# A case report of cStage IIIB squamous cell lung carcinoma completely resected after downstaging with neoadjuvant therapy

**Li, Jijia; Zu, Peng; Jakopović, Marko; Legras, Antoine; Saji, Hisashi; Onodera, Ken; Schlachtenberger, Georg; Liu, Hongxu**

*Source / Izvornik:* **Journal of Thoracic Disease, 2024, 16, 3503 - 3511**

**Journal article, Published version**
**Rad u časopisu, Objavljena verzija rada (izdavačev PDF)**

https://doi.org/10.21037/jtd-24-522

*Permanent link / Trajna poveznica:* https://urn.nsk.hr/urn:nbn:hr:105:320848

*Rights / Prava:* Attribution-NonCommercial-NoDerivatives 4.0 International/Imenovanje-Nekomercijalno-Bez prerada 4.0 međunarodna

*Download date / Datum preuzimanja:* **2025-02-07**


*Repository / Repozitorij:*

Dr Med - University of Zagreb School of Medicine Digital Repository

Case Report: iMDT Corner

# A case report of cStage IIIB squamous cell lung carcinoma completely resected after downstaging with neoadjuvant therapy

**Jijia Li[1], Peng Zu[1], Marko Jakopović[2], Antoine Legras[3], Hisashi Saji[4], Ken Onodera[5], Georg Schlachtenberger[6], Hongxu Liu[1]**

[1]Department of Thoracic Surgery, Liaoning Cancer Hospital & Institute, Shenyang, China; [2]Department for Respiratory Diseases Jordanovac, University Hospital Centre Zagreb, Zagreb, Croatia; [3]Department of Thoracic Surgery, Tours University Hospital, Tours, France; [4]Department of Chest Surgery, St. Marianna University School of Medicine, Kanagawa, Japan; [5]Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Miyagi, Japan; [6]Department of Cardiothoracic Surgery, University Hospital of Cologne, Cologne, Germany

*Contributions:* (I) Conception and design: J Li; (II) Administrative support: H Liu; (III) Provision of study materials or patients: J Li; (IV) Collection and assembly of data: P Zu; (V) Data analysis and interpretation: P Zu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Hongxu Liu, MD. Department of Thoracic Surgery, Liaoning Cancer Hospital & Institute, No. 44 Xiaoheyan Road, Shenyang 110042, China. Email: hongxuliu@qq.com.

**Background:** The most effective method and length of time for administering adjuvant immunotherapy after surgery for non-small cell lung cancer (NSCLC) are still unknown. Various clinical trials have utilized diverse strategies for adjuvant treatment. In this case, we explore the potential benefits of neoadjuvant immunotherapy combined with chemotherapy in managing locally advanced lung squamous carcinoma, which often poses challenges for treatment. This multimodal approach aims to downstage tumors and optimize surgical outcomes.

**Case Description:** Following a diagnosis of stage IIIB lung cancer, the patient underwent three cycles of neoadjuvant therapy using sintilimab, Abraxane, and Lobaplatin, resulting in a significant 45% reduction in tumor size. Subsequently, a right lower lobe lobectomy and systematic lymphadenectomy were performed using a uniportal video-assisted thoracic surgery (VATS) approach. Postoperative analysis revealed negative lymph nodes, with only a 5-mm residual tumor in the tumor bed, downstaging the cancer to IA1. Remarkably, the patient experienced a smooth recovery without any postoperative complications. One cycle of adjuvant therapy was administered following the operation to further support the patient's recovery and minimize the risk of disease recurrence. This comprehensive treatment approach underscores the importance of neoadjuvant therapy in optimizing surgical outcomes and improving long-term prognosis for patients with locally advanced lung cancer.

**Conclusions:** For patients with stage III locally advanced lung squamous carcinoma, the combination of Sintilimab and Platinum-based drugs can be used as a neoadjuvant therapy which can reduce the difficulty of the operation.

**Keywords:** Case report; neoadjuvant therapy; squamous cell lung carcinoma; sintilimab

Submitted Mar 28, 2024. Accepted for publication May 15, 2024. Published online May 29, 2024.
doi: 10.21037/jtd-24-522
**View this article at:** https://dx.doi.org/10.21037/jtd-24-522

## Introduction

The mortality of lung cancer is still the highest worldwide (1). Non-small cell lung cancer (NSCLC) is the main pathological type, including squamous cell carcinoma, adenocarcinoma, etc. (2). Sintilimab is a human immunoglobulin monoclonal antibody G4 (IgG4) jointly developed by Innovent Bio and Eli Lilly and Company. In the year of 2018, sintilimab was officially approved by Chinese National Medical Products

© Journal of Thoracic Disease. All rights reserved.

