Original Article

Sleeve lobectomy versus lobectomy after neoadjuvant chemo-immunotherapy for non-small cell lung cancer invading the lobar bronchial orifice: a multicenter retrospective cohort study

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Background: For non-small cell lung cancer (NSCLC) invading lobar bronchial orifice, sleeve lobectomy is the preferred surgical option. Neoadjuvant chemo-immunotherapy may allow R0 resection with lobectomy. This study aims to compare the long-term outcome of sleeve lobectomy and lobectomy after neoadjuvant chemo-immunotherapy.

Methods: We retrospectively screened patients undergoing neoadjuvant chemo-immunotherapy followed by lobectomy or sleeve lobectomy for NSCLC invading lobar bronchial orifice from March 2019 and April 2022. Event-free survival (EFS) was compared between sleeve lobectomy and lobectomy groups in the original cohort and the inverse probability of treatment weighting (IPTW) adjusted cohort. Cox regression was conducted for the potential association between surgical type and EFS.

Results: We initially enrolled 248 patients. According to the inclusion criteria, the final analysis included 68 (27.4%) patients: 38 undergoing lobectomy and 30 undergoing sleeve lobectomy. The 2-year EFS was 83.3% versus 60.5% in sleeve and lobotomy groups, respectively [hazard ratio (HR) =0.46, 95% confidence interval (CI): 0.210–1.005; P=0.057]. In Cox regression analysis, improved EFS was associated with pathological complete response (pCR) (HR =0.31, 95% CI: 0.11–0.90; P=0.03) but not surgical types (HR =0.54, 95% CI: 0.22–1.5; P=0.20). In the subgroup analysis including pCR patients (n=31), median EFS was not reached (NR) in either group (P=0.8) before and after IPTW. In the non-pCR subgroup (n=37), median EFS was 21 months (95% CI: 13–NR) in lobectomy group versus not achieved (95% CI: 25–NR) in sleeve lobectomy group (P=0.04) after IPTW.

Conclusions: Lobectomy could be feasible for pCR patients and there is survival advantage with sleeve lobectomy in patients failing to achieve pCR after neoadjuvant chemo-immunotherapy.

Keywords: Neoadjuvant therapy; sleeve lobectomy; lobectomy; event-free survival (EFS); immunotherapy

Submitted Oct 09, 2024. Accepted for publication Jan 09, 2025. Published online Feb 25, 2025.
doi: 10.21037/tlcr-24-925
View this article at: https://dx.doi.org/10.21037/tlcr-24-925

Introduction

Sleeve lobectomy is the preferred surgical option for locally advanced non-small cell lung cancer (NSCLC) that invades the bronchial orifice of the lungs (1). In comparison to lobectomy, sleeve lobectomy is technically more challenging, and associated with longer operation time and thus increased risk of peri-operative complications.

Chemo-immunotherapy has also been increasingly used as an alternative modality for neoadjuvant therapy for NSCLC due to advantage in reducing tumor size and micrometastasis burden before operation versus neoadjuvant chemotherapy (2-4). Tumor regression after neoadjuvant chemo-immunotherapy may allow for R0 resection with lobectomy. We conducted a retrospective analysis to compare sleeve lobectomy versus lobectomy in patients undergoing neoadjuvant chemo-immunotherapy for NSCLC that invaded lobar bronchial orifice. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-925/rc).

Highlight box

Key findings

- Pathological complete response (pCR) is the essential element for surgical modification after neoadjuvant chemo-immunotherapy for non-small cell lung cancer (NSCLC) invading lobar bronchial orifice. Lobectomy is a feasible surgical plan when patients achieve pCR after neoadjuvant chemo-immunotherapy and sleeve lobectomy was associated with improved event-free survival (EFS) if pCR is not achieved.

What is known and what is new?

- Sleeve lobectomy was typically chosen for NSCLCs invading the bronchial opening to ensure R0 resection. However, after neoadjuvant chemo-immunotherapy, tumor regression at the lobar bronchial orifice may allow for R0 resection via lobectomy.
- This is a study exploring the impact of surgical modification on prognosis after tumor regression due to neoadjuvant chemo-immunotherapy for patients with NSCLC invading lobar bronchial orifice.

What is the implication, and what should change now?

- From a clinical perspective, evaluating the pathological response to neoadjuvant chemo-immunotherapy before surgery is essential when choosing between sleeve lobectomy and lobectomy. The increased rates of major pathological response and pCR achieved with neoadjuvant chemo-immunotherapy appear to discourage the need for more extensive surgical interventions.

Methods

Data source

Participants for this study were enrolled from four participating centers. The study protocol was approved by the institutional review committees of Affiliated Hospital of Xuzhou Medical University (No. XYFY2023-KL162-01), Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University (No. 2024DZKY-007-01), Shanghai Chest Hospital [No. KS(Y)23082] and Shandong Cancer Hospital and Institute (No. SDTHEC2023006011). Informed consent was waived by the review committees on the condition of patient anonymity. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

For inclusion in the final analysis, the lesion must be located in a single lobe as assessed using computed tomography (CT), and had invaded the bronchial orifice as determined by bronchoscopy prior to but not after neoadjuvant chemo-immunotherapy. Brain magnetic resonance imaging (MRI), abdominal ultrasound, bone scan and positron emission tomography/CT (PET/CT) were used to rule out distant metastases. Disease staging was conducted using the tumor-node-metastasis (TNM) system of the eighth edition of American Joint Cancer Committee (AJCC) (5).

Responses to neoadjuvant therapy was evaluated after 2 cycles of neoadjuvant therapy using the Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 (6). The decision to perform surgery, conduct additional cycles of neoadjuvant therapy, or switch to radiotherapy was made by a multidisciplinary tumor board.

