

Prognosis analysis of lobectomy and sublobar resection in patients ≥75 years old with pathological stage I invasive lung adenocarcinoma of ≤3 cm: a propensity score matching-based analysis

Chunji Chen^{1#}, Qiming Ni^{2#}, Yubo Shi^{3#}, Shijie Fu¹, Xufeng Pan¹, Yiyang Wang¹, Jun Yang¹, Rui Wang¹

¹Department of Thoracic Surgery, ²Department of Radiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; ³Department of Thoracic Surgery, Yantaishan Hospital, Yantai 264000, China

Contributions: (I) Conception and design: R Wang, C Chen; (II) Administrative support: R Wang, S Fu; (III) Provision of study materials or patients: J Yang, Q Ni, Y Shi, R Wang; (IV) Collection and assembly of data: C Chen, Q Ni; (V) Data analysis and interpretation: C Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Rui Wang; Jun Yang. Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 West Huaihai Road, Shanghai 200030, China. Email: rui_wang788@163.com; YJ_yangjun@hotmail.com.

Background: To determine the clinical prognosis after sublobectomy versus lobectomy in elderly patients \geq 75 years old with stage I invasive lung adenocarcinoma \leq 3 cm in size.

Methods: In patients \geq 75 years old, 255 patients were diagnosed with stage I invasive lung adenocarcinoma \leq 3 cm in size between 2010 and 2014 in Shanghai Chest Hospital, they were all treated with sublobectomy or lobectomy. Potential confounding factors that consisted in the baseline characteristics of these two groups was balanced by the method of propensity score matching (PSM). The stratified analysis was conducted to compare the relapse-free survival (RFS) and lung cancer special survival (LCSS) rates in the sublobectomy and lobectomy groups.

Results: As for the 255 patients, 112 cases conducted sublobectomy and 143 with lobectomy. Significant difference existed in RFS before (P=0.002) and after (P=0.010) PSM. Similarly, we still recognized significant difference in LCSS between the two groups before (log-rank P<0.001) or after (log-rank P=0.002) PSM. We still identified different RFS or LCSS rates between the stratified tumor size group and the stratified lymph node dissection group after adjustment of PSM.

Conclusions: Lobectomy showed a survival advantage for sublobectomy for patient \geq 75 years old with stage I lung adenocarcinoma \leq 3 cm in size. Considering that lobectomy could get a better prognosis, it should be preferable for the treatment of patient \geq 75 years old with stage I lung adenocarcinoma \leq 3 cm in size.

Keywords: Sublobectomy; lobectomy; patients ≥75 years old; pathological stage I invasive lung adenocarcinoma

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Introduction

Lung cancer remains one of the leading causes of cancerrelated mortality worldwide and its incidence is still now increasing (1,2). With aging population and development in imaging technology, more and more elderly with early stage lung cancers are being diagnosed than in the past (3). For patients with early-staged non-small cell lung cancer (NSCLC), surgical resection may provide a potential therapeutic approach (4). As we known, the NCCN guidelines recommend lobectomy combining with mediastinal lymph node dissection as the standard treatment for patients with stage I NSCLC (5). However, for the high-risk patients, sublobectomy is considered to be a compromising solution by many more thoracic surgeons because they can retain more of lung function, especially for the elderly patients with simultaneous multiple primary lung cancer which sublobectomy may preserved a greater possibility for the second primary lung cancer resection (6,7). In addition, sublobectomy may be more appropriate to reduce postoperative morbidity and mortality and prolong the life expectancy in elderly patients. Many observational studies have shown that sublobar resection was comparable to lobectomy in patients with early-stage NSCLC and was more pronounced in older populations (1,8,9). In contrast, a large number of studies have not supported sublobectomy since the only randomized controlled trial (RCT) report in 1995 (10-12). Therefore, it is controversial whether sublobectomy can achieve the same tumor prognosis as lobectomy in elderly patients.

In this study, we utilized the database of the Department of Thoracic Surgery of Shanghai Chest Hospital to investigate the prognosis following sublobectomy versus lobectomy in elderly patients \geq 75 years old with stage I lung adenocarcinoma \leq 3 cm in size.

Methods

The study was approved by the Institutional Review Board of our hospital [ID: KS(Y)1668] and limited to patients with age \geq 75 and diagnosed with pathological stage I invasive lung adenocarcinoma between 2010 and 2014 in our hospital. Patients who met the following criteria will be excluded: (I) lung cancer was not the first primary malignancy; (II) patients who received radiation therapy prior to surgery; (III) patients did not leave the hospital after surgery or died within 30 days of surgery.

Finally, 255 patients met the inclusion criteria, and the following data for each patient were collected: sex, age at diagnosis, tumor size, tumor location, tumor laterality, pathologic stage, predominant histology subtype, number of lymph nodes examined, surgery resection, lymphatic invasion (LVI), visceral pleural invasion (VPI), adjuvant therapy, relapse-free survival (RFS), lung cancer specific survival (LCSS).

Statistical analyses

Baseline characteristics between the groups of sublobectomy

and lobectomy are compared. Pearson χ^2 test was performed for categorical covariates and student's *t*-test was performed for continuous ones. Using Kaplan-Meier method to calculate the distribution of RFS and LCSS and the logrank test was used to probe the significance between these two categories. Univariable and multivariable analyses were performed by a Cox proportional hazards model.

Propensity score matching (PSM) was used to adjust for potential differences in baseline characteristics between patients receiving different surgical procedures. A logistic regression model, including variables of age (treated as a continuous variable), gender, laterality, tumor location, tumor size (treated as a continuous variable) and T stage, was performed to estimate the propensity of undergoing sublobectomy. Then a 1:1 nearest-neighbor matching was established to improve accuracy without a corresponding increase in bias. The matching tolerance value was 0.01.

All the clinicopathologic data and distributions of survival were analyzed by SPSS 23.0 software package (SPSS Inc., Chicago, IL, USA) or Prism 5 (Graphpad Software Inc., La Jolla, CA, USA). The curves of RFS and LCSS, as well as their comparisons, were calculated by Kaplan-Meier method and the log-rank test. All tests were two-tailed, and P<0.05 was considered statistically significant.

Results

A total of 255 patients with median age of 77.3 years were included in this study, 112 underwent sublobectomy and another 143 received lobectomy. The baseline characteristics of our patients before or after PSM were listed in *Table 1*. There was a significant difference between these two groups in age (P=0.019), tumor size (P=0.007), tumor location (P=0.028), tumor laterality (P=0.010), p-T stage (P=0.006), and the number of harvested lymph node (P<0.001). Baseline bias of preoperative variables was balanced after adjusting for PSM.

The average follow-up time was 60.2 months (1.3–99.8 months) before PSM. In our analysis, all of the patient's death was LCSS, therefore the LCSS in the study is equivalent to the overall survival (OS). Univariable and multivariable analyses for RFS before and after PSM were summarized in *Tables 2,3*. We identified gender (log-rank P=0.005) and surgical resection (log-rank P=0.002) were all significant prognostic factors for RFