Case Report: iMDT Corner

Single-port video-assisted thoracoscopic sleeve lobectomy after neoadjuvant immunochemotherapy: a case report

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Background: The morbidity and mortality of lung cancer have always ranked first among malignant tumors (MTs). Previous studies have shown that neoadjuvant chemotherapy can improve the 5-year survival rate of patients with non-small cell lung cancer (NSCLC), but the benefit is limited. Studies have proven that neoadjuvant immunotherapy combined with chemotherapy has unique advantages in prolonging patient survival, reducing distant recurrence, and inducing antitumor immunity. However, its impact remains to be more comprehensively investigated.

Case Description: A 59-year-old male who was admitted to the hospital with a primary complaint of repeated cough and expectoration for 6 months. Preoperative assessment showed right upper lung squamous cell carcinoma with multiple hilar and mediastinal lymph node metastasis, and the clinical stage was cT2aN2M0 stage (IIIA). After three cycles of pembrolizumab + carboplatin + paclitaxel therapy were administered, the reexamination of the tumor was evaluated as partial response (PR), and a sleeve lobectomy of the right upper lung was performed under single-port thoracoscopic surgery. The operation proceeded smoothly without conversion to thoracotomy, and R0 resection was successfully achieved. Postoperative pathological stage was ypT1bN0M0 stage IA, and postoperative pathological remission was evaluated as major pathological response (MPR). After the operation, three cycles of immunotherapy combined with chemotherapy were completed, which was followed by maintenance therapy with pembrolizumab monotherapy for 1 year, and no signs of tumor recurrence and metastasis have been found in follow-up thus far.

Conclusions: Through this case, we believe that for locally advanced NSCLC sleeve lobectomy after neoadjuvant therapy may be a safe and feasible treatment option, can avoid pneumonectomy, protect the lung function of patients, and still ensure the R0 resection rate. Moreover, it may does not significantly increase the difficulty of surgical operation or reduce safety. However, further research is needed to confirm our conclusion. And then, neoadjuvant therapy in the perioperative period may induce a series of side effects or adverse reactions, and thus greater attention should be paid to its timely management.

Keywords: Neoadjuvant immunotherapy combined with chemotherapy; pembrolizumab; single-port thoracoscopy; sleeve lobectomy; case report

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Introduction

The morbidity and mortality of lung cancer have always ranked first among malignant tumors (MTs) (1). Radical surgical resection of early non-small cell lung cancer (NSCLC) is the preferred local treatment method (2,3). For locally advanced lung cancer, there are many treatment options for resectable stage III NSCLC; however, there is considerable controversy concerning the best treatment mode. The 5-year overall survival (OS) rates for IIIA, IIIB and IIIC were 36%, 26%, and 13% respectively (4). Relevant studies have shown that neoadjuvant + surgery + adjuvant therapy may yield the longest OS in patients with advanced NSCLC (5,6), and in the National Comprehensive Cancer Network (NCCN) guidelines on resectable stage III NSCLC, all recommendations indicate neoadjuvant chemotherapy or chemoradiotherapy + surgery + postoperative adjuvant therapy (6).

The 2010 and 2014 NSCLC meta-analysis cooperative group studies established the status of neoadjuvant and adjuvant chemotherapy. Previous studies have shown that neoadjuvant and adjuvant chemotherapy can improve the 5-year survival rate of patients with NSCLC, but only by about 5% (7,8), with limited benefit and high toxicity. In contrast, immunotherapy has shown significant efficacy in advanced NSCLC. Related studies have shown that immunotherapy can significantly extend the OS and progression-free survival (PFS) of patients (9-12). But the benefits of neoadjuvant immunotherapy are still being examined. Neoadjuvant immunotherapy further utilizes the primary tumor as an antigen source recognized by the immune system to induce or enhance systemic anti-tumor immunity to target and eliminate distant micrometastases that may become postoperative recurrence. The study by Topalian *et al.* reported that two difference mechanisms. First, anti-programmed cell death protein (death-ligand) 1 [anti-PD-(L)1] rejuvenates tumor-specific cytotoxic T cells already present in the tumor microenvironment (TME), leading to their activation, proliferation, and translocation into micrometastatic deposits. Second, anti-PD-(L)1 enhances the stimulation of tumor-specific T cell production or partially reverses tolerance. Activated T cells enter the circulation system through efferent lymphatic vessels and then reach micrometastases in the tissue (13). Compared with adjuvant therapy, some research has shown that neoadjuvant immunotherapy is superior to adjuvant immunotherapy in prolonging patient survival, reducing distant recurrence, and inducing antitumor immunity (14).