Surgery

Sleeve lobectomy was conducted as previously reported (7-9). In sleeve lobectomy group, patients who underwent bronchial sleeve resection, as well as one patient who had double sleeve resection, were included. No patients who only

received arterial sleeve resections were included. All patients underwent systematic lymph node dissection. Strategy for lymph node dissection was identical in the two groups: for NSCLC on the right side, groups 2, 3, 4, 7, 8, 9, 10 and 11 were dissected; for NSCLC on the left side, groups 4, 5, 6, 7, 8, 9, 10 and 11 were dissected. Stationing of the lymph nodes was conducted according to the guidelines of the AJCC and the International Association for Lung Cancer Research (5). Surgical complications were classified based on the Clavien-Dindo classification system (10).

Pathological response

Major pathological response (MPR) was defined as ≤10% viable tumor cells in the primary lesion. Pathological complete response (pCR) was defined as absence of viable tumor cells in resected tissues (11).

Outcomes

The primary outcome was the event-free survival (EFS), which is calculated from the time from surgery to recurrence (either local or distant), death, or the date of last follow-up. The secondary outcome was the perioperative complications.

Statistical analysis

Categorical variables were compared between the two groups using χ^2 test or Fisher exact probability test, and presented as number and percentage. Continuous variables following normal distribution were compared between the two groups using Student's *t*-test and presented as mean ± standard deviation. Due to the small population and the difference in population between sleeve lobectomy group and lobectomy group, the propensity scored based inverse probability of treatment weighting (IPTW) was performed (12). Stabilized weights were calculated for each case based on the estimated propensity score (13). We calculated the propensity score for each variable through logistic regression model by the following variables: age, gender, body mass index (BMI), smoking, diabetes, hypertension, tumor location, histology, clinical T stage, clinical N stage, clinical TNM stage, pathological response and R0 resection. The standardized mean difference (SMD) was used to assess the balance of baseline characteristics between groups. An SMD less than or equal to 0.1 was regarded as an ideal balance. The median EFS was estimated by the Kaplan-Meier method before and after IPTW adjustments. The weighted cox proportional hazard regression was conducted to identify risk factors associated with EFS, and the results are shown as hazard ratio (HR) and 95% confidence interval (CI). P<0.05 (two-sided) was considered statistically significant. All statistical analyses were conducted using R (v4.3.1).

Results

Baseline characteristics

We initially enrolled 248 patients. After data cleaning according to the inclusion criteria, the final analysis included 68 (27.4%) patients (mean age: 60.4 years; 62 men): 38 in the lobectomy group and 30 patients in the sleeve lobectomy group (*Figure 1*). Majority of the patients had stage III disease (75%; *Table 1*). After IPTW, demographic and other clinicopathological characteristics of the two groups were generally balanced, with all SMD less than 0.1 except for clinical N stage (SMD =0.192) and clinical TNM stage (SMD =0.101, *Figure 2*).

Perioperative outcomes

The sleeve lobectomy group had longer operation time before (184.07±43.30 versus 154.45±44.81 min, P=0.008) and after matching (IPTW: 184.72±38.77 versus 155.15 ±45.34 min, P=0.005), and higher rate of thoracotomy before (53.3% versus 15.8%, P=0.002) after matching (57.6% versus 12.6%, P<0.001) (*Table 2*). Estimated blood loss did not differ between the two groups. The rate of grade II–V postoperative complications was 23.3% (7/30) in the sleeve lobectomy group versus 13.2% (5/38) in the lobectomy group (P=0.64). There was no perioperative death. The rate of R0 resection was 93.3% (28/30) in sleeve lobectomy group versus 97.4% (37/38) in lobectomy group (P=0.83) before and after IPTW (P>0.99) (*Table 3*). The pCR rate was 50.9% in the sleeve lobectomy group versus 48.7% in the lobectomy group (P=0.87, *Table 3*) after IPTW and postoperative TMN stage (pStage, *Table 3*) was also balanced after IPTW. Details of complications are shown in *Table 2* and the postoperative characteristics are shown in *Table 3*.

Adjuvant therapy

All patients received the same chemotherapy and

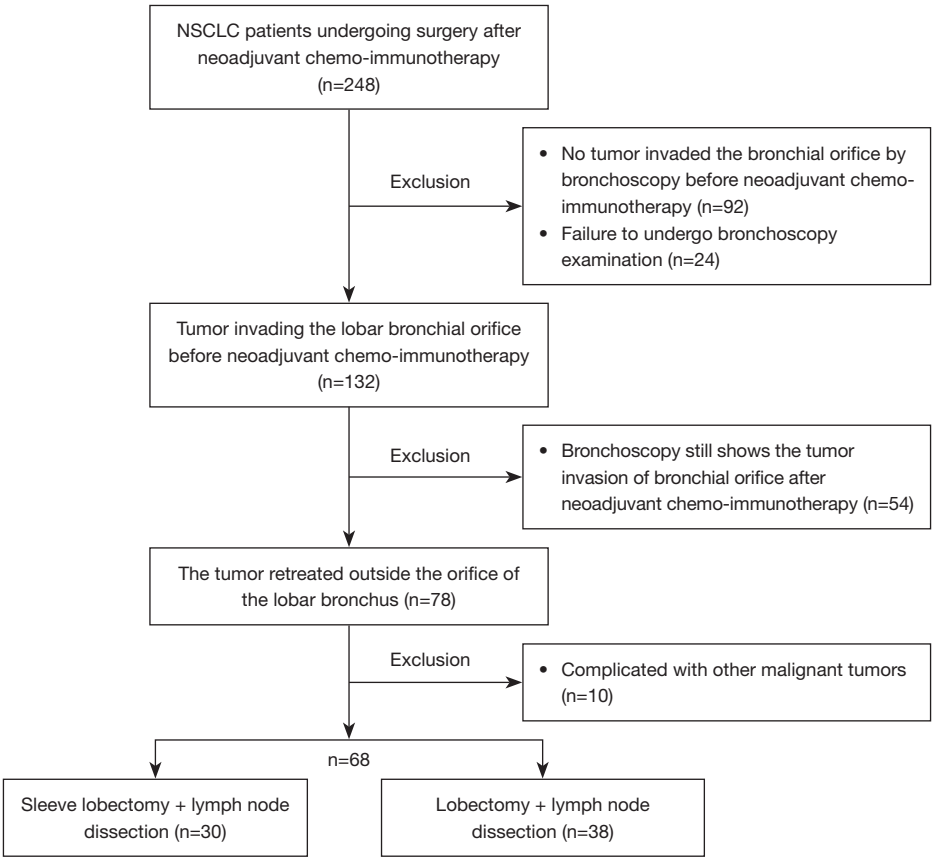

Figure 1 Flow diagram of patient selection in this study. NSCLC, non-small cell lung cancer.