Administration (NMPA) with the National Drug Approval No. S20180016. Although there are guidelines about Neoadjuvant nivolumab therapy recommended for stage III patients according to CheckMate-816 (3) and the study of Provencio *et al.* (4). However, there are no guidelines for preoperative neoadjuvant Sintilimab for resectable stage III NSCLC, and relevant clinical trials have been conducted. At the 55th American Society of Clinical Oncology (ASCO) Annual Meeting, preliminary data from the open, single-center, single-arm, phase Ib study (registration number: ChiCTR-OIC-17013726) on the neoadjuvant therapy of sintilimab monotherapy for resectable NSCLC carried out by Gao *et al.* were published (5). The data confirmed the feasibility of sintilimab monotherapy as neoadjuvant therapy.

### Highlight box

**Key findings**

- For stage III lung squamous cell carcinoma, the use of sintilimab in combination with platinum-based chemotherapy as neoadjuvant therapy is feasible.

**What is known and what is new?**

- Immunotherapy can improve the prognosis of lung cancer patients. In advanced lung cancer, it has been confirmed that immunotherapy combined with platinum-containing chemotherapy can prolong patients' survival. In patients with locally advanced lung cancer, immunotherapy combined with chemotherapy as a neoadjuvant approach can benefit patients.
- Combining immunotherapy with other modalities of treatment may benefit some operable patients with locally advanced lung cancer. However, the specific neoadjuvant and adjuvant regimens and duration of treatment vary among different clinical trials, thus further phase III clinical trials are needed.

**What is the implication, and what should change now?**

- Regarding new adjuvant therapies, variations exist in medication regimens, duration, and postoperative adjuvant therapy methods across immunotherapy-related clinical trials. Achieving a unified standard swiftly is challenging due to significant individual differences in immunotherapy responses compared to chemotherapy. Immunotherapy's complex mechanism and potential impact of surgery on the immune microenvironment emphasize the unequal weight of neoadjuvant and adjuvant therapy. Whether prolonged neoadjuvant therapy affects surgical procedures warrants exploration. This case proposes a clinically feasible approach with minimal patient burden and short treatment cycle, meriting further research.
- If it is possible to conduct programmed cell death 1 ligand 1 expression testing on patients before initial treatment, and to monitor real-time immune microenvironment and blood circulating tumor DNA during each cycle, it can serve as a reference for medication regimens.

In ORIENT-12 (6), it was confirmed that patients with lung squamous cell carcinoma can benefit from the combination of sintilimab and platinum-based chemotherapy. Currently, there are few reports about combination of immunotherapy and chemotherapy as neoadjuvant therapy. This paper reports 1 case of IIIB squamous lung carcinoma treated in our hospital with neoadjuvant therapy before operation. Description and discussion of the intraoperative conditions after neoadjuvant therapy using these medicines is unique. We present this article in accordance with the CARE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-522/rc).

## Case presentation

A 53-year-old man, who presented with chest tightness, went to the local hospital for computed tomography (CT) scan 20 days ago. CT scan showed a pulmonary tumor in the lower lobe of right lung. With no treatment, the patient was admitted to Liaoning Cancer Hospital & Institute. Enhanced CT scan of chest showed a mass in the lower lobe of the right lung, which was irregular in shape, about 77 mm × 70 mm × 70 mm in size and with uneven enhancement. The bronchus of the posterior basal segment of the right lower lobe was cut off. CT scan also revealed mediastinal and right hilar adenopathy with obstructive pneumonia (*Figure 1*). Fiber bronchoscope showed that the tumor blocked the basal segment of the right lung lower lobe, and the pathological results were squamous carcinoma (*Figure 2*). The clinical stage was cT4N2M0, stage IIIB. The patient had smoked 30 cigarettes per day for 35 years (52.5 pack/years) and quitted smoking for 3 years. The patient had a family history of malignant tumor, and his sister was also a lung cancer patient. The patient has no history of diabetes, coronary artery diseases, hypertension, hepatitis, drug allergy, previous trauma, or operation. Tumor markers were detected as the following: squamous cell carcinoma antigen (SCC): 1.2 ng/mL (normal range, ≤1.5 ng/mL), carcinoembryonic antigen (CEA): 1.68 ng/mL (normal range, 0–5 ng/mL), cytokeratin-19 (CYFRA21-1): 70.68 ng/mL (normal range, <3.3 ng/mL), and neuron specific enolase (NSE): 44.24 μg/L (normal range, <16.3 μg/L). Cardiopulmonary function, brain MRI, bone scan, liver, gallbladder and spleen ultrasound showed no abnormalities. No programmed cell death 1 ligand 1 (PD-L1) test was done.

Starting from July 10$^{th}$, 2020, the patient received 3 cycles of neoadjuvant therapy using sintilimab (200 mg/q3w, d1), albumin-bound paclitaxel (Abraxane) (450 mg/q3w, d1)

© Journal of Thoracic Disease. All rights reserved.

