Effective induction immunotherapy minimizes surgical invasiveness for locally advanced lung cancer

Bao, Feichao; Wang, Jiaming; Shen, Chen; Yu, Fenghao; Jakopović, Marko; Hao, Xiuxiu; Chen, Yang; Wang, Yiyang; Gu, Zhitao; Fang, Wentao

Original Article

Effective induction immunotherapy minimizes surgical invasiveness for locally advanced lung cancer

Feichao Bao[1#], Jiaming Wang[1#], Chen Shen[1#], Fenghao Yu[1], Marko Jakopović[2,3], Xiuxiu Hao[1], Yang Chen[1], Yiyang Wang[1], Zhitao Gu[1], Wentao Fang[1]

[1]Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Department for Respiratory Diseases Jordanovac, University Hospital Centre Zagreb, Zagreb, Croatia; [3]School of Medicine, University of Zagreb, Zagreb, Croatia

Contributions: (I) Conception and design: F Bao, J Wang, C Shen, Z Gu, W Fang; (II) Administrative support: Y Wang, F Yu; (III) Provision of study materials or patients: Y Chen; (IV) Collection and assembly of data: F Bao, X Hao; (V) Data analysis and interpretation: F Bao, J Wang, C Shen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Wentao Fang, MD; Zhitao Gu, MD. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, No. 241, West Huaihai Road, Shanghai 200030, China. Email: vwtfang@hotmail.com; guzhitao0717@hotmail.com.

Background: Immunotherapy has been recommended for neoadjuvant therapy in patients with locally advanced non-small cell lung cancer (NSCLC). However, its effect on surgical resection has not yet been examined. This study aimed to examine the effect of induction immunotherapy on surgical resection in terms of the surgical approach, resection extent, and perioperative recovery.

Methods: We performed a real-world study comprising consecutive patients with clinical stage IB–IIIB NSCLC who received surgical resection after induction immunotherapy from January 2019 to September 2021. The perioperative outcomes were compared in terms of the surgical approach and resection extent.

Results: Among 68 patients, 37 (54.4%) achieved a clinical objective response. Standard resection was performed in 37 patients (54.4%), while extended resection was necessary in the other 31 patients (45.6%). Minimally invasive surgery (MIS) was attempted in 37 cases (54.4%), with only 1 (2.7%) conversion. MIS was significantly more commonly accomplished in patients with a clinical objective response than those without (67.6% *vs.* 35.5%, P=0.008). Patients with a clinical objective response were more likely to have their tumors removed via MIS and/or standard resection (75.7% *vs.* 51.6%, P=0.04), while those without a clinical objective response more often required extended resection using an open approach. Patients receiving standard resection or MIS had significantly better perioperative outcomes than those who underwent extended resection or thoracotomy (all P<0.05).

Conclusions: The results of this large single-center retrospective cohort indicate that in terms of a better clinical response, effective induction immunotherapy could help reduce the resection extent and/or provide more opportunities to perform MIS, resulting in better recovery.

Keywords: Immunotherapy; non-small cell lung cancer (NSCLC); minimally invasive surgery (MIS); resection extent

Submitted May 28, 2024. Accepted for publication Jul 03, 2024. Published online Jul 18, 2024.
doi: 10.21037/tlcr-24-470
View this article at: https://dx.doi.org/10.21037/tlcr-24-470

Introduction

Because of their favorable toxicity profile and effectiveness in advanced non-small cell lung cancer (NSCLC) patients (1), immune checkpoint inhibitors (ICIs) have begun to be used as neoadjuvant alternatives for locally advanced diseases in potential surgical candidates (2). In recent phase III trials, neoadjuvant immunotherapy plus chemotherapy resulted in significantly longer event-

free survival and a higher pathological complete response (pCR) rate compared with chemotherapy alone (3,4). This treatment approach did not increase the incidence of adverse events or impede the feasibility of surgery; however, there was still more than 15% of patients who were unable to proceed with surgery due to various reasons. Effective induction therapy may reduce local invasion and improve the resectability of the tumor; however, severe hilar fibrosis and dense adhesions caused by immunotherapy may also increase the difficulty of surgical resection (5). To investigate the effect of immunotherapy on surgical resection, we performed a literature search to retrieve prospective clinical trials examining the outcomes of neoadjuvant immunotherapy in patients with resectable NSCLC. Some of these trials were documented in Table S1 (2-4,6-14). The majority of these articles focused on the pathological response and survival outcomes of the patients, and provided very limited information on the surgical approaches, resection extent, or perioperative outcomes. Thus, in this real-world study, we aimed to confirm whether the effective induction of immunotherapy could minimize surgical invasiveness in terms of the surgical approach, resection extent, and postoperative outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-470/rc).