immunotherapy agents used in the neoadjuvant therapy during adjuvant therapy. Among the sleeve lobectomy group, 12 patients (40.0%) continued adjuvant therapy with immunotherapy for more than 1 year, with 10 (33.3%) patients receiving 2 cycles of chemotherapy and at least 1 cycle of immunotherapy. In the lobectomy group, 17 (44.7%) patients adhered to adjuvant therapy with immunotherapy for over 1 year, while 8 (21.1%) patients received 2 cycles of chemotherapy and at least 1 cycle of immunotherapy (P=0.51, Table S1).

Survival outcomes

The median follow-up was 32 months. The median EFS was not reached (NR) in the sleeve lobectomy group, and was 32 months (95% CI: 22–NR) in the lobectomy group (HR =0.46, 95% CI: 0.210–1.005, P=0.057; *Figure 3*). After IPTW, the KM curve and result were similar to (*Figure 3*). The 1- and 2-year recurrence rate was 7.4% versus 11.4% and 14.8% versus 34.3% in the sleeve and lobectomy groups, respectively (*Table 4*).

Subgroup analysis

Kaplan-Meier analysis showed longer EFS in patients with pCR both in original cohort and the IPTW-adjusted cohort (P=0.003, *Figure 4*). In the subgroup analysis that only included patients with pCR, median EFS was NR in either group (P=0.80) before and after IPTW. In the subgroup analysis that only included patients without pCR, the median EFS was 21 months (95% CI: 13–NR) in the lobectomy group versus not achieved (95% CI: 35–NR) in the sleeve lobectomy group (P=0.04), in the IPTW-adjusted cohort, the sleeve lobectomy was still associated with longer EFS but the median EFS was not achieved (95% CI: 25–NR, *Figure 5*).

In the subgroup analysis that included patients with stage I/II disease only, the median EFS was not achieved in both group (P=0.31). In the subgroup analysis that included patients with stage III disease only, the median EFS was not

Table 1 Demographic and clinical characteristics in the overall and IPTW-adjusted cohort

Characteristics	Unmatched				IPTW			
	Lobectomy (n=38)	Sleeve lobectomy (n=30)	P	SMD	Lobectomy (n=37.78)	Sleeve lobectomy (n=28.41)	P	SMD
Age (years)	59.45 (9.21)	61.67 (7.19)	0.28	0.269	60.59 (8.53)	60.68 (8.00)	>0.99	0.011
BMI (kg/m^2)	23.53 (2.54)	24.26 (2.27)	0.22	0.303	23.78 (2.58)	23.94 (2.19)	0.79	0.069
Sex			0.90	0.138			0.81	0.059
Female	4 (10.5)	2 (6.7)			3.3 (8.6)	2.0 (7.1)		
Male	34 (89.5)	28 (93.3)			34.5 (91.4)	26.4 (92.9)		
Smoking			0.29	0.324			0.86	0.046
Never	13 (34.2)	15 (50.0)			15.1 (39.9)	12.0 (42.2)		
Current or ever	25 (65.8)	15 (50.0)			22.7 (60.1)	16.4 (57.8)		
Diabetes			0.60	0.198			0.73	0.088
No	31 (81.6)	22 (73.3)			30.4 (80.4)	21.8 (76.8)		
Yes	7 (18.4)	8 (26.7)			7.4 (19.6)	6.6 (23.2)		
Hypertension			0.51	0.224			0.79	0.069
No	28 (73.7)	19 (63.3)			27.2 (72.0)	19.6 (68.8)		
Yes	10 (26.3)	11 (36.7)			10.6 (28.0)	8.9 (31.2)		
Tumor location			0.26	0.343			0.93	0.023
Left	19 (50.0)	10 (33.3)			16.3 (43.2)	11.9 (42.0)		
Right	19 (50.0)	20 (66.7)			21.5 (56.8)	16.5 (58.0)		
Histology			0.51	0.237			0.76	0.077
Adenocarcinoma	10 (26.3)	5 (16.7)			8.1 (21.5)	5.2 (18.4)		
Squamous cell carcinoma	28 (73.7)	25 (83.3)			29.7 (78.5)	23.2 (81.6)		
Clinical T stage			0.94	0.154			>0.99	0.043
T1	6 (15.8)	5 (16.7)			5.2 (13.7)	4.0 (13.9)		
T2	14 (36.8)	9 (30.0)			15.0 (39.6)	10.7 (37.8)		
T3	14 (36.8)	12 (40.0)			14.1 (37.3)	10.8 (38.1)		
T4	4 (10.5)	4 (13.3)			3.5 (9.3)	2.9 (10.2)		
Clinical N stage			0.83	0.241			0.86	0.192
N0	8 (21.1)	7 (23.3)			8.7 (23.0)	5.7 (20.2)		
N1	3 (7.9)	2 (6.7)			2.4 (6.5)	1.7 (6.1)		
N2	26 (68.4)	21 (70.0)			26.1 (69.0)	20.9 (73.7)		
N3	1 (2.6)	0 (0.0)			0.6 (1.5)	0.0 (0.0)		
Clinical TNM stage			0.83	0.15			0.93	0.101
I	3 (7.9)	3 (10.0)			3.9 (10.3)	2.9 (10.3)		
II	7 (18.4)	4 (13.3)			6.6 (17.5)	3.9 (13.9)		
III	28 (73.7)	23 (76.7)			27.3 (72.1)	21.5 (75.8)		

Data are presented with mean (SD) or n (%). IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; BMI, body mass index; TNM, tumor-node-metastasis; SD, standard deviation.

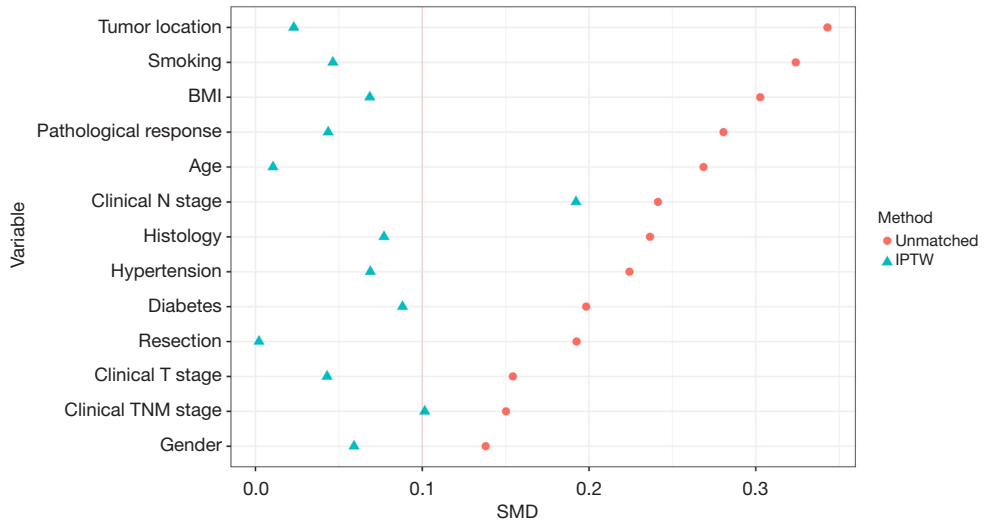

Figure 2 Standard mean difference after IPTW. BMI, body mass index; TNM, tumor-node-metastasis; IPTW, inverse probability of treatment weighting; SMD, standard mean difference.

achieved in the both group (P=0.10, Figure S1).

In multivariate regression analysis, improved EFS was associated with pCR (HR =0.31, 95% CI: 0.11–0.90; P=0.03) but not surgical types (HR =0.54, 95% CI: 0.22–1.5; P=0.20) after IPTW (*Table 5*).

Discussion

Tumor size reduction and pathological downstaging by neoadjuvant chemo-immunotherapy in NSCLC patients has been confirmed by several trials, including Keynote-671, Checkmate-816, NADIM II and Aegean (14-17). In patients undergoing sleeve lobectomy for NSCLC with invasion to the lobar bronchial orifice, lobectomy was also able to achieve R0 resection after neoadjuvant chemo-immunotherapy in our study. As there are no published studies examining the influence of modifying surgical type on long-term survival, although the tumor at the orifice of the bronchus regresses after neoadjuvant chemo-immunotherapy, most thoracic surgeons still prefer a more conservative sleeve lobectomy rather than lobectomy.

In the current study, although the statistically significant difference is not achieved, there was a trend for numerically longer EFS in the sleeve lobectomy group than the lobectomy group. Subgroup analysis indicated that lobectomy could be feasible for pCR patients and there was survival advantage with sleeve lobectomy in patients who did not achieve pCR after neoadjuvant chemo-immunotherapy. The IPTW analysis revealed that all results were robust after balancing clinical characteristics between the two groups. The 2-year EFS rate in the lobectomy group in the current study (60.5%) was comparable to that reported in the Checkmate-816 trial (63.8%), in which >80% of the patients underwent surgery (15) and in the Keynote-671 trial (62.4%) (14) adding support for the validity and perhaps generalizability of the findings in the current study.

The pCR rate in the current study (53.3% and 39.5% in the sleeve lobectomy and lobectomy groups, respectively) was higher than that reported by the Checkmate-816 trial (24.0%) and Keynote-671 trial (18.1%) (14,15). The differences could be attributed to the fact that up to 77.9% (53/68) of patients (Checkmate-816: 48.6%; Keynote-671: 43.1%) were diagnosed with squamous cell carcinoma which had high chemo-immunotherapy thorough response. In the Rationale 315 research, 79.2% patients were diagnosed with squamous cell carcinoma and the pCR rate was 40.7%, which was similar to our research (45.6%) (18).

In the multivariate Cox regression analysis, improved EFS was associated with pCR (HR =0.31, 95% CI: 0.11–0.90; P=0.03) but not surgical types (HR =0.54, 95% CI: 0.22–1.5; P=0.20) after IPTW. Exploratory analysis in the Neotorch trial also showed that patients who achieved pCR or MPR had significantly longer event-survival free compared to those who failed to achieve pathological response (HR =0.16 and 0.24, respectively) (19). Similarly, patients in pCR group had a favorable EFS than non-pCR group (patients who failed to achieve pCR) after IPTW

Table 2 Neoadjuvant and perioperative outcomes in the unmatched and IPTW-adjusted cohort

