Thoracic surgical challenges after neoadjuvant immunotherapy for non-small cell lung cancer: a narrative review

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Background and Objective: Lung cancer is the leading cause of cancer-related death, with an increasing incidence in both sexes and all ages. Locally advanced non-small cell lung cancer (NSCLC) should be considered as a systemic disease that requires a multimodal approach. Neoadjuvant regimens including chemotherapy, radiotherapy and immunotherapy are widely available options in several centers. The impact of neoadjuvant immunotherapy on surgery is a hot topic for thoracic surgeon because of the technical feasibility of lung resection, especially with a minimally invasive approach, after treatment. The aim of this review is to describe the peri-operative outcomes in patients who underwent neoadjuvant immunotherapy treatment.

Methods: We performed a literature research in PubMed, Medline, Embase, CENTRAL and CINAHL databases. Papers reporting surgical-related complications after neoadjuvant immunotherapy were included. Following terms were used: NSCLC, lung resection, neoadjuvant immunotherapy, survival, feasibility of lung surgery after neoadjuvant treatment, lung surgery after immunotherapy. Only papers written in English were included.

Key Content and Findings: Hilar and mediastinal fibrosis were commonly reported as surgical challenges. These challenges resulted in conversion to thoracotomy in some case but minimally invasive approaches of 67% were reported. Complete resection was achieved in 79.9% to 100% of cases.

Conclusions: Surgery after neoadjuvant treatment is challenging although feasible in selected patients. Hilar and mediastinal fibrosis can render dissection demanding resulting in higher conversion rates.

Keywords: Immunotherapy; neoadjuvant immunotherapy; lung surgery; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the principal cause of cancer-related death in developed countries and is associated with one of the lowest survival rates together with liver and pancreatic cancer (1,2).

Although several improvements in surgical techniques, chemotherapy, immunotherapy and radiotherapy, lung cancer is still associated with modest overall 5-year survival rates and thus remains the leading cause of cancer death in 87 countries in men and 26 countries in women (3). Several therapeutic options are nowadays available for patients affected by non-small cell lung cancer (NSCLC) depending on stage of the disease and its particular molecular pathologic features. Therapeutic management of early and metastatic stages is well-established in international guidelines (4). On the contrary, optimal therapy of locally advanced NSCLC is to date controversial. Moreover, the

term "locally advanced" NSCLC includes several clinical presentations. According to the eighth edition of the tumor-node-metastasis (TNM) classification, stage III NSCLC, for example, represents a heterogeneous group of locally advanced lung cancers with various involvement of N stations (single-, multi-level, bulky disease, controlateral) (5). Consequently, many aspects of the management are poorly established with controversial recommendations within different countries.

Significance of available data is limited. For instance, we have often limited data regarding patients with stage IIIA disease, with several studies that include heterogeneous population with limited follow up.

Histology along with TNM classification are mostly relevant for the prognosis. As Asamura and colleagues showed, number of involved nodal stations and their distribution are a well-defined prognostic indicator in patients with lung malignancies. The reported 5-year survival rates according to the cN and pN status were 60% and 75% for N0, 37% and 49% for N1, 23% and 36% for N2, and 9% and 20% for N3, respectively. For patients with N1 and N2 disease, 5-year published survival rates were: 59% in N1a (single N1 station involved), 50% in N1b (multiple N1 stations involved), 54% in N2a1 (single station N2 involved without N1 status), 43% in N2a2 (single station N2 with N1 involvement) and 38% in N2b disease (multiple N2 stations involved) (6-9).

In the last years, a better understanding of cancer immunology led to the development of several targeted therapies, which can be used in adjuvant or neoadjuvant settings (10).

Because of the difficulties to enroll large numbers of patients in neoadjuvant immunotherapy studies, major pathological response (MPR) has been used to predict the efficacy of neoadjuvant immunotherapy (11). Although complete [pathological complete response (pCR)] or MPR occurs in 19–57% of patients with stage IB-IIIA NSCLC, the real impact of neoadjuvant treatment, especially immunotherapy, on perioperative surgical outcomes has still not been thoroughly elucidated (12,13). The inflammatory reaction caused by neoadjuvant treatment could potentially trigger a fibrosis which can turn surgery into a big challenge for thoracic surgeons. The safety and feasibility of lung surgery, especially with minimal invasive approach, after neoadjuvant immunotherapy is still a matter of debate. We present the following article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-77/rc).