There are few reports on patients with locally advanced lung squamous cell carcinoma who have undergone sleeve lobectomy after pembrolizumab combined with chemotherapy. Here, we report a case of stage IIIA locally advanced driver gene mutation-negative NSCLC treated with neoadjuvant chemo-immunotherapy. After three cycles of pembrolizumab neoadjuvant therapy, a single-port thoracoscopic right upper lung sleeve resection was successfully completed, which was evaluated as R0 resection. Moreover, the pathological report indicated a major pathological response (MPR). We present this article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-859/rc).

Highlight box

Key findings

- Sleeve lobectomy after neoadjuvant therapy is a safe and feasible treatment option, can still ensure the operation rate and R0 resection rate, and does not significantly increase the difficulty of surgical operation or reduce safety.

What is known and what is new?

- Neoadjuvant immunotherapy has advantages in prolonging patient survival, reducing distant recurrence, and inducing antitumor immunity.
- Single-port sleeve lobectomy and neoadjuvant immunotherapy combined with chemotherapy is technically feasible and has advantages of minimal invasiveness. The difficulty of surgery is not significantly increased due to the addition of immunotherapy.

What is the implication, and what should change now?

- Sleeve lobectomy after neoadjuvant immunotherapy combined with chemotherapy is safe and feasible for resectable locally advanced non-small cell lung cancer.

Case presentation

The patient, a 59-year-old male, was admitted to the hospital with a primary complaint of repeated cough and expectoration for 6 months. He had a history of gout for 15 years, with attacks 2–3 times a year, which were controlled by self-medication. There was history of dermatitis lasting 1 month, and mometasone furoate cream was used for symptomatic treatment. No history of surgery or allergy to diclofenac sodium was reported, and a family history of related tumors was denied. Auxiliary examination revealed the following on chest computed tomography (CT) (*Figure 1A*): (I) there was