Highlight box

Key findings

- In terms of a better clinical response, effective induction immunotherapy could help to reduce the resection extent and/or provide more opportunities to perform minimally invasive surgery (MIS), resulting in better recovery.

What is known, and what is new?

- Previous research suggests that neoadjuvant immunotherapy improves the clinical outcomes of patients with operable locally advanced non-small cell lung cancer (NSCLC). The effect of induction immunotherapy on surgical resection has yet to be explored.
- Patients with a clinical objective response were more likely to have their tumors removed via MIS and/or standard resection, while those without such a response more often needed extended resection via an open approach. Patients receiving standard resection or MIS had significantly better perioperative outcomes than those who underwent either extended resection or thoracotomy.

What is the implication, and what should change now?

- Surgical resection after induction immunotherapy for locally advanced NSCLC is safe and feasible in general.

Methods

Patients

All consecutive patients with clinical stage IB–IIIB NSCLC who underwent pulmonary resection after intentional induction immunotherapy at the Shanghai Chest Hospital from January 2019 to September 2021 were included in this real-world study, except those involved in ongoing clinical trials on induction immunotherapy. Patients who did not proceed to surgery were also excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Shanghai Chest Hospital (No. IS21113). Informed consent was obtained from all the patients before treatment to use their clinical information for research purposes. The patients' charts and images were individually reviewed, and data related to the patients' demographics, tumor characteristics, detailed perioperative outcomes, and survival outcomes were retrospectively collected.

Neoadjuvant therapy and surgical technique

All patients underwent a comprehensive preoperative staging protocol, which included pretreatment tumor biopsy, contrast-enhanced computed tomography scan of the chest, magnetic resonance imaging of brain, positron emission tomography/computed tomography scan, and invasive mediastinal nodal staging with endobronchial ultrasound or mediastinoscopy as clinically indicated. Tumor staging was performed according to the tumor-node-metastasis staging system of the American Joint Committee on Cancer (8th edition) (15). Induction therapy was considered for patients with high tumor T stage or hilar or mediastinal lymph node metastasis, based on the discretion of the treating physicians. The immunotherapy treatments included programmed cell death protein 1 or programmed cell death ligand 1 inhibitors (nivolumab, pembrolizumab, sintilimab, durvalumab, tislelizumab, atezolizumab, and toripalimab), which were used in combination with or without chemotherapy. Tumor response after induction was evaluated by imaging studies according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (16).

Surgical resection of the primary tumor and lymph

nodes was performed by either minimally invasive surgery (MIS), including video-assisted thoracoscopic surgery (VATS), and robotic-assisted thoracoscopic surgery, or the open approach, including posterolateral thoracotomy or median sternotomy. The choice of surgical approach was determined based on individual surgeon's assessment of resectability and their experience in minimally invasive procedures. The resection extent was defined as a standard resection (anatomical segmentectomy or lobectomy), or an extended resection (the resection of more than one lobe, including a bilobectomy, sleeve lobectomy, lobectomy with super vena cava resection, and reconstruction and pneumonectomy). Complete resection (R0 resection) was defined according to the recommendations of the International Association for the Study of Lung Cancer [2005] (17).

Data collection and evaluation

Postoperative complications were described and counted according to the Common Terminology Criteria for Adverse Events Version 5.0 (18). The rates of postoperative complications, duration of chest drainage, postoperative length of stay and other factors were compared between groups to evaluate patients' recovery. On histological examination, the major pathological response (MPR) was defined as less than 10% of viable tumor cells remaining, while the pCR was defined as no viable residual tumor in the resected specimen. Overall survival (OS) was calculated from the date of operation to the date of death from any cause. Progression-free survival (PFS) in all patients was defined as the time between surgery and tumor progression or death from any cause. Disease-free survival (DFS) in patients with complete surgical resection was defined as the time from surgery to recurrence or death from any cause.

Statistical analysis

The continuous variables were compared using the two-tailed Student's *t*-test or the Mann-Whitney *U* test as appropriate. The categorical variables were compared using the Pearson's chi-square test or Fisher exact test as appropriate. The Kaplan-Meier curve and the log-rank test were used to estimate and compare OS, PFS, and DFS between the groups. A competing-risks proportional hazards model was used to analyze survival outcomes, with non-lung cancer-related deaths considered competing events. Predictors were examined using the Fine-Gray proportional hazards model. Multivariable analyses were performed in a forward stepwise manner for factors identified in univariate analyses with P<0.10. A P value less than 0.05 was considered statistically significant. All the statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA).

