapy-related rash is potentially associated with pathological outcomes in NSCLC patients after neoadjuvant chemo-immunotherapy, suggesting easy-to-find irAEs, such as rash, can be used as indicators to predict response to neoadjuvant chemo-immunotherapy.

Clinical trial registration: clinicaltrials.gov/, identifier NCT04606303.

KEYWORDS

immune-related adverse events, neoadjuvant, Toripalimab, non-small cell lung cancer, immunotherapy

Introduction

Lung cancer counts as the leading cause of cancer-related death worldwide (1). Only one-quarter of patients with non–small-cell lung cancer (NSCLC) are diagnosed with early-stage disease and eligible for curative-intent surgery (2). The emergence of neoadjuvant therapy made it possible for locally advanced patients to accept surgical resection (3), and the addition of immunotherapy further improve the pathological outcomes of these patients in CheckMate 816 trial (4) and several single arm clinical trials compared with mono-chemotherapy (5–10). Immunotherapy, a significant treatment emerging in the past decade, has changed the paradigm of lung cancer treatment and brought great benefits to patients with PD-L1-expressing, locally advanced or metastatic NSCLC and locally advanced patients after radical resection or concurrent chemoradiotherapy (11–15).

As to neoadjuvant treatment, it was reported in the CheckMate-816 clinical trial that the median event-free survival was 31.6 months with nivolumab plus chemotherapy, and the percentage of patients with a pathological complete response (pCR) was 24.0% (4). Zhao et al. (9) found that Toripalimab, a PD-1 monoclonal antibody, plus platinum-based doublet chemotherapy yields a substantial major pathological response (MPR) rate (50% in the per-protocol population) with manageable toxicity and feasible resection in stage III NSCLC. Toripalimab combined with stereotactic body radiation therapy (SBRT) is also effective as a neoadjuvant regimen (16). There are also a larger number of clinical trials of neoadjuvant chemotherapy combined with immunotherapy (shown in the following chart). The pCR rates and treatment-related adverse events (TRAE) occurrence differ from 9% to 71% and 23% to 92.6%.

It is often observed in clinical practice that patients with immune-related adverse events (irAEs) may be more likely to achieve pCR after neoadjuvant immunotherapy. Some literature has pointed out that the irAEs happened due to the activation of T cells, which could help to kill the tumor cell. A retrospective study reported that patients with irAEs showed improved effectiveness over patients without irAEs (17, 18). To elucidate the association between the occurrence of irAEs and the pCR/MPR rate after R0 resection, data was analyzed among resectable locally advanced NSCLC patients to determine whether irAE could act as a prognostic factor to predict the efficacy of immunotherapy.

Methods

Patients

We enrolled patients with resectable stage IIB-IIIB NSCLC (according to the staging criteria of the American Joint Committee

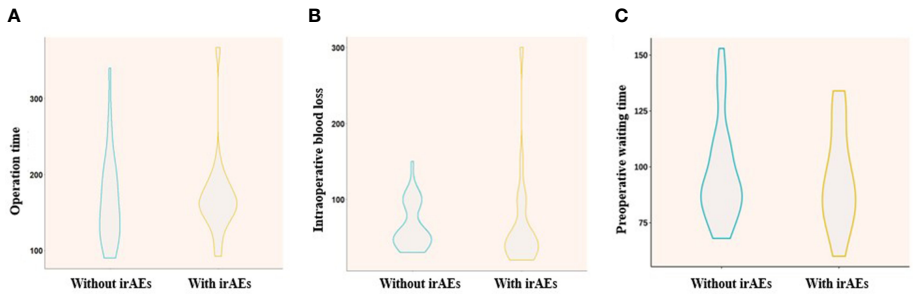

FIGURE 1
Comparison of operation time **(A)**, intraoperative blood loss **(B)**, and preoperative waiting time **(C)** between "with irAEs" and "without irAEs".

on Cancer, 8th edition) without previous anticancer therapy, an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale in which higher scores reflect greater disability) without EGFR/ALK mutation. Patients had to have measurable disease according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and pretreatment tumor tissue available to assess the expression of programmed death ligand 1 (PD-L1). Patients with known ALK translocations or EGFR mutations were excluded. The inclusion criteria were: 1) cytological or histological confirmation of NSCLC; 2) primary staged as clinical or pathological stage IIB-IIIB; 3) completed at least one cycle of immunotherapy. The exclusion criteria were 1) EGFR/ALK mutation, 2) important organ dysfunction before treatment; 3) did not complete a follow-up visit of the first cycle at the time of data collection; 4) previously accepted anti-tumor treatment.

Trial design and treatment

In the prospective study, NSCLC patients were treated with neoadjuvant Toripalimab (240mg, every 3 weeks) plus double platinum-based chemotherapy from December 2020 to March 2022 at Peking University Cancer Hospital. Patients received cisplatin 75mg/m2 and pemetrexed 500 mg/m2 for adenocarcinoma, or cisplatin 75mg/m2 and nab-paclitaxel 260 mg/m2 for other subtypes on day 1-2 of each 21-day cycle. And intravenous Toripalimab was used on day 1 with chemotherapy of each 21-day cycle. Surgical resection was performed 6-8 weeks afterward. We analyzed the data of patients in the Renaissance study and explored the association between clinical outcomes and irAEs after the commencement of neoadjuvant Toripalimab treatment. The study was approved by the Peking University Ethic board (2020YJZ58) and registered at https://clinicaltrials.gov/ as NCT04606303. All patients signed written informed consent forms, and all data were deidentified.

End points and assessments

All patients were staged according to the 8th Edition American Joint Committee on Cancer staging system. Characteristics of patients were summarized, including age, sex, pathological type, smoking history, tumor-node-metastasis (TNM) stage, immunotherapy-related adverse events (irAEs), and residual viable tumor (RVT).

The primary endpoints were major pathological response (MPR) rate (19) (≤10% residual viable tumor cells in the primary tumor and sampled lymph nodes). The second end points were the emergence of irAEs, pathological complete response (pCR) rate (0% residual viable tumor cells in the primary tumor and sampled lymph nodes), objective response rate, R0 resection rate, perioperative safety, and event-free survival.

Definition

IrAEs were defined as having a potential immunological basis that required more frequent monitoring and potential intervention assessed by a multidisciplinary team of physicians, surgeons, and radiologists. IrAEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (20) and were handled according to the guidelines on the management of immunotherapy-related toxicities (21, 22). The time to onset of irAE was defined as the time from the start of immunotherapy to the occurrence of irAE. Event-free survival (EFS) was defined as the time from the start of immunotherapy to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression of disease in the absence of surgery, or death from any cause.

Statistical analysis

Descriptive statistics of baseline, clinicopathological, and operation-related characteristics were listed. The pCR, MPR, R0 resection rate, the occurrence of irAEs, the time interval between Toripa, limab use and the occurrence of irAE, and event-free survival were calculated. SPSS 26.0 (IBM, Armonk, NY, USA) was used for statistical analysis. The continuous data were presented as medians (ranges) and analyzed using the Mann-Whitney U-test. The categorical data were presented as numbers (percentages) and analyzed using the chi-square or Fisher's exact test. And the survival outcome data were presented as average (ranges) and analyzed by the Cox proportion risk regression model. The Kaplan-Meier curve was analyzed by Log-Rank analysis. Reported P values are two-sided, and the significance level was set at 0.05 for all analyses unless otherwise noted.

Results

Patient characteristics

From December 2020 to March 2022, 55 patients met the inclusion criteria, the median age was 62 years old (IQR 55-66 years old) (Figure 2). Overall, 50 patients (90.9%) were men, 49 patients (89.1%) had a smoking history, 16 patients (29.1%) were stage IIB, 31 patients (56.4%) were stage IIIA, 8 patients (14.5%) were stage IIIB. Nine patients (16.4%) were staged as N0, 16 patients (29.1%) were staged as N1, and 30 patients (54.5%) were staged as N2. Forty-four patients were diagnosed with squamous cell carcinoma (80%), nine patients were diagnosed with adenocarcinoma (16.4%), and 2 patients were proven to have adenosquamous lung cancer.

Treatments and TRAE outcomes, especially irAEs outcomes

About 69.1% of patients accepted 2 cycles of neoadjuvant Toripalimab plus chemotherapy, 14 patients accepted 3 cycles of neoadjuvant Toripalimab plus chemotherapy (25.5%), one patient received 4 cycles of neoadjuvant Toripalimab plus chemotherapy (1.8%), and 2 patient received one cycle of neoadjuvant Toripalimab plus chemotherapy (3.6%) (Table 1) One of the 2 patients that only

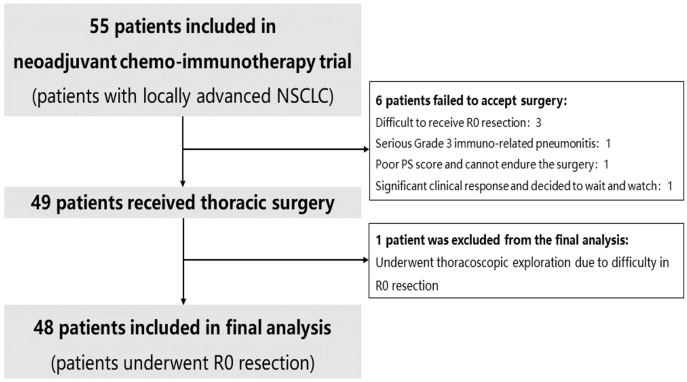

FIGURE 2
Flow chart of including patients.

take 1 cycle was due to bile tract infection, another patient suffered severe immune-related enteritis and can't continue immunotherapy. TRAE occurred in 53 patients (96.4%), which contains myelosuppression, vomiting, nausea, alopecia, acroanesthesia, anorexia, hepatic function impairment, etc. Among them, 17 patients (30.9%) suffered Grade 3-4 TRAE. While there were 22 patients (40%) involved in this clinical trial were diagnosed with irAEs. Immune-related thyroid dysfunction, rash/pruritus, enteritis, and pneumonitis occurred in 12 patients (21.8%), 7 patients (12.7%), 2 patients (3.6%), and 1 patient (1.8%), respectively. Among these 22 patients, 6 patients suffered Grade 2-3 irAEs. The common Grade 2-3 irAEs were rash and pruritus (9.1%), immune-related enteritis (9.1%), immune-related pneumonitis (4.5%), and thyroid dysfunction (4.5%) (Table 2). The median time between the commencement of Torapalimab and diagnosis of irAEs was 28.5 days (IQR: 18.3-77.5 days). And the median time interval between the commencement of Torapalimab and diagnosis of grade 1, grade 2, and grade 3 irAEs were 32.5 days,21 days, and 62 days. Grade 1-2 irAEs appear to occur earlier than Grade 3 (Figure 3). Grade 1-2 rash was usually treated withsteroids ointment and oral antihistamines. Grade 1-2 thyroid dysfunction was treated with thyroid hormone supplements. While immune-related pneumonitis and enteritis were treated with intravenous steroids injection and sequentially dose decreased till suspension, symptomatic treatment was also used when patients suffered serious dyspnea or diarrhea. In our research, two patients with grade 2 irAEs (9.1%) and 3 patients with grade 3 irAEs (13.6%) were treated with glucocorticoid therapy. The median glucocorticoid-using time duration was 12 days (IQR: 7-79 days).

Patients received surgery

Forty-eight of 55 patients finally received thoracic surgery with a median time interval of 67 days (IQR 39-113 days) after neoadjuvant treatment. Pathology confirmed that 31 (64.6%) patients achieved MPR and 24 (50.0%) patients achieved pCR.

In a total of 48 patients who received R0 resection, eleven patients suffered from thyroid dysfunction, of which six patients achieved MPR and 5 patients achieved pCR, the median time from treatment initiation to onset was 45 days (IQR 21-91 days). Six

TABLE 1 Characteristics of included patients.

	N (%)
Age (IQR)	61.5 (55-66)
Gender	
male	50 (90.9%)
female	5 (9.1%)
Smoking history	
Yes	49 (89.1%)
No	6 (10.9%)
Staging	
IIB	16 (29.1%)
IIIA	31 (56.4%)
IIIB	8 (14.5%)
Staging of Lymph nodes	
N0	9 (16.4%)
N1	16 (29.1%)
N2	30 (54.5%)
Pathology	
Squamous cell carcinoma	44 (80.0%)
Adenocarcinoma	9 (16.4%)
Adeno-squamous carcinoma	2 (3.6%)
Cycles of Neoadjuvant Therapy	
1	2 (3.6%)
2	38 (69.1%)
3	14 (25.5%)
4	1 (1.8%)

TABLE 2 irAE of all 55 patients involved in trial.

Type of irAEs	Any Grade	Grade 2-3	Median Time Interval (Days)
Hyperthyroidism	12	1 (4.5%)	45.5(IQR 21-96.3)
Rash/pruritus	7	2 (9.1%)	8(IQR 6-29)
Enteritis	2	2 (9.1%)	45
Pneumonitis	1	1 (4.5%)	62
Total	22	6 (27.3%)	28.5 (IQR 18.3-77.5)

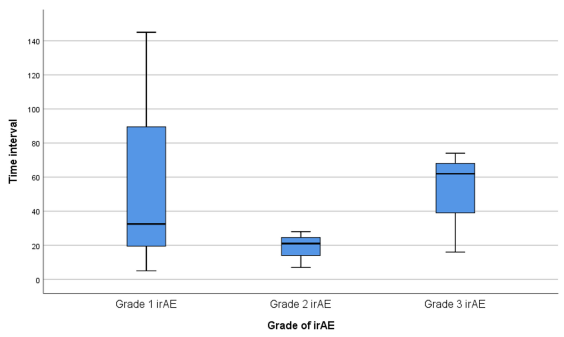

FIGURE 3
Comparison of the time interval between commencement of Torapalimab and diagnosis of different grades of irAEs. irAEs refers to immunotherapy-related adverse events.

patients with rash or pruritus achieved MPR, and 5 patients achieved pCR, the median time to onset was 8 days (IQR 6-29 days). One patient with enteritis achieved pCR, and the time interval between treatment and the onset of enteritis was 16 days. Among these patients with irAEs, three patients suffered grade 2-3 irAEs and achieved pCR(Table 3).

