

Surgery for Stage IV Non-Small Cell Lung Cancer: Lobectomy or Sub-lobar Resection?

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Abstract

Background : A survival benefit was observed in metastatic non-small cell lung cancer (NSCLC) patients that underwent operation. But no evidence to support whether lobectomy would further prolong these patients' live than sub-lobar resection.

Methods: Patients that underwent primary tumor resection with metastatic NSCLC were identified from the Surveillance, Epidemiology and End Results (SEER) database and then divided into lobectomy and sub-lobar resection groups. A 1:1 propensity score matching (PSM) was performed to balance characters. Cancer specific survival (CSS) was estimated.

Results: A total of 24,268 patients with metastatic NSCLC were identified; 4,114 (16.95%) received primary tumor surgery, of which 2,045 (49.71%) underwent lobectomy and 1,766 (42.93%) underwent sub-lobar resection. After PSM, 644 patients in each group were included. Lobectomy was independently correlated with longer median CSS time (HR=0.70, 95% CI 0.61-0.80, P<0.001). The 1, 2 and 3-year survival rate after PSM also favored the lobectomy group. However, no significant survival difference was found in wedge resection and segmentectomy (HR=0.96, 95% CI 0.70-1.31, P=0.490). The 1, 2 and 3-year survival rate after PSM also showed no difference within the sub-lobar group. We explore whether lymph node dissection would provide a further survival benefit for stage IV NSCLC patients. According to the multivariate Cox analysis of the matched population, lymph node dissection was independently associated with better CSS (HR=0.76, 95% CI 0.66-0.88, P<0.001) and OS (HR=0.74, 95% CI 0.65-0.86, P<0.001). We confirmed this result in different types of surgery and found lymph node dissection group persist to have better survival outcomes both in lobectomy group and sub-lobar resection population. According to subgroup analysis, except for stage T4 and brain metastasis patients, all subtype of patients would benefit more from lobectomy than sub-lobar resection.

Conclusions: Lobectomy brings survival benefit in metastatic NSCLC patients compared with sub-lobar resection.

Background

Lung cancer is one of the leading causes of cancer death worldwide,[1] approximately 85% subtype patients of which are non-small cell lung cancer (NSCLC) [2] The 5-year survival rate of these patients was only 4–6% and 40% of which were diagnosed as stage IV disease at the first visit to hospital.[3]

The recommended treatment for stage IV NSCLC is systemic therapy (chemotherapy, molecular targeted therapy or immune therapy). [4] Traditionally, stage IV treatment strategy for NSCLC have not included curative-intent local therapy (surgery or radiation), given therapeutic goals which have focused on disease control, palliation and optimization of life quality. But more recently several clinical studies have shown that local consolidative therapy may be beneficial for stage IV non-small cell lung cancer (NSCLC) patients and improve their survival.[5, 6] Daniel et al.[7] conducted the first phase II clinical trial considering the effects of local consolidative therapy in combination with systemic treatment. The updated long-term outcomes indicated local consolidative therapy favored progression free survival (PFS) (14.2 months vs 4.4 months; p = 0.022) and overall survival (OS) (41.2 months vs 17.0 months; p = 0.017).

Lobectomy and systematic lymph node dissection is the cornerstone for early stage of NSCLC. Recently, evidences from real world studies showed primary tumor resection would also be beneficial for stage IV NSCLC patients and improve their survival.[8–10] However, no study explore which surgery type (lobectomy or sub-lobar resection) would provide more survival benefit for these patients.

To address this unresolved issue, we performed a population-based study to examine whether lobectomy or sub-lobar resection in stage IV NSCLC patients who underwent surgery with the most benefit.

Methods

SEER Database

The Surveillance, Epidemiology and End Results (SEER) database is a national population-based reporting system that collects tumor-related data, covering approximately 28% of the US population.[11] The SEER data is publicly available for studies of cancer-based epidemiology and survival analysis. We received permission to access the data used for this research (SEER-Stat username: 11136-Nov2018).

Cases of lung cancer (C34.0-34.9) diagnosed from 2004 to 2016 were extracted from the SEER database (SEER-Stat 8.3.6) according to the site code classifications. This range was selected because the American Joint Committee on Cancer (AJCC) TMN stage and Collaborative Stage (CS) information became available in 2004. We reclassified the TNM stage according to AJCC 8th edition. Patients who underwent primary tumor resection diagnosed at stage IV and histologically confirmed as NSCLC were enrolled. Patients were excluded if the surgery to primary site record was unknown. Other exclusion criteria were as follows: less than 18 years old, unknown TNM stage, unknown time of survival, unknown treatment modality, not the first tumor and not only one tumor.

Statistical analysis

The study sample was divided according to surgical resection strategy for primary tumor: Lobectomy versus sub-lobar resection. The propensity-score matching (PSM) generated from the logistic regression were performed to minimize the differences in confounding variables and facilitate matching patients in the two treatment groups (R software version 2.15.1, <https://cran.r-project.org/>). Variables that could influence the outcomes of treatment were used to generate a propensity score, including age, gender, histology, TNM stage, differentiation grade and tumor position. Patients were 1:1 matched on the basis of PSM using the nearest-neighbor method on the logit scale. The caliper was set at 0.01. After PSM, standardized mean differences (SMD) before and after PSM were calculated. Confounding variables was considered comparable when SMD below 0.10.

Overall survival (OS), cancer specific survival (CSS) and survival months were extracted from the SEER database. OS was the time from diagnosis to death from any cause; living patients were excluded at the time of last recording. CSS was calculated from the date of diagnosis to the date of cancer specific death. OS and CSS were estimated by the Kaplan– Meier (K-M) method and compared with the log-rank test. Univariate and multivariate Cox proportional hazard regression was used to determine independent prognostic factors. Hazard ratios (HRs) were calculated with 95% confidence interval (CI).

The normality of the data was assessed by the Shapiro-Wilk test. Continuous variables were given as mean and standard deviation. Student's t-test or Mann-Whitney test was performed to compare differences between groups with continuous variables. Distribution of categorical variables was presented as a count and percentage. The χ^2 test or Fisher exact test for small samples was used to compare categorical variables. Subgroup analysis was conducted according to different clinical types of population. Statistical analysis was performed with SPSS 24.0 (IBM Corp., Armonk, NY, USA), statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics before and after PSM

In total, 476,757 NSCLC patients were identified from 2004 to 2016 in the SEER database, of which, 24,268 stage IV NSCLC patients met the inclusion criteria, the screening process is shown in Fig. 1. Of all eligible patients, 4,114 (16.95%) underwent surgical treatment to primary tumor site, 2,045 (49.71%) of these patients underwent lobectomy and

1,766 (42.93%) received sub-lobar resection, others underwent pneumonectomy and biopsy, which were not included in this analysis. Obvious differences in age, histology, differentiation, tumor position, TNM stage, radiation chemotherapy and distant surgery were noted between the lobectomy and sub-lobar resection groups. (Table 1) This indicated that the baseline characteristics of the two groups were not balanced. Specifically, lobectomy group was associated with lower T stage patients. After the 1:1 PSM, 1,288 stage IV NSCLC patients treated with lobectomy (n = 644) or sub-lobar resection (n = 644) were enrolled in the survival analysis. Baseline characteristics were all well balanced (Table 1).