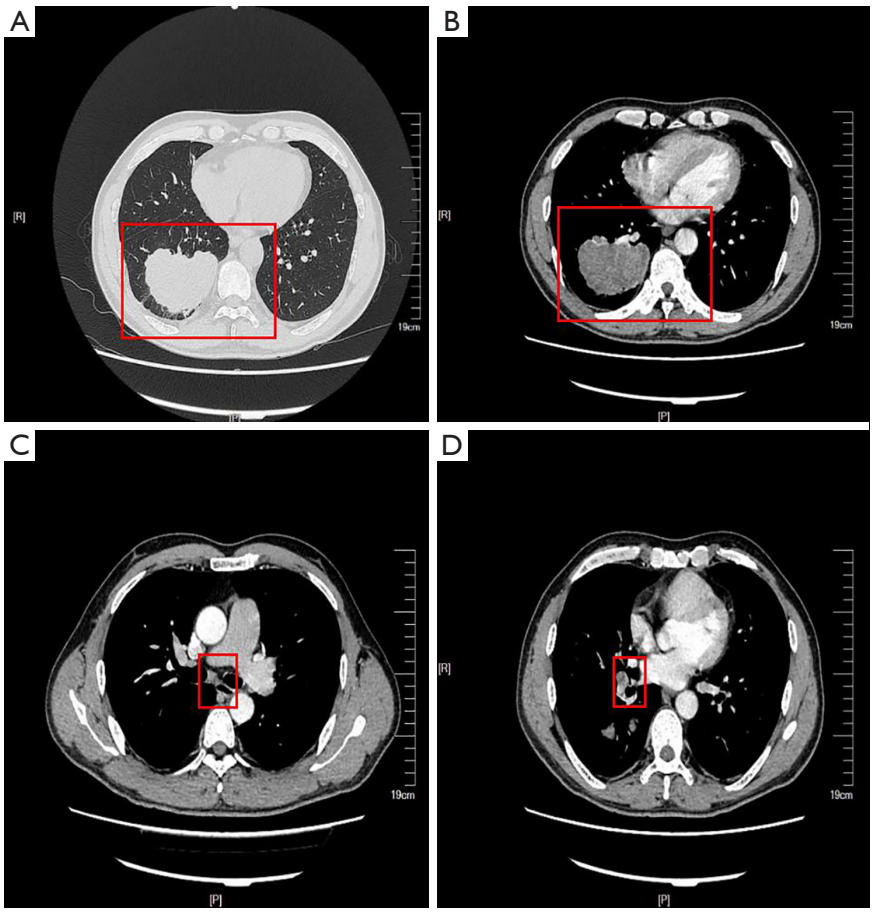


**Figure 1** Before neoadjuvant therapy. (A) The maximum dimension of the lesion (red box) in the right lower lobe on chest CT lung window. (B) The maximum dimension of the lesion (red box) in the right lower lobe on chest CT mediastinal window. (C) The suspicious subcarinal lymph node (red box) for metastasis, mediastinal window. (D) The suspicious hilar lymph node (red box) for metastasis, mediastinal window. CT, computed tomography.

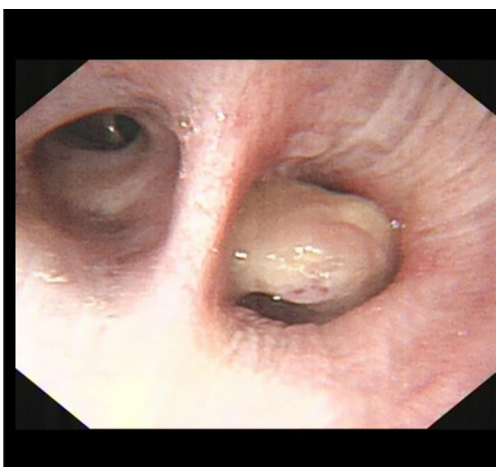

**Figure 2** New organisms can be seen in the basal segment of the right lung lower lobe.

and Lobaplatin (a kind of platinum-based antineoplastic) (90 mg/q3w, d1) before surgery with an interval of 21 days between each cycle. Each cycle remains 1 day. Then the patient underwent a CT re-examination, which revealed that the mass in the right lung lower lobe became smaller, with the tumor size of about 42 mm × 30 mm (*Figure 3*) and the efficacy appraisal was partial response (PR). The cTNM changed down to cT2BN0M0, stage IIA. After that, right lower lobectomy and lymph node dissection were performed via uniportal video-assisted thoracic surgery (VATS) approach on the patient on September 12$^{th}$, 2020.

With the patient in the left lateral decubitus position, a 4 cm incision was inserted in the fifth intercostal space (ICS). Ultrasonic knife (Harmonic, Ethicon Inc., USA) was used to expose vessels and trachea of the right lung lower lobe,

© Journal of Thoracic Disease. All rights reserved.