Furthermore, as to the safety of thoracic surgery after neoadjuvant Toripalimab plus chemotherapy, irAEs showed no significant influence on the operation time (170.6 min vs 165.7 min, p=0.775) (Figure 1A), intraoperative blood loss (67.4 mL vs 64.3 mL, p=0.831) (Figure 1B) and preoperative waiting time (93 days vs 97 days, p=0.630) (Figure 1C). The pathological response outcomes of different stage of NSCLC was presented in Table 4. It showed that Stage IIB to IIIA might benefit mostly from neoadjuvant immunochemotherapy, and no significant difference was found between clinical stage and pathological response (p=0.27).

We also analyzed the time-onset of irAE and the time interval between the last cycle of neoadjuvant therapy and surgery (Figure 4), the p-value didn't show a significant difference, which further confirms that the occurrence of irAE would not delay surgery and neoadjuvant immuno-chemotherapy could be estimated as dependable and safe.

Patients failed to receive surgery

There is one patient who decided to watch and wait after complete clinical response (CCR) (Figure 5). This patient was diagnosed with lung adenocarcinoma, cT2N2M0, stage IIIA. His CT examination in May 2021 revealed truncated bronchial stenosis in the upper lobe of the right lung, irregular soft tissue foci next to the hilum, about 32*22mm, with distal lung tissue atelectasis. There were also multiple enlarged lymph nodes in the mediastinum and the right hilum. Bronchoscopy showed a bulge around 2/3 circumference of the right main bronchus, with the upper edge about 5mm from the bulge. Pathological biopsy suggested moderately differentiated squamous carcinoma. He was treated with 1 cycle of ABP (albumin- bounded paclitaxel) + cisplatin + Toripalimab in 2021/6/25. The next cycle of treatment was canceled due to the development of severe immune-related enteritis which was treated at Peking Union Medical College Hospital subsequently. On 2021-9-22 his chest CT showed: the soft tissue masses near the right hilum disappeared. Multiple enlarged lymph nodes were reduced in size. PET-CT of the right pulmonary hilum did not show hypermetabolism. In 2021-12-16, he reviewed bronchoscopy and the biopsy reported mild chronic inflammation of the mucosa of the pseudostratified ciliated columnar epithelium, with two heterogeneous cells visible in the interstitium, considered to be cancer. In 2022-4-13, we reviewed the bronchoscopy again, and the biopsy showed no definite clue of lung cancer. In 2022-12-16, we retested the chest CT: it showed that the soft tissue thickening in upper lobe of the right lung near the hilum was as before, either was the bronchial stenosis in the right upper lobe.

There were also 6 other patients who failed to receive surgery, of which three patients failed to receive surgery for the poor performance in radiological imaging, as well as 2 patients' surgery were canceled respectively for the anatomical adhesion during surgical exploration and poor physical performance. Notably, one

TABLE 3 irAE of 48 patients received R0 resection.

Type of irAEs	Any Grade	Grade 2-3	Median Time Interval (IQR)	pCR	pCR rate	MPR	MPR rate
Hyperthyroidism	11	0	45 days(21-91 days)	5	45.5%	6	54.5%
Rash/pruritus	7	2	8 days(6-29 days)	5	71.4%	6	85.7%
enteritis	1	1	16 days	1	100%	1	100%
pneumonitis	0	0	0	0	0	0	0
Total	19	3	22 days (16-46 days)	11	57.9%	13	68.4%

TABLE 4 The results of pathological response for different clinical stage of NSCLC.

Clinical Stage /pathological response	IIB	IIIA	IIIB	Total
pCR	7	16	1	24
MPR not pCR	2	4	1	7
Non-MPR	4	8	5	17

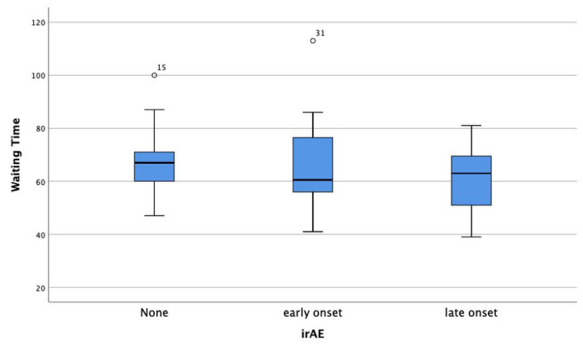

FIGURE 4
Comparison of waiting time after the last cycle of immunotherapy between early, late-onset or no occurrence of irAEs.

patient's surgery was canceled for grade 3 immuno-related pneumonitis. This patient has diagnosed with stage IIIB adenocarcinoma without ALK translocation and EGFR mutation in the left lower lobe (Figure 6A), thus three cycles of neoadjuvant Toripalimab combined with chemotherapy were used for the surgical opportunity. While reduced exercise tolerance come out after the third cycle, he simultaneously had intermittent fever during hospitalization, chest computed tomography showed large-area ground-glass opacity with consolidation (Figure 6B), which confirmed the diagnosis of immuno-related pneumonitis. Arterial blood gas analysis showed an arterial partial pressure of oxygen of 68.2 mmHg. After standard treatment of glucocorticoid therapy combined with continued antibiotic treatment, the patient recovered from the server pneumonitis with continuous oxygen therapy. The patients achieved great improvement for 18 months from the treatment start (Figure 6C). And recently computed tomography showed that the tumor completely disappeared.

Patients underwent adjuvant therapy

There are 14 patients who took adjuvant therapy, which includes chemo-immunotherapy with/without sequential immunotherapy for maintenance treatment, or directly adjuvant immunotherapy. There are 34 patients who didn't take adjuvant therapy, the result of adjuvant therapy were presented in Table 5.

Survival analysis

The average EFS of patients without irAE (33 patients) was 22.7 months (95%CI 21.3-24.2 months). The median EFS of patients with irAE (22 patients) was 23.5 months (95%CI 21.0-25.9 months), and both median times were not reached, The log-rank analysis showed that the p-value was 0.61.

6 patients arrived at the end point of our study, 3 of them had encountered local recurrence, 2 of them had been diagnosed with metastatic lung cancer, and only 1 patient died during our study.

We separated the patients with irAE into the early-onset and late-onset, each separately included 14 and 8 patients. The watershed between them was 3 months. Due to the small sample size, the HR of early-onset irAE had no significant difference, and the HR of late-onset irAE was 4.53 (p=0.065, 95%CI 0.91-22.5). While the log-rank analysis of the K-M curve showed a significant difference (p=0.021) (Figure 7).

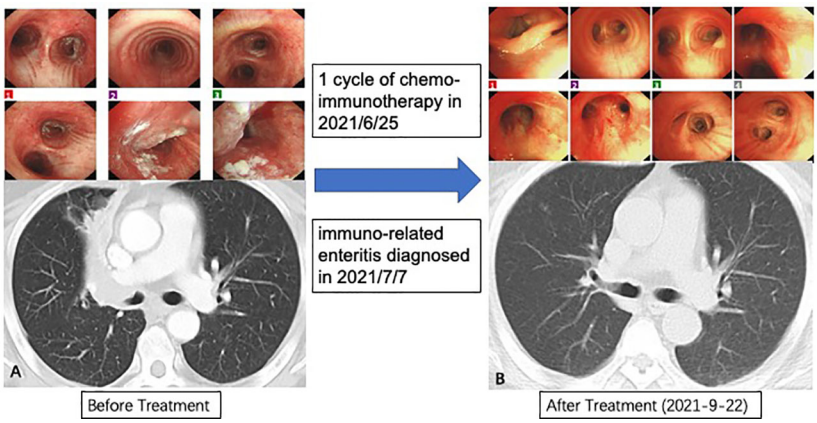

FIGURE 5
Procedures of treatment and response. **(A)** Baseline characteristic of lungs; **(B)** Great clinical response in bronchoscopy and computed tomography.

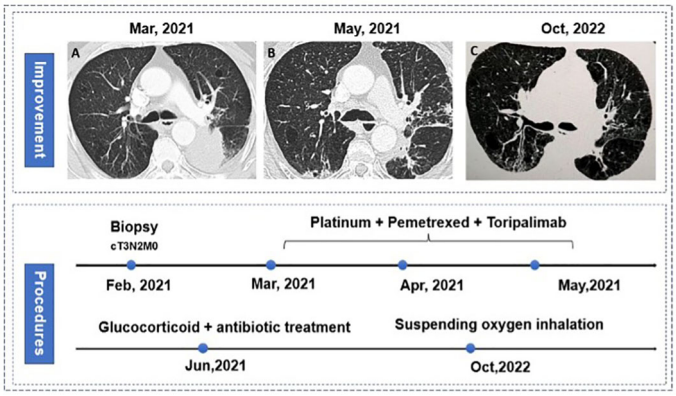

FIGURE 6
Procedures of treatment and pneumonitis. **(A)** baseline characteristic of lungs; **(B)** immune-related pneumonitis **(C)** great improvement in tumor and pneumonitis in bilateral lungs.

Discussion

Immunotherapy, targeting T-cell regulatory pathways, is widespreadingly recommended as first-line therapy for advanced lung cancer, which has been heralded as a promising treatment when combined with chemotherapy. Several international clinical trials provided the evidence that neoadjuvant immunotherapy plus chemotherapy performed well with higher rates of pathological response and controllable side effects (Table 6).

According to the NADIM study, the MPR rate of all patients involved was 45% (7). As the CheckMate 816 trial found out: the pCR rate of Stage IIIA NSCLC was 23%, and the pCR rate of squamous cell carcinoma was slightly higher than adenocarcinoma, without significant difference (4).

Moreover, a large number of patients with NSCLC in China were diagnosed with non-squamous carcinoma (26). Epidermal growth factor receptor (EGFR) mutation is currently the most common target; EGFR mutations were more common in Chinese patients than in American patients (27), which might result in our patients that accepted immunotherapy of non-squamous NSCLC (11/55, 20%) is less than of squamous cell carcinoma (44/55, 80%). As a single-center study, our patients cannot present for the whole population in Beijing or China, which contributes to the inevitable selection bias of our study.

Previous articles reported that immunochemotherapy obtained shorter operative time, a higher rate of en bloc resection, and minimal invasion (4). As validated in our study, patients with irAE showed similar preoperative waiting time, operation time, and intraoperative blood loss, confirming its safety and reliability of neoadjuvant immunochemotherapy. The relationship between the irAEs and pathological response was explored as the predictor for the combination treatment. Hyperthyroidism, rash, and pruritus were the common adverse events reported in recent articles on immunochemotherapy. Intriguingly, rash and pruritus always come out early, and most of these patients were proven pCR finally. Moreover, some literature did confirm that irAE is connected with better OS in melanoma (28), non-squamous NSCLC (29) and ESCC (30). The specific types of irAE might predict better prognosis as well, such as colitis and diarrhea (31). Our initial idea was to find the association between the occurrence of specific irAE with a better pathological response. Unfortunately, no significant P value was found between irAE and pathological response. It had been reported that 3 months could serve as a watershed to identify the early-onset or late-onset irAEs (32), as we estimated, the median

TABLE 5 The results of the of adjuvant therapy of 48 patients.

Pathological response /Adjuvant Therapy	Chemo-immunotherapy	Immunotherapy	None
pCR	1	2	21
MPR not pCR	2	1	4
Non-MPR	5	3	9
Total	8	6	34

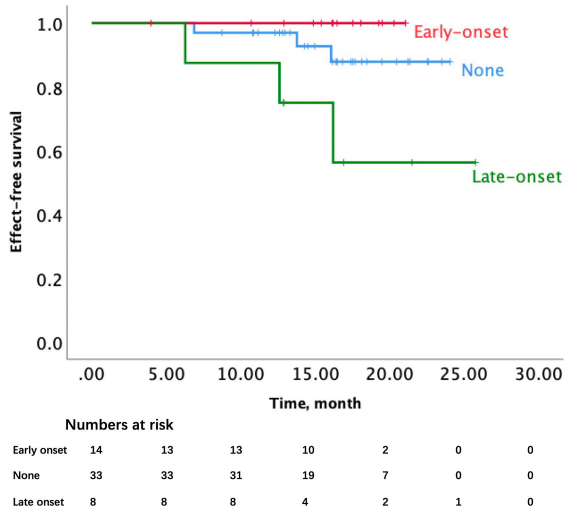

FIGURE 7
Event-free survival by early or late onset of irAE in all 55 patients.

TABLE 6 The results of the terminated neoadjuvant immunotherapy trials for resectable NSCLC.