Group	Unmatched			IPTW		
	Lobectomy (n=38)	Sleeve lobectomy (n=30)	P	Lobectomy (n=37.78)	Sleeve lobectomy (n=28.41)	P
Tumor size, cm	3.42 (0.91)	3.39 (0.78)	0.88	3.39 (0.86)	3.42 (0.82)	0.91
Anti-PD-1 agents			0.24			0.32
Pembrolizumab	3 (7.9)	8 (26.7)		3.4 (8.9)	8.3 (29.1)	
Tislelizumab	13 (34.2)	7 (23.3)		11.1 (29.4)	5.9 (20.8)	
Sintilimab	10 (26.3)	6 (20.0		9.5 (25.2)	6.5 (22.7)	
Camrelizumab	9 (23.7)	5 (16.7)		10.1 (26.7)	4.4 (15.6)	
Nivolumab	3 (7.9)	4 (13.3)		3.7 (9.8)	3.3 (11.8)	
Chemotherapy regimens with ICIs			0.24			0.19
Paclitaxel + platinum	28 (73.7)	23 (76.7)		26.5 (70.2)	22.5 (79.2)	
Pemetrexed disodium + platinum	7 (18.4)	2 (6.7)		8.0 (21.1)	1.6 (5.6)	
Gemcitabine + platinum	3 (7.9)	5 (16.7)		3.3 (8.7)	4.3 (15.1)	
Cycles of ICIs	2.29 (0.57)	2.30 (0.84)	0.95	2.34 (0.58)	2.36 (0.88)	0.95
Adverse event, Grade 3–5			0.53			0.56
Neutropenia	3 (7.9)	1 (3.3)		2.4 (6.4)	2.2 (7.6)	
Pneumonia	1 (2.6)	1 (3.3)		0.6 (1.6)	0.7 (2.5)	
Skin rash	2 (5.3)	3 (10.0)		1.6 (4.2)	3.1 (10.9)	
Diarrhea	0 (0.0)	1 (3.3)		0 (0.0)	1.5 (5.4)	
Elevated ALT/AST	1 (2.6)	0 (0.0)		0.8 (2.2)	0 (0.0)	
Radiological response			0.52			0.58
CR	1 (2.6)	1 (3.3)		0.9 (2.4)	0.6 (2.0)	
PR	37 (97.4)	28 (93.3)		36.9 (97.6)	27.3 (96.2)	
PD	0 (0.0)	1 (3.3)		0 (0.0)	0.5 (1.8)	
Surgery approach			0.002			<0.001
MIA	32 (84.2)	14 (46.7)		33.0 (87.4)	12.1 (42.4)	
Thoracotomy	6 (15.8)	16 (53.3)		4.7 (12.6)	16.4 (57.6)	
Surgical time (min)	154.45 (44.81)	184.07 (43.30)	0.008	155.15 (45.34)	184.72 (38.77)	0.005
Estimated blood loss (mL)	106.58 (28.88)	110.00 (19.30)	0.58	104.95 (32.10)	109.05 (18.39)	0.56
Postoperative drainage (mL)	567.90 (83.40)	580.90 (63.37)	0.48	565.43 (86.91)	588.75 (64.95)	0.25
Grade 2 or higher complications			0.64			0.49
Atelectasis	1 (2.6)	2 (6.7)		0.8 (2.1)	1.7 (6.0)	
Atrial fibrillation	1 (2.6)	0 (0.0)		0.9 (2.5)	0.0 (0.0)	
Pleural effusion	2 (5.3)	3 (10.0)		1.5 (4.1)	3.2 (11.3)	
Pneumonia	1 (2.6)	1 (3.3)		1.1 (2.8)	0.7 (2.4)	
Prolonged air leak	0 (0.0)	1 (3.3)		0.0 (0.0)	0.9 (3.0)	

Data are presented with mean (SD) or n (%). Paclitaxel chemotherapy included, abraxane, paclitaxel liposome, docetaxel; platinum-based chemotherapy included, carboplatin, nedaplatin, lobaplatin and cisplatin. IPTW, inverse probability of treatment weighting; PD-1, programmed cell death 1; ICI, immune checkpoint inhibitor; ALT, alanine transaminase; AST, aspartate transaminase; CR, complete Response; PR, partial response; PD, progressive response; MIA, minimally invasive approach.

Table 3 Postoperative characteristics in the overall and IPTW-adjusted cohort

Characteristics	Unmatched			IPTW		
	Lobectomy (n=38)	Sleeve lobectomy (n=30)	P	Lobectomy (n=37.78)	Sleeve lobectomy (n=28.41)	P
Resection			0.83			>0.99
R0	37 (97.4)	28 (93.3)		35.5 (94.1)	26.7 (94.1)	
R1	1 (2.6)	2 (6.7)		2.2 (5.9)	1.7 (5.9)	
pT			0.24			0.22
0	20 (52.6)	17 (56.7)		23.4 (62.0)	15.5 (54.6)	
1	4 (10.5)	1 (3.3)		3.1 (8.2)	0.5 (1.8)	
2	9 (23.7)	3 (10.0)		6.4 (16.8)	2.6 (9.3)	
3	4 (10.5)	8 (26.7)		4.0 (10.6)	8.4 (29.6)	
4	1 (2.6)	1 (3.3)		0.9 (2.3)	1.4 (4.8)	
pN			0.75			0.89
0	24 (63.2)	21 (70.0)		26.2 (69.4)	20.4 (71.8)	
1	2 (5.3)	2 (6.7)		1.4 (3.8)	1.5 (5.4)	
2	12 (31.6)	7 (23.3)		10.1 (26.8)	6.5 (22.8)	
pStage			0.35			0.35
0	15 (39.5)	16 (53.3)		18.4 (48.7)	14.5 (50.9)	
I	5 (13.2)	1 (3.3)		4.6 (12.1)	0.8 (3.0)	
II	7 (18.4)	7 (23.3)		5.7 (15.0)	8.0 (28.1)	
III	11 (28.9)	6 (20.0)		9.2 (24.2)	5.1 (18.0)	
Pathological response			0.37			0.87
Non-pCR	23 (60.5)	14 (46.7)		19.4 (51.3)	13.9 (49.1)	
pCR	15 (39.5)	16 (53.3)		18.4 (48.7)	14.5 (50.9)	

Data are presented with mean (SD) or n (%). IPTW, inverse probability of treatment weighting; pT, postoperative T stage; pN, postoperative N stage; pStage, postoperative stage; pCR, pathological complete response.

in our study (P=0.003). Therefore, a subgroup analysis that included only patients who achieved pCR showed no difference in EFS between the sleeve lobectomy and lobectomy groups, indicating sleeve lobectomy is not associated with survival benefit in patients who achieve pCR after neoadjuvant chemo-immunotherapy. For patients failed to achieve pCR, however, sleeve lobectomy was associated with longer EFS than lobectomy after IPTW (median EFS: NR versus 21 months, P=0.04). In a retrospective study of patients undergoing surgery after neoadjuvant chemo-immunotherapy, the group with a small surgical extent (e.g., sleeve lobectomy versus pneumonectomy and lobectomy versus bilobectomy) was associated with longer PFS (HR =0.29, 95% CI: 0.10–0.85; P=0.047) (20). The contradicting findings may be attributed to higher pCR rate in the small surgical extent group (44.4% versus 29.2%, P<0.001).