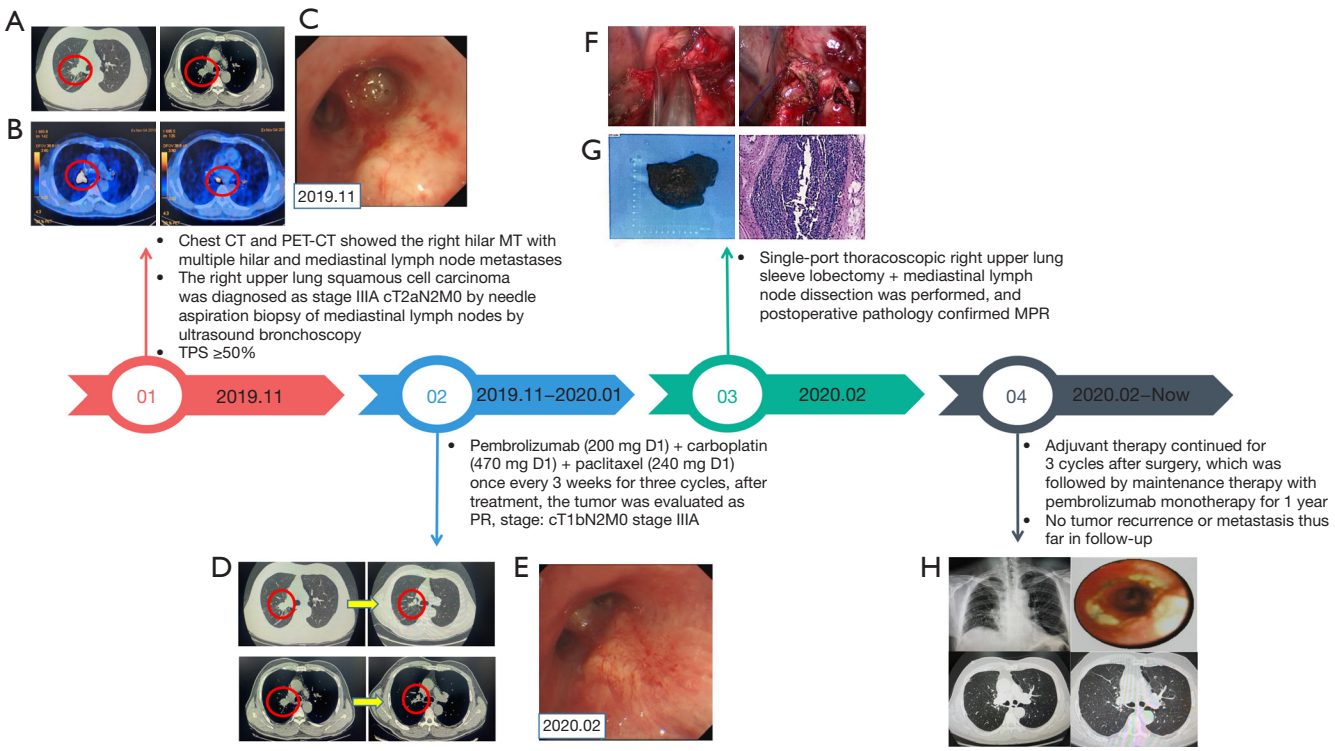

Figure 1 Diagnosis and treatment timeline of the patient. Chest CT revealed right hilar MT and enlarged lymph nodes in the hilum and mediastinum (A). PET-CT revealed mild metabolic lesions next to the mediastinum in the upper lobe of the right lung and multiple lymph nodes with increased metabolism in the right hilum (B). Preoperative bronchoscopy revealed tumor invasion to the right upper lobe of the bronchial ostium (C). After 3 cycles of neoadjuvant immunotherapy combined with chemotherapy, chest CT was used to evaluate the tumor shrinkage (PR) (D). After 3 cycles of neoadjuvant immunotherapy combined with chemotherapy, reexamination under bronchoscopy showed remaining neoplasms in the right main bronchial ostiumed (E). Intraoperative bronchial stump trimming and anastomosis (F). Postoperative pathology showed that a small amount of nonkeratinizing squamous cell carcinoma remained under the microscope, and most of the tumor cells were necrotic and had disappeared; no metastatic cancer was found in any lymph nodes (H&E staining, ×40) (G). Regular follow-up and reexamination after operation showed no tumor recurrence or distant metastasis (H). The red circle on (A,B,D) indicates the location of the primary tumor. CT, computed tomography; PET, positron emission tomography; MT, malignant tumor; TPS, tumor cell proportion score; MPR, major pathologic response; PR, partial response; H&E, hematoxylin and eosin.

a soft tissue shadow in the right hilum, about 3.5 cm × 1.3 cm in size. The bronchi in the right upper lobe were narrowed, the tube wall was thickened, and the lesion was enhanced; (II) mediastinal and right hilar lymph nodes appeared enlarged with calcification. Positron emission tomography (PET)-CT (*Figure 1B*) showed a right upper hilar hypermetabolism mass, which was considered to be MT; right upper lobe paramediastinal mild metabolic lesion; and a possible right hilar lymph node metastasis. Electronic bronchoscopy (*Figure 1C*) revealed that in the bronchus of the posterior segment of the right upper lobe, there were yellow-white neoplasms blocking the lumen and invading the bronchial orifice of the right upper lobe, while the surface mucosa was congested and edematous. Microscopic pathology indicated squamous cell carcinoma. Head magnetic resonance imaging (MRI), whole body scan, color ultrasound of the whole abdomen, and color ultrasound of the neck and supraclavicular lymph nodes showed no signs of metastasis. In order to clarify the pathological diagnosis and staging, needle aspiration biopsy of mediastinal lymph nodes and ultrasound bronchoscopy were performed. Postoperative pathology showed squamous cell carcinoma in the lymph nodes of groups 10 and 7. The PD-L1 was ≥50%. Given with the patient's medical history and related examinations, the diagnosis was right upper lung squamous cell carcinoma

with hilar and mediastinal lymph node metastasis cT2aN2M0 IIIA [according to American Joint Committee on Cancer (AJCC) 8th edition staging system].

After the relevant examinations were completed, we immediately organized a multidisciplinary team (MDT) consultation. After detailed discussions with the thoracic surgery, respiratory medicine, oncology, radiotherapy, pathology, and other departments, we recommended that the patient undergo neoadjuvant immunotherapy combined with chemotherapy. The specific plan was as follows pembrolizumab (200 mg D1) + carboplatin (470 mg D1) + paclitaxel (240 mg D1) once every 3 weeks for three cycles, which was combined with phlegm reduction, atomization, airway relaxation, and lung function exercises.

On February 11, 2020, the patient returned to the hospital for reexamination. Chest CT (*Figure 1D*) showed an occupying space in the right hilar area, and MT was considered. Additionally, the lesion is smaller than before (1.5 cm × 0.6 cm), the bronchi of the right upper lobe had narrowed, and the tube wall appeared thickened. Review under electronic bronchoscopy (*Figure 1E*) showed that the bronchial lumen of the posterior segment of the right upper lung apex was unobstructed, and new organisms (it's considered a tumor) were present on the right main bronchus orifice. According to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (13), we evaluated that it's partial response (PR) of the primary tumor and as stage IIIA (cT1bN2M0). In line with surgical indications, we decided to perform surgical operation. On February 25, 2020, with the patient under general anesthesia, sleeve lobectomy of the right upper lung under single-port thoracoscopic surgery + mediastinal lymph node dissection was performed (*Figure 1F*). The patient had an antibiosis 30 minutes before surgery and surgery time exceeding 3 hours. And the patient discharged after one week after surgery.

In postoperative pathology (*Figure 1G*), microscopy showed only 1% remnant nonkeratinizing squamous cell carcinoma and that most of the tumor cells were necrotic and disappeared. No metastatic cancer was found in any of the lymph nodes, as follows: station 2: 0/5, station 4: 0/2, station 7: 0/5, station 10: 0/1, station 12: 0/1, station 13: 0/2, station 14: 0/1. The postoperative pathological stage was ypT1bN0M0 IA2 (according to AJCC 8th edition staging system). After discussion, we decided to continue with three cycles of combined immunotherapy after surgery with the following protocol: (pembrolizumab 200 mg D1) + (carboplatin 470 mg D1) + (paclitaxel 240 mg D1) once every 3 weeks. After 3 cycles of adjuvant therapy, pembrolizumab monotherapy was changed to maintain for 1 year. Pembrolizumab monotherapy was maintained for 1 year, during which time regular follow-up examinations were conducted (*Figure 1H*). At the 1-month follow-up visit, the lungs appeared well recruited and the anastomosis was well healed. No recurrence or metastasis was found during the follow-up period.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Patient perspective

During the diagnosis and treatment process, I have been fully informed of the regimen, advantages and disadvantages, risks, and side effects of neoadjuvant immunotherapy combined with chemotherapy, as well as the surgical plan and follow-up treatment arrangements. During the perioperative period, I was able to carry out daily work and engage in social and day-to-day life. I was highly satisfied with the diagnosis and treatment, and I had confidence in the follow-up treatment.