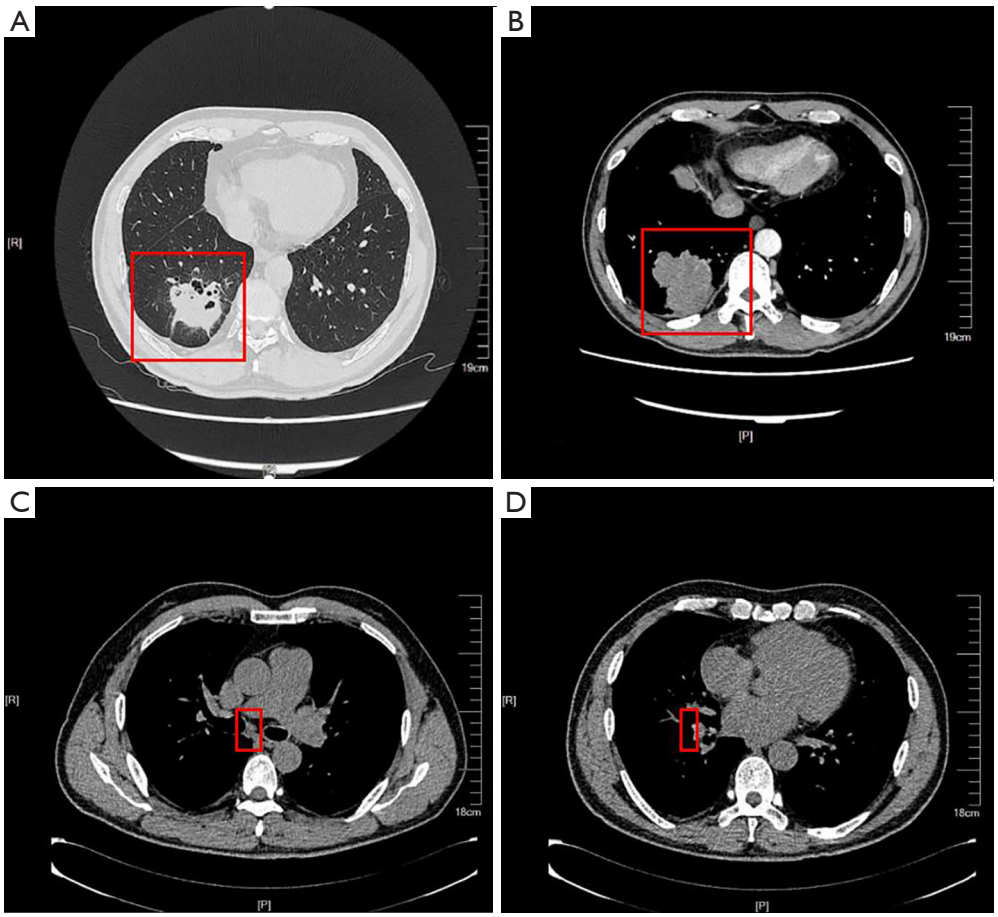


**Figure 3** After neoadjuvant therapy. (A) The maximum dimension of the lesion (red box) in the right lower lobe on chest CT lung window. (B) The maximum dimension of the lesion (red box) in the right lower lobe on chest CT mediastinal window. (C) The suspicious subcarinal lymph node (red box) for metastasis, mediastinal window. (D) The suspicious hilar lymph node (red box) for metastasis, mediastinal window. CT, computed tomography.

as well as dissect the lymph nodes by the surgeon. Despite the swollen hilar lymph nodes, they did not infiltrate the pulmonary arteries and trachea, it was not difficult to expose the arteries and trachea. The operation went smoothly and lasted about 90 min. The mediastinal lymph node dissection includes 2R#, 4R#, 7#, 8#, and 9#. The drainage tube was removed after 2 days of operation and the patient was discharged 4 days postoperatively. The patient had an uneventful recovery without postoperative complications. The postoperative pathology was squamous carcinoma with post-treatment changes. The cancer cells in the tumor bed were 5 mm in diameter. The pathological result showed all the removed lymph nodes were negative and the final pathological stage was ypIA1. MPR was reached. After surgery, the patient received the same adjuvant therapy as before. At present, the patient has cooperated well and the review is normal (*Figure 4*).

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.

## iMDT discussion

In the present case, combination of immunotherapy and chemotherapy as neoadjuvant treatment was well tolerated

© Journal of Thoracic Disease. All rights reserved.