Trial	Identifier	Phase	Stage	Sample Size	Primary Endpoint	Treatment	R0 Rate	pCR	TRAE	MPR
LCMC	NCT02927301	II	IB–IIIB	181	MPR	atezolizumab monotherapy	76%	NA	41%	20%
Long et al.	NCT04304248	II	III	33	MPR	toripalimab	96.7%	45.5%	NA	60.6%
CheckMate159	NCT02259621	II	I-IIIA	22	Safety	Nivo	91%	15%	23%	45%
NADIM	NCT03081689	II	IIIA	46	PFS	Nivo	89%	71%	93%	85%
SAKK 16/14	NCT02572843.	II	IIIA(N2)	68	MPR	Durvalumab	93%	18%	88%	62%
J.Lei et al. (23)	NCT04338620.	II	IIIA, IIIB-N2	14	MPR	camrelizumab	50%	57.1%	NA	85.9%
Gao et al.	ChiCTR-OIC-17013726	1b	IA-IIIB	40	MPR	Sintilimab	92.5%	16.2%	52.5%	40.5%
H.Duan et al. (24)	–	II	IIA-IIIB	20	ORR	PD-1 inhibitors	95%	30%	NA	50%
Checkmate816	NCT02998528	III	IB-IIIA	358	EFS/pCR	Nivolumab	83.2%	24%	92.6%	NA
A.Tfayli et al. (25)	NCT03480230	II	IB-IIIA	15	ORR	Avelumab	73%	9%	NA	27%

time between the commencement of Toripalimab and surgery was nearly 3 months, either. Thus we did a survival analysis of the onset of irAE and event-free survival and got a positive outcome, which might proclaim the early-onset irAE as a biomarker of better outcomes among locally advanced NSCLC patients with neoadjuvant immune-chemotherapy modality. Early-onset irAEs were mainly composed of rash/pruritus and thyroid dysfunction, both were easily monitored and handled during the preoperative treatment period. Patients with early-onset irAEs including rash or pruritus in neoadjuvant immunotherapy were more likely to achieve better event-free survival compared to late-onset irAEs. We only came out with this conclusion based on our 55-patient retrospective trial in our hospital, more rigorous randomized clinical trials are needed to find the association between them for neoadjuvant immunotherapy in locally advanced NSCLC.

To our best knowledge, immune checkpoint inhibitors are designed to attack malignancies by targeting the ligands, leading to T-cell activation for the attack against malignant cells. These ligands included cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death protein 1 (PD-1), and programmed death ligand-1 (PD-L1). These corresponding medications upregulate the immune system and cause irAEs (33). Some adverse events may be mild, 14 patients with lung cancer who received immunotherapy reported that their hair turned black, and another case reported that one patient with metastatic cutaneous melanoma developed eyelash poliosis after undergoing treatment with combination immunotherapy with ipilimumab and nivolumab (34). In a responder analysis, an increase in overall survival was seen in patients with the related adverse event of special interest (AESI) compared with those with no related AESIs. About 57% of responding patients with a related AESI reported the AESI before documentation of response (35). Patients with rash/pruritus always had a higher proportion of major pathological responses. Researchers found that T cells that reacted to antigens shared in NSCLC lesions and the skin-mediated autoimmune skin toxic effects. These T cells may also have mediated the tumor regression in patients who responded to therapy (17). Compared with immune-related pneumonitis, rash/pruritus happened earlier and was easier to be detected, which may lessly hinder thoracic surgery for its stable nature. Thus, more active surgical treatment should be adopted when confronted with certain irAE such as rash/pruritus.

Immunotherapy efficacy predictors were explored recently; serum biomarkers or others were regarded as powerful predictors. For example, phenotype markers were explored in an end-staged solid tumor, like PD-L1 expression, TILs (36), or LAG3 (37), etc. And there are also genomic markers such as MSI-H, TMB (38), specific gene mutation (39), and ctDNA. Inflammatory biomarkers are also explored to predict the efficacy of neoadjuvant immunotherapy (40). However, there was still lacking authoritative clinical evidence for these predictors. Based on previous studies, ctDNA could count as promising and dependable marker of neoadjuvant immune-checkpoint inhibitors used in resectable locally advanced NSCLC (4, 41, 42). But the cost and fundamental establishments made it less useful in our clinical practice. Other biomarkers like TMB, MIS-H or PD-L1 expression couldn't effectively predict the outcome of neoadjuvant immunotherapy (5, 7). As the pooled analysis published in February 2023 on JAMA Oncology found out, irAE did bring out better OS and PFS in Stage IV non-squamous NSCLC patients who underwent Atezo treatment (29). Our study also found that early-onset irAEs were associated with better event-free survival in resectable NSCLC patients who underwent neoadjuvant Toripalimab treatment.

Nevertheless, some severe irAE like immune-related pneumonitis or enteritis could stop patients from getting regular preoperative treatment or even surgery. Early-onset irAEs were mainly composed of rash/pruritus and thyroid dysfunction, both

were easily monitored and handled during the preoperative treatment period, which also highly alleviated the anxiety of these patients. Thus, we finally came out with this conclusion: Easy-to-find irAEs, such as rash, can be used as indicators to predict response to neoadjuvant chemo-immunotherapy.

According to the other accomplished clinical trials of neoadjuvant immunotherapy, TRAE happened in 23%-93% of patients, but they barely mentioned specifically about irAEs. One literature reported the occurrence rate of irAE in the atezo-containing arm in Stage IV non-squamous NSCLC as 48% (29). The reported incidence of any-grade irAEs associated with ICI treatment ranges widely across agents and trials, from approximately 15% to 90% (43, 44).

A meta-analysis studied by De Velasco et al. reported the incidence of the most common irAEs of 21 randomized phase II/III trials from 1996 to 2016, which included a total of 6528 patients who received monotherapy (45). Within this cohort, across all ICIs, incidence of all-grade irAE was 30.4%, and the incidence of grade 3/4 events was 1.5% for colitis, 1.5% for liver toxicity, 1.1% for rash, 0.3% for hypothyroidism, and 1.1% for pneumonitis, added up to 5.8% grade3/4 occurrence.

The present study has several limitations. Firstly, this was a single-center study, not a randomized controlled trial, and the results were subjective to the inherent shortcomings of the single-center study. Patients in preparation for lung cancer surgery were enrolled, which may introduce a selection bias. Additionally, the difference was not significant perhaps due to the small sample size, the confounding effects of limited sample size cannot be ruled out. Secondly, different PD-1 inhibitors might result in different irAEs and lead to different efficiency, only Toripalimab was used in this cohort. Our study only included the use of Toripalimab, different kinds of immune-checkpoint inhibitors might result in the different modalities of irAEs. Thus, the results may not be proper for other PD-1 inhibitors, which need more evidence from randomized controlled trials. Finally, all the irAEs were assessed by investors in our hospital, limited by a paucity of irAEs evaluation criteria, which may cause subjective judgment bias.

In conclusion, some irAEs may point to the positive treatment effect, which may not be affected by the treatment cycles. The importance of accurately identifying irAEs that may benefit from neoadjuvant immunotherapy is critical, given the potentially positive indicator on treatment-associated results.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Peking University Ethic board (2020YJZ58). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NW and SY supervised the study. NW, SY, YT, and XL conceived of and designed the study. YT and XL did the statistical analysis and wrote the drafted report. NW, SY, YT, XL, YW, and JC critically revised the manuscript. BL, JW, and CL organized and screened patients. All authors had access to all the raw datasets. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Advances in efficacy prediction and monitoring of neoadjuvant immunotherapy for non-small cell lung cancer

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The use of immune checkpoint inhibitors (ICIs) has become mainstream in the treatment of non-small cell lung cancer (NSCLC). The idea of harnessing the immune system to fight cancer is fast developing. Neoadjuvant treatment in NSCLC is undergoing unprecedented change. Chemo-immunotherapy combinations not only seem to achieve population-wide treating coverage irrespective of PD-L1 expression but also enable achieving a pathological complete response (pCR). Despite these recent advancements in neoadjuvant chemo-immunotherapy, not all patients respond favorably to treatment with ICIs plus chemo and may even suffer from severe immune-related adverse effects (irAEs). Similar to selection for target therapy, identifying patients most likely to benefit from chemo-immunotherapy may be valuable. Recently, several prognostic and predictive factors associated with the efficacy of neoadjuvant immunotherapy in NSCLC, such as tumor-intrinsic biomarkers, tumor microenvironment biomarkers, liquid biopsies, microbiota, metabolic profiles, and clinical characteristics, have been described. However, a specific and sensitive biomarker remains to be identified. Recently, the construction of prediction models for ICI therapy using novel tools, such as multi-omics factors, proteomic tests, host immune classifiers, and machine learning algorithms, has gained attention. In this review, we provide a comprehensive overview of the different positive prognostic and predictive factors in treating preoperative patients with ICIs, highlight the recent advances made in the efficacy prediction of neoadjuvant immunotherapy, and provide an outlook for joint predictors.

KEYWORDS

non-small cell lung cancer, neoadjuvant immunotherapy, chemo-immunotherapy, efficacy prediction, biomarkers

1 Introduction

Lung cancer has one of the highest incidence rates worldwide and is responsible for the most deaths (1). Non-small cell lung cancer (NSCLC) is a major type of lung cancer accounting for approximately 85% of lung cancer cases; only 30%–40% of patients diagnosed with NSCLC present with resectable disease (2, 3). Surgical resection is the cornerstone for the treatment of early-stage NSCLC and is also one of the most effective means for the treatment of stage IIIA disease for attaining resectable status by neoadjuvant chemotherapy (4–6). Preoperative chemotherapy improves both progression-free survival (PFS) and overall survival (OS); however, it improves the 5-year survival rate by only 5% and fails to meet clinical needs (7). Recently, activating the human immune system to fight cancer, including NSCLC, by blocking inhibitory immune checkpoints has gained attention. Several phase III trials have confirmed the role of pembrolizumab, an immune checkpoint inhibitor (ICI), as a standard first-line treatment for patients with locally advanced or metastatic NSCLC (8–10). Notably, compared with monotherapy, ICIs plus platinum-based chemotherapy resulted in significantly longer OS and PFS regardless of PD-L1 expression (11–14).

Given the effectiveness of immunotherapy, an increasing number of clinical trials evaluating these agents are rapidly moving from advanced NSCLC to earlier stages of the disease (15). These trials have shown a high percentage of patients with resectable NSCLC achieving a major pathological response (MPR) of up to 86% and a pathological complete response (pCR) of approximately 9%–63% (16, 17). These data suggest the feasibility and efficacy of neoadjuvant immunotherapy in tumor down-staging in patients without increasing the incidence of adverse effects or surgical delay (18). In early 2022, National Comprehensive Cancer Network (NCCN) updated its guidelines for neoadjuvant systemic therapy according to the result of CheckMate 816 presented at the 2021 AACR annual meeting (19). The regimen of nivolumab plus platinum-doublet chemotherapy was first added to the guidelines as neoadjuvant systemic therapy. The preliminary efficacy of chemo-immunotherapy in NSCLC patients is being widely discussed and has prompted research worldwide (15–18). Based on the limited data currently available, as many as 17 different clinical trials about neoadjuvant immunotherapy are currently registered in ClinicalTrials.gov (20). These landmark clinical trials of neoadjuvant immunotherapy have ushered in a new era in NSCLC therapy.

Regardless of the benefits of neoadjuvant immunotherapy, not all patients will experience favorable responses to treatment. Different clinical trials reveal wide efficacy gaps (17). There exists a significant population of patients who do not sufficiently respond to ICIs and may even suffer severe immune-related adverse effects (irAEs) or hyperprogression (21). The heterogeneous objective response rate (ORR) in NSCLC patients who received immunotherapy indicated that the selection of effective biomarkers to better stratify patients for immunotherapy is important. Preliminary data generated by clinical trials for advanced NSCLC patients treated with ICIs have disclosed some biomarkers that are associated with response to immunotherapy (22). These can be roughly divided into the following four categories (23): 1) tumor-intrinsic biomarkers, including programmed cell death ligand 1 (PD-L1), tumor mutational burden (TMB), and specific gene alterations; 2) tumor microenvironment biomarkers, including tumor-associated immune cells (TAICs), and T-cell receptor (TCR) repertoire; 3) liquid biopsies, including peripheral blood cells and circulating tumor DNA (ctDNA); 4) host-related biomarkers, including clinical characteristics, sex, and human leukocyte antigen-1 (HLA-I).

The study of predictive factors associated with the efficacy of neoadjuvant immunotherapy is still in its infancy, and most explorations of neoadjuvant-related biomarkers are built upon existing biomarkers that have been identified in studies on ICI monotherapy. However, factors underlying the therapeutic efficacy of combination therapy and monotherapy may differ and, thus, cannot be generalized. Due to its short therapeutic cycles, periodic image reviewing, and definitive assessment of pathological responses, neoadjuvant immunotherapy is an ideal pattern for research biomarkers. This pattern can provide more opportunities to observe and assess biological changes at different times of neoadjuvant immunotherapy.

In this review, we summarize the positive prognostic and predictive factors that have been used to predict the efficacy of neoadjuvant immunotherapy in NSCLC patients, as well as the recent advances in the development of biomarkers that can be used to better facilitate patient selection.

2 Controversial biomarkers for predicting neoadjuvant immunotherapy efficacy

2.1 PD-L1 and tumor mutational burden

PD-L1 is a key protein in the advancement and development of immunotherapy. PD-L1 expression assessed by immunohistochemistry (IHC) was the first Food and Drug Administration (FDA)-approved companion or complementary diagnostic test for ICI monotherapy in NSCLC patients (24, 25). Owing to data from several studies, nivolumab was approved for NSCLC patients irrespective of the PD-L1 status (26).

Currently, PD-L1 has been investigated as a biomarker in several clinical trials of neoadjuvant immunotherapy. The phase 2 Lung Cancer Mutation Consortium 3 (LCMC3) trial showed that MPR was associated with baseline PD-L1 tumor proportion score (TPS) in NSCLC patients treated with atezolizumab monotherapy; a considerably higher pathological response was observed in patients with TPS ≥ 50% compared with those with TPS < 50% (27, 28). In CheckMate 816 trial, a greater event-free survival (EFS) and pCR benefit with nivolumab plus chemotherapy were seen across subgroups of a tumor PD-L1 expression level of over 1% (29). The NEOSTAR trial showed that those who achieved MPR or high radiographic response had higher PD-L1 expression (30). A similar result was seen in another trial of nivolumab plus ipilimumab in patients under the same dose and interval therapy (31).