Results

From January 2019 to September 2021, a total of 68 consecutive patients who received induction immunotherapy followed by surgical resection were identified for inclusion in the study (*Table 1*). Among them, 61 patients (89.7%) received immunotherapy plus chemotherapy, and 7 patients (10.3%) received either single or double agent ICI treatment. Squamous cell carcinoma was the most common histological subtype (n=42, 61.8%), and most of the tumors were centrally located (n=42, 61.8%). According to the RECIST, we observed a partial response (PR) in 37 (54.4%) patients after induction treatment, radiological stable disease (SD) in 31 (45.6%) patients, and an overall objective response rate (ORR) of 54.4% (Figure S1). Complete resection was successfully achieved in 60 (88.2%) patients. Postoperative complications occurred in 20 (29.4%) patients, the most common of which were air leak and atrial fibrillation (Table S2). Air leak was particularly frequent among patients undergoing sleeve lobectomy. Only 1 patient died from non-ICI related respiratory failure after bilobectomy via thoracotomy. Thus, the study had a 30-day mortality rate of 1.5%.

In 37 patients (54.4%) the tumors were able to be removed by standard resection. However, extended resection was necessary in the other 31 patients (45.6%), including bilobectomy in 7 cases, sleeve lobectomy in 18 cases, pneumonectomy in 4 cases, and lobectomy with super vena cava resection and reconstruction in 2 cases (*Table 1*). There were more centrally located tumors (93.5% *vs.* 35.1%, P<0.001) and squamous cell carcinomas (83.9% *vs.* 43.2%, P<0.001) in the patients receiving extended resection than those receiving standard resection (*Table 2*). The ORR was higher in the standard resection patients than the extended resection patients (59.5% *vs.* 48.4%, P=0.36), but the difference was not statistically significant. The complete resection rates were similar after both extended and standard resection (90.3% *vs.* 86.5%, P=0.72). Extended resection was associated with a significantly

Table 1 Clinical and pathological characteristics of 68 patients with clinical stage IB–IIIB non-small cell lung cancer

Characteristics	Value
Age (years), median [range]	62 [33–76]
Male sex, n (%)	61 (89.7)
Comorbidity, n (%)	
Yes	32 (47.1)
No	36 (52.9)
Smoking history, n (%)	
Current/former	53 (77.9)
Never	15 (22.1)
Clinical stage, n (%)	
IB	2 (2.9)
IIA	3 (4.4)
IIB	9 (13.2)
III	54 (79.4)
Pathology, n (%)	
Adenocarcinoma	18 (26.5)
Squamous cell	42 (61.8)
Adenoid cystic carcinoma	1 (1.5)
Adenosquamous carcinoma	1 (1.5)
Not specified	6 (8.8)
Tumor location, n (%)	
Central	42 (61.8)
Peripheral	26 (38.2)
Radiological response, n (%)	
Partial response	37 (54.4)
Stable disease	31 (45.6)
Extent of resection, n (%)	
Standard resection	37 (54.4)
Extended resection	31 (45.6)
Bilobectomy	7 (10.3)
Sleeve lobectomy	18 (26.5)
Pneumonectomy	4 (5.9)
Lobectomy + SVC replacement	2 (2.9)
Surgical approach, n (%)	
Open	32 (47.1)
MIS	36 (52.9)
Resection status, n (%)	
R0	60 (88.2)
R1	4 (5.9)
R2	4 (5.9)

SVC, super vena cava; MIS, minimally invasive surgery.

higher volume of blood loss (200 *vs.* 100 mL, P=0.005), higher postoperative complication rate (51.6% *vs.* 10.8%, P<0.001), longer chest-drainage duration (median 6 *vs.* 4 days, P<0.001), and longer postoperative length of stay (median 7 *vs.* 5 days, P<0.001) than standard resection.

MIS was attempted in 37 patients (54.4%), and was successfully completed in 36 patients (97.3%). Only 1 case (2.7%) was converted from VATS to thoracotomy. The surgical approach was found to be significantly associated with the ORR (*Figure 1A*). MIS was found to be more accomplished in patients with a PR (25/37, 67.6%) than those with SD (11/31, 35.5%) after induction (P=0.008) (*Table 3*). Standard resection was more often performed via MIS than the open approach (78.4% *vs.* 22.6%, P<0.001) (*Figure 1B*). However, extended resection was still able to be accomplished via MIS in 22.6% of the patients (7 of 31, including 4 cases of sleeve lobectomy and 3 cases of bilobectomy), among these patients, six achieved a PR after induction immunotherapy. Compared to the patients who underwent open surgery, those who underwent MIS had significantly fewer postoperative complications (16.7% *vs.* 43.8%, P=0.03), a shorter chest-drainage duration (median: 4 *vs.* 5 days, P=0.009), and a shorter postoperative length of stay (median: 5 *vs.* 6 days, P=0.003) (*Table 3*). The patients with a PR had more opportunities to have their tumors removed via MIS and/or standard resection (75.7% *vs.* 51.6%, P=0.04), while those with SD more frequently required extended resection via the open approach (*Figure 1C*).

On histological examination, a MPR was observed in 34 patients (50.0%), and a pCR was observed in 18 patients (26.5%) (Figure S2). However, the pathological response was not associated with the radiologic response. Among the 34 MPR patients, 8 patients achieved SD according to the radiological evaluation. Conversely, 11 of the 37 PR patients did not achieve an MPR. Further, the pathological response was not found to be associated with either the surgical approach or resection extent (*Tables 2,3*).

After a median follow-up period of 15 months (range, 7–37 months), 64 patients (94.1%) were alive and 9 (13.2%) had developed recurrent disease. The OS and PFS rates at 2-year post surgery were 94.0% and 80.7%, respectively, for the entire cohort. There was a trend toward better 2-year PFS in the MPR patients than the non-MPR patients (93.0% *vs.* 59.4%), with a borderline significant difference (P=0.06). However, the ORR was found not to be associated with PFS (P=0.98) or OS (P=0.46). Multivariable Fine-Gray analysis (*Table 4*) results showed that R0 resection was the only independent predictor of better PFS [hazard ratio (HR)

Table 2 Oncological characteristics and surgical outcomes between the extended resection group and standard resection group

Characteristics	Extended resection (n=31)	Standard resection (n=37)	P value
Pathology			<0.001
Adenocarcinoma	1 (3.2)	17 (45.9)	
Squamous cell carcinoma	26 (83.9)	16 (43.2)	
Others	4 (12.9)	4 (10.8)	
Tumor location			<0.001
Central	29 (93.5)	13 (35.1)	
Peripheral	2 (6.5)	24 (64.9)	
Radiology response			0.36
Partial response	15 (48.4)	22 (59.5)	
Stable disease	16 (51.6)	15 (40.5)	
Pathological response			0.33
MPR	18 (58.1)	16 (43.2)	
Non-MPR	13 (41.9)	21 (56.8)	
cStage at presentation			0.82
I/II	6 (19.4)	8 (21.6)	
III	25 (80.6)	29 (78.4)	
ycStage after induction			0.31
I/II	12 (38.7)	15 (40.5)	
III	19 (61.3)	22 (59.5)	
Surgical approach			<0.001
Open	24 (77.4)	8 (21.6)	
MIS	7 (22.6)	29 (78.4)	
Resection status			0.72
R0	28 (90.3)	32 (86.5)	
R1/R2	3 (9.7)	5 (13.5)	
Operation time, min	154.5 [59–329]	152 [41–203]	0.12
EBL, mL	200 [100–1,500]	100 [100–200]	0.005
Complication	16 (51.6)	4 (10.8)	<0.001
Intra-operative mortality	0	0	N/A
30-day mortality	1 (3.2)	0	0.46
Duration of chest drainage, days	6 [2–20]	4 [2–9]	<0.001
POS, days	7 [3–20]	5 [3–10]	<0.001

Data are presented as n (%) or median [range]. MPR, major pathological response; cStage, clinical stage; ycStage, clinical stage after induction; MIS, minimally invasive surgery; EBL, estimated blood loss; N/A, not applicable; POS, postoperative length of stay.

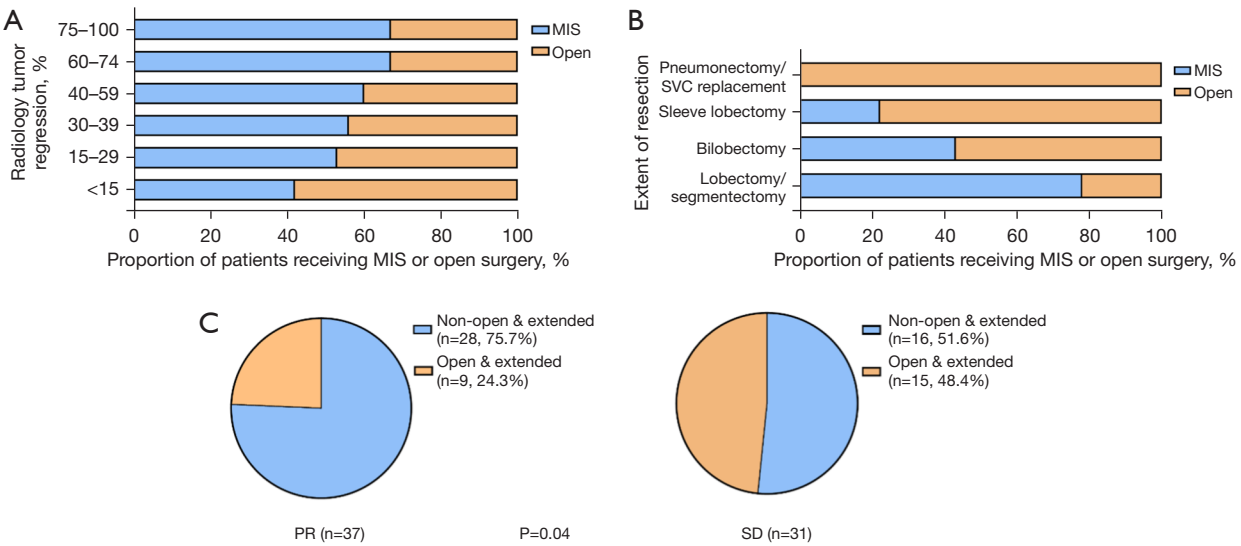

Figure 1 Proportions of patients receiving different types of surgery. (A) Proportions of patients receiving MIS or open surgery with different levels of radiology tumor regression. (B) Proportions of patients receiving MIS or open surgery with different resection extents. (C) Proportions of patients receiving extended resection via the open approach with different radiological responses. Open & extended, patients receiving extended resection via open surgery; non-open + extended, patients receiving minimally invasive surgery or standard resection. MIS, minimally invasive surgery; SVC, super vena cava; PR, partial response; SD, stable disease.

=0.18, 95% confidence interval (CI): 0.05–0.62, P=0.006] and better OS (HR =0.14, 95% CI: 0.03–0.62, P=0.01). For patients who underwent R0 resection, OS and DFS were similar between those who received the MIS and open approach (*Figure 2A,2B*), and between those who received extended resection and standard resection (*Figure 2C,2D*).

Discussion

Recent research suggests that neoadjuvant immunotherapy improves the clinical outcomes of patients with operable locally advanced NSCLC (3). However, to date, no research has been conducted on the effect of induction immunotherapy on surgical resection, especially in relation to the resection extent and surgical approach. In this real-world study, we retrospectively included a large number of patients who received surgery after induction immunotherapy at a single-center and focused on the surgical outcomes in terms of the surgical approach and resection extent. We found that surgical resection after induction immunotherapy was safe and feasible in general, with a high R0 resection rate and satisfactory perioperative outcomes. Complete resection was the only independent predictor of better PFS and OS. Meanwhile, surgical invasiveness in terms of the surgical approach and resection extent was minimized by the effective induction of immunotherapy as shown by the objective radiological response, resulting in diminished surgical risks and better patient recovery.

Surgical resection after neoadjuvant immunotherapy for locally advanced NSCLC can be challenging. The effect of induction immunotherapy on surgical complexity has not yet been well explored. Dense fibrosis may develop in patients who respond to immunotherapy, resulting in increased difficulty for mediastinal and hilar dissection (5). However, it has been reported that only 8.1% (3 of 37) of operations after induction immunotherapy were “very complex” due to fibrotic change caused by immunotherapy (19). Conversely, many locally advanced NSCLCs are centrally located with local hilum invasion and thus resection is technically difficult. The effective induction of immunotherapy may lead to tumor regression and reduce invasion to the hilar structures. The results of the Checkmate-816 (3) trial suggested that the surgical outcomes of patients who received immunotherapy plus chemotherapy were more favorable than those who received chemotherapy alone. Specifically, there were fewer cases of pneumonectomy and a higher use of MIS in the patients who received immunotherapy plus chemotherapy (3). The higher MPR and pCR might account for better patient

Table 3 Oncological characteristics and surgical outcomes between the open approach group and minimally invasive surgery group