From a practice viewpoint (the choice of sleeve lobectomy versus lobectomy), it is critically important to assess pathologic response to neoadjuvant immunochemotherapy at the time of surgery. Higher rate of MPR and pCR with neoadjuvant chemo-immunotherapy, apparently discourage more extensive surgery. Currently, there is no reliable model to accurately predict pCR before surgery, but the use of functional imaging and biomarkers has greatly improved the accuracy of pCR prediction (21,22). In the SANO trial for esophageal cancer, the overall survival (OS) of patients in the active surveillance group was not

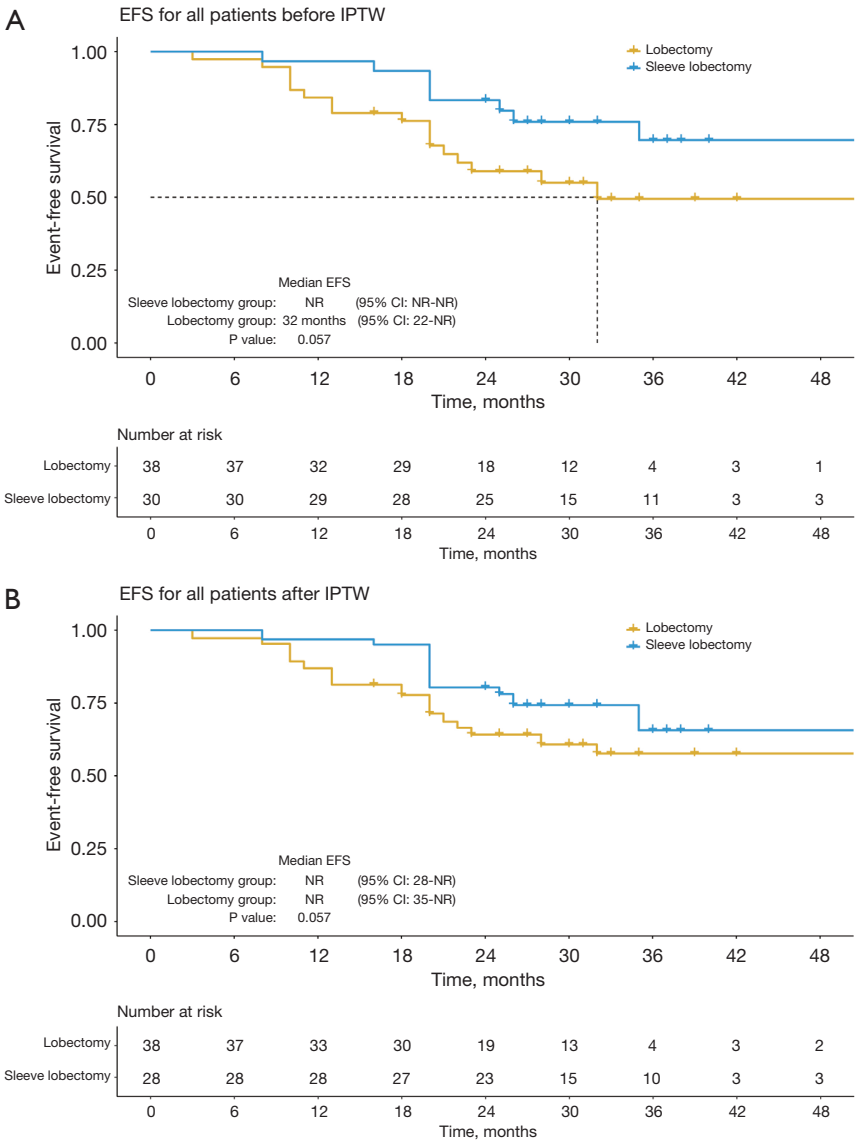

Figure 3 EFS for all patients before or after IPTW. (A) Comparison of EFS between the sleeve lobectomy group and the lobectomy group before IPTW. (B) Comparison of EFS between the sleeve lobectomy group and the lobectomy group after IPTW. IPTW, inverse probability of treatment weighting; EFS, event-free survival; NR, not reached; CI, confidence interval.

inferior to that of the standard surgical group when patients achieved clinically complete response (cCR) in both groups, which also provided key references for organ therapy strategies (23). We conservatively suggest lobectomy could be performed for the organ preservation strategy like SANO trial when the patients achieve cCR rather than pCR, as the technology for preoperative diagnosis of pCR is not yet mature. However, cCR is currently inefficient as a basis for modifying surgical types and the accurate preoperative diagnosis of pCR will become a key point in reducing the scope of surgery and implementing organ protection strategies in the future.