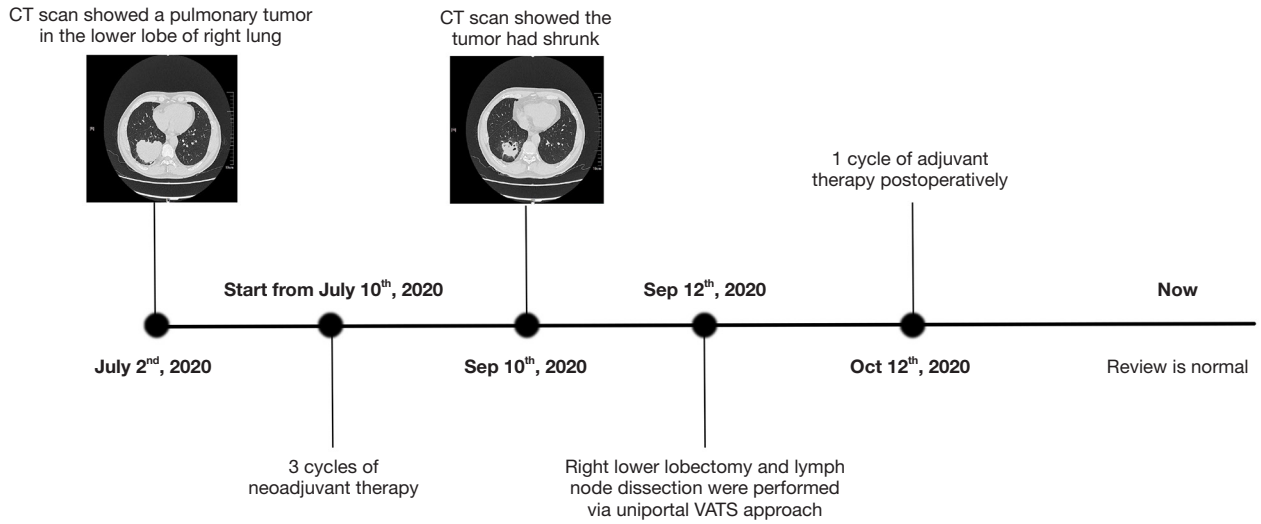


**Figure 4** Timeline. CT, computed tomography; VATS, video-assisted thoracic surgery.

by the patient with no occurrence of treatment-related adverse events. In addition, the operation time was not delayed due to adverse effects of combined neoadjuvant therapy. Moreover, the tumor shrunk significantly after preoperative treatment and the clinical stage was downgraded from cT4N2M0, stage IIIB to ypIA1. The operation of single-port thoracoscopy requires the lung lobe to be clamped with an oval clamp and gauze on one side to expose the vascular area. If the tumor is too large, it may obstruct the surgical field from certain angles. The baseline of the tumor is 77 mm × 70 mm × 70 mm. If the tumor is removed from the chest cavity, it will inevitably cause damage to the ribs or disrupt the integrity of the tumor. The surgery lasted for 90 min, and there was no increase in the difficulty of the surgical procedure. In addition, compared to open surgery, single-port thoracoscopy has at least shortened the time for thoracotomy and closure. Our neoadjuvant regimen is similar to the clinical trial protocol proposed by Forde *et al.* (3) and Provencio *et al.* (7). In this case, no adverse events occurred, and the conclusion that it did not increase surgical difficulty is consistent with Forde *et al.*'s (3) and Provencio *et al.*'s (7) researches. The limitations of this case report are listed as follows: (I) this patient did not take PD-L1 test. In the research by Gao *et al.* (5), it was confirmed that the expression of PD-L1 in the primary lesion is related to the percentage of pathological response of the primary lesion. This study was a single-arm study. Only sintilimab monotherapy as a neoadjuvant regimen was investigated. Not conducting PD-L1 testing on patients is a shortcoming. However, in Forde *et al.*'s study (3), it was confirmed that regardless of PD-L1 expression, immune combination therapy can significantly improve pathological complete response (pCR). Therefore, we believe that the test results would not change the treatment regimen. (II) This patient did not take EGFR test either. The probability of mutation in squamous cell carcinoma is extremely small. (III) Another shortcoming is that we did not conduct pathological examination on the mediastinal lymph nodes. This patient refused positron emission tomography/computed tomography (PET-CT) scans due to economic reasons. Lymph node metastasis was determined solely based on the morphology of chest CT, which could potentially lead to false positive results. (IV) No guideline is provided for this type of patient on postoperative therapy. All studies with perioperative treatment are done regardless of response to neoadjuvant therapy. Only in CheckMate-816, neoadjuvant treatment was applied. More and longer adjuvant therapy may obtain a better outcome. For stage IIIB lung cancer that can be completely resected, Chinese Society of Clinical Oncology (CSCO) currently still recommends surgical resection (8). In recent years, literatures demonstrated that immunotherapy based on PD-1/PD-L1 blockage improved the survival rate of some patients with advanced lung cancer (9,10). In terms of neoadjuvant therapy for lung cancer, although PD-L1 is not currently recommended in all guidelines, such clinical trials like CheckMate 159, LCMC3, NEOSTAR, JCSE01.10, etc. have been written in the comment section of CSCO due to significant progress in

© Journal of Thoracic Disease. All rights reserved.

phase II trials (7). Among them, JCSE01.10 is sintilimab as a neoadjuvant. The major pathological remission rate (MPR) reached 40.5% without delaying the operation time. It was confirmed in a study that immunotherapy combined with chemotherapy could amplify the effect of immunotherapy, which is better than chemotherapy or immunotherapy alone (11). For the present case, after using the neoadjuvant immunotherapy combined with chemotherapy, it is not clear whether the combination therapy amplifies the therapeutic effect, which needs to be confirmed by randomized clinical trials with large sample sizes in the future.