Characteristics	Open (n=32)	MIS (n=36)	P value
Pathology			0.04
Adenocarcinoma	4 (12.5)	15 (41.6)	
Squamous cell carcinoma	23 (71.9)	19 (52.8)	
Others	5 (15.6)	2 (5.6)	
Tumor location			0.04
Central	27 (84.4)	15 (41.7)	
Peripheral	5 (15.6)	21 (58.3)	
Radiology response			0.008
Partial response	12 (37.5)	25 (69.4)	
Stable disease	20 (62.5)	11 (30.6)	
Pathological response			0.33
MPR	14 (43.8)	20 (55.6)	
Non-MPR	18 (56.3)	16 (44.4)	
cStage at presentation			0.21
I/II	4 (12.5)	10 (27.8)	
III	28 (87.5)	26 (72.2)	
ycStage after induction			0.02
I/II	8 (25.0)	19 (52.8)	
III	24 (75.0)	17 (47.2)	
Resection status			0.14
R0	26 (81.2)	34 (94.4)	
R1/R2	6 (18.8)	2 (5.6)	
Operation time, min	153 [41–329]	152.5 [80–248]	0.59
EBL, mL	200 [100–1,500]	100 [100–200]	0.002
Complication	14 (43.8)	6 (16.7)	0.03
30-day mortality	1 (3.1)	0	0.47
Duration of chest drainage, days	5 [2–20]	4 [2–10]	0.009
POS, days	6 [3–20]	5 [3–16]	0.003

Data are presented as n (%) or median [range]. cStage, clinical stage; ycStage, clinical stage after induction; MPR, major pathological response; EBL, estimated blood loss; POS, postoperative length of stay.

survival in the immunotherapy arm; however, the study did not investigate whether the pathological response was also the underlying reason for the reduced resection extent and the higher use of MIS in that trial (3). In the current study, we found that the clinical response in terms of the ORR was not directly associated with the pathological response of the patients receiving neoadjuvant immunotherapy. However, the clinical response in terms of the PR provided the patients with more opportunities to have their tumors removed via MIS and/or standard resection (75.7% *vs.* 51.6%, P=0.04). The pathological response in terms of the MPR was not associated with either the resection extent or the surgical approach. Therefore, while post-treatment fibrosis may occur to some extent after induction

Table 4 Univariable and multivariable Fine-Gray proportional hazards model for survival of patients after resection

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
PFS						
Female versus male	1.78	0.14–2.22	0.41			
Age (per 1 year old increase)	1.02	0.94–1.10	0.65			
Non-SCC versus SCC	1.45	0.40–5.24	0.57			
PR versus SD	0.98	0.28–3.49	0.98			
Standard versus extended	1.75	0.44–7.01	0.43			
MIS versus open	0.51	0.13–2.01	0.34			
R0 versus non-R0	0.16	0.04–0.54	0.003	0.18	0.05–0.62	0.006
MPR versus non-MPR	0.09	0.01–0.72	0.02	0.11	0.02–1.06	0.06
pCR versus non-pCR	0.28	0.04–2.17	0.22			
OS						
Female versus male	2.48	0.05–3.39	0.40			
Age (per 1 year old increase)	1.16	1.05–1.29	0.04	1.51	0.77–2.97	0.23
Non-SCC versus SCC	0.01	0.00–116.00	0.36			
PR versus SD	0.42	0.04–4.25	0.46			
Standard versus extended	0.01	0.00–57.07	0.35			
MIS versus open	0.01	0.00–67.16	0.41			
R0 versus non-R0	0.09	0.01–0.80	0.03	0.14	0.03–0.62	0.01
MPR versus non-MPR	0.25	0.03–3.08	0.31			
pCR versus non-pCR	0.49	0.08–18.06	0.97			

HR, hazard ratio; CI, confidential interval; PFS, progression-free survival; SCC, squamous cell carcinoma; SD, stable disease; PR, partial response; MIS, minimally invasive surgery; MPR, major pathological response; pCR, pathological complete response; OS, overall survival.

immunotherapy, the resection extent and feasibility of MIS largely depend on the effectiveness of tumor regression by neoadjuvant therapy.