Table 1
Demographic Information for Patients with Stage IV NSCLC before and after PSM

	Before PSM			After PSM		
	Sub-lobectomy (n = 1766)	Lobectomy (n = 2045)	SMD	Sub-lobectomy (n = 644)	Lobectomy (n = 644)	SMD
Age						
< 60	540 (30.6)	685 (33.5)	0.566	201 (31.2)	184 (28.6)	< 0.001
60–75	879 (49.8)	1062 (51.9)		326 (50.6)	342 (53.1)	
> 75	347 (19.6)	298 (14.6)		117 (18.2)	118 (18.3)	
Gender						
Male	862 (48.8)	1008 (49.3)	< 0.001	322 (50.0)	309 (48.0)	< 0.001
Female	904 (51.2)	1037 (50.7)		322 (50.0)	335 (52.0)	
Histology						
Squamous cell carcinoma	205 (11.6)	336 (16.4)	0.016	83 (12.9)	89 (13.8)	< 0.001
Adenocarcinoma	1330 (75.3)	1312 (64.2)		468 (72.7)	445 (69.1)	
Other	231 (13.1)	397 (19.4)		93 (14.4)	110 (17.1)	
Differentiation						
Well	195 (11.1)	162 (7.9)	0.023	59 (9.2)	69 (10.7)	< 0.001
Moderately differentiated	541 (30.6)	628 (30.6)		194 (30.1)	182 (28.3)	
Poory differentiated	595 (33.7)	905 (44.3)		248 (38.5)	246 (38.2)	
undifferentiated	55 (3.1)	81 (4.0)		23 (3.6)	26 (4.0)	
Unknown	380 (21.5)	269 (13.2)		120 (18.6)	121 (18.8)	
Position						
Bronchus	13 (0.7)	10 (0.5)	0.057	4 (0.6)	2 (0.3)	< 0.001
Lobe	1450 (82.1)	1883 (92.1)		557 (86.5)	558 (86.6)	
Overlapping lesion	35 (2.0)	52 (2.5)		11 (1.7)	16 (2.5)	
Unknown	268 (15.2)	100 (4.9)		72 (11.2)	68 (10.6)	
AJCC T status						
T1	304 (17.2)	381 (18.6)	0.497	138 (21.4)	158 (24.5)	< 0.001
T2	375 (21.3)	872 (42.7)		195 (30.3)	195 (30.3)	
T3	308 (17.4)	350 (17.1)		107 (16.6)	107 (16.6)	
T4	779 (44.1)	442 (21.6)		204 (31.7)	184 (28.6)	

PSM, propensity score matching; NSCLC, non-small cell lung cancer; LN, lymph node; AJCC, American Joint Committee on Cancer

	Before PSM			After PSM		
AJCC N status						
N0	947 (53.6)	1070 (52.3)	0.148	340 (52.8)	364 (56.5)	0.023
N1	145 (8.2)	382 (18.7)		64 (9.9)	77 (12.0)	
N2	537 (30.4)	542 (26.5)		205 (31.9)	170 (26.4)	
N3	137 (7.8)	51 (2.5)		35 (5.4)	33 (5.1)	
AJCC M status						
M1a	475 (26.9)	373 (18.3)	0.856	141 (21.9)	149 (23.1)	< 0.001
M1b	390 (22.1)	575 (28.1)		148 (23.0)	148 (23.0)	
M1	901 (51.0)	1097 (53.6)		355 (55.1)	347 (53.9)	
LN dissection						
No	1243 (70.5)	231 (57.8)	0.308	194 (30.1)	211 (32.8)	0.041
Yes	523 (29.5)	1814 (88.7)		450 (69.9)	433 (67.2)	
Radiation						
No	1245 (70.5)	1181 (57.8)	0.953	423 (65.7)	422 (65.5)	0.002
Yes	521 (29.5)	864 (42.2)		221 (34.3)	222 (34.5)	
Chemotherapy						
No/Unknown	722 (40.9)	892 (43.6)	0.261	270 (41.9)	290 (45.0)	< 0.001
Yes	1044 (59.1)	1153 (56.4)		374 (58.1)	354 (55.0)	
Surgery to metastasis site						
No	1021 (57.8)	1374 (67.2)	0.118	313 (48.6)	359 (55.7)	0.033
Yes	745 (42.2)	671 (32.8)		331 (51.4)	285 (44.3)	
PSM, propensity score matching; NSCLC, non-small cell lung cancer; LN, lymph node; AJCC, American Joint Committee on Cancer						

Logistic analysis was performed to evaluate which variables were associated with lobectomy (Table 2). Compared with patients under 60 years old, patients over 75 years old tend to receive more sub-lobar resection than lobectomy (HR = 0.71, 95% CI 0.55–0.91, P = 0.007). In addition, T4 patients received less lobectomy compared with T1 or T2 patients. Patients who received radiation therapy also receive more lobectomy than patients with no radiotherapy (HR = 1.30, 95% CI 1.08–1.56, P = 0.005).

Table 2

Logistic Regression Model for stage IV NSCLC patients underwent lobectomy or sub-lobar resection

Characteristic	Univariate Analysis		Multivariate Analysis	
	Odds Ratios		Odds Ratios	
	(95%CI)	P Value	(95%CI)	P Value
Age				
< 60	1.00 (reference)		1.00 (reference)	
60–75	0.94 (0.78–1.34)	0.531	0.94 (0.78–1.14)	0.551
> 75	0.70 (0.54–0.90)	0.006	0.71 (0.55–0.91)	0.007
Gender				
Male	1.00 (reference)		/	/
Female	1.02 (0.86–1.20)	0.859	/	/
Histology				
Squamous cell carcinoma	1.00 (reference)		1.00 (reference)	
Adenocarcinoma	0.66 (0.52–0.85)	0.001	0.67 (0.52–0.85)	0.001
Other	1.06 (0.77–1.45)	0.732	1.05 (0.78–1.43)	0.742
Differentiation				
Well	1.00 (reference)		/	/
Moderately differentiated	0.96 (0.71–1.31)	0.805	/	/
Poory differentiated	0.98 (0.72–1.33)	0.884	/	/
Undifferentiated	0.84 (0.49–1.45)	0.535	/	/
Unknown	1.06 (0.75–1.50)	0.731	/	/
Position				
Bronchus	1.00 (reference)		1.00 (reference)	
Lobe	1.44 (0.49–4.27)	0.509	1.42 (0.48–4.20)	0.526
Overlapping lesion	1.80 (0.53–6.05)	0.344	1.77 (0.53–5.97)	0.356
Unknown	0.75 (0.25–2.30)	0.616	0.75 (0.24–2.30)	0.749
AJCC T status				
T1	1.00 (reference)		1.00 (reference)	
T2	1.62 (1.28–2.06)	< 0.001	1.61 (1.27–2.04)	< 0.001
T3	1.18 (0.89–1.56)	0.244	1.17 (0.89–1.55)	0.257
T4	0.76 (0.60–0.97)	0.029	0.76 (0.60–0.97)	0.025
AJCC N status				
NSCLC, non-small cell lung cancer; AJCC, American Joint Committee on Cancer				