Methods

We performed a literature search in PubMed/Medline/Embase/CENTRAL/CINAHL using the following search words alone or in combination: NSCLC, lung resection, feasibility of lung surgery after neo-adjuvant treatment, lung surgery after immunotherapy. We included all the studies where surgery-related complications after neoadjuvant immunotherapy were reported. Only papers in English language were included (*Table 1*).

Due to the narrative design of the review, a certain subjectivity in choice of studies included is likely.

Results

Feasibility of surgery after neoadjuvant immunotherapy

The first series reporting lung cancer resection after T-cell checkpoint inhibitors was published in 2017 by Chaft *et al.* Five patients were initially treated with anti-programmed cell death 1 and its ligand (anti-PD-1/L-1) therapies with or without anti-CTLA-4 inhibitors and after that, they underwent lung resection. Surgery was considered safe and feasible even if the authors reported that mediastinal and hilar dissection can be technically challenging due to the fibrosis following immunotherapy (14).

Forde and colleagues published in 2018 a pilot study in which they showed that the PDL-1 inhibitor nivolumab, administered in a neoadjuvant setting, was associated with few side effects, did not delay surgery and induced an MPR in 45% of resected tumors. The authors reported that a surgical complete resection was achieved in 95% of the patients. Despite the reported encouraging results, no information about perioperative outcomes were provided (12).

Similarly, no treatment-related delays for patients undergoing surgery after 1 infusion of atezolizumab were reported in the phase II PRINCEPS Trial and therefore Besse and colleagues concluded that surgery is safe after neoadjuvant treatment with atezolizumab (15).

Bott *et al.* conducted a retrospective analysis on 19 patients showing that surgery after immunotherapy could be feasible with a reasonable rate of minor complications (16).

One year later Bott conducted a phase I trial with nivolumab followed by lung resection and, interestingly, 7 of 13 minimally invasive procedures (thoracoscopic or robotic surgeries) were converted to thoracotomy, often because of hilar inflammation and fibrosis, which were almost certainly treatment related (17).

The multi center LCMC3 trial tested the outcomes of

Table 1 Search characteristics

Items	Specification
Date of search	Search performed between 14th and 24th June 2021
Databases and other sources searched	PubMed/Medline/Embase/CENTRAL/CINAHL
Search terms used	1# NSCLC [Mesh]
	2# lung resection [Mesh]
	3# feasibility of lung surgery after neo-adjuvant treatment OR lung surgery after immunotherapy
Timeframe	Not specified
Inclusion and exclusion criteria	Inclusion criteria:
	1. Studies analyzing surgical outcomes after neo-adjuvant immunotherapy
	2. All surgical approaches (open, video-assisted or robotic-assisted thoracoscopic surgery)
	Exclusion criteria:
	1. Overlapping patient cohorts (inclusion of the latest study only to avoid duplication of data)
	2. Editorials, commentaries, case reports
	3. Language other than English
	4. Full text unavailable
Selection process	Initially, records were screened by title and abstract and then duplicate studies were identified and removed using EndNote X9
	For the second stage of screening, we performed full text review of all eligible studies from the title and abstract screening. Both stages were performed by two authors (FM, FA). In case of disagreements the other members of the team were consulted

NSCLC, non-small cell lung cancer.

atezolizumab followed by surgical resection 30–50 days later in patients with NSCLC stage IB to selected IIIB. The study showed a good tolerability of atezolizumab along with reduced unresectability from 12% to 4%. One hundred and fifty-nine patients received surgery with an acceptable rate of intraoperative complications (5/159, 3%) and with R0 resections of 91% (18).

With a more recent case series, Song reported that, in patients who underwent salvage surgery after targeted therapy (erlotinib, icotinib, gefitinib or crizotinib), R0 resection was achieved in all patients included in the study (n=9) with a 67% rate of minimally invasive approaches (19).