International MDT (iMDT) discussion

Discussion among physicians from Fujian Medical University Union Hospital

Pembrolizumab is a high-affinity humanized immunoglobin (Ig)G4 monoclonal antibody targeting the programmed cell death protein 1 (PD-1 protein), which can block the interaction of PD-1 with PD-L1 and then mediate the tumor killing effect (15). Pembrolizumab is currently one of the PD-1/PD-L1 immune checkpoint inhibitors (ICIs) with the most approved indications and the widest coverage of tumor types. The 5-year follow-up data of the KEYNOTE-001 study confirmed, for the first time, that pembrolizumab for treatment-naive or treatment-experienced advanced NSCLC can provide long-term survival benefits, with a 29.6% five-year survival rate being reported (16). KEYNOTE-021 compared the efficacy, safety, and PD-L1 status of pembrolizumab combined with

standard chemotherapy and chemotherapy alone in patients with advanced nonsquamous NSCLC. The results of the study showed that the objective response rate (ORR) (58% *vs.* 33%) and PFS (median 24.5 *vs.* 9.9 months; hazard ratio 0.54, 95% confidence interval: 0.35–0.83) were significantly improved (17). In addition, the KEYNOTE-024 and KEYNOTE-042 studies found that in patients with advanced NSCLC with PD-L1 ≥50% or PD-L1 ≥1%, pembrolizumab improved the overall lifetime and had higher safety compared with platinum-based chemotherapy (18-20). The KEYNOTE-021, KEYNOTE-189, and KEYNOTE-407 trials also verified that the combination therapy of pembrolizumab and chemotherapy can provide patients an extended OS and PFS than can chemotherapy alone, regardless the PD-L1 expression (21-23).

Previous studies have established the role of immunotherapy in the treatment of advanced NSCLC. However, in recent years, greater attention has gradually been afforded to neoadjuvant immunotherapy. Many neoadjuvant immunotherapy strategies are currently available, such as neoadjuvant immunotherapy monotherapy (examined in the CheckMate 159 trial), immunotherapy double-drug therapy (examined in the NEOSTAR trial) (*Table 1*), immunotherapy combined with chemotherapy (examined in the NADIM, NADIM II, Checkmate-816 and AEGEAN trial) (*Table 1*). The regimen of immunotherapy combined with chemotherapy seems to perform better in terms of R0 resection rate, pathological complete response (pCR) rate, major pathologic response (MPR) rate, and ORR rate (26-30).

The newly published results of the KEYNOTE-671 (*Table 1*) study reported that in patients with resectable stage II, IIIA, or IIIB (N2) NSCLC, pembrolizumab + cisplatin + gemcitabine/pemetrexed neoadjuvant treatment followed by surgical resection and postoperative pembrolizumab monotherapy significantly improved MPR and pCR (30.2% *vs.* 11.0%, 18.1% *vs.* 4.0%). And the event-free survival (EFS) at 24 months was 62.4% in the pembrolizumab group and 40.6% in the placebo group (24). Checkmate-816 (*Table 1*) is a global multicenter, open-label, phase 3 trial. It has found that the combination of neoadjuvant nivolumab plus chemotherapy significantly prolongs event free survival, has a higher pCR rate, and the addition of nivolumab to neoadjuvant chemotherapy does not increase the incidence of adverse events or hinder the feasibility of surgery (25).

Although neoadjuvant immunotherapy combined with chemotherapy has shown good therapeutic effects in many studies regardless of the treatment plan, its safety has been a consistent concern. Zhou *et al.* conducted a meta-analysis and found that the combination group's PFS, ORR, and OS were significantly better than those of the chemotherapy-alone group, but the combination group's grade 3–5 adverse events (AEs) were also significantly increased in the treatment group (31). Liang *et al.* included and indirectly compared 11 randomized controlled trials and found that regardless of the degree of PD-L1 expression, immunotherapy combined with chemotherapy was recommended as first-line treatment; however, they noted that side effects should be closely monitored (32). The study by Fujiwara *et al.* also reported that the addition of immune checkpoint blockers to perioperative therapy was associated with an increase in grade 3–4 treatment-related adverse events and adverse events leading to treatment discontinuation. Although immunotherapy has brought us huge benefits in clinical treatment, the safety issues it brings have also attracted our attention. We need to detect related adverse reactions early and make corresponding treatments (33). Although hilar and mediastinal lymph node fibrosis and thoracic adhesions after neoadjuvant therapy may affect operation, relevant studies show that the surgical rate of patients after neoadjuvant immunotherapy is 81–95% while the R0 resection rate is as high as 100%, and the complications of surgery after neoadjuvant immunotherapy for early-stage lung cancer do not appear to be significantly increased (26,29,30,34).