In contrast, correlative data from some other trials of neoadjuvant immunotherapy did not show a relationship between PD-L1 status and the clinical benefits of NSCLC patients. Forde et al. and Altorki et al. found no association between PD-L1 tumor status and MPR (32, 33). Interestingly, when NSCLC patients were treated with typical ICIs like atezolizumab or nivolumab combined with paclitaxel and carboplatin, tumor PD-L1 expression tended to show no correlation with pathological response (34, 35). These results are in contrast to those of early studies on monotherapy (28, 30).

TMB, as a genetic characteristic of tumorous tissue, is emerging as a potential predictive biomarker of response to ICIs. TMB could be processed to neo-antigens, and higher TMB resulted in more effective T-cell recognition, which is correlated with better ICI outcomes (36). Although the US FDA approved pembrolizumab for TMB-high solid tumors, including unresectable NSCLC in 2020, there are both pros and cons to the clinical utility of TMB in neoadjuvant immunotherapy (37, 38). Previous trials, including the KEYNOTE-021, 189, and 407, have shown that TMB is not associated with the efficacy of chemo-immunotherapy, suggesting that treatment with ICIs combined with chemo-agents may confound the application of TMB (36, 39). Similarly, the LCMC3, NEOSTAR, and NADIM trials revealed that TMB was not significantly associated with MPR or patient survival (28, 31, 35). The CheckMate 816 trial also incorporated TMB into analyses and found that pCR benefit was seen with nivolumab plus chemotherapy regardless of TMB value (29). Only in patients in the NCT02259621 trial were a high mean of TMB predicted MPR and the mutation-associated neoantigen burden associated with pathological response (32); however, there was no significant correlation between TMB and PD-L1 expression (32).

2.2 Specific gene alterations

NSCLC with epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase rearrangements, or ROS1 mutations is currently recognized as a negative predictor of immunotherapy efficacy (40, 41). NSCLC patients harboring EGFR mutations benefit less from ICI treatment despite high PD-L1 expression (42). Several studies have shown that PD-L1 expression is regulated by complex mechanisms, including EGFR. Chen et al. found that EGFR activation upregulated PD-L1 via phosphorylating ERK and c-Jun pathway (43). Data from experimental studies showed that EGFR mutations could also upregulate PD-L1 through a variety of pathways, including NF-kB, YAP, JAK/STAT, and PI3K/AKT/mTOR (44, 45). Therefore, EGFR mutation may cause immune escape through the upregulation of PD-L1 expression. Moreover, EGFR mutation may also influence immune cell infiltration. EGFR mutational activation might reduce the MHC-I expression through the ERK-MEK pathway, resulting in a decreased number of infiltrating $CD8^+$ T cells, which may then contribute to the poor response to ICIs (46). However, the application of EGFR as a negative biomarker to predict the efficacy of immunotherapy remains controversial, and the underlying mechanisms and interactions with ICI therapy are complex (47). Different benefits of ICI therapy could be observed in different subtypes of EGFR mutations. Patients with EGFR L858R had better benefits from immunotherapy than those with 19Del (40).

In contrast, patients with KRAS mutations or BRAF V600E mutations might have a higher response to ICIs (48). These patients were found to have increased PD-L1 expression and high TMB burden (49). The potential mechanism may involve that RAS mutations can stabilize the mRNA encoding the PD-L1 protein through downstream signals; thus, tumor cells continue to synthesize PD-L1. There are limited data on the impact of oncogenic driver genes on the response to immunotherapy in patients with early-stage NSCLC since most clinical trials have excluded patients with tumors with mutations in the oncogenic genes.

The cohort in the LCMC3 trial observed that patients without STK11/LKB1 mutations or Keap1 mutations more frequently achieved MPR (27). Moreover, the most recent data published from the LCMC3 trial showed that co-mutant STK11 and KRAS portended worse pathological responses (28). Significantly, NSCLC patients with tumors with mutant STK11 not only have no radiographic or pathological response (34) but also suffered progressive disease when STK11 is co-mutated with KRAS (31). Tumor intrinsic pathways including STK11/LKB1 and KEAP1 are associated with non-T cell-inflamed tumor microenvironment (TME), which is also called a "cold" tumor, thus impairing the clinical efficacy of immunotherapy (50). Inactivation of STK11 signaling stimulates cancer cells to produce G-CSF, CXCL7, IL-6, and IL-1β, thereby recruiting tumor-associated neutrophils, which results in suppression of cytotoxic T-cell activity (51, 52). While all of these results have been mutually verified in different studies, conclusions are limited given the small number of patients in each clinical trial. Further clinical trials that include large panels of specific gene alterations will help investigate novel therapies to overcome STK11 mutation-mediated resistance to neoadjuvant immunotherapy.

2.3 Blood parameters and host-related markers

Blood parameters represent attractive biomarkers because blood is easily accessible and can be analyzed repeatedly over time. Some metrics and ratios of complete blood count (CBC) have been suggested as markers for predicting the efficacy of ICIs and patient outcomes. In studies on advanced NSCLC patients, Diem et al. and Ren et al. reported that high values of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) before treatment are prognostic markers significantly correlating with poor survival and lower response rates in patients treated with nivolumab monotherapy (53, 54). NADIM trials incorporated NLR and PLR to study the association of these parameters with the degree of pathological response and found that only decreased PLR after neoadjuvant treatment was associated with pCR (55). Moreover, lactate dehydrogenase (LDH) or peripheral blood tumor marker carcinoembryonic antigen (CEA) might also be a reliable biomarker to predict immunotherapy efficacy in NSCLC patients (56–58). However, chemo-agents used in neoadjuvant immunotherapy may affect patients' blood parameters, making the applicability of blood-related biomarkers uncertain.

Host-related markers contain various factors about the patients' clinical characteristics, such as sex, age, body mass index, smoking, personal history, and HLA complex (59–62). Several studies have shown that the efficacy of ICI monotherapy is better in men than in women, even in the case of high PD-L1 expression NSCLC (62, 63). In contrast, women benefit significantly more from ICIs plus chemotherapy than men with advanced lung cancer (64, 65). The sex-based difference in antitumor immune response relies on a complex interplay between immune evasion mechanisms, hormones, genes, and behavioral factors (66, 67). In CheckMate 816 trial, both male and female patients benefitted more from nivolumab plus chemotherapy over chemotherapy alone. Interestingly, median EFS was longer in women than in men in both arms (29). Additionally, elder patients may achieve poor immunotherapy efficacy due to immunosenescence. Whether the benefit of immunotherapy is age-dependent remains controversial (68–71). Further clinical research should take host-related factors into account to eliminate bias, explore potential mechanisms, and stratify populations that benefit from neoadjuvant immunotherapy.

3 Potential biomarkers for predicting neoadjuvant immunotherapy efficacy

3.1 Tumor-associated immune cells and tertiary lymphoid structures

The unique advantage of neoadjuvant therapy compared with other advanced NSCLC treatments is that pre- and post-neoadjuvant immunotherapy tissue specimens can be obtained during the whole treatment cycle. The different types of tumor-infiltrating lymphocytes (TILs) in the TME can be used to predict the prognosis and response to immunotherapy (72). TILs, as part of tumor-associated immune cells, can be assessed in tumor tissues using immunohistochemistry or other high-plex multiplex immunofluorescence.

The NEOSTAR trial analyzed immune profiling of resected tumor tissues and found that $CD3^+$ TILs, $CD3^+CD8^+$ TILs, and $CD3^+CD8^+CD45RO^+$ memory TILs were significantly higher in tumors treated with nivolumab + ipilimumab than in those treated with monotherapy. However, these increases were irrespective of MPR (30). Immunologic analyses from the LCMC3 trial revealed that lower frequencies of $ILT2^+NKG2A^+$ and $ILT2^+NKG2A$ NK cells, and $ILT2^+$ NK-like T cells were strongly associated with MPR in NSCLC patients (73). The pCR patients from the NADIM trial had a higher percentage of $CD3^+$ $CD4^+$ $PD\text{-}1^+$ cells at diagnosis than non-pCR patients (74). The validity of this cell subset as a predictive marker had also been verified, with an area under the curve (AUC) of 0.728. Furthermore, patients with complete pathologic response (cPR) also had higher levels of NKG2D expression on $CD56^+$ T cells, CD25 expression on $CD4^+CD25hi^+$ cells, and CD69 expression on intermediate monocytes when compared to non-cPR patients (74). The above studies indicate that the different types of TILs could predict the response to neoadjuvant immunotherapy to some extent.

The TME not only plays an important role in TILs and mediates the initiation and progression of tumors but also participates in the aggregation of immune cells that developed in non-lymphoid tissues at the tumor site (75). These organized cellular aggregates, composed of B cells, T cells, dendritic cells, and high endothelial venules are called tertiary lymphoid structures (TLSs). Several studies have shown that the presence of TLSs is associated with favorable responses and prognosis to immunotherapy in most solid tumors including NSCLC (76, 77). Cottrell et al. assessed the specific immunologic features of TLS in NSCLC patients treated with neoadjuvant nivolumab using quantitative immune-related pathological response criteria and demonstrated that TLSs are important in the antitumor immune response in pCR and MPR patients (78). Large-scale studies are still needed to understand the complex relationship between immune cell profiles and patient outcomes.

3.2 T-cell receptor sequencing

TCR is a unique protein complex found on the surface of T cells that is responsible for recognizing fragments of antigens, including tumor neoantigens (79). Emerging evidence has indicated that TCR sequencing could be used as a dynamic biomarker of ICI response (80). Chemotherapy is the cornerstone of neoadjuvant immunotherapy. Chemo-agents have the great capability of tumor debulking and releasing neoantigens while killing cancer cells. The interplay between neoantigens and TCR plays a critical role in tumor-specific T cell-mediated antitumor immune response (81).

A trial of neoadjuvant administration of nivolumab monotherapy in patients with early-stage lung cancer revealed that MPR patients had a higher frequency of T-cell clones in both the tumor and peripheral blood than non-MPR patients (32). One patient's cPR neoantigen-specific T-cell clones rapidly increased in peripheral blood and were maintained for up to 4 weeks after treatment (32). In a study using samples obtained from the same clinical trial (NCT02259621), Caushi et al. found that some specific T-cell clonotypes for mutation-associated neoantigens (MANAs) were expanded and detected in MPR patients, suggesting that there were differences between MANA-specific TIL in ICI-responsive versus ICI-resistant NSCLC (82).

With the development of high-throughput sequencing technology, the TCR repertoire can be assessed through various features, including density, diversity, and clonality. In one exploratory analysis of the NADIM trial, next-generation TCR sequencing was performed using pre-treatment and post-treatment peripheral blood and tissues obtained from NSCLC patients (83). Baseline tissue TCR unevenness was associated with cPR to neoadjuvant chemo-immunotherapy. Moreover, compared with TPS (AUC of 0.767) and TMB (AUC of 0.550) as biomarkers, the top 1% clonal space of TCR achieved a higher diagnostic potential, with an AUC of 0.967, to identify cPR patients (83). The TCR repertoire showed good performance in predicting response to neoadjuvant immunotherapy. Further studies are warranted in larger cohorts to precisely identify specific TCR repertoire.

3.3 Circulating tumor DNA

CtDNAs are short DNA fragments released from tumors into peripheral blood and can be quantified in liquid biopsies to predict tumor recurrence (84). The detection and sequencing of ctDNA may reveal minimal residual disease (MRD) and identify NSCLC patients who are at high risk of recurrence (85–88).

One large-scale, multicenter prospective cohort study showed that ctDNA-MRD positivity was an independent risk factor for shortened recurrence-free survival in lung cancer surgery patients (89). The NADIM trial evaluated ctDNA levels before and after neoadjuvant treatment and found that patients with low ctDNA levels at baseline had significantly improved PFS and OS than those with high ctDNA levels; moreover, patients with undetectable ctDNA after treatment were significantly associated with long PFS and OS (35, 90). In CheckMate 816 trial, a higher percentage of patients showed ctDNA clearance with chemo-immunotherapy than with chemotherapy alone, and these patients had longer EFS than those without ctDNA clearance (29). Moreover, ctDNA is correlated with cPR (29). Although there are limited data on the predictive power of ctDNA for assessing neoadjuvant chemo-immunotherapy efficacy, several clinical trials have revealed that ctDNA is a potential biomarker for predicting patients' survival outcomes. Dynamic ctDNA monitoring may be useful for designing new clinical trials.

3.4 Gut microbiota

Gut microbiota is also one of the currently investigated biomarker objects, which can modulate the host immune system and maintain tissue homeostasis (91). Accumulating evidence seems to show the gut microbiota as a potential diagnostic tool to predict response or resistance to ICIs through its extensive influence on local and systemic immune systems (92). Gut microbiota has been assessed in the NEOSTAR trial using targeted 16S ribosomal RNA gene sequencing to explore the link between MPR status and the composition of gut microbiota. *Paraprevotella* and *Akkermansia* spp. were associated with MPR in neoadjuvant patients, and *Dialister* sp. was associated with a decrease in nivolumab toxicity (30). The gut microbiota can alter the efficacy and toxicity of ICI agents. Currently, the NADIM study and other trials are also exploring gut microbiota.