A phase II clinical trial investigating the therapeutic effect of two cycles of PD-1 inhibitor pembrolizumab was published in 2021. Eichhorn and colleagues included fifteen patients with NSCLC stage II-IIIA who underwent surgery without a relevant increase of peri operative morbidity (20).

Zhao and colleagues reported in a study published in 2021 that the dissection of pulmonary vessels in 14 patients who underwent surgery after neoadjuvant therapy with erlotinib was more difficult due to fibrosis of the hilum but the conversion rate was 0%. A comparison with a control group of 15 patients receiving neoadjuvant chemotherapy showed no difference in minimally invasive approach's resection rate (P=0.924). Similarly, any significant difference was observed in 1- and 3-year overall or disease-free survivals between the 2 groups (21).

A recent meta-analysis analyzed five clinical trials focusing its attention on the role of neoadjuvant epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) targeted therapy for patients with EGFR-mutant NSCLC. Even if only phase II trials were included, the authors reported a surgical resection and R0 resection rates of 79.9% (95% CI: 65.3–94.5%) and 64.3% (95% CI: 43.8–84.8%). No intraoperative mortality was observed and no intraoperative difficulties were reported (22).

A meta-analysis published in 2020 included 252 patients from seven studies and compared efficacy and safety of neoadjuvant chemotherapy versus neoadjuvant immunotherapy. The pooled odds ratio evaluated the

Table 2 Key points of the analyzed studies

Study	Key points
Chaft *et al*. 2017	Surgery safe and feasible, mediastinal and hilar fibrosis affecting dissection
Forde *et al*. 2018	No delay of surgical treatment, MPR 45%, complete resection in 95% of patients
Bott *et al*. 2019	High conversion rate to open procedure due to hilar inflammation and fibrosis
LCMC3 trial 2019	Complete resection in 91% of patients, acceptable rate of intraoperative complications
Song *et al*. 2020	67% of minimally invasive approaches, complete resection achieved in 100% of patients
Sun *et al*. 2020	Complete resection in 79.9% of cases, no intraoperative difficulties or complications were reported
Jia *et al*. 2020	Better outcomes than neoadjuvant chemotherapy in terms of treatment delay, treatment-related adverse events and surgical complications
Chen *et al*. 2020	No difference in feasibility of sleeve lobectomy compared to surgery alone
Shu *et al*. 2020	Complete resection in 87% of patients, no intraoperative complications reported
Zhao *et al*. 2021	Challenging dissection due to fibrosis of the hilum, 0% conversion rate to open approach
Eichhorn *et al*. 2021	No relevant increase in perioperative morbidity
Spicer *et al*. 2021	No delay in surgical procedure in 83% of the patients in the chemo/immunotherapy group and 75% in the last group with a conversion rate from minimally invasive to open surgery of 11% *vs.* 16%
Jiang *et al*. 2022	Neoadjuvant chemoimmunotherapy improves MPR compared to neoadjuvant immunotherapy alone, no increase in adverse events or surgical delay observed

MPR, major pathological response.

incidence of treatment-related adverse events, incidence of surgical complications and surgical delay rate (0.19, 0.41 and 0.03, respectively). These latter outcomes were better than those for neoadjuvant chemotherapy (95 % CI: 0.04–0.90; 0.22–0.75; 0.01–0.10, respectively) (23).

When immunotherapy regimen is added to chemotherapy in a neoadjuvant setting, surgery seems to be safe and feasible.

Chen and colleagues analyzed the feasibility of sleeve lobectomy in patients who received already chemo/immunotherapy and found no difference in complication rate between sleeve lobectomies after neo-adjuvant chemo-immunotherapy and surgery alone (24).

Furthermore, a combination of neoadjuvant chemo/immunotherapy was investigated in a multicenter study including 30 subjects by Shu *et al*. The outcomes of atezolizumab plus chemotherapy in stage IB-IIIA disease were investigated in this group of patients. The majority of patients (97%) underwent surgery, of which 87% had a radical resection without surgical complications attributable to the neoadjuvant treatment (25).

Similar outcomes were observed by Provencio *et al*. in 41 patients who underwent lung resection after chemo/immunotherapy. All tumors were resectable at time of surgery and a R0 resection was obtained in all cases (26).