Generally, most patients for whom induction immunotherapy is planned have centrally located NSCLC, and this trend was also observed in our study. Extended resection was often inevitable, even after preoperative therapy. In the Checkmate-816 trial, 16.8% of the patients received pneumonectomy after immunotherapy (3). We found that extended resection was associated with worse perioperative outcomes than standard resection. Most of the extended resection cases required an open approach (77.4%). Conversely, in the standard resection cases, the open approach was necessary in only 21.6% of the patients. Not surprisingly, extended resection was associated with worse perioperative outcomes than standard resection. Nevertheless, the perioperative outcomes of the extended resection were generally acceptable. More importantly, extended resection achieved a similar rate of complete resection as that of standard resection. The multivariable analysis results showed that complete resection was associated with improved survival. Based on the acceptable perioperative outcomes and a high rate of complete resection, which is critical for oncological outcomes, extended resection should not be denied to patients after induction immunotherapy.

MIS has already been attempted in patients with locally advanced NSCLC after induction treatment (3). The reported conversion rates after induction immunotherapy have been quite high (11–54%) (2-4,6-14), which might be

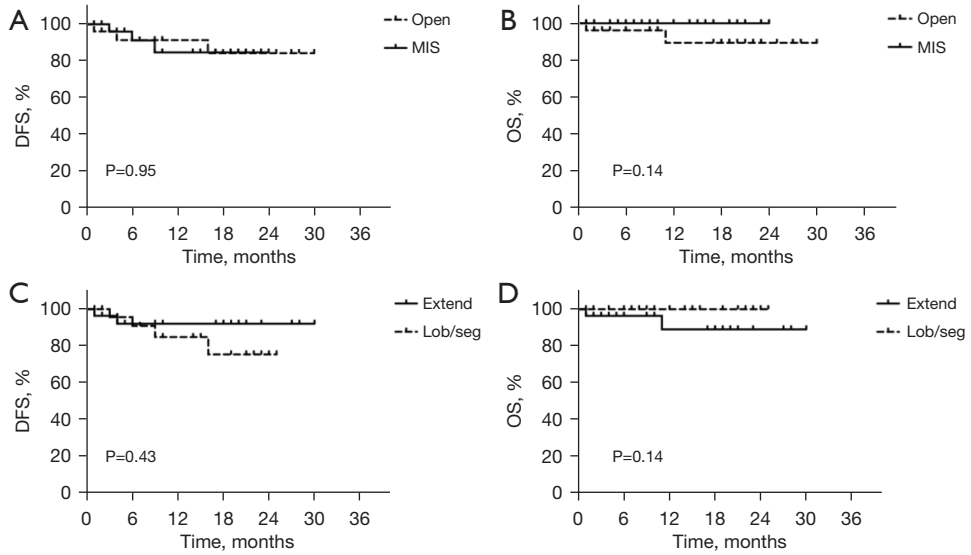

Figure 2 Survival outcomes of patients after R0 resection. (A) DFS of patients receiving MIS or open surgery; (B) OS of patients receiving MIS or open surgery; (C) DFS of patients with different resection extents; (D) OS of patients with different resection extents. Extend, extended resection; Lob/seg, lobectomy/segmentectomy; DFS, disease-free survival; MIS, minimally invasive surgery; OS, overall survival.

because of the central tumor location and/or dense adhesion after induction. The conversion rate in the present study was only 2.7% (n=1), which was due to sufficient previous experience in MIS pulmonary resection after induction therapies at our center (20). For extended resection, 22.6% of the cases (7/31) were still able to be accomplished by MIS. To date, no study has compared the surgical outcomes of patients receiving MIS with those receiving open surgery after induction immunotherapy. In this study, MIS was found to be performed in more than half of the patients (52.9%), with a similar complete resection rate to that of the open approach. Compared with the open approach the MIS approach resulted in better perioperative outcomes. As MIS may help achieve better surgical outcomes and improve postoperative recovery, without compromising the completeness of the resection, it should be attempted in well-selected cases after immunotherapy.

In this study, we found that the effective induction of immunotherapy, represented by an objective radiological response before surgery, was associated with a higher proportion of standard resection and/or MIS in patients with locally advanced NSCLC. Patients with a PR after the effective induction of immunotherapy had more opportunities to receive MIS than those with SD (67.6% *vs.* 35.5%, P=0.008). When the resection extent was taken into consideration, the patients with a PR were significantly less likely to endure extended resection by the open approach than those with SD (24.3% *vs.* 48.4%, P=0.04). Therefore, the effective induction of immunotherapy in terms of a better radiological response could help to minimize surgical trauma by reducing the resection extent and/or increasing the use of MIS, and thus improving the perioperative recovery of patients. The radiological evaluation of the treatment response is helpful in deciding the resection extent and surgical approach. This supports our previous findings after induction targeted therapy for N2/stage IIIA NSCLC patients, which also showed that the effective induction of this therapy increased the use of VATS and reduced the resection extent, resulting in better perioperative outcomes (20).