Therefore, considering the patient's condition in this case, the choice of surgical procedure after neoadjuvant treatment represented a substantial challenge for us. Considering the protection of the patient's lung function, after multidisciplinary discussion, we selected single-port thoracoscopic-assisted sleeve lobectomy. From the perspective of clinical efficacy and safety, a retrospective study found that sleeve lobectomy is an effective treatment option after neoadjuvant therapy for NSCLC of all stages and does not increase perioperative complications or recurrence (35). Other research indicates that the long-term survival rate is better than that of pneumonectomy (35,36). Through an analysis of surgical difficulty and feasibility, Chen *et al.* found that the surgical difficulty and postoperative complication rate of sleeve lobectomy after neoadjuvant immunotherapy combined with chemotherapy were similar to those of surgery alone. Another study demonstrated that sleeve lobectomy after neoadjuvant therapy is effective and safe in patients with NSCLC (37). The study by Liang *et al.* reported that sleeve lobectomy for advanced NSCLC after neoadjuvant immunotherapy

Table 1 Clinical trials evaluating neoadjuvant ICIs in resectable NSCLC

Characteristics	KEYNOTE-671 (24)	CHECKMATE-816 (25)	NEOSTAR (26)	NADIM II (27)	AEGEAN (28)
Stage	Resectable II to select IIIB (N2)	Resectable IB to IIIA	Resectable I to IIIA	Resectable IIIA and IIIB	Resectable IIA to select IIIB (N2)
Regimens	Pembrolizumab + cisplatin + gemcitabine/ pemetrexed as neoadjuvant prior to surgery and pembrolizumab monotherapy as adjuvant after surgery	Nivolumab + ipilimumab (closed to enrollment)	Nivolumab + ipilimumab (D1, D15, D29)	Nivolumab + chemotherapy and nivolumab monotherapy as adjuvant after surgery (adjuvant treatment with nivolumab for 6 months who had R0 resections)	Durvalumab + platinum-based chemotherapy (followed by durvalumab q4w, for an additional 12 cycles post-surgery)
	Placebo + cisplatin + gemcitabine/ pemetrexed as neoadjuvant prior to surgery and placebo as adjuvant after surgery	Nivolumab + platinum-doublet chemotherapy	Nivolumab monotherapy (D1, D15, D29)	Chemotherapy alone (observation for 6 months)	Placebo + platinum-based chemotherapy (followed by placebo monotherapy q4w, for an additional 12 cycles post-surgery)
	–	Platinum-doublet chemotherapy alone	Surgery was planned to occur within 6 weeks after the completion of neoadjuvant treatment	–	–
	–	Surgery was planned to occur within 6 weeks after the completion of neoadjuvant treatment	–	–	–
Cycles	4	3	3	3	4
Surgery	82%	83%	Nivo 96%	91%	81%
			Nivo + ipi 81%		
ORR	NR	54%	Nivo 22%	74%	NR
			Nivo + ipi 19%		
MPR	30%	37%	Nivo 22%	52%	33%
			Nivo + ipi 38%		
pCR	18%	24%	Nivo 9%	36%	17%
			Nivo + ipi 29%		

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; ORR, objective response rate; MPR, major pathological response; pCR, pathological complete response; D, day; nivo, nivolumab; ipi, ipilimumab; NR, not reported.

combined with chemotherapy increased the difficulty of surgery but did not delay postoperative recovery (38).