Based on the result of our research and other researches, we also have some suggestions. In neoSCORE trial, the rate of MPR rate and pCR was higher after three than only two cycles neoadjuvant treatment (41.4% versus 26.9% and 24.1% versus 19.2%, respectively) (24). In a retrospective study of 115 patients with locally advanced NSCLC, more cycles (3 or 4) of neoadjuvant chemo-immunotherapy were associated with higher probability of

Table 4 Recurrence characteristics

Characteristic	Sleeve lobectomy (n=27)	Lobectomy (n=35)
Follow-up (months)	33	27
Recurrence within 1 year	2 (7.4)	4 (11.4)
Recurrence within 2 years	4 (14.8)	12 (34.3)
Recurrence site	6 (22.2)	13 (37.1)
Bone	2 (7.4)	3 (8.6)
Bone and lung	1 (3.7)	2 (5.7)
Lung	0 (0.0)	2 (5.7)
Lymph node	3 (11.1)	4 (11.4)
Others	0 (0.0)	2 (5.7)

Data are presented with median or n (%).

achieving MPR than with only 2 cycles (25). Considering the important role of lymph nodes in the effectiveness of immunotherapy (26) and the adverse impact of expanded lymphadenectomy on adjuvant therapy (27), we believe that more cycles of neoadjuvant chemo-immunotherapy should be attempted for high pCR rate and organ preservation strategy.

We did not observe significant difference in postoperative complications between the two groups after IPTW (P=0.49), likely due to the small sample size. However, the sleeve lobectomy group in the current study had longer operation time and higher rate of thoracotomy. Accordingly, lobectomy should be considered for patients who are likely to achieve pCR after neoadjuvant chemo-immunotherapy.

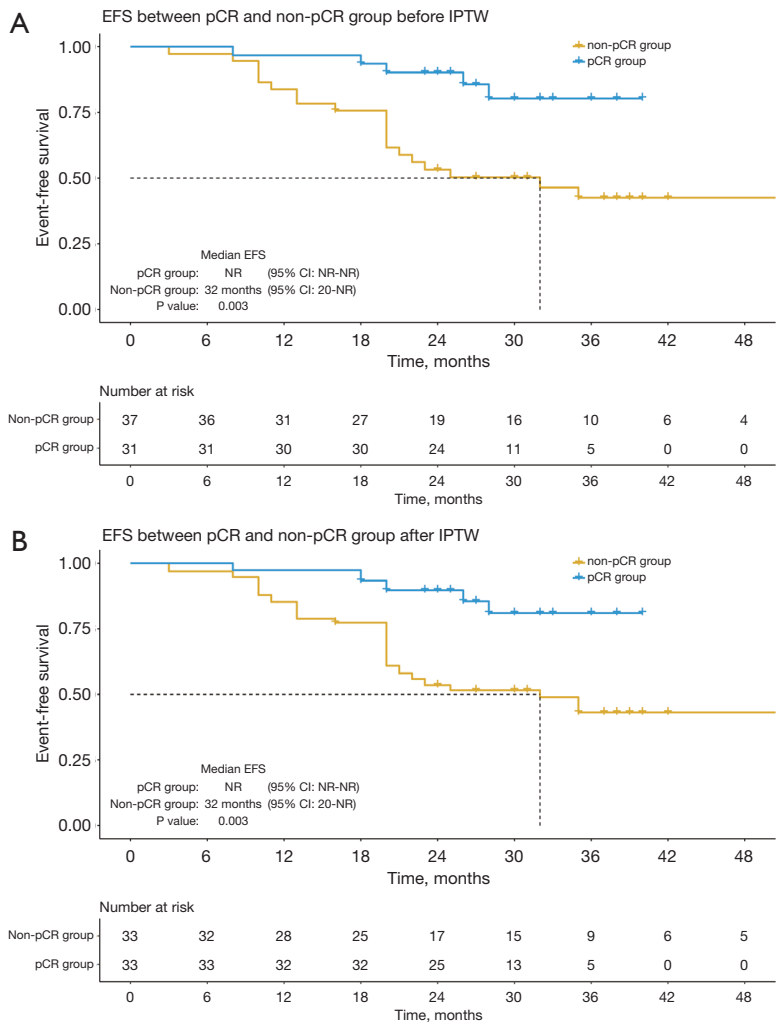

Figure 4 EFS between pCR and non-pCR group before or after IPTW. (A) Comparison of EFS between the pCR group and the non-pCR group before IPTW. (B) Comparison of EFS between the pCR group and the non-pCR group after IPTW. pCR, pathological complete response; IPTW, inverse probability of treatment weighting; EFS, event-free survival; NR, not reached; CI, confidence interval.