4 Cutting-edge progress in biomarker exploration

4.1 Multi-omics

With the rapid development of omic methods (genomics, proteomics, transcriptomics, metabolomics), massive omics data have become available for clinical analysis (93). Rich et al. described a blood-based host immune classifier (HIC) proteomic testing to classify NSCLC patients. HIC classification could predict survival with ICI-based therapy and select NSCLC patients who were responding to immunotherapy (94). Zhang et al. integrated multi-omics analysis in one NSCLC patient after neoadjuvant immunotherapy and revealed that specific genomic phenotypes and lower immunogenicity were attributed to an inferior immunotherapy efficacy (95). Different omics or diverse genomic phenotypes could be influenced by each other. Some unique homologous recombination deficiency events in combination with TMB, TME, or various intratumor heterogeneity ultimately influence the therapeutic outcomes of neoadjuvant immunotherapy in NSCLC patients (96). Multi-omics data can identify different molecular subtypes associated with different prognoses in NSCLC patients treated with ICIs (97). There is still a lack of research and clinical trials to standardize the acquisition of and analysis tools for omics data in neoadjuvant immunotherapy. Further, neoadjuvant-related studies should investigate the potential applications of omics tools in chemo-immunotherapy.

4.2 Image features

Tumor computational imaging can extract a wealth of information about the entire tumor burden, cancer lesion, and para-carcinoma tissues, which may reflect immune response in NSCLC. Khorrami et al. developed a unique feature set called delta-radiomic analysis (DelRADx), which identified the changes in the radiomic texture of CT patterns from the intra- and peri-tumoral regions before and after immunotherapy. Using DelRADx features, the model achieved an AUC of 0.88 in distinguishing responders from non-responder to immunotherapy and was also associated with OS in NSCLC (98). Yang et al. utilized PET-CT to investigate the correlation between radiological, metabolic (^{18}F-FDG), and pathological responses in lung cancer patients who underwent neoadjuvant immunotherapy plus surgery (99). The ^{18}F-FDG-reflected metabolic activity revealed the presence of invaded tumor-draining lymph nodes (TDLNs) that are associated with poor pathological responses. Their work showed the potential utility of PET-CT in predicting the pathological response to ICIs (99). Recently, with the help of machine learning algorithms, computational imaging has achieved impressive successes in stratifying and quantifying the radiomic features of NSCLC. As will be detailed in the following sections, machine learning algorithms show powerful prediction performance.

4.3 Machine learning

Machine learning (ML) is a branch of artificial intelligence (AI) involving algorithms that can be trained to make predictions by analyzing data. Although there is a lack of prospective studies on the application of ML in predicting neoadjuvant efficacy, some studies have made impressive attempts to build prediction models by combining machine learning and various data.

AI algorithms can automatically quantify radiographic characteristics from CT data of NSCLC patients. AI-based characterization of lung cancer lesions can be used as non-

invasive radiomic biomarkers, which had a good predictive ability for predicting good immunotherapy response in advanced NSCLC patients receiving immunotherapy and could also predict OS with an AUC of up to 0.76 (100). Yoo et al. constructed a high-performance ML model with AUC over 0.97 from ^{18}F-FDG PET-CT radiomics features to predict pCR after neoadjuvant chemo-immunotherapy in NSCLC (101). The accuracy of the prediction using the ML model was significantly higher than that derived using conventional image features (101, 102).

Several types of omics data, such as RNA expression levels, immune-related gene panels, and immune-related biomarkers, from peripheral blood samples or tumor tissues of NSCLC patients treated with ICIs, could be combined with bioinformatics and ML techniques to improve the predictive performance of the model (103, 104). ML has also been applied in some clinical trials. In exploratory analyses of the LCMC3 trial, more than 100 pre-treatment blood samples were used to construct a predictive model for MPR by evaluating immune cell subsets. The final multiparametric model was significantly correlated with MPR with an AUC in the test set of 0.726 (28). Wu et al. integrated data from eight atezolizumab clinical trials to construct a mortality prediction model using different ML algorithms (105). The results showed that random forest (RF) with an AUC of 0.844 reached the highest performance in prediction tasks. Similarly, Benzekry et al. found that RF (AUC of 0.74) was the best ML model to predict disease control rate using NSCLC patients' simple clinical and hematological data (106). ML algorithms are good at handling non-linear problems and massive calculations. Prelaj et al. integrated real-world data and the blood microRNA signature classifier to develop a new predictive model of ICI response in NSCLC (107). Vanguri et al. developed a dynamic deep attention-based multiple-instance learning model with masking (DyAM) using a cohort of 247 NSCLC patients with multimodal data including radiological, histopathologic, and genomic features and known outcomes to immunotherapy (108). However, these high-volume data did not help much in performance boosting. The AUC value of these ML-based models was between 0.8 and 0.87.

5 Discussion

Neoadjuvant immunotherapy has gradually become a mainstay in the treatment of NSCLC. The promising results of neoadjuvant immunotherapy in resectable NSCLC have been confirmed by several prospective randomized controlled trials. While some patients respond to chemo-immunotherapy, a considerable proportion of NSCLC populations fail to benefit from it. It seems all the more necessary today to discover and develop reliable biomarkers for efficacy prediction when chemo-immunotherapy seems to achieve population-wide treating coverage irrespective of PD-L1 expression.

Based on previous and ongoing clinical trials, we summarized the biomarkers that benefit the prediction of neoadjuvant immunotherapy efficacy and highlight the potential biomarkers for efficacy prediction; we envision the cutting-edge progress made in improving the performance of biomarker-related models (Figure 1). These advances in biomarker-directed therapy have led to improvements in OS.

The accuracy of tumor-intrinsic biomarkers such as PD-L1 and TMB has decreased with the addition of chemotherapeutic regimens in NSCLC neoadjuvant immunotherapy that are mutagenic and may thus induce a higher TMB score. The cutoff for TMB evaluation to select NSCLC patients for treatment with ICIs is still currently controversial and may be due to differences in tumor biology and the microenvironment. It is still not routinely used in clinical practice due to the poor reproducibility of TMB results. Therefore, different clinical trials gave different cutoff TMB values (28, 31, 35). PD-L1 is key in immunotherapy, while various posttranslational modifications of PD-L1 protein may affect clinical detection and treatment efficacy. Lee et al. found that heavy glycosylation of PD-L1 could lead to false-negative readouts in clinical bioassays, and deglycosylated PD-L1 is a more reliable biomarker to guide immunotherapy (109). With the widespread application of immunotherapy, the bioassays of tumor-intrinsic biomarkers should also be revolutionized.

With the continuous development of immunofluorescence, flow cytometry, and next-generation sequencing technology, new kinds of potential biomarkers such as TILs, TLS, TCR, or ctDNA are being recognized. Nevertheless, it is difficult to standardize a cutoff for those biomarkers. There is a drift between statistical findings and clinical applications due to the lack of prospective validation studies. Further clinical trials should incorporate AUC, C-index, and calibration to validate the predictive efficacy of these biomarkers. The cost of bioassays is equally of concern. Enrolling high-volume multi-omics data and modifying ML algorithms can improve the performance of prediction tasks. Most data are obtained from retrospective studies, and further studies should consider randomized clinical trials, prospective cohorts, or real-world data for inclusion.

First-line neoadjuvant chemo-immunotherapy is starting to and will revolutionize the current paradigm of resectable NSCLC treatment. Identifying biomarkers for chemotherapy or immunity may be more difficult in combination models. The interaction and crosstalk within chemo-agents and ICIs make it more variable to explore. The advantage of exploring biomarkers under neoadjuvant therapy is that it can better combine the association between dynamic biomarkers in pre- and post-treatment and patient outcomes. Selecting pCR patients or long-term survival patients to further analyze the key factors benefitting them seems promising to explore. It may be beneficial to identify key biomarkers backward to better stratify patients receiving neoadjuvant immunotherapy.

Biological processes are dynamically altered depending on tumor burden and treatment. Tumor-associated immune cells, TME, or tumor neoantigens might change rapidly with tumor debulking under chemo-immunotherapy. Thus, dynamic biomarkers could be used to escalate or de-escalate preoperative

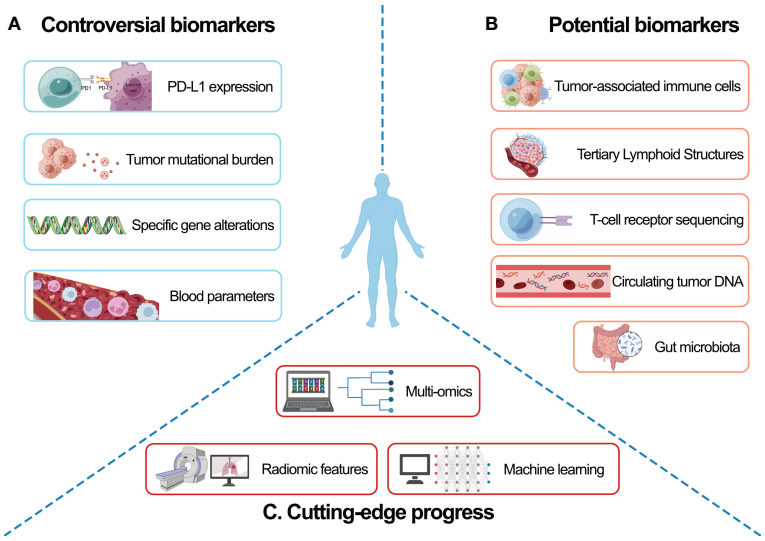

FIGURE 1
Summary of biomarkers for predicting neoadjuvant immunotherapy efficacy in NSCLC. Biomarkers were grouped by predictive ability: **(A)** controversial biomarkers, **(B)** potential biomarkers, and **(C)** cutting-edge progress in biomarker exploration. Graph drawing created with BioRender.com and Figdraw (https://www.figdraw.com/static/index.html, access date 14 Jan 2023). NSCLC, non-small cell lung cancer.

therapeutic strategies. The development and validation of dynamic and easy-monitored biomarkers are less explored. A composite biomarker incorporating multiple other variables may be a novel direction for future research.

Author contributions

Conception and design: YW, SH, and ZH. Administrative support: ZZ and ZH. Collection and assembly of reference: XF, WX, RL, and QZ. Graph drawing: YW and SH. Manuscript writing: all authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pathological complete response to long-course neoadjuvant alectinib in lung adenocarcinoma with EML4-ALK rearrangement: report of two cases and systematic review of case reports

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Objective: Despite the promising efficacy and tolerability of alectinib in treating advanced anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC), the role of alectinib in neoadjuvant setting remains understudied in ALK-rearranged resectable lung cancer.

Methods: Our report concerns two cases of early-stage NSCLC with complete pathologic responses to off-label use of long-course neoadjuvant alectinib. PubMed, Web of Science, and Cochrane Library were searched comprehensively for ALK-positive resectable cases with neoadjuvant alectinib. The papers were chosen following PRISMA recommendations. Seven cases from the literature and two present cases were evaluated.

Results: Two cases with stage IIB (cT3N0M0) EML4-ALK lung adenocarcinoma received long-course (more than 30 weeks) of neoadjuvant alectinib followed by R0 lobectomy with the complete pathological response. In our systematic review, 74 studies were included in the original search. Application of the screening criteria resulted in 18 articles deemed eligible for full-text reading. Following the application of the exclusion criteria, out of six papers, seven cases were selected for inclusion in the final analysis and were included in the systematic review. None of the studies were included in the quantitative analysis.

Conclusion: We report two cases of lung adenocarcinoma with resectable ALK-positive that achieved pCR with long-course neoadjuvant alectinib. Our cases and a systematic review of the literature support the feasibility of neoadjuvant alectinib treatment for NSCLC. However, large clinical trials must be conducted in the future to determine the treatment course and efficacy of the neoadjuvant alectinib modality.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO, identifier CRD42022376804.

KEYWORDS

lung adenocarcinoma, ALK rearrangement, neoadjuvant therapy, alectinib, pathological complete response

Introduction

Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangement, also known as the ALK-positive variant, is one of the significant driver mutations in non-small-cell lung cancer (NSCLC) and accounts for about 5% of NSCLC (1–3). This alteration leads to the uncontrolled growth and spread of the tumor cells, which is a crucial reason why ALK-positive NSCLC is more aggressive and resistant to traditional chemotherapy treatment than NSCLC without this alteration (4). In addition, ALK rearrangements are found more often in younger never smokers and in people with adenocarcinoma, the most common pathological type of NSCLC (4, 5).

We are fortunate that there have been advances in ALK tyrosine kinase inhibitor (ALK-TKI) targeted therapies for ALK-positive lung cancer over the last decade. Now, various drugs can be used for first-line treatment options in advanced lung cancer with ALK rearrangement, from the initial generation of crizotinib to the second generation of ceritinib, alectinib, and brigatinib, to the third generation of lorlatinib (6–10).

Previous studies suggest that in resectable non-small cell lung cancer, neoadjuvant chemotherapy, radiotherapy, immunotherapy, and combination therapy play an important role. Early meta-analysis suggests that neoadjuvant chemotherapy can lead to an absolute survival improvement of 5% at five years, from 40% to 45% in stage I-III resectable cases (11). In addition, the newly published CheckMate 816 study suggests that neoadjuvant chemotherapy in combination with nivolumab compared with chemotherapy alone can further improve the pathological complete response (pCR) and event-free survival (EFS) in the stage IB (≥4 cm) to IIIA resectable NSCLC patients, according to the seventh edition staging criteria of the American Joint Committee on Cancer(AJCC) (12). Based on the available evidence (12, 13), in the current eighth edition staging system of the AJCC, stage IIA-IIIA resectable NSCLC patients without EGFR mutations or ALK fusions are the target population for neoadjuvant chemotherapy in combination with immunotherapy.

For resectable NSCLC with a specific oncogenic driver positive, the published neoadjuvant study focused mainly on the epidermal growth factor receptor (EGFR) pathway. The early randomized phase 2 study of CTONG1103 showed that neoadjuvant erlotinib is more effective than neoadjuvant chemotherapy in EGFR-positive patients with stage IIIA-N2 NSCLC (14). According to previous studies, ALK-rearranged lung cancer patients have similar or worse survival outcomes than EGFR-mutated patients (15, 16). In advanced lung cancer, similar to EGFR tyrosine kinase inhibitor (EGFR-TKI) for EGFR-mutated patients, ALK-TKI has a higher objective response rate (ORR) and longer progression-free survival (PFS) for ALK-rearranged patients compared to traditional chemotherapy (6, 7), so neoadjuvant therapy for ALK-positive patients also worth exploring. However, previous neoadjuvant treatments for ALK-positive patients have mostly been clinical studies or case reports in small samples (17, 18). The ongoing phase II ALNEO trial assesses the activity of oral 8-week neoadjuvant alectinib in potentially resectable stage III ALK-positive NSCLC (any T stage with N2 or T4N0-1) (19). The other ongoing NAUTIKA1 study is a multiple cohorts perioperative trial in patients with resectable stage II-III NSCLC, which investigates neoadjuvant and adjuvant alectinib in the ALK-positive cohort (20).

Alectinib is a highly selective ALK inhibitor currently used as the front-line or second-line treatment for advanced ALK-positive NSCLC (6, 21). However, alectinib's activity as neoadjuvant therapy in resectable ALK-positive NSCLC has yet to be investigated despite promising efficacy and tolerability in treating advanced ALK-positive NSCLC.

Although several previous studies have reported cases receiving neoadjuvant treatment with alectinib (19, 22), given that there are no published results of strictly designed and implemented large trials of patients with neoadjuvant alectinib, the preoperative regimens and treatment timing of alectinib have not been well studied. Furthermore, no case has been reported or studied regarding long courses of neoadjuvant alectinib therapy. Herein, firstly, we report two cases of resectable ALK-positive lung adenocarcinoma receiving more than six months of alectinib as neoadjuvant therapy followed by radical surgical resection to achieve pathological complete responses. Subsequently, we systematically reviewed previously reported cases of neoadjuvant treatment with alectinib.

Case presentation

Case one

A 51-year-old male heavy-smoker patient presented to our hospital in July 2021 with chest pain for two months. In contrast-enhanced computerized tomography (CT) of the chest, a mass of approximately 53 mm in length was found in the left lower lobe, along with an isolated nodule of 6 mm in the same lung lobe (Figure 1). Serum oncological marker results showed an elevated level of carcinoembryonic antigen (CEA, 8.96 ng/ml, reference value <6 ng/ml). Fiberoptic bronchoscopy showed no significant abnormalities. The patient had a CT-guided percutaneous lung biopsy and was diagnosed with pulmonary adenocarcinoma (Figure 2). Immunohistochemical testing results (D5F3 assay, Ventana-Roche Diagnostics, Mannheim, Germany) confirmed

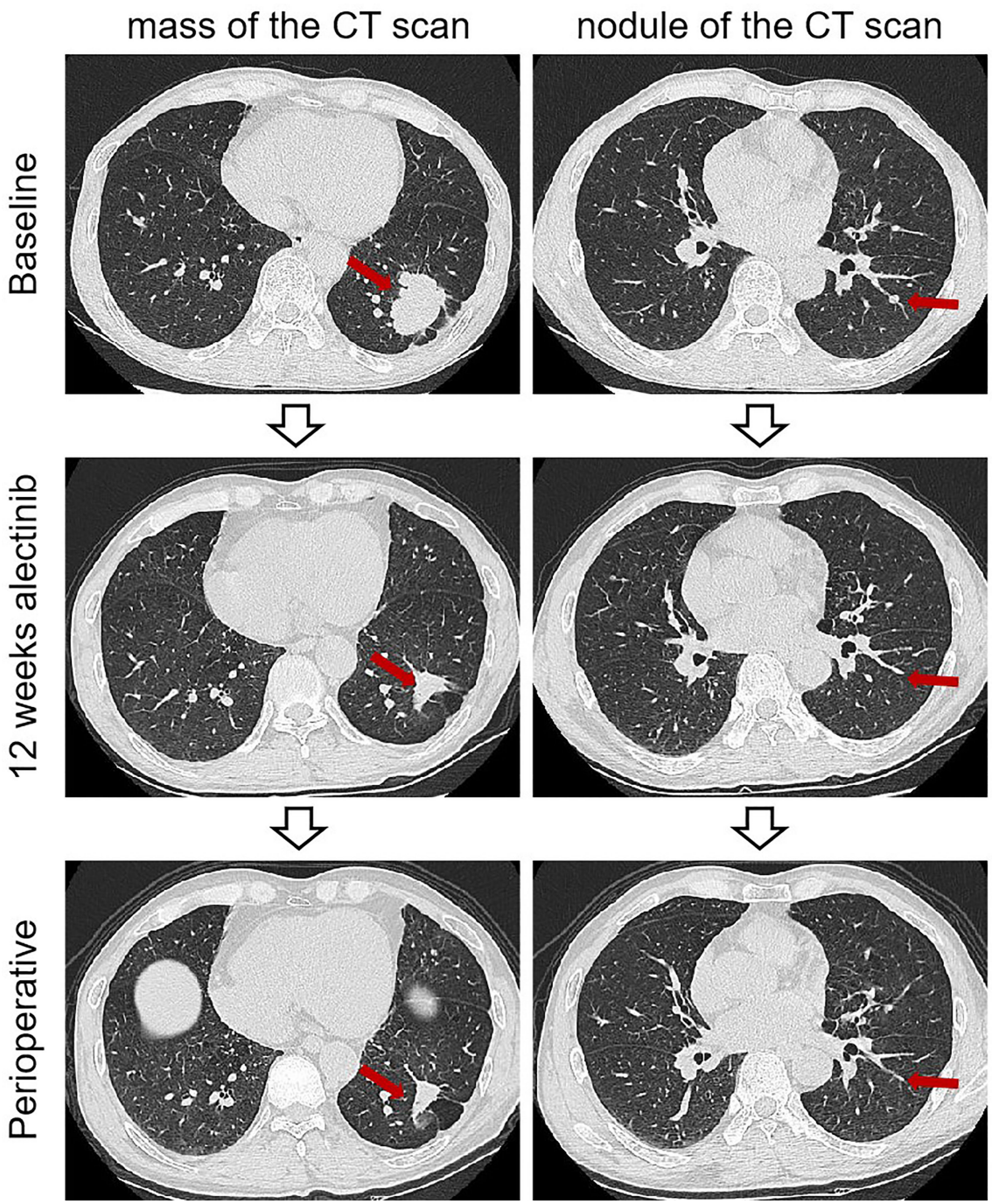

FIGURE 1
Imaging findings of case 1. The computed tomography scan of before and after neoadjuvant alectinib. CT, computed tomography.

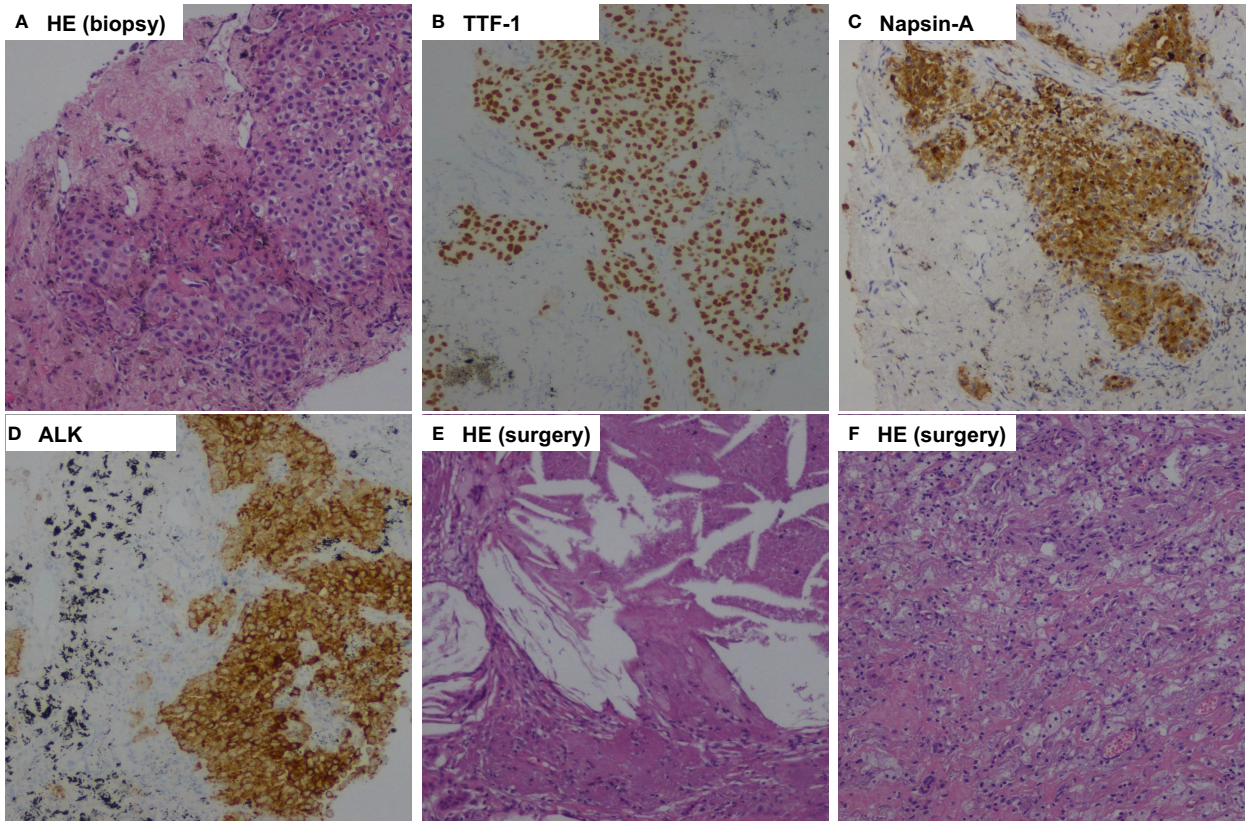

FIGURE 2
Pathologic findings of case 1. **(A)**, Percutaneous lung biopsy of the mass before treatment showed pulmonary adenocarcinoma (Hematoxylin-eosin, HE, 100x); **(B)**, Tumor cells positive by immunohistochemistry for TTF-1 (100x); **(C)**, Tumor cells positive by immunohistochemistry for Napsin-A (100x); **(D)**, Immunohistochemical testing results (D5F3 assay) confirmed strong positivity of ALK (100x); **(E, F)**, Postoperative pathology examination showed pathological complete response to neoadjuvant alectinib with no residual viable tumor cell. (HE, 100x).

anaplastic lymphoma kinase (ALK) positivity (Figure 2). In addition, Echinoderm microtubule-associated protein-like 4 (exon 13)-ALK (exon 20) fusion (variant 1) was detected in tumor specimen with a 60-gene panel next-generation sequencing. A whole-body bone scan, contrast-enhanced magnetic resonance imaging (MRI) scan of the head, and CT scan of the abdomen were performed to rule out distant metastases.

The patient was recommended to receive neoadjuvant alectinib therapy followed by surgical resection after a multidisciplinary discussion. Alectinib was given at 600 mg twice daily for three cycles (12 weeks) from July 15, 2021. Imaging evaluation of the efficacy showed a partial response, the patient was advised to consider receiving surgical treatment, but the patient refused surgery, continued with oral alectinib treatment, and the patient's mass continued to shrink. After 30 weeks of therapy, A CT scan was performed to assess the efficacy of neoadjuvant therapy. A partial response was achieved after neoadjuvant therapy, with 66% shrinkage of the mass (18 mm×15 mm), and the solitary nodule in the left lower lobe disappeared (Figure 1). Repeated serial serum CEA results showed that CEA gradually declined. Only grade 1 anemia was observed during the neoadjuvant therapy. A lobectomy of the left lower lobe and systemic lymphadectomy under a video-assisted thoracoscopic approach was successfully performed on March 1, 2022. During the surgical procedure, mild tissue adhesions were found, and no significant hilar fibrosis or significant adhesions of lymph nodes were detected. The duration of the surgery was 153 minutes, with 100 ml of intraoperative bleeding without blood transfusion. The thoracic drain was removed on postoperative day 5. The patient was discharged on postoperative day 10. Postoperative pathology shows chronic inflammation of lung tissue, more histiocytic infiltration, multinucleated giant cell reaction, and cholesterol crystals. As per IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy (23), the components of the primary tumor bed are 0% viable tumor, 10% necrosis, and 90% stroma, consistent with pCR (Figure 2). In addition, no metastatic carcinoma was seen in any lymph nodes resected in stations 4L, 5L, 7, 8, 10L, and 11L (a total of 9 lymph nodes). Postoperative pathological TNM stage down to ypT0N0M0. He continued to receive alectinib after discharge and did not report any specific discomfort at the 13-month follow-up (until April 2023). The CT scan showed the cancer had not returned at the last follow-up after the surgery. The repeated examination of the patient's CEA levels showed they were all within the normal range.

Case two

A 48-year-old man with no smoking history was referred to the hospital with an asymptomatic mass in the middle lobe of the right lung. An enhanced computed tomography scan revealed a large mass with a diameter of 58 mm and an additional nodule (5 mm) on the right interlobar pleural in the same lobe (Figure 3). Bronchoscopy showed a neoplasm obstructed the medial segment of the right middle lobe bronchus (Figure 3). Bronchoscopic biopsy pathology suggested lung adenocarcinoma, containing an acinar subtype component. Tumor cells were positive by immunohistochemistry for TTF-1 and Napsin-A (Figure 4). ALK fusion status was positive by immunohistochemistry with a monoclonal antibody (D5F3, Ventana-Roche Diagnostics, Mannheim, Germany) and next-generation sequencing with a 60-gene panel (Novogene Bioinformatics Technology, Beijing, China). NGS disclosed an ALK rearrangement with EML4-ALK fusion (variant 3). After a detailed staging examination, which included brain contrast-enhanced MRI, whole-body bone imaging, and contrast-enhanced CT of the chest and abdomen, no distant metastases were found.