	Univariate Analysis		Multivariate Analysis	
N0	1.00 (reference)		1.00 (reference)	
N1	1.46 (1.23–1.90)	0.004	1.45 (1.12–1.88)	0.005
N2	0.81 (0.66–0.98)	0.029	0.80 (0.66–0.97)	0.02
N3	0.55 (0.37–0.84)	0.005	0.55 (0.36–0.83)	0.005
AJCC M status				
M1a	1.00 (reference)		1.00 (reference)	
M1b	1.25 (0.97–1.61)	0.088	1.24 (0.96–1.60)	0.002
M1	1.04 (0.84–1.30)	0.705	1.04 (0.84–1.29)	0.723
Lymph-nodes dissection				
No	1.00 (reference)		1.00 (reference)	
Yes	15.47 (12.91–18.54)	< 0.001	15.32 (12.82–18.30)	< 0.001
Radiation				
No	1.00 (reference)		1.00 (reference)	
Yes	1.31 (1.09–1.58)	0.005	1.30 (1.08–1.56)	0.005
Chemotherapy				
No	1.00 (reference)		/	/
Yes	0.95 (0.79–1.13)	0.537	/	/
NSCLC, non-small cell lung cancer; AJCC, American Joint Committee on Cancer				

Impact of surgery types on survival outcomes in IV NSCLC patients

Kaplan-Meier analyses and log-rank test were used in the matched population, patients who underwent lobectomy enjoyed longer CSS and OS compared with sub-lobar resection. The median CSS time was 29 months for patients who underwent lobectomy and 18 months for patients who received sub-lobar resection after PSM (HR = 0.70, 95% CI 0.61–0.80, P < 0.001) (Fig. 2A). The median OS was 25 and 16 months in lobectomy group and sub-lobar resection group (HR = 0.73, 95% CI 0.65–0.83, P < 0.001) (Fig. 2B), respectively. The 1, 2 and 3-year survival rate after PSM also favored the lobectomy group. (Table 3)

Table 3
Survival rate of stage IV NSCLC patients according to different types of surgery

Cancer Specific Survival		Overall Survival		
	Sub-lobectomy VS. Lobectomy	P value	Sub-lobectomy VS. Lobectomy	P value
1-year survival rate	59.0% vs. 72.7%	< 0.001	56.7% vs. 70.3%	< 0.001
2-year survival rate	43.2% vs. 54.9%	< 0.001	40.9% vs. 51.5%	< 0.001
3-year survival rate	31.9% vs. 44.8%	0.001	29.1% vs. 41.0%	0.001
NSCLC, non-small cell lung cancer				

Primary tumor lobectomy as an independent prognostic factor for survival in IV NSCLC patients

In multivariate Cox analysis (Table 4) of the matched population, lobectomy persisted to be independently associated with better CSS (HR = 0.67, 95% CI 0.58–0.77, P < 0.001) and OS (HR = 0.69, 95% CI 0.61–0.79, P < 0.001). Age, gender, TNM stage, histology, differentiation, lymph node dissections, chemotherapy, radiotherapy were all independent factors for survival of stage IV NSCLC patients.

Table 4

Cox Proportional Hazards Regression Model for Lung Cancer– Specific Survival in Patients with NSCLC with surgery

Characteristic	Cancer Specific Survival				Overall Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P Value	(95%CI)	P Value	HR (95%CI)	P Value	(95%CI)	P Value
Age								
< 60	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
60–75	1.13 (0.97–1.32)	0.112	1.22 (1.04–1.43)	0.017	1.16 (1.00–1.35)	0.045	1.24 (1.06–1.44)	0.007
> 75	1.27 (1.04–1.55)	0.02	1.53 (1.24–1.90)	< 0.001	1.38 (1.14–1.66)	0.001	1.63 (1.33–1.99)	< 0.001
Gender								
Male	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Female	0.67 (0.59–0.77)	< 0.001	0.72 (0.62–0.82)	< 0.001	0.66 (0.58–0.75)	< 0.001	0.71 (0.62–0.81)	< 0.001
Histology								
Squamous cell carcinoma	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Adenocarcinoma	0.72 (0.59–0.87)	0.001	0.80 (0.65–0.98)	0.03	0.67 (0.56–0.80)	< 0.001	0.75 (0.62–0.91)	0.004
Other	0.93 (0.73–1.18)	0.54	0.86 (0.67–1.11)	0.245	0.92 (0.73–1.15)	0.444	0.86 (0.68–1.09)	0.223
Differentiation								
Well	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Moderately differentiated	1.42 (1.09–1.84)	0.01	1.29 (0.99–1.70)	0.061	1.34 (1.05–1.71)	0.018	1.24 (0.97–1.59)	0.09
Poory differentiated	1.87 (1.45–2.41)	< 0.001	1.49 (1.14–1.95)	0.003	1.81 (1.43–2.29)	< 0.001	1.45 (1.13–1.85)	0.003
Undifferentiated	2.49 (1.67–3.70)	< 0.001	2.12 (1.39–3.24)	< 0.001	2.47 (1.71–3.57)	< 0.001	2.10 (1.42–3.11)	< 0.001
PSM, propensity score matching; NSCLC, non-small cell lung cancer; LN, lymph node; AJCC, American Joint Committee on Cancer								

	Cancer Specific Survival				Overall Survival			
Unknown	1.73 (1.31–2.28)	< 0.001	1.41 (1.06–1.88)	0.018	1.60 (1.24–2.08)	< 0.001	1.31 (1.00–1.71)	0.047
Position								
Bronchus	1.00 (reference)		/	/	1.00 (reference)		/	/
Lobe	1.61 (0.52–5.02)	0.409	/	/	1.39 (0.52–3.72)	0.51	/	/
Overlapping lesion	2.78 (0.83–9.29)	0.097	/	/	2.36 (0.82–6.80)	0.113	/	/
Unknown	1.54 (0.49–4.86)	0.462	/	/	1.28 (0.47–3.47)	0.631	/	/
AJCC T status								
T1	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
T2	1.46 (1.21–1.77)	< 0.001	1.42 (1.17–1.72)	< 0.001	1.38 (1.16–1.65)	< 0.001	1.35 (1.13–1.62)	0.001
T3	1.47 (1.18–1.84)	0.001	1.52 (1.20–1.92)	< 0.001	1.40 (1.14–1.72)	0.001	1.45 (1.17–1.81)	0.001
T4	1.59 (1.32–1.93)	< 0.001	1.49 (1.22–1.82)	< 0.001	1.48 (1.24–1.77)	< 0.001	1.44 (1.19–1.73)	< 0.001
AJCC N status								
N0	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
N1	1.64 (1.32–2.02)	< 0.001	1.78 (1.43–2.21)	< 0.001	1.48 (1.21–1.82)	< 0.001	1.66 (1.35–2.06)	< 0.001
N2	1.83 (1.58–2.13)	< 0.001	1.83 (1.55–2.15)	< 0.001	1.72 (1.49–1.99)	< 0.001	1.76 (1.51–2.06)	< 0.001
N3	1.98 (1.48–2.65)	< 0.001	2.04 (1.50–2.76)	< 0.001	1.91 (1.45–2.52)	< 0.001	2.02 (1.51–2.70)	< 0.001
AJCC M status								
M1a	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	