After neoadjuvant therapy in this case, the operation time and difficulty were reduced. CT images before the operation revealed a large number of enlarged lymph nodes which the clinical diagnosis was N2. After the treatment, the lymph nodes showed no changes in size, but the postoperative pathology confirmed that the lymph nodes were negative. Pathological remission occurs after neoadjuvant therapy, which has a positive effect on the prognosis of patients (12,13). The patient was given neoadjuvant treatment due to the clinical diagnosis of N2. Intraoperative exploration revealed that the patient had enlarged hilar lymph nodes (10#), inferior mediastinal lymph nodes (8# and 9#), and superior mediastinal lymph nodes (2# and 4#). It was easy to expose the branch of right lower pulmonary arteries and inferior tracheal protuberance because the swollen lymph nodes did not infiltrate the pulmonary arteries and trachea. The surgical procedure was uneventful. The surgical incision was 4-cm long, which indicates that the neoadjuvant therapy not only benefited the patient's condition, reduced surgical trauma, but also improved the probability of radical resection.

Four weeks after the operation, the preoperative plan was performed again to supplement with adjuvant therapy for one cycle. The patient did not continue treatment for financial reasons. At present, the patient has no progression for 5 months after surgery.

In conclusion, for patients with resectable stage IIIB lung squamous carcinoma, as a viable treatment option, neoadjuvant immunotherapy combined with chemotherapy will reduce the difficulty of the surgery, expand indications for surgery and improve the success rate of surgery.

### *Discussion among physicians from Liaoning Cancer Hospital & Institute*

This case provides a novel feasible neoadjuvant approach. Currently, there is no measurable indicator to determine the duration and efficacy of immunotherapy as a neoadjuvant treatment. Therefore, despite the favorable outcome in this case, large-scale experiments are still required. Additionally, a drawback of this case is the lack of preoperative lymph node pathological examination.

### *Several issues regarding the diagnosis and treatment of this patient were further discussed below*

**How many circles should postoperative immunotherapy last for surgical patients with immunochemotherapy as neoadjuvant therapy?**

- Expert opinion 1: Antoine Legras. We cannot answer this question today. Some studies will be conducted with consolidation ICI after surgery. However, based on previous studies after chemo-radiation therapy, the duration should be several months.
- Expert opinion 2: Georg Schlachtenberger. Adjuvant therapy for patients already receiving neoadjuvant treatment is not intended. However, additional adjuvant therapy can be considered if vital tumor cells remain postoperatively after neoadjuvant treatment. To date, only nivolumab has been approved for perioperative immunotherapy. Provencio *et al.* applied four cycles as neoadjuvant and two as adjuvant treatment (4). Therefore, I recommend this therapy.
- Expert opinion 3: Hisashi Saji. I guess, 1 year for Pt. with non-pCR. No postoperative immunotherapy for Pt. with pCR.
- Expert opinion 4: Ken Onodera. Immunochemotherapy as neoadjuvant therapy showed a favorable prognosis in event-free survival with hazard ratio 0.63 compared to the chemotherapy in CheckMate-816 trial. This is comparable to the results of sandwich trials such as KEYNOTE-671 and AEGEAN. Therefore, I believe that postoperative immunotherapy using the same agents as neoadjuvant therapy is not worthwhile. However, it is clear that there are patients for whom neoadjuvant immunochemotherapy alone is inadequate, and I believe that other treatment strategies are necessary postoperatively.
- Expert opinion 5: Marko Jakopović. This is not quite clear yet. There are data for 6 months of adjuvant immunotherapy after neoadjuvant Io plus chemotherapy then surgery (NADIM II) (7) and there are data of 12 months (AEGEN, CheckMate-77T, Keynote 671). Today, stronger data are available for 1 year adjuvant treatment.

© Journal of Thoracic Disease. All rights reserved.