After multi-disciplinary team consultation and acquiring informed consent from the patient, the patient began to receive treatment with neoadjuvant alectinib at 600 mg twice daily. After eight weeks of treatment with alectinib, this patient was evaluated as having a partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

After 32 weeks of alectinib treatment, a re-evaluation showed a 70% reduction of the tumor in the right middle lobe, with no pleural nodules detected (Figure 3). Moreover, the patient tolerated well and only experienced grade 1 elevated aminotransferase. An R0 right middle lobectomy and systemic lymphadenectomy under a video-assisted thoracoscopic approach were performed one week after the last dose of alectinib. During surgery, moderate tissue adhesions were found during the separation of vessels and bronchi. Postoperative pathology shows chronic inflammation of resected lung tissue, fibrous tissue hyperplasia, infiltration of multinucleated

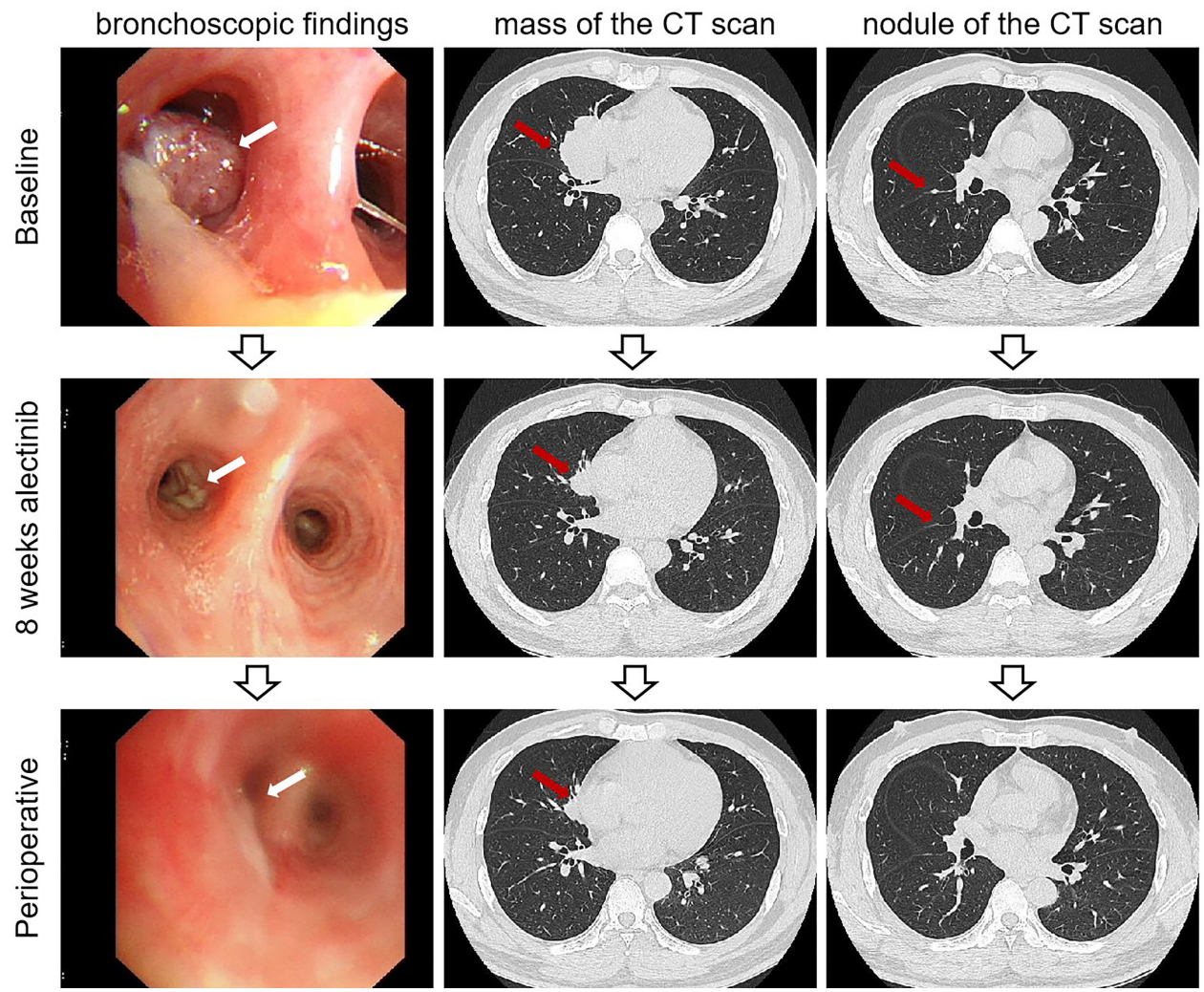

FIGURE 3
Imaging findings of case 2. The bronchoscopic findings and computed tomography scan of baseline and after neoadjuvant alectinib. CT, computed tomography.

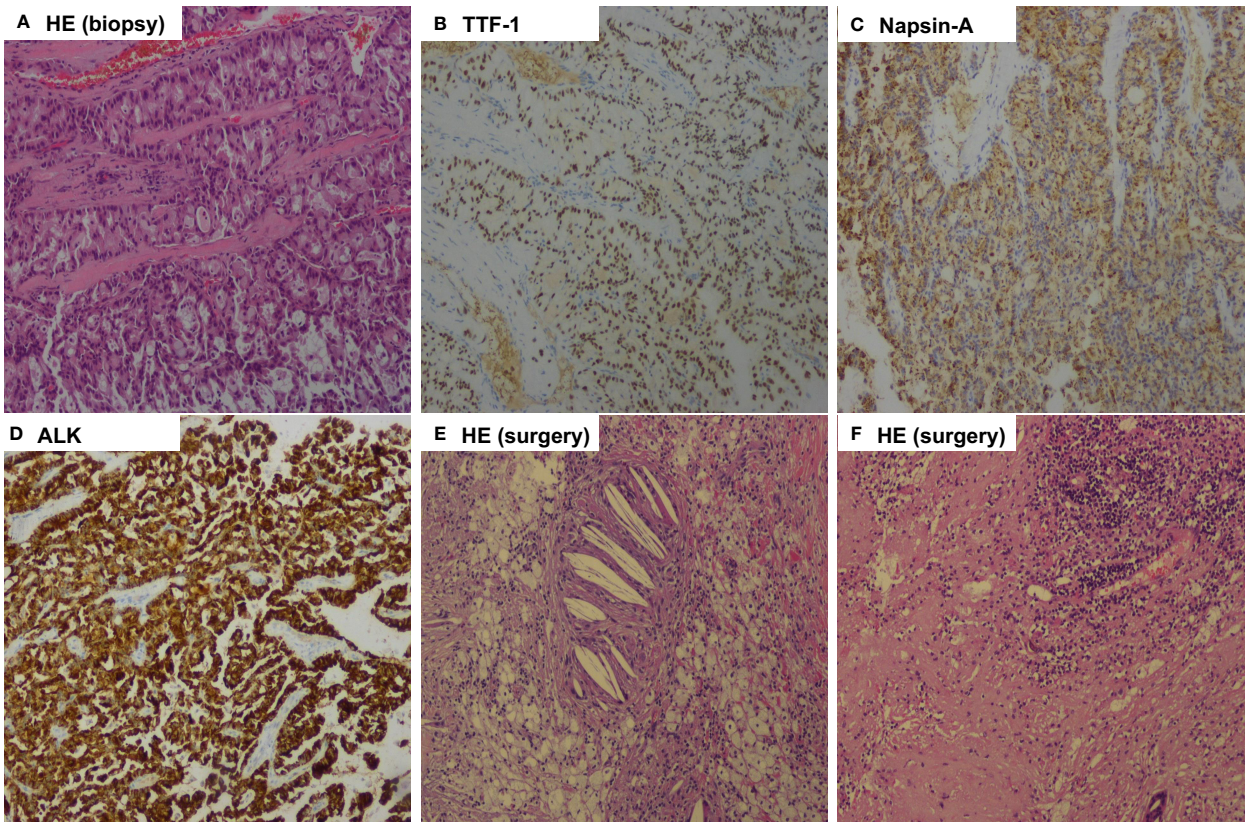

FIGURE 4
Pathologic findings of case 2. **(A)**, Bronchoscopic biopsy of the mass before treatment showed pulmonary adenocarcinoma (Hematoxylin-eosin, HE, 100x); **(B)**, Tumor cells positive by immunohistochemistry for TTF-1 (100x); **(C)**, Tumor cells positive by immunohistochemistry for Napsin-A (100x); **(D)**, Immunohistochemical testing results (D5F3 assay) confirmed strong positivity of ALK (100x); **(E, F)**, Postoperative pathology examination showed pathological complete response to neoadjuvant alectinib with no residual viable tumor cell. (HE, 100x).

giant cells, lymphocytes, and more foam cells, necrosis, and cholesterol crystals. Per IASLC 2020 methodology (23), the components of the primary tumor bed are 0% viable tumor, 25% necrosis, and 75% stroma. No metastatic carcinoma was found in the lymph nodes resected in stations 2R, 4R, 7R, 8R, 10R, 11R, 12R, and 13R (a total of 18 lymph nodes). In addition, the pathology of the resected nodule on the right interlobar pleural in the right middle lobe suggests chronic inflammation of fibrous connective tissue. Postoperative histologic examination demonstrated a complete pathological response (Figure 4). The patient was recommended to take alectinib for two more years after surgery and did not experience a recurrence during the twelve months of follow-up (until April 2023).

Materials and methods

Protocol and registration

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (Table S1 in Supplementary Materials) (24). In addition, this systematic review protocol was registered with the international prospective register of systematic reviews (PROSPERO) online database (PROSPERO Identifier: CRD42022376804).

Search strategy

We established our search strategy in PubMed by leveraging Medical Subject Headings (MeSH) terms for case reports and case series study types involving neoadjuvant alectinib in lung adenocarcinoma with EML4-ALK rearrangement. The generated search strategy was then transferred to the Web of Science and Cochrane Library using a Polyglot translator (25). The last search ran on 18th October 2022. The Supplementary Materials provide a detailed description of each database's search methodology.

Eligibility criteria

We included case reports, case series, or letters that met all of the following criteria (1): cases with NSCLC, (2) with confirmed presence of EML4-ALK rearrangement, (3) with neoadjuvant alectinib treatment, (4) with pathological response outcome. There were no patient demographics or language restrictions, and no publication date restrictions were placed on the included studies.

Study screening and selection

Titles and abstracts were screened for the records obtained during the literature search. Two reviewers (LS and SH-G) separately screened titles and abstracts, and consensus settled discrepancies. After that, the full texts of eligible papers were retrieved and independently double-screened, with any discrepancies being forwarded to a third reviewer (ZL).

Data extraction

The following information was extracted from the included articles: age of the reported case, gender, smoking status, symptoms, baseline cTNM stage, EML4-ALK variant status, neoadjuvant treatment course, radiologic response, pathologic response, and adverse effects. All of the identified studies were listed by the authors, as well as the year of publication. Data extracted from each study was conducted by two reviewers independently (LS and SH-G), with any inconsistencies referred to a third reviewer (ZL). The data was summarized and compiled into an online Excel spreadsheet for the authors to access.

Quality of studies

Case reports are biased by their nature. However, standardized techniques have been developed to evaluate the methodological quality of case reports. We utilized the Newcastle-Ottawa Scale (NOS), as modified by Murad et al., to rate the quality of the case series and reports included in the study (26). This tool evaluates the four domains of selection, ascertainment, causality, and reporting using a set of 8 questions. The tool's questions 4, 5, and 6 were omitted since they primarily apply to the kind of adverse medication events listed therein and have no bearing on our subject (26). The remaining five questions' total scores were used to categorize the remaining articles' bias risks as "high risk," "medium risk," or "low risk." We deemed case reports or case series to have a low risk of bias if they received 4 or 5 points on the quality evaluation questions. A score of 3 indicated a medium risk of bias in an article, whereas a score of less than 3 indicated a high risk of bias.

Data analysis

Each article's data included in our systematic review was retrieved, compiled, and shown in a table. The cases were then described narratively in the text to combine and highlight the similarities and differences between them and to draw conclusions finally. We used descriptive statistics to summarize demographics and clinical characteristics due to the descriptive nature of this systematic review and the small number of cases. Continuous variables were reported using means, while dichotomous variables were reported using frequencies and percentages.

We used descriptive statistics to summarize demographics and clinical features due to the descriptive nature of this systematic review and the small number of cases. Continuous variables were reported using means or median, while dichotomous variables were reported using frequencies and percentages.

Results

Study selection

A PRISMA flow diagram that depicts the study selection procedure is shown in Figure 5. First, 74 manuscripts were identified: 26 from PubMed, 38 from the Web of Science, and ten from Cochrane Library. After removing any papers that were duplicates, 49 papers remained. Of those, 31 were excluded after the title and abstract screening, leaving 18 studies for full-text screening. Next, we obtained the full text for all 18 records and screened them for eligibility. After excluding twelve articles for the reasons shown in Figure 5, we were left with six manuscripts, including seven cases, which we analyzed (19, 22, 27–30).