Overall, it appears that sleeve lobectomy after neoadjuvant immunotherapy combined with chemotherapy is safe and feasible. The studies by our team also found that sleeve lobectomy under single-port thoracoscopic surgery is safe and feasible. During the mean follow-up was 7.5 months. There were no tumor recurrences or bronchial anastomotic complications. The modified bronchial anastomosis technique is to use a single 3-0 prolene suture to made a stitch on the posterior bronchial wall and a knot outside the lumen, and then suture 1/4 of

the both sides. The other two bilateral quarters were then similarly sutured. Finally, the procedure was completed with a final knot outside the lumen (39,40). The modified bronchial anastomosis technique was an end-to-end bronchial anastomosis that performs with continuous suturing using a single 3-0 prolene suture, and confers the advantages of continuous suture and interrupted suture and is widely used in minimally invasive surgery. Compared with the anastomosis methods, this bronchial anastomosis technology has the advantages of simple operation, fewer surgical sutures, reduced suture entanglement, and shortened bronchial anastomosis time. At the same time, it has universality in minimally invasive surgery, and the adequate planning and mature bronchial anastomosis technology can help to reduce the difficulty of single-port thoracoscopic sleeve lobectomy (39,40).

Several issues in the diagnosis and treatment of this patient were further discussed as follows

(I) How can the efficacy of neoadjuvant immunotherapy be assessed? In addition to PD-1/PD-L1, are there any potential markers that can help predict treatment response?

Expert opinion 1: Dr. Antonio Rossi

pCR and MPR might be considered short-term outcomes for the assessment of the potential efficacy of neoadjuvant immunotherapy, being considered also as a potential surrogate of survival results. EFS, and OS are among the long-term outcomes for the evaluation of the efficacy of this treatment. Preliminary data coming from clinical trials for immunotherapy in early-stages NSCLC patients showed the potential role of some markers such as PD-L1, TMB, specific gene alterations, TME biomarkers [tumor-associated immune cells (TAICs), and T-cell receptor (TCR) repertoire], peripheral blood cells and circulating tumor DNA (ctDNA), etc. Among these, although there are still limited data, as baseline value and/or as dynamic monitoring, ctDNA seems to be a very promising potential biomarker to predict treatment response and survival outcomes for neoadjuvant immunotherapy.

Expert opinion 2: Dr. Duilio Divisi

In patients with advanced but resectable NSCLC, neoadjuvant immunotherapy or chemo-immunotherapy is safe and efficacious option treatment improving pathologic response rates and PFS/OS, particularly in patients who had tumors that expressed PD-L1. Despite these recent advances in neoadjuvant chemoimmunotherapy, there is still a significant proportion of patients who have an inadequate response to ICIs and may even experience severe immune-related adverse effects (irAEs) or excessive progression (41).

A few biomarkers that may be related to immunotherapy response have been identified from preliminary data in clinical trials for patients with advanced NSCLC treated with ICIs (42,43).

Four categories can be used to group as follow:

(I) Tumor-intrinsic biomarkers: such as PD-L1/PD-1, tumor mutational burden (TMB), and specific gene alterations;
(II) Tumor microenvironment biomarkers: it can be consisted of TAICs, and TCR repertoire;
(III) Liquid biopsies: among them, the peripheral blood cells and ctDNA were the most widely used;
(IV) Host-related biomarkers: including clinical characteristics, human leukocyte antigen-I (HLA-I), and so on.

(II) Given the variety of neoadjuvant immunotherapy regimens available, is there an optimal way to choose the suitable neoadjuvant immunotherapy regimen for patients in clinical practice? And how to choose the surgical plan after neoadjuvant therapy?

Expert opinion 1: Dr. Antonio Rossi

To date no head-to-head comparison between different ICIs in neoadjuvant setting are available. It has not been observed that the efficacy of one ICI was significantly better than the other. To date, the choice of the suitable neoadjuvant immunotherapy regimen should be based on the results from the available trials looking at the outcomes, toxicity, schedule of administration, neoadjuvant/perioperative trial, and regulatory approvals. In the lack of direct ICI comparisons in this setting, future mature data coming from the already performed trials and those that will be available from the ongoing studies, might better define if we can consider a potentially better ICI to administer in the neoadjuvant therapy. In terms of clinical efficacy, retrospective study found that in various stages and subgroups with or without neoadjuvant therapy, sleeve lobectomy had the long-term survival rate is better than that of pneumonectomy without increasing perioperative complications or recurrence (35,36).