With the CheckMate 816 trial, patients with stage IB-IIIA NSCLC were randomized to induction nivolumab plus platinum-doublet chemotherapy (149 patients) versus chemotherapy alone (135 patients). Any delay in surgical procedure was observed in 83% of the patients in the chemo/immunotherapy group and 75% in the last group with a conversion rate from minimally invasive to open surgery of 11% *vs.* 16%. Length of surgery was not influenced by the addition of nivolumab to the chemotherapy regimen (27).

A recent meta-analysis showed that neoadjuvant chemoimmunotherapy can improve the pathological response (MPR rate: 53.3% *vs.* 28.6%; pCR rate: 28.6% *vs.* 9.9%) compared with those receiving neoadjuvant single-agent immunotherapy, without increasing the incidence of adverse events (18.0% *vs.* 12.3%) or surgical delay rate (3.8% *vs.* 7.4%) (28). The keypoints of the analyzed studies are summarized in *Table 2*.

Discussion

After neoadjuvant immunotherapy treatment, hilar fibrosis to some extent is a common intraoperative finding and additionally the pulmonary artery, vein and trachea may

show an increased frailty (29). Therefore, lung resection can potentially be very challenging.

Furthermore, the occurrence of complications after neoadjuvant treatment (e.g., toxicity of drugs, adverse reactions, etc.) can result in a delay of subsequently planned surgery even if some studies have not found such delays (25,30,31).

In view of the above mentioned studies, a minimally invasive approach appears to be valid and safe in the treatment of locally advanced NSCLC with neoadjuvant immunotherapy. Particular care during patient selection must be taken to the presence of bulky tumors infiltrating the mediastinum or the pulmonary vessels because maneuverability is reduced due to tumor location and infiltration of important structures. Although VATS lobectomy seems to result in comparable oncological outcomes and has the advantage of reducing the length of stay as well as postoperative pain and major complications, the approach should be chosen and offered to the patient according to the surgeon's technical capabilities. The dictum "primum non nocere" should be always kept in mind, particularly, but not only, by less experienced surgeon. "Better one conversion than one complication" appears, in this case, to be an appropriate motto.

The optimal timing of the surgical intervention after neoadjuvant therapy is not standardized and has to be still established (32). In order to perform a successful but also safe surgery the timing of transition from inflammation to fibrosis should be investigated because the hilar fibrosis could make vessel dissection more difficult and thus the risk for conversion or intraoperative complications including major blood loss.

Relying on the above mentioned results of the current literature, it seems to be safe and feasible to:

- ❖ Administer neoadjuvant immunotherapy for 2–4 cycles;
- ❖ Perform a CT scan after last cycle and use the Response Evaluation Criteria in Solid Tumours (RECIST);
- ❖ Discuss the CT scans in a multidisciplinary setting;
- ❖ Consider central bulky tumors and infiltration of surrounding structures as possible predictors of conversion from VATS to thoracotomy.

Conclusions

Neoadjuvant treatment regimens potentially improve the benefit of curative surgery in well selected patients with locally advanced NSCLC. Nevertheless, its impact on safety and feasibility of surgery must be elucidated on the basis of prospective, large sample trials.

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Footnote

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Minervini F, Scarci M. Lung cancer screening: where do we stand? Precis Cancer Med 2019;2:34.