**How should non-R0 resection patients with immunochemotherapy as neoadjuvant therapy be treated after surgery?**

- Expert opinion 1: Antoine Legras. R1: radiation therapy 66 Gy.
  Run: depends on the reason for Run (Insufficient lymph nodes? Pleural lavage cytology?...)
- Expert opinion 2: Georg Schlachtenberger. Non-R0 resection is not an option, in my opinion. Nevertheless, I would recommend including radiation therapy in the discussion if R1 resection is inevitable.
- Expert opinion 3: Hisashi Saji. Post-operative radiotherapy followed by adjuvant immunochemotherapy.
- Expert opinion 4: Ken Onodera. Local control is necessary to prevent recurrence in non-R0 resection patients. Immunochemotherapy is excellent for distant control, but may be inadequate for prevention of recurrence in non-R0 resection patients. Specifically, additional resection or radiation therapy should be considered.
- Expert opinion 5: Marko Jakopović. I believe that this patient should receive concomitant chemo and radiotherapy followed by immunotherapy for 1 year (in case there is no distant metastasis).

**What's the operational difficulties and precautions for the surgery on patients with immunochemotherapy as neoadjuvant therapy?**

- Expert opinion 1: Antoine Legras. No specific difficulties.
- Expert opinion 2: Georg Schlachtenberger. The tissue of patients after immunotherapy is more fragile than in patients without therapy. Otherwise, there is not a big difference.
- Expert opinion 3: Hisashi Saji. I guess, interlobar bulky LN metastasis in whom should be needed sleeve lobectomy or pneumonectomy.
- Expert opinion 4: Ken Onodera. Although it is not common to encounter severe adhesions during surgery after neoadjuvant immunochemotherapy, severe adhesions may be seen in cases in which vascular or bronchial invasion was suspected, or preoperative radiation therapy. In such cases, a thorough preoperative surgical plan should be planned and bronchoplasty or angioplasty should be considered.
- Expert opinion 5: Marko Jakopović. In vast majority of patients treated with neoadjuvant immune-chemotherapy, there are no difficulties and precautions. In some minor percentage of patients (below 15% in my experience), there was short delay in surgery. In surgical point, there were some difficulties with resection because of scaring tissue in patients with MPR or pCR. The problem is that 15% to 20% of patients who receive neoadjuvant therapy never get to the surgery. That is the problem in earlier stages of the disease (for example stages IB and IIA) which are considered operable upfront.

**What method can be used to determine R0 resection on patients who have negative lymph nodes after immunochemotherapy as neoadjuvant therapy?**

- Expert opinion 1: Antoine Legras. IASLC criteria for R0/Run/R1.
- Expert opinion 2: Georg Schlachtenberger. In my opinion, patients who underwent neoadjuvant therapy should primarily receive a lobectomy. By performing lobectomy, R0 resection is quite probable if a segmentectomy is suitable for the location of the tumor and the patient. A frozen section of the resection margins should be performed.
- Expert opinion 3: Hisashi Saji. Preoperatively PET. Postoperatively pathological report.
- Expert opinion 4: Ken Onodera. If no PET-positive lymph node remains and negative lymph node is proved pathologically, the patient is determined R0 resection; if PET-positive lymph node remains, the patient may be determined R0 resection if negative lymph node is proved pathologically by sampling or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).
- Expert opinion 5: Marko Jakopović. Pathological examination of the resected specimen is the gold standard for determination of R0 resection in surgically treated lung cancer patients. Besides exploration of R0 resection, responses to therapy (pCR and MPR) should be also determined because this is important for decision if adjuvant treatment is needed (no data for that yet).

**Should the postoperative treatment be based on pTNM or ypTNM?**

- Expert opinion 1: Antoine Legras. Probably based on ypTNM.
- Expert opinion 2: Georg Schlachtenberger. In my opinion, definitely on ypTNM. Otherwise, every patient would receive perioperative chemoimmunotherapy. In my opinion, overtreatment is just as bad as undertreatment.
- Expert opinion 3: Hisashi Saji. I think ypTNM should be better.

© Journal of Thoracic Disease. All rights reserved.

- Expert opinion 4: Ken Onodera. There is no clear evidence for additional adjuvant immunotherapy after neoadjuvant immunochemotherapy. It is controversial whether postoperative treatment is necessary in patients with pCR. Therefore, we believe that postoperative treatment should be based on ypTNM.
- Expert opinion 5: Marko Jakopović. This is a million-dollar question. I think that in future we will consider ypTNM much more than pTNM (as mentioned before 30% of patients after neoadjuvant chemo-immunotherapy are having MPR or pCR). The other issue is that in lung cancer patients, we are not having true pTNM before starting any treatment, and therefore, since we have significant proportion of patients with excellent responses to neoadjuvant therapy, I believe in the future we should consider much more ypTNM.

The clinical extent of disease is needed before deciding about appropriate treatment approach and should be recorded for cancer registries, the anatomic extent of disease as described by the ypTNM classification after preoperative therapy is of great prognostic significance.