Study and clinical characteristics of patients with neoadjuvant alectinib treatment

A summary of the characteristics is presented in Table 1. Of the seven previously reported cases treated with neoadjuvant alectinib, four cases were non-smokers, and three cases were former smokers. In addition, five patients were clinically staged as stage cIIIA, and two were clinically staged as stage cIIIB. Regarding the length of neoadjuvant alectinib treatment, two patients were treated for six weeks, three for eight weeks, and two for 12 weeks, with a mean of 8.6 weeks. After neoadjuvant targeted therapy, the best imaging outcome was PR in six cases, and CR was achieved in one case.

All patients underwent lobectomy combined with mediastinal lymph node dissection and had R0 resection. Postoperative pathological results suggested pCR in 2 cases (28.6%), major pathological response (MPR) in 3 cases (42.9%), and non-MPR in 2 cases (28.6%).

We could not do a quantitative meta-analysis due to the case report or case series nature of the studies on this subject.

Quality assessment

The quality of case reports and case series were assessed using Murad et al.'s standardized tool. According to the risk of bias score and classification rules mentioned above, five cases were scored 5, two cases were scored 4, and all cases were evaluated as low-risk of bias. A detailed quality assessment for each case is available in Table S2 of the Supplementary Materials.

Discussion

Main findings

Our case report is the first to document a long-course of neoadjuvant alectinib treatment. Two patients with ALK-positive

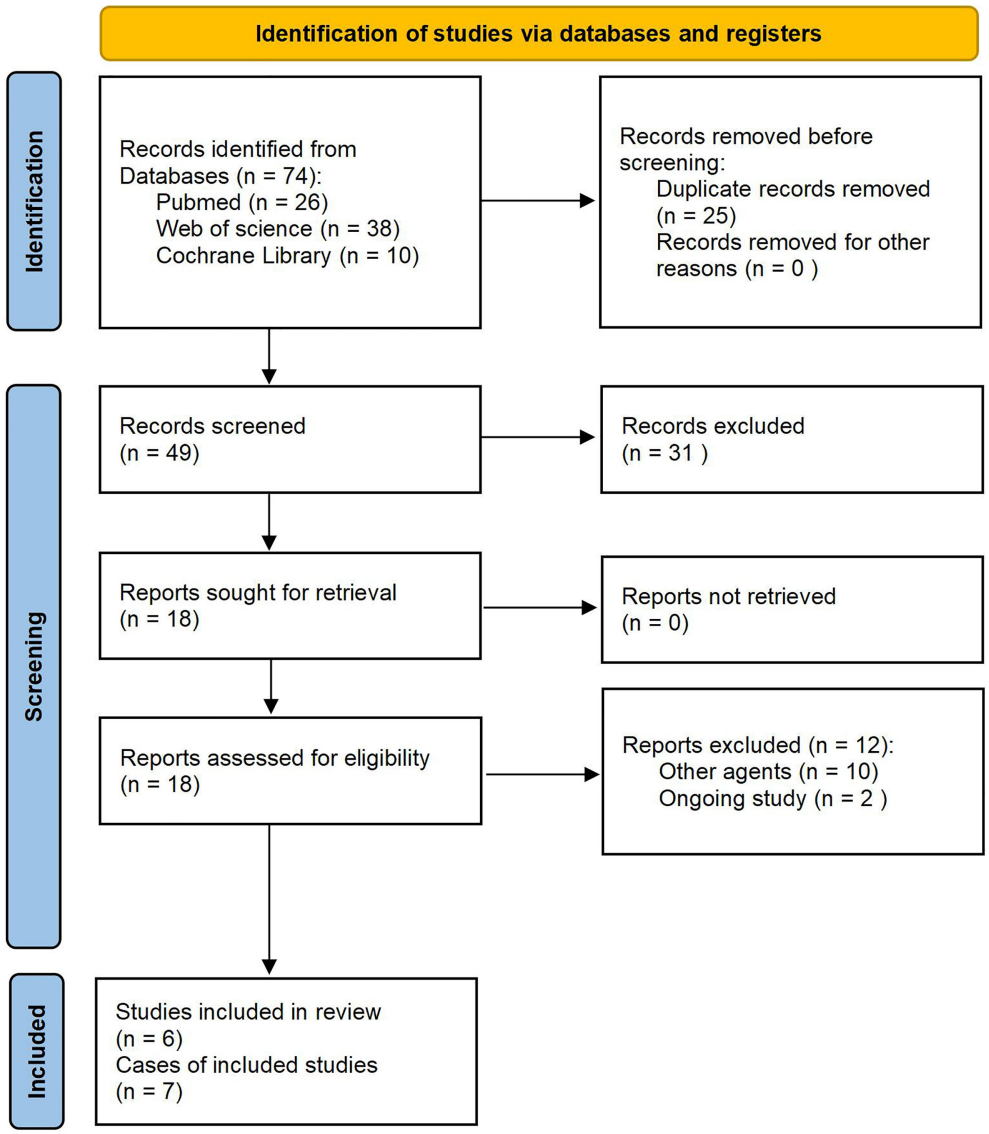

FIGURE 5
PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

stage IIB NSCLC received more than six months of induction alectinib treatment and then had surgery for R0 resection after imaging evaluation showed the best shrinkage. Pathological evaluation after surgery showed that the treatment achieved pCR. In addition, there were no severe treatment-related adverse reactions (TRAEs) or severe perioperative adverse events. The patient had oral alectinib as postoperative adjuvant therapy, and follow-up showed no recurrence or metastasis.

Based on the case reports we have presented, we have conducted a systematic review of seven cases from six studies, including cases with neoadjuvant alectinib. In our systematic review, all patients with stage IIIA-IIIB NSCLC treated with a short-course of preoperative alectinib (6-12 weeks) had a postoperative pathological evaluation. Two patients had pCR, three had MPR, and two had non-MPR. There were no reported severe TRAEs. Compared with previous cases, our reported cases of long-course neoadjuvant alectinib had similar therapeutic safety and surgical feasibility. In addition, the pathological response evaluation of our reported cases reached pCR after surgery, which may bring long-term survival benefits to patients.

Current topics in practice

One of the most critical questions is what kind of patient should receive neoadjuvant targeted therapy for ALK-positive NSCLC. In addition, the choice of therapeutic drugs and treatment cycles is another critical question.

The first neoadjuvant treatment exploration of ALK-TKI was a small sample of retrospective studies of crizotinib. In the study, all

TABLE 1 Summary of reported cases receiving neoadjuvant alectinib therapy in ALK-positive lung adenocarcinoma.

Case	Author	Age (year)/ Gender	Smoking status	Symptoms	Location	Baseline cTNM	EML4-ALK variant	Alectinib dosage	Treatment course	Radiologic response	Extent of resection	Pathologic response	Adverse effects	Adjuvant treatment	Follow-up
1	Zhang et al.	46/Male	None	Cough and hemoptysis	Left lower lobe	cIIIb (cT3N2M0)	variant 3	600 mg BID	8 weeks	PR	Lobectomy	non-MPR	Grade 1 constipation	NA	NA
2	Yue et al.	51/Male	Former	Asymptomatic	Right upper lobe	cIIIa (cT2N2M0)	NA	600 mg BID	6 weeks	PR	Lobectomy	non-MPR	None	Alectinib, PORT	6 months without Recurrence
3	Leonetti et al.	62/Male	None	NA	Left upper lobe	cIIIa (cT2aN2M0)	NA	600 mg BID	8 weeks	PR	Lobectomy	MPR	None	Alectinib	NA
4	Gu et al.	67/Male	None	Hoarseness	Left upper lobe	cIIIb (cT4N2M0)	NA	150 mg BID	12 weeks	CR	Lobectomy	MPR	None	NA	NA
5	Hu et al.	58/ Female	None	Hemoptysis	Right lower lobe	cIIIa (cT2bN2M0)	NA	600 mg BID	8 weeks	PR	Bilobectomy	pCR	Grade 1 constipation Grade 1 erythema	Alectinib	8 months without Recurrence
6	Sentana-Lledo et al.	61/NA	Former	Asymptomatic	Left lingular lobe	cIIIa (cT1bN2M0)	variant 3	600 mg BID	6 weeks	PR	Lobectomy	pCR	NA	Alectinib	3 months without Recurrence
7	Sentana-Lledo et al.	65/NA	Former	Asymptomatic	right middle lobe	cIIIa (cT3N2M0)	variant 2	600 mg→450mg BID	12 weeks	PR	Lobectomy	MPR	Transaminases increased	Without	recurrence at 12 months mark
8	Present case 1	51/Male	Former	Chest pain	Left lower lobe	cIIb (cT3N0M0)	variant 1	600 mg BID	30 weeks	PR	Lobectomy	pCR	Grade 1 anemia	Alectinib	13 months without Recurrence
9	Present case 2	48/Male	Former	Asymptomatic	right middle lobe	cIIb (cT3N0M0)	variant 3	600 mg BID	32 weeks	PR	Lobectomy	pCR	Grade 1 transaminases increased	Alectinib	12 months without Recurrence

EML4-ALK, echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase; PR, partial response; CR, complete remission; MPR, major pathological response; pCR, pathological complete response; NA, not available; PORT, postoperative radiotherapy.

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11 patients were cases with N2 (stage IIIA or IIIB) who received crizotinib for 28-120 days before surgery. The study found that 10 out of 11 patients (91.0%) had a partial response, while one had a stable disease. Additionally, two patients (18.2%) achieved pCR (17).

With the iterations of ALK-TKI, from first-generation to third-generation drugs, we also have more available TKIs for neoadjuvant strategy against the ALK pathway. More stringent requirements are necessary for choosing drugs with higher objective response rates (ORR), remission depth, and better safety for neoadjuvant therapy, with the purpose of the neoadjuvant therapy per se. The SAKULA study showed the clinical benefit of ceritinib for neoadjuvant therapy. The study included seven patients with ALK-positive stage II-III NSCLC who received two cycles (28 days per cycle) of ceritinib induction therapy followed by surgery, with a 57% MPR and 2 cases achieving pCR (29%). However, it was worrying that all seven patients had treatment interruptions due to adverse events, and five cases experienced dose downregulation (31).

A series of studies on the front-line alectinib in advanced NSCLC showed that alectinib has a higher ORR and a greater tumor remission depth than crizotinib and may be more valuable for neoadjuvant therapy (9, 32, 33). Therefore, the neoadjuvant exploration of alectinib is also reasonably expected. The earliest case report suggests that alectinib for neoadjuvant therapy resulted in tumor shrinkage. A 46-year-old male with clinical stage IIIB (cT3N2M0) lung adenocarcinoma received neoadjuvant alectinib at 600 mg twice daily for two cycles (56 days), and imaging results after two cycles of treatment evaluated PR, with tumor shrinkage of 47%. After induction of alectinib, the TNM stage was downstaged as IB (ypT1aN0M0) (22). The cases of other previous small samples also suggested the value of alectinib in neoadjuvant therapy. However, neoadjuvant targeted therapy data is relatively scarce, and clinicians primarily rely on their experience. There is a need for more research to improve current data.

Most reported cases in our review were locally advanced patients with initial clinical stage III. However, the two cases we reported were stage IIB patients with suspicious intrapulmonary metastatic nodules (T3) at initial evaluation and recommended to receive induction therapy after multidisciplinary discussion. Notably, our patients had a smaller tumor load and earlier clinical stage than previously reported cases, which may have contributed to the eventual postoperative pathological evaluation to achieve pCR.

Additionally, studies included in our review had administered targeted therapy for 2-3 months, while few cases had received long cycles of alectinib preoperatively. Our reported cases, however, received more than six months of alectinib each, and both patients underwent surgery after achieving the best objective response when the tumor reached maximum remission. The earlier initial clinical stage is another critical factor contributing to our cases' postoperative pCR. However, this hypothesis requires further confirmation through strictly designed clinical trials.

The current NAUTIKA1 trial involving the neoadjuvant treatment of alectinib is enrolling patients with resectable stage II, IIIA, or selective IIIB (T3N2 only) ALK-positive NSCLC. These patients will receive alectinib induction therapy for eight weeks, followed by surgery (20). The other ALNEO study, which includes cases of potentially resectable stage III (any T with N2, T4N0-1) NSCLC, will also receive alectinib induction therapy for eight weeks (19, 34). These prospective clinical trials deserve our expectations.

Strength and weaknesses

Our study is the first to focus on long-course neoadjuvant alectinib in lung adenocarcinoma with the EML4-ALK variant. It aims to integrate all available cases from the literature in a systematic review with a standardized quality appraisal. While our review is a crucial starting point for understanding the preoperative ALK-TKI therapy strategy, its findings need to be expanded upon by more rigorous studies in prospective clinical trials. However, our narrative synthesis of case reports has several weaknesses, including subjectivity and a lack of detailed patient information and long-term follow-up data to judge overall survival accurately. Additionally, the small sample size of seven cases prevented a thorough quantitative synthesis, and generalizability is limited due to missing cases and publication bias. Furthermore, our analysis of neoadjuvant therapy findings was restricted by the lack of control over reported pathological response results.

Conclusion

We present two cases of resectable ALK-positive lung adenocarcinoma that had a pCR following long-course neoadjuvant alectinib treatment. Our cases, along with a systematic review, show that neoadjuvant alectinib treatment is a feasible option for NSCLC. However, large clinical trials are necessary in order to determine the treatment course and efficacy of neoadjuvant alectinib.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the institutional review board (IRB)/ethics committee of Beijing Chest Hospital, Capital Medical University.

Author contributions

ZL, LS, and SG contributed to the study's conception, data interpretation, and manuscript writing. LS, SG, LT, QM, SZ, DY,

YD, and ZL analyzed the patient data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1120511/full#supplementary-material

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