PSM, propensity score matching; NSCLC, non-small cell lung cancer; LN, lymph node; AJCC, American Joint Committee on Cancer

	Cancer Specific Survival				Overall Survival			
M1b	1.50 (1.20– 1.87)	< 0.001	1.44 (1.14– 1.81)	0.002	1.49 (1.21– 1.85)	< 0.001	1.47 (1.18– 1.83)	0.001
M1	1.45 (1.20– 1.74)	< 0.001	1.43 (1.18– 1.74)	< 0.001	1.44 (1.21– 1.72)	< 0.001	1.44 (1.20– 1.74)	< 0.001
Primary surgery								
Sub-lobectomy	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Lobectomy	0.70 (0.61– 0.80)	< 0.001	0.67 (0.58– 0.77)	< 0.001	0.73 (0.65– 0.83)	< 0.001	0.69 (0.61– 0.79)	< 0.001
Lymph nodes dissection								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.79 (0.69– 0.91)	0.001	0.76 (0.66– 0.88)	< 0.001	0.78 (0.68– 0.89)	< 0.001	0.74 (0.65– 0.86)	< 0.001
Radiation								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	1.39 (1.21– 1.60)	< 0.001	1.33 (1.14– 1.55)	< 0.001	1.36 (1.19– 1.55)	< 0.001	1.31 (1.13– 1.52)	< 0.001
Chemotherapy								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.97 (0.85– 1.11)	0.644	0.74 (0.64– 0.87)	< 0.001	0.90 (0.80– 1.03)	0.114	0.71 (0.62– 0.83)	< 0.001
PSM, propensity score matching; NSCLC, non-small cell lung cancer; LN, lymph node; AJCC, American Joint Committee on Cancer								

Impact of sub-lobar resection on survival outcomes in IV NSCLC patients

We divided sub-lobar resection population into wedge resection and segmentectomy groups, the PSM analysis was conducted to balance the demographic information, which was shown in Supplementary materials. Kaplan-Meier analyses and log-rank test were used in the matched population, patients who underwent wedge resection had similar CSS and OS compared with segmentectomy. The median CSS time was 16 months for patients who underwent wedge resection and 17 months for patients who received segmentectomy after PSM (HR = 0.96, 95% CI 0.70–1.31, P = 0.490) (Fig. 2C). The median OS was 14 and 16 months in wedge resection group and segmentectomy group (HR = 0.96, 95% CI 0.71–1.30, P = 0.390) (Fig. 2D), respectively. The 1, 2 and 3-year survival rate after PSM also showed no difference between the sub-lobar group. (Table 5)

Table 5
Survival rate of stage IV NSCLC patients in the Sublobar Resection cohort

	Cancer Specific Survival		Overall Survival	
	Wedge resection VS. Segmentectomy	P value	Wedge resection VS. Segmentectomy	P value
1-year survival rate	54.7% vs. 61.7%	0.103	51.6% vs. 61.0%	0.103
2-year survival rate	42.7% vs. 41.7%	0.779	40.3% vs. 40.4%	0.792
3-year survival rate	32.1% vs. 32.2%	0.876	29.3% vs. 30.1%	0.876
NSCLC, non-small cell lung cancer				

Impact of lymph node dissection on survival outcomes in IV NSCLC patients

We explore whether lymph node dissection would provide a further survival benefit for stage IV NSCLC patients. According to the multivariate Cox analysis (Table 4) of the matched population, lymph node dissection was independently associated with better CSS (HR = 0.76, 95% CI 0.66–0.88, $P < 0.001$) and OS (HR = 0.74, 95% CI 0.65–0.86, $P < 0.001$). We confirmed this result in different types of surgery and found lymph node dissection group persist to have better survival outcomes both in lobectomy group and sub-lobar resection population. (Fig. 3A-D) We further divided all patients into two groups according to lymph node dissection number (< 9 or ≥ 9). (Fig. 4A-D) The results showed over 9 lymph node dissection only improved survival in sub-lobar resection population (CSS HR = 0.66, 95% CI 0.50–0.87, $P = 0.011$), but not in lobectomy patients (CSS HR = 0.97, 95% CI 0.70–1.35, $P = 0.89$).

Subgroup analysis

We further explored whether lobectomy was associated with better survival outcomes in different subtypes of populations. Both CSS (Fig. 5A) and OS (Fig. 5B) outcomes showed similar results. Except for stage T4 and brain metastasis patients, all subtype of NSCLC patients would benefit more from lobectomy than sub-lobar resection.

Discussion

There is growing evidence to support the value of primary tumor resection for advanced NSCLC patients in recent years. However, no study with the primary aim to compare survival outcomes in relation to surgical strategies (lobectomy or sub-lobar resection) were found. Few evidences for best surgery strategy could be referred when surgeons performed operation on metastasis NSCLC patients. This is a population-based propensity score matching study to assess the value of lobectomy or sub-lobar resection in stage IV NSCLC patients. The results indicated that lobectomy can independent significantly improve both cancer specific and overall survival rate compared with sub-lobar resection. Subgroup analysis revealed that comparing with sub-lobar resection, except for stage T4 patients, all subgroup patients would benefit from lobectomy.

According to National Comprehensive Cancer Network (NCCN) guidelines, patients who have single brain or adrenal metastasis, but the primary tumor is T1-2, N0-1 or T3, N0, local treatment of the metastasis followed by resection of the primary tumor is recommended.[12] The guidelines also recommend contralateral lung nodule can be resected. However, published evidences related to local management strategies for stage IV NSCLC are generally single-institution retrospective studies. As such, surgeons have extremely limited evidence to provide a patient an estimate of their prognosis with an aggressive therapy. Yang et al. [13] explored the treatment effect of surgery for metastasis NSCLC

with the use of National Cancer Data Base (NCDB), indicating operative for cT1-2, N0-1, M1 or cT3, N0, M1 disease is associated with a 5-year survival of 25%, supporting guidelines that recommend surgery for very select patients with stage IV disease. In the subgroup analysis, comparing with lobectomy, pneumonectomy (HR = 1.58, 95% CI 1.31–1.90, $P < 0.001$), segmentectomy (HR = 1.36, 95% CI 1.08–1.71, $P = 0.009$) and wedge resection (HR = 1.70, 95% CI 1.55–1.88, $P < 0.001$) were all associated with worse survival outcomes in stage IV NSCLC patients. It is noticeable, this subgroup analysis did not balance the patients' baseline characters, potential patient selection bias could be existed. The proper surgery type for stage IV NSCLC patients remains to be answered. Based on SEER database and using propensity score matching analysis, our study found that lobectomy should be considered in majority surgery for stage IV NSCLC, except for stage T4 patients, and lymph node dissection may further provide survival benefit.