### *Summarizing the discussion*

The optimal approach and duration for adjuvant immunotherapy following surgery in NSCLC remain uncertain. Various clinical trials have employed different adjuvant treatment strategies. In NADIM II study, postoperative adjuvant therapy consisted of a 6-month course of single-agent immunotherapy (7). In NeoSCORE study (14), dual-agent immunotherapy combined with platinum-based chemotherapy is administered for 2–3 cycles, followed by maintenance with single-agent immunotherapy until the progression of disease occurs. The CheckMate-816 trial did not incorporate immunotherapy in the adjuvant therapy (3). The ongoing studies, such as CheckMate-77T and AEGEAN studies, utilized single-agent immunotherapy as adjuvant therapy for a duration of 1 year. The Neotorch trial included one cycle of dual-agent immunotherapy combined with platinum-based chemotherapy, followed by 1 year of continued single-agent immunotherapy as the adjuvant treatment approach. All of these clinical trials were conducted without circulating tumor DNA (ctDNA) testing on patients, regardless of whether the patient achieved MPR or PCR. As not all these experiments recorded overall survival (OS) outcomes, specific cases should be discussed in a multidisciplinary team (MDT) context, taking into account their individual characteristics.

If R0 resection is not achieved, radiotherapy is indispensable. Subsequently, the continuation of treatment with an adjuvant therapy should be conducted.

The tissues of patients who receive immunotherapy are more fragile than those who do not. Based on this, many clinical trials set the time of surgery to 4–8 weeks after the last dose to give these tissues time to recover. If tumors or lymph nodes are evaluated for vascular or bronchial invasion prior to treatment, preparations should be made in advance for tracheal or angioplasty.

Before neoadjuvant therapy, patients should be thoroughly evaluated, including PET-CT and EBUS-TBNA, to ensure accurate preoperative staging. It provides a basis for treatment efficacy and postoperative adjuvant regimens.

The currently recognized adjuvant therapy is based on ypTNM staging. However, all clinical trials are predefined treatment regimens.

## Conclusions

For individuals diagnosed with resectable stage IIIB squamous cell lung carcinoma, incorporating neoadjuvant immunotherapy combined with chemotherapy presents a viable treatment option. This approach aims to reduce surgical complexities, broaden eligibility criteria for surgery, and enhance the overall success rate of surgical interventions.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-522/rc

*Peer Review File:* Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-522/prf

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-522/coif). H.S. receives payment for lectures from MSD, Boehringer Ingelheim, ETHICON, Covidien, Chugai-pharm, Astellas Pharma, FUJIFILM Medical, Bristol-Myers Squibb, Takeda, AstraZeneca, CSL Behring, and TAIHO. The other authors have no conflicts of interest to declare.

© Journal of Thoracic Disease. All rights reserved.

*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.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

## References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Watzka FM, Fottner C, Miederer M, et al. Surgical therapy of neuroendocrine neoplasm with hepatic metastasis: patient selection and prognosis. Langenbecks Arch Surg 2015;400:349-58.
3. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
4. Provencio M, Nadal E, González-Larriba JL, et al. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:504-13.
5. Gao S, Li N, Gao S, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol 2020;15:816-26.
6. Zhou C, Wu L, Fan Y, et al. Sintilimab Plus Platinum and Gemcitabine as First-Line Treatment for Advanced or Metastatic Squamous NSCLC: Results From a Randomized, Double-Blind, Phase 3 Trial (ORIENT-12). J Thorac Oncol 2021;16:1501-11.
7. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol 2022;40:2924-33. Erratum in: J Clin Oncol 2022;40:3785.
8. Hanna NH, Schneider BJ, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. J Clin Oncol 2020;38:1608-32.
9. Yu H, Boyle TA, Zhou C, et al. PD-L1 Expression in Lung Cancer. J Thorac Oncol 2016;11:964-75.
10. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
11. Rocco D, Della Gravara L, Battiloro C, et al. The role of combination chemo-immunotherapy in advanced non-small cell lung cancer. Expert Rev Anticancer Ther 2019;19:561-8.
12. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-71.
13. Koshy M, Fedewa SA, Malik R, et al. Improved survival associated with neoadjuvant chemoradiation in patients with clinical stage IIIA(N2) non-small-cell lung cancer. J Thorac Oncol 2013;8:915-22.
14. Shao M, Yao J, Wang Y, et al. Two vs three cycles of neoadjuvant sintilimab plus chemotherapy for resectable non-small-cell lung cancer: neoSCORE trial. Signal Transduct Target Ther 2023;8:146.

**Cite this article as:** Li J, Zu P, Jakopović M, Legras A, Saji H, Onodera K, Schlachtenberger G, Liu H. A case report of cStage IIIB squamous cell lung carcinoma completely resected after downstaging with neoadjuvant therapy. J Thorac Dis 2024;16(5):3503-3511. doi: 10.21037/jtd-24-522

© Journal of Thoracic Disease. All rights reserved.