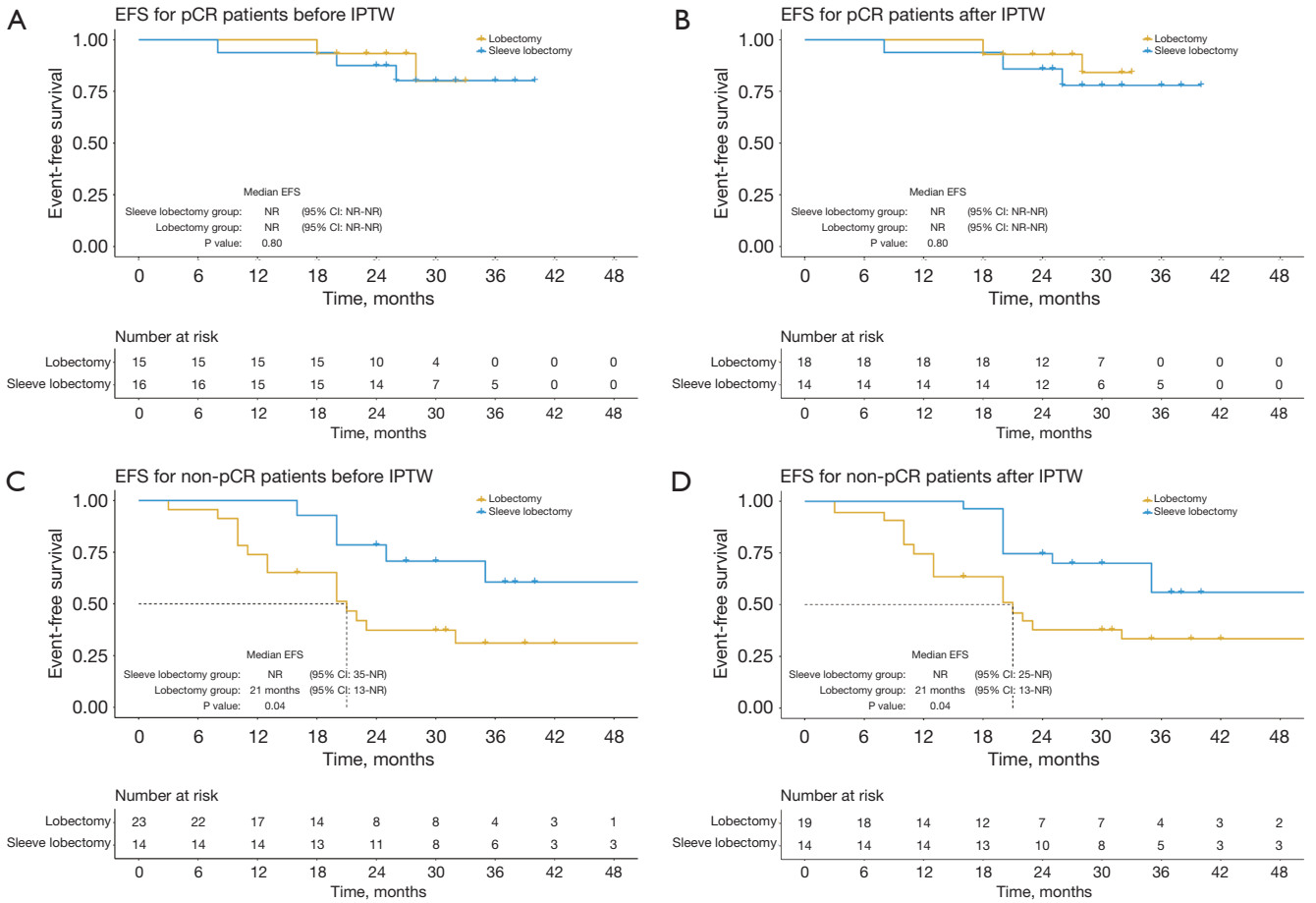

Figure 5 EFS for patients in term of postoperative pathology before or after IPTW. (A) Comparison of EFS between the sleeve lobectomy group and the lobectomy group for pCR patients before IPTW. (B) Comparison of EFS between the sleeve lobectomy group and the lobectomy group for pCR patients after IPTW. (C) Comparison of EFS between the sleeve lobectomy group and the lobectomy group for non-pCR patients before IPTW. (D) Comparison of EFS between the sleeve lobectomy group and the lobectomy group for non-pCR patients after IPTW. pCR, pathological complete response; IPTW, inverse probability of treatment weighting; EFS, event-free survival; NR, not reached; CI, confidence interval.

Table 5 Multivariable Cox regression analysis in the unmatched and IPTW-adjusted cohort

Group	Unmatched		IPTW	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Histology (squamous cell carcinoma *vs.* adenocarcinoma)	1.28 (0.48, 3.14)	0.70	1.05 (0.34, 3.23)	>0.99
Clinical TNM stage (stage III *vs.* stage I–II)	1.12 (0.41, 3.09)	0.80	1.21 (0.42, 3.50)	0.70
Surgical types (sleeve lobectomy *vs.* lobectomy)	0.45 (0.19, 1.07)	0.07	0.54 (0.22, 1.5)	0.20
Pathological response (pCR *vs.* non-pCR)	0.31 (0.11, 0.86)	0.03	0.31 (0.11, 0.90)	0.03
Tumor size	1.52 (0.99, 2.35)	0.056	1.45 (0.95, 2.22)	0.09

IPTW, inverse probability of treatment weighting; CI, confidence interval; TNM, tumor-node-metastasis; pCR, pathological complete response.

Limitation

A key limitation in the current study is the retrospective design and the unknown bias in selection of one over another type of surgery. Also, the sample size is relatively small to support multivariate regression analysis and subgroup analysis in patients with versus without pCR. Indeed, we failed to show an association between EFS with some of the baseline characteristics that are known to be associated with EFS in patients with locally advanced NSCLC (e.g., disease stage).

Conclusions

In conclusion, sleeve lobectomy was associated with improved EFS in comparison to lobectomy in non-pCR patients who completed neoadjuvant chemo-immunotherapy for NSCLC that invaded orifice of the lobar bronchus. Subgroup analysis, however, suggested that lobectomy could be feasible for patients who achieved pCR.

Acknowledgments

We sincerely acknowledge that the preliminary findings of this study were presented at the ESMO Asia Congress 2024, which provided valuable feedback and insights from experts in the field. We extend our gratitude to the organizing committee of the Congress for the opportunity to share our work. Additionally, we thank all collaborators, colleagues, and participants who contributed to this research. Writing and editorial assistance was provided by Kehong Zhang from Ivy Medical Editing (Shanghai, China).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-925/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-925/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-925/prf

Funding: This study was supported by the Social Development Projects of Key R&D Programs in Xuzhou City (KC22097 and KC22252).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-925/coif). All authors report that this study was supported by the Social Development Projects of Key R&D Programs in Xuzhou City (KC22097 and KC22252). The authors have no other conflicts of interest to declare.

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. The study protocol was approved by the institutional review committees of Affiliated Hospital of Xuzhou Medical University (No. XYFY2023-KL162-01), Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University (No. 2024DZKY-007-01), Shanghai Chest Hospital [No. KS(Y)23082] and Shandong Cancer Hospital and Institute (No. SDTHEC2023006011). Informed consent was waived by the review committees on the condition of patient anonymity. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Ma T, Yi J, Ge Y, Yang H, Wang J, Li S, Ma R, Zhang G, Peng H, Song P, Yao F, Zhang H. Sleeve lobectomy versus lobectomy after neoadjuvant chemo-immunotherapy for non-small cell lung cancer invading the lobar bronchial orifice: a multicenter retrospective cohort study. Transl Lung Cancer Res 2025;14(2):408-421. doi: 10.21037/tlcr-24-925