This study had certain limitations. First, it was retrospective in nature and thus had unavoidable intrinsic biases. For example, the surgeon's preference and experience might influence the perioperative surgical outcomes. However, in this real-world study, all consecutive patients treated during the study period were included to reduce potential selection biases. Second, patients who underwent induction immunotherapy but did not proceed to surgery were not included in this study, and the reasons for the cancelled surgeries were not analyzed. Third, different regimens of immunotherapy were used for induction, which might have effects on survival and recurrence; however, the main purpose of our study was to investigate the effect of immunotherapy on surgical resection. To further validate

our findings derived from a single center experience, a future multi-center real-world study utilizing prospectively collected data with similar objectives should be conducted.

Conclusions

In conclusion, surgical resection after the effective induction of immunotherapy for locally advanced NSCLC is safe and feasible in general. The complete removal of the disease is associated with better survival outcomes; however, extended resection is often necessary to achieve this goal. Our results suggest that the effective induction of immunotherapy in terms of a better radiological response could help to minimize surgical invasiveness by reducing the resection extent and/or increasing the feasibility of MIS, resulting in better patient recovery. Thus, immunotherapy should be further explored in the inductive setting for patients with locally advanced lung cancers.

Acknowledgments

Funding: This work was supported by the Major Clinical Research Project of Shanghai Shenkang Hospital Development Center (No. SHDC2020CR1023B) and the National Multi-disciplinary Treatment Project for Major Diseases of China (No. 2020NMDTP).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-470/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-470/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-470/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-470/coif). M.J. receives consulting fees from MSD, Pfizer, AstraZeneca, J&J, Amgen; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from MSD, Pfizer, AstraZeneca, J&J, Amgen, Roche; and support for attending meetings and/or travel from MSD, Roche, AstraZeneca. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Shanghai Chest Hospital (No. IS21113) and informed consent was obtained from all the patients.

References

1. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Ann Oncol 2021;32:881-95.
2. Provencio M, Nadal E, Insa A, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21:1413-22.
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. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:491-503.
5. Sepesi B, Zhou N, William WN Jr, et al. Surgical outcomes after neoadjuvant nivolumab or nivolumab with ipilimumab in patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 2022;164:1327-37.
6. Reuss JE, Anagnostou V, Cottrell TR, et al. Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer. J Immunother Cancer 2020;8:e001282.
7. 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.
8. Cascone T, William WN Jr, Weissferdt A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. Nat Med 2021;27:504-14.
9. Rothschild SI, Zippelius A, Eboulet EI, et al. SAKK 16/14: Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients With Stage IIIA(N2) Non-Small-Cell Lung Cancer-A Multicenter Single-Arm Phase II Trial. J Clin Oncol 2021;39:2872-80.
10. Lee J, Chaft J, Nicholas A, et al. PS01.05 surgical and clinical outcomes with neoadjuvant atezolizumab in resectable stage IB–IIIB NSCLC: LCMC3 trial primary analysis. J Thorac Oncol 2021;16:S59-61.
11. Gao S, Li N, Gao S, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol 2020;15:816-26.
12. Wislez M, Mazieres J, Lavole A, et al. Neoadjuvant durvalumab for resectable non-small-cell lung cancer (NSCLC): results from a multicenter study (IFCT-1601 IONESCO). J Immunother Cancer 2022;10:e005636.
13. Provencio-Pulla M, Nadal E, Larriba JLG, et al. Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: Primary endpoint results of pathological complete response (pCR) from phase II NADIM II trial. J Clin Oncol 2022;40:8501.
14. Zhang P, Dai J, Sun F, et al. Neoadjuvant Sintilimab and Chemotherapy for Resectable Stage IIIA Non-Small Cell Lung Cancer. Ann Thorac Surg 2022;114:949-58.
15. Amin MB, Edge SB, Greene FL, et al. editors. AJCC Cancer Staging Manual (8th ed.). New York, NY: Springer, 2017.
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
17. Rami-Porta R, Wittekind C, Goldstraw P, et al. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25-33.
18. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Published November 27, 2017.
19. 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.
20. 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.

Cite this article as: Bao F, Wang J, Shen C, Yu F, Jakopović M, Hao X, Chen Y, Wang Y, Gu Z, Fang W. Effective induction immunotherapy minimizes surgical invasiveness for locally advanced lung cancer. Transl Lung Cancer Res 2024;13(8):1964-1974. doi: 10.21037/tlcr-24-470