3. de Groot PM, Wu CC, Carter BW, et al. The epidemiology of lung cancer. Transl Lung Cancer Res 2018;7:220-33.
4. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv1-iv21.
5. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
6. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:1675-84.
7. Wei S, Asamura H, Kawachi R, Sakurai H, Watanabe S. Which is the better prognostic factor for resected non-small cell lung cancer: the number of metastatic lymph nodes or the currently used nodal stage classification? J Thorac Oncol 2011;6:310-8.
8. Rena O. The "N"-factor in non-small cell lung cancer: staging system and institutional reports. J Thorac Dis 2016;8:3049-52.
9. Martins RG, D'Amico TA, Loo BW Jr, et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. J Natl Compr Canc Netw 2012;10:599-613.
10. Yeh J, Marrone KA, Forde PM. Neoadjuvant and consolidation immuno-oncology therapy in stage III non-small cell lung cancer. J Thorac Dis 2018;10:S451-9.
11. Uprety D, Mandrekar SJ, Wigle D, et al. Neoadjuvant Immunotherapy for NSCLC: Current Concepts and Future Approaches. J Thorac Oncol 2020;15:1281-97.
12. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med 2018;378:1976-86.
13. Chaft JE, Rimner A, Weder W, et al. Evolution of systemic therapy for stages I-III non-metastatic non-small-cell lung cancer. Nat Rev Clin Oncol 2021;18:547-57.
14. Chaft JE, Hellmann MD, Velez MJ, et al. Initial Experience With Lung Cancer Resection After Treatment With T-Cell Checkpoint Inhibitors. Ann Thorac Surg 2017;104:e217-8.
15. Besse B, Adam J, Cozic N, et al. 1215O - SC Neoadjuvant atezolizumab (A) for resectable non-small cell lung cancer (NSCLC): Results from the phase II PRINCEPS trial. Ann Oncol 2020;31:S794.
16. Bott MJ, Cools-Lartigue J, Tan KS, et al. Safety and Feasibility of Lung Resection After Immunotherapy for Metastatic or Unresectable Tumors. Ann Thorac Surg 2018;106:178-83.
17. Bott MJ, Yang SC, Park BJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2019;158:269-76.
18. Kwiatkowski DJ, Rusch VW, Chaft JE, et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): interim analysis and biomarker data from a multicenter study (LCMC3). J Clin Oncol 2019;37:8503.
19. Song W, Di S, Liu J, et al. Salvage surgery for advanced non-small cell lung cancer after targeted therapy: A case series. Thorac Cancer 2020;11:1061-7.
20. Eichhorn F, Klotz LV, Kriegsmann M, et al. Neoadjuvant anti-programmed death-1 immunotherapy by pembrolizumab in resectable non-small cell lung cancer: First clinical experience. Lung Cancer 2021;153:150-7.
21. Zhao W, Chen T, Ji C, et al. Feasibility of Surgical Resection After Induction Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Therapy for N2 Lung Adenocarcinomas. Ann Thorac Surg 2021;111:290-5.
22. Sun L, Guo YJ, Song J, et al. Neoadjuvant EGFR-TKI Therapy for EGFR-Mutant NSCLC: A Systematic Review and Pooled Analysis of Five Prospective Clinical Trials. Front Oncol 2020;10:586596.
23. Jia XH, Xu H, Geng LY, et al. Efficacy and safety of neoadjuvant immunotherapy in resectable nonsmall cell lung cancer: A meta-analysis. Lung Cancer 2020;147:143-53.
24. Chen Y, Zhang L, Yan B, et al. Feasibility of sleeve lobectomy after neo-adjuvant chemo-immunotherapy in non-small cell lung cancer. Transl Lung Cancer Res 2020;9:761-7.
25. Shu CA, Gainor JF, Awad MM, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:786-95.
26. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemo-immunotherapy for the treatment of stage IIIA resectable non-small-cell lung cancer (NSCLC): A phase II multicenter exploratory study—Final data of patients who underwent surgical assessment. J Clin Oncol 2019;37:8509.
27. Spicer J, Wang C, Tanaka F, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) +

platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). Clin Oncol 2021;39:8503.
28. Jiang J, Wang Y, Gao Y, et al. Neoadjuvant immunotherapy or chemoimmunotherapy in non-small cell lung cancer: a systematic review and meta-analysis. Transl Lung Cancer Res 2022;11:277-94.
29. Gao SJ, Corso CD, Wang EH, et al. Timing of Surgery after Neoadjuvant Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:314-22.
30. Cascone T, William WN, Weissferdt A, et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. J Clin Oncol 2019;37:8504.
31. Li N, Ying J, Tao X, et al. P1.18-06 Efficacy and Safety of Neoadjuvant PD-1 Blockade with Sintilimab in Resectable Non-Small Cell Lung Cancer. J Thorac Oncol 2019;14:S627-8.
32. Ahern E, Solomon BJ, Hui R, et al. Neoadjuvant immunotherapy for non-small cell lung cancer: right drugs, right patient, right time? J Immunother Cancer 2021;9:e002248.

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