The role of surgery for advanced stage NSCLC is always commonplace for diagnostic and palliative purposes.[14, 15] As personalized medicine has taken a more prominent role in the care of advanced NSCLC patients and treatment decisions are now based on histological molecular subtypes, surgeons are more commonly performing operations to acquire adequate tissue for enabling detailed subtyping of NSCLC. Sub-lobar resection is enough to get adequate biopsy for diagnostic and palliative purposes; however, lobectomy and lymph node dissection means a more aggressive comprehensive reduction of primary tumor, which might be associated with a better survival outcome. Mitchell et al.[5] found that T stage is also the significant prognostic factor in stage IV NSCLC patients, and comprehensive local consolidative therapy would bring survival benefit both according to OS (HR = 0.67, 95% CI 0.46–0.97, $P = 0.034$). These evidences also supported a more aggressive and thorough local treatment strategy for metastasis NSCLC.

Oligometastatic NSCLC is one of the most proper indications to receive local consolidative therapy.[16] Ashworth et al [17] indicated survival outcomes for patients with oligometastatic NSCLC are highly variable, and half of patients progress within approximately 12 months; however, long-term survivors do exist. Definitive treatment of the primary lung tumor and low-burden thoracic tumors are strongly associated with improved long-term survival. Many studies have focus on local treatments for oligometastatic NSCLC, with the use of surgery and radiation, both for primary tumor and metastasis sites. Numerous single institution studies have demonstrated that surgical management of patients with oligometastatic NSCLC to the brain, adrenal gland and contralateral lung is associated with superior long-term survival. [18–20] Although surgery are not recommended by NCCN guidelines for management of metastatic NSCLC with pleural dissemination,[12] several cohorts also observed survival benefit for this population.[21] In this population based analysis, we found except for stage T4 patients, all subgroup patients would significant gain more survival benefit from lobectomy than sub-lobar resection. However, clinical information of oligometastatic NSCLC and patients with pleural dissemination were not available in SEER database, we were unable to verify the treatment effect of lobectomy on these populations. Further real-world studies should focus more on this population.

Several potential mechanisms may explain the survival benefit of the aggressive surgical strategy. First, possible larger and comprehensive extend resection would reduce the de novo resistant malignant cells that cannot be killed or inhibited by initial and maintenance systemic therapy, in consequence, life expectance is prolonged.[22, 23] Second, thorough primary tumor resection would potentiate the effects of perioperative systemic therapy; for example, in a mouse model, after neoadjuvant immunotherapy, these mice received primary tumor resection could get the long survival, while mice did not receive local treatment have a reduced survival time.[24] Third, primary tumor after systemic therapy would promote the growth of distant micrometastatic,[25] by reducing the primary tumor burden in maximum, the growth of distant micrometastatic disease can also be decreased. Notably, these mechanisms are not mutually exclusive, and more than one could contribute to the benefits of lobectomy for advanced NSCLC.

Although this population-based analysis suggested the long-term survival beneficial clinical efficacy of lobectomy and lymph node dissection for patients with stage IV NSCLC, the data should be interpreted with caution as: first, information on preoperative comorbidities for patients were lacking which might lead to a selection bias for the treatment choice;

second, detailed information and distribution of patients' metastatic disease is not available, and this would impede us to explore whether oligometastasis disease will affect the benefit of lobectomy; third, data on systemic therapies were not available. This lack of information regarding target therapies and immunotherapy is a limitation of the current study; Although, the number of stage IV patients that underwent primary tumor resection is limited in each medical center, to explore the curative effect of lobectomy for these patients are challenging, SEER database is the only comprehensive population-based database with open access worldwide providing the most ideal approach to study the survival of such patients. Prospective randomized trials are needed to further validate the benefit of surgery types in metastasis NSCLC patients.

Conclusions

In conclusion, our study showed lobectomy for primary tumor may further improve the survival of stage IV NSCLC patients compared with sub-lobar resection. Future clinical trials should focus on optimal candidates for such surgery in metastasis NSCLC patients.

Abbreviations

Non-small cell lung cancer (NSCLC); Epidemiology and End Results (SEER); American Joint Committee on Cancer (AJCC); Collaborative Stage (CS); Propensity-score matching (PSM); progression free survival (PFS); Overall survival (OS); Cancer specific survival (CSS); Kaplan Meier (K-M); Hazard ratio (HR); Confidence intervals (CI); National Cancer Date Base (NCDB).

Declarations

Ethics approval and consent to participate

This study is approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University. The committee of the First Affiliated Hospital of Guangzhou Medical University waiver the consent for its retrospective nature.

Consent for publication

All authors agree with publication

Availability of data and material

For original deidentified individual patient data please contact drjianxing.he@gmail.com. Data will be made available for a period of 5 years after the publication date.

Competing interests

None

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Authors' contributions

- Conception and design: H-L, Y-Z, W-L, J-H; (II) Administrative support: J-H, W-L, J-L; (III) Provision of study materials: H-L, Y-Z, S-X, B-C; (IV) Collection and assembly of data: W-W, J-H, C-L, Y-L, G-L-, Z-H; (V) Data analysis and interpretation: H-L, J-L, J-H; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors

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Figures

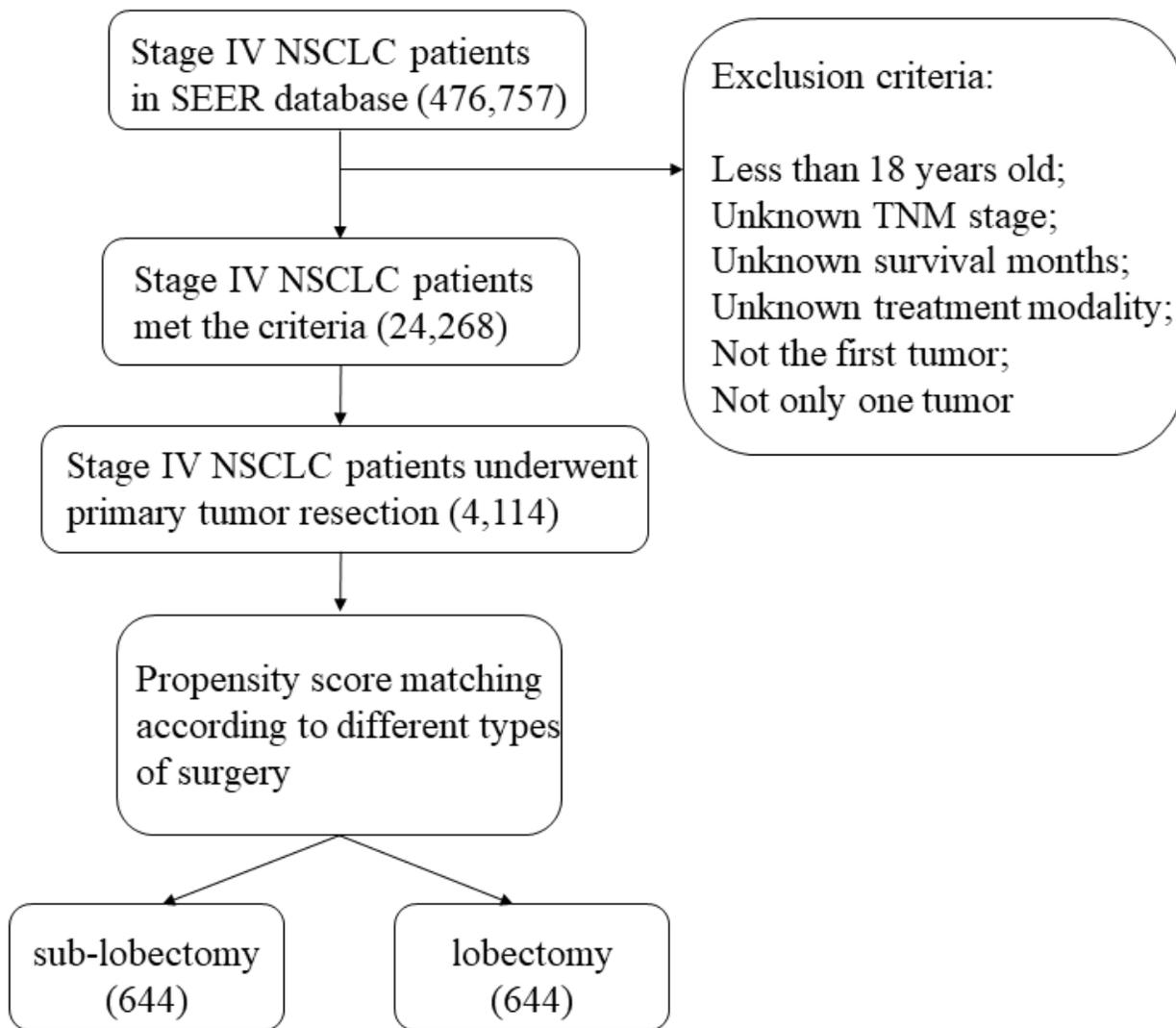


Figure 1

Flow chart of patient screening

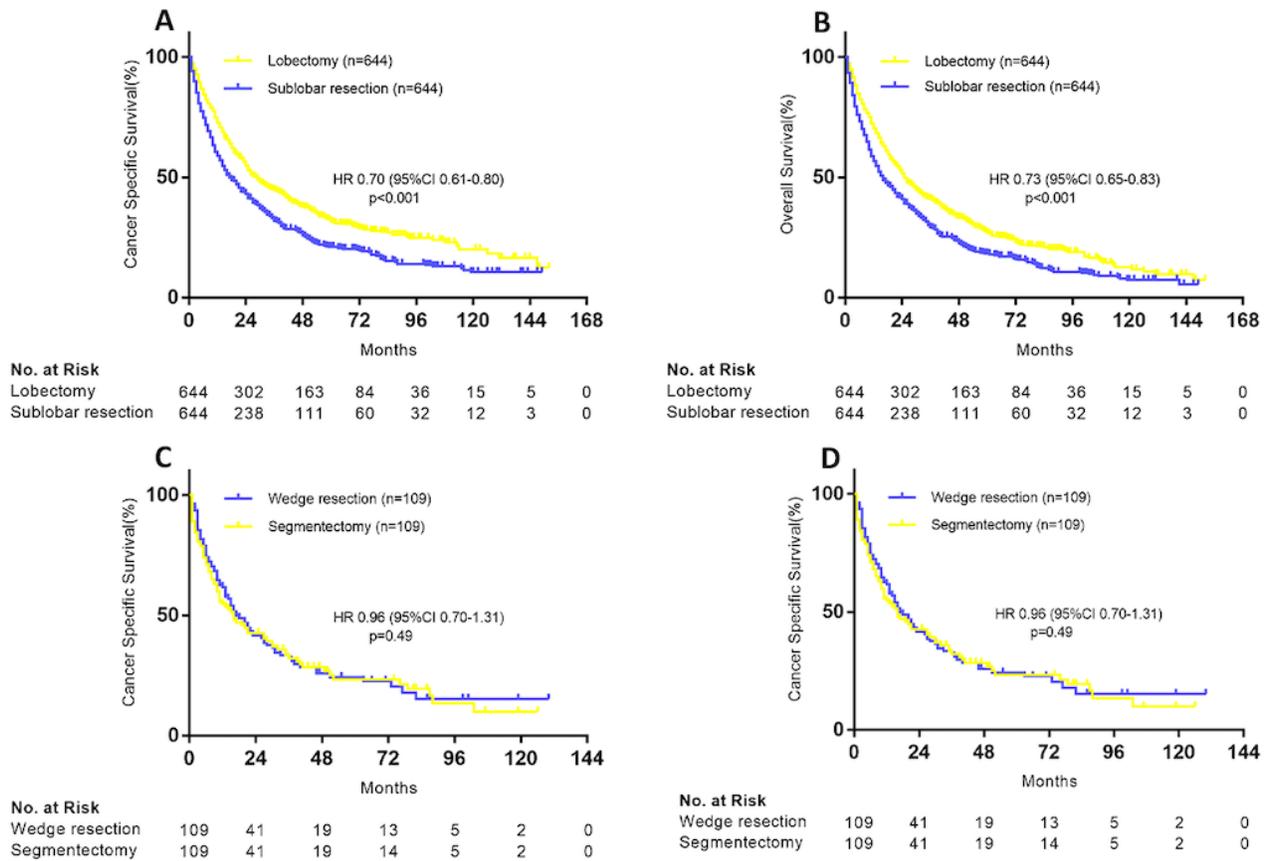
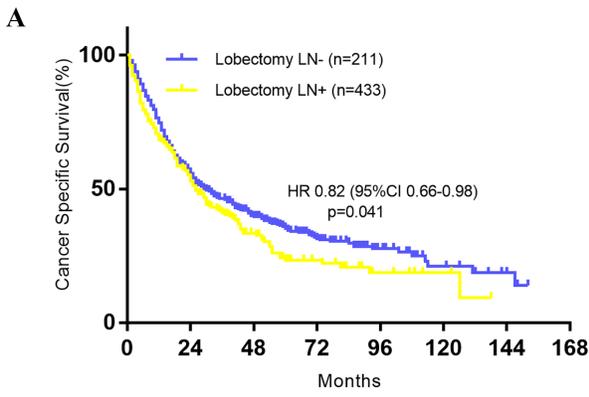


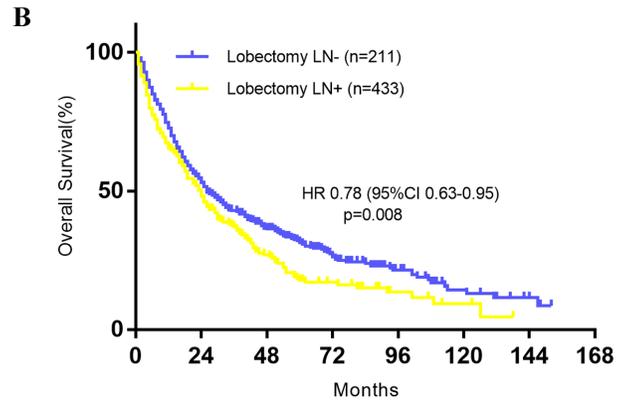
Figure 2

Kaplan-Meier plot of survival outcomes for stage IV NSCLC patients according to surgery types. (A) Cancer specific survival of lobectomy versus sublolar resection; (B) Overall survival of lobectomy versus sublolar resection; (C) Cancer specific survival of wedge resection versus segmentectomy; (D) Overall survival of wedge resection versus segmentectomy;