Expert opinion 2: Dr. Duilio Divisi

To date, we have several ongoing clinical trials able to offer the possibility to choose between different neoadjuvant treatment option in NSCLC: immunotherapy alone, double agent immunotherapy or chemo-immunotherapy

association.

The choice of the optimal treatment depends on the patient's ability to tolerate any immunotherapy or even chemotherapy toxicities. In addition, to the classic chemotherapy toxicity (nausea, vomiting, diarrhea), ICIs have different toxicity profiles involving multiple organs like myocarditis, rash, pneumonia, neuromuscular toxicity, hypothyroidism, etc. (44,45). Adverse reactions related to immunity or chemotherapy may lead to delayed surgery and may increase the risk of perioperative complications. Even in some cases, surgical delays caused by immune related adverse reactions may lead to tumor progression. Therefore, an adequate patient selection (good performance status, age, absence of other autoimmune disease, good organ function) is necessary to select between immunotherapy and chemotherapy or in combination. A retrospective analysis found that surgical difficulty and postoperative complication rate of sleeve lobectomy after neoadjuvant immunotherapy combined with chemotherapy were similar to those of surgery alone. Although there is currently controversy over the impact of neoadjuvant therapy on surgical difficulty, it is widely recognized that the surgical approach after neoadjuvant therapy is safe and feasible (37).

(III) Does neoadjuvant immunotherapy affect the safety, feasibility, and choice of surgical methods? When is the best time to perform surgery after neoadjuvant immunotherapy? What are the advantages of the modified bronchial anastomosis technique?

Expert opinion 1: Dr. Antonio Rossi

Based on the results of each trial and their meta-analysis, neoadjuvant immunotherapy was confirmed to be safe with treatment-related adverse events and the mean surgical resection rate similar to those reported by neoadjuvant chemotherapy, with no conclusive evidence that might affect surgical procedures or their safety. There is no clear evidence to confirm the optimal surgical time after neoadjuvant immunotherapy, also considering that early surgery may lead to serious surgical complications, while delayed surgery may lead to tumor progression. The existing data should recommend surgery within 4–6 weeks after the last neoadjuvant immunotherapy cycle.

The modified bronchial anastomosis technique places the first stitch at this location can help to tighten the anastomotic from the back wall to the front wall, and then adjust the tightness of the suture before tying the knot. By using this method, the anastomotic tension and anastomotic complications can be efficiently reduced (39,40).

Expert opinion 2: Dr. Duilio Divisi

Neoadjuvant immunotherapy causes fibrosis at the level of the hilar and mediastinal structures, associated with vascular fragility and interstitial lung disease (46). In this way, spirometry before and after immunotherapy treatment is always recommended in order to evaluate the impairment of gas exchange which could determine a contraindication to surgery. The percentage rate of thoracotomies and conversions to muscle sparing thoracotomy appears to be increased compared to minimally invasive surgery [VATS and robot-assisted thoracic surgery (RATS)] (47).

The time-to-surgery does not appear to have any particular effects on the efficacy and safety of surgery (48). The tendency is to wait 4–6 weeks after the last cycle of chemoimmunotherapy (49). Although there are not specific experiences and randomized studies in this regard, personally I believe that bringing forward surgery to the third week could reduce the impact on the pulmonary interstitium and vascular brittleness.

For the modified bronchial anastomosis technique, the working process is simple and convenient because it is a substantially modified continuous suture technique. The modified bronchial anastomosis technique is simple and can reduce operative time, little tying of knots is required. And then the good exposure of the operative view is maintained (39,40).

Conclusions

The successful diagnosis and treatment of this patient suggests that sleeve lobectomy after neoadjuvant immunotherapy combined with chemotherapy may be safe and feasible for resectable locally advanced NSCLC. Sleeve lobectomy after neoadjuvant therapy may did not significantly increase the difficulty of operation or reduce safety. With this approach, the R0 resection rate can be ensured, pneumonectomy can be avoided, and the lung function of patients protected, creating good conditions for patients to tolerate subsequent treatment, and further research is needed to confirm our conclusion.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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