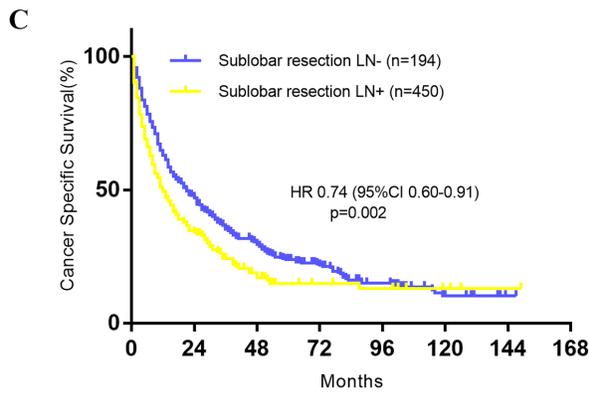
No. at Risk

Lobectomy LN-	211	95	46	20	9	4	1	0
Lobectomy LN+	433	207	118	65	29	12	5	0



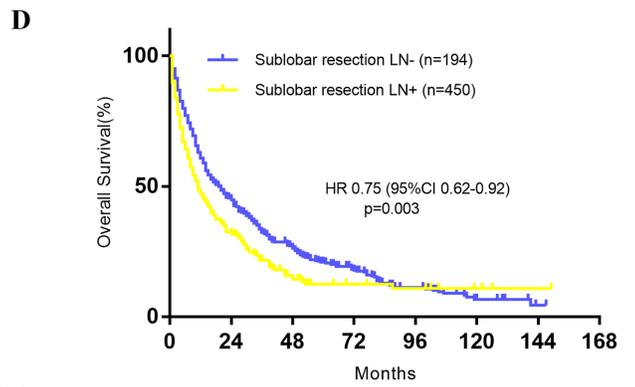
No. at Risk

Lobectomy LN-	211	95	46	20	9	4	1	0
Lobectomy LN+	433	207	118	65	29	12	5	0



No. at Risk

Sublobar resection LN-	194	55	21	10	8	4	2	0
Sublobar resection LN+	450	183	90	51	25	9	2	0



No. at Risk

Sublobar resection LN-	194	55	21	10	8	4	2	0
Sublobar resection LN+	450	183	90	51	25	9	2	0

Figure 3

The impact of lymph node dissection on survival outcomes. (A) Cancer specific survival of lobectomy; (B) Overall survival of lobectomy; (C) Cancer specific survival of sub-lobar resection; (D) Overall survival of sub-lobar resection.

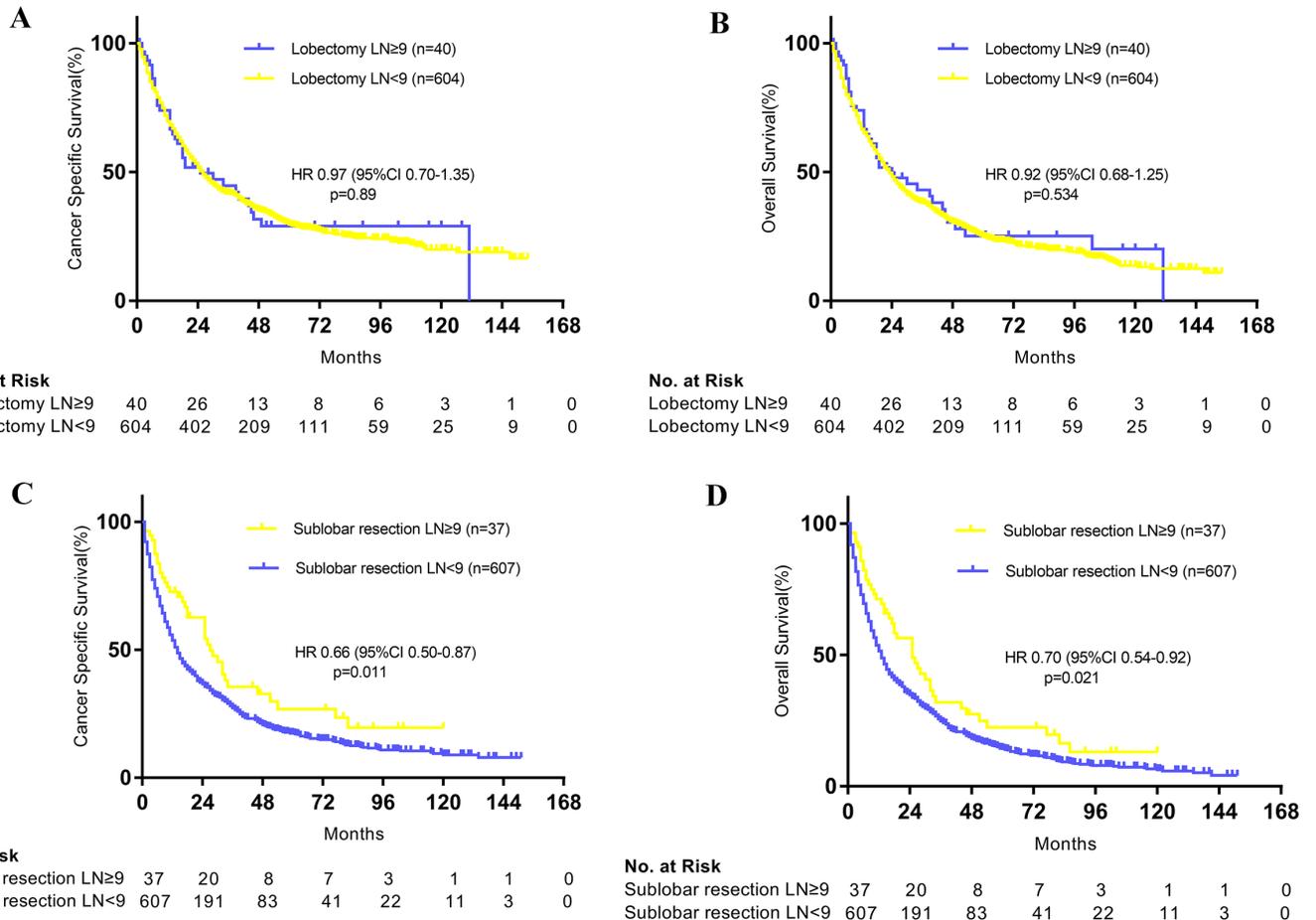


Figure 4

The impact of lymph node dissection number on survival outcomes. (A) Cancer specific survival of lobectomy; (B) Overall survival of lobectomy; (C) Cancer specific survival of sub-lobar resection; (D) Overall survival of sub-lobar resection.

Subgroup	Sublobar resection no. of events (%)	Lobectomy no. of events (%)	Hazard Ratio (95% CI)	P Value
Overall	644 (50.0)	644 (50.0)	0.67 (0.58-0.77)	<0.001
Age				
<60	201 (31.2)	184 (28.6)	0.64 (0.49-0.84)	0.001
60-75	326 (50.6)	342 (53.1)	0.79 (0.65-0.96)	0.017
>75	117 (18.2)	118 (18.3)	0.50 (0.35-0.70)	<0.001
Gender				
Male	322 (50.0)	309 (48.0)	0.68 (0.56-0.82)	<0.001
Female	322 (50.0)	335 (52.0)	0.66 (0.54-0.81)	<0.001
Histology				
Squamous carcinoma	83 (12.9)	89 (13.8)	0.45 (0.29-0.69)	<0.001
Adenocarcinoma	468 (72.7)	445 (69.1)	0.74 (0.63-0.88)	<0.001
Others	93 (14.4)	110 (17.1)	0.56 (0.39-0.80)	0.001
AJCC T status				
T1	138 (21.4)	158 (24.5)	0.59 (0.43-0.81)	0.001
T2	195 (30.3)	195 (30.3)	0.52 (0.40-0.68)	<0.001
T3	107 (16.6)	107 (16.6)	0.61 (0.42-0.88)	0.008
T4	204 (31.7)	184 (28.6)	0.86 (0.67-1.11)	0.239
AJCC N status				
N0	340 (52.8)	364 (56.5)	0.72 (0.59-0.88)	0.001
N1	64 (9.9)	77 (12.0)	0.60 (0.38-0.96)	0.032
N2	205 (31.8)	170 (26.4)	0.66 (0.52-0.85)	0.001
N3	35 (5.4)	33 (5.1)	0.38 (0.17-0.84)	0.017
AJCC M status				
M0	141 (21.9)	149 (23.1)	0.51 (0.35-0.74)	<0.001
M1b	148 (23.0)	148 (23.0)	0.53 (0.38-0.75)	<0.001
M	355 (55.1)	347 (53.9)	0.75 (0.63-0.90)	0.002
Location of metastasis (after 2010)				
Bone	41 (14.6)	56 (16.4)	0.64 (0.49-0.79)	<0.001
Brain	73 (26.0)	69 (20.2)	0.77 (0.62-0.97)	0.051
Liver	34 (12.1)	48 (14.0)	0.69 (0.55-0.83)	0.004
Pleural/Peritoneal effusion	110 (39.1)	131 (38.3)	0.44 (0.29-0.59)	<0.001
Contralateral lung nodules	23 (8.2)	38 (11.1)	0.51 (0.39-0.65)	<0.001
Metastasis number (after 2010)				
Only one	199 (70.8)	239 (70.0)	0.45 (0.30-0.61)	<0.001
More than one	51 (18.2)	67 (19.6)	0.65 (0.55-0.76)	<0.001
More than three	31 (11.0)	36 (10.4)	0.78 (0.65-0.90)	0.032
Radiation				
No/Unknown	423 (65.7)	422 (65.5)	0.62 (0.49-0.81)	0.021
Yes	221 (34.3)	222 (34.5)	0.77 (0.60-0.87)	0.019
Chemotherapy				
No/Unknown	270 (41.9)	290 (45.0)	0.65 (0.55-0.82)	0.03
Yes	374 (58.1)	354 (55.0)	0.70 (0.57-0.81)	0.031
Surgery to metastasis site				
No/Unknown	313 (48.6)	359 (55.7)	0.71 (0.58-0.87)	0.005
Yes	331 (51.4)	285 (44.3)	0.64 (0.54-0.81)	0.03

Subgroup	Sublobar resection no. of events (%)	Lobectomy no. of events (%)	Hazard Ratio (95% CI)	P Value
Overall	644 (50.0)	644 (50.0)	0.69 (0.61-0.79)	<0.001
Age				
<60	201 (31.2)	184 (28.6)	0.67 (0.52-0.87)	0.002
60-75	326 (50.6)	342 (53.1)	0.77 (0.64-0.93)	0.006
>75	117 (18.2)	118 (18.3)	0.57 (0.42-0.78)	0.001
Gender				
Male	322 (50.0)	309 (48.0)	0.70 (0.59-0.84)	<0.001
Female	322 (50.0)	335 (52.0)	0.68 (0.56-0.82)	<0.001
Histology				
Squamous carcinoma	83 (12.9)	89 (13.8)	0.45 (0.30-0.67)	<0.001
Adenocarcinoma	468 (72.7)	445 (69.1)	0.75 (0.64-0.88)	<0.001
Others	93 (14.4)	110 (17.1)	0.63 (0.45-0.88)	0.006
AJCC T status				
T1	138 (21.4)	158 (24.5)	0.58 (0.43-0.77)	<0.001
T2	195 (30.3)	195 (30.3)	0.57 (0.44-0.73)	<0.001
T3	107 (16.6)	107 (16.6)	0.66 (0.47-0.93)	0.017
T4	204 (31.7)	184 (28.6)	0.88 (0.69-1.12)	0.307
AJCC N status				
N0	340 (52.8)	364 (56.5)	0.73 (0.61-0.88)	0.001
N1	64 (9.9)	77 (12.0)	0.63 (0.40-0.99)	0.043
N2	205 (31.8)	170 (26.4)	0.69 (0.55-0.88)	0.003
N3	35 (5.4)	33 (5.1)	0.41 (0.19-0.86)	0.018
AJCC M status				
M0	141 (21.9)	149 (23.1)	0.58 (0.41-0.82)	0.002
M1b	148 (23.0)	148 (23.0)	0.57 (0.42-0.79)	0.001
M	355 (55.1)	347 (53.9)	0.75 (0.64-0.89)	0.001
Location of metastasis (after 2010)				
Bone	41 (14.6)	56 (16.4)	0.65 (0.51-0.79)	<0.001
Brain	73 (26.0)	69 (20.2)	0.81 (0.65-1.01)	0.028
Liver	34 (12.1)	48 (14.0)	0.70 (0.55-0.82)	0.003
Pleural/Peritoneal effusion	110 (39.1)	131 (38.3)	0.45 (0.30-0.61)	<0.001
Contralateral lung nodules	23 (8.2)	38 (11.1)	0.51 (0.38-0.65)	<0.001
Metastasis number (after 2010)				
Only one	199 (70.8)	239 (70.0)	0.49 (0.33-0.67)	<0.001
More than one	51 (18.2)	67 (19.6)	0.64 (0.56-0.74)	0.002
More than three	31 (11.0)	36 (10.4)	0.79 (0.65-0.91)	0.034
Radiation				
No/Unknown	423 (65.7)	422 (65.5)	0.63 (0.48-0.81)	0.017
Yes	221 (34.3)	222 (34.5)	0.77 (0.61-0.86)	0.022
Chemotherapy				
No/Unknown	270 (41.9)	290 (45.0)	0.68 (0.55-0.85)	0.02
Yes	374 (58.1)	354 (55.0)	0.71 (0.57-0.82)	0.028
Surgery to metastasis site				
No/Unknown	313 (48.6)	359 (55.7)	0.69 (0.56-0.87)	0.008
Yes	331 (51.4)	285 (44.3)	0.66 (0.55-0.80)	0.01

Figure 5

Subgroup analysis for stage IV NSCLC patients according to surgery types. (A) Cancer specific survival; (B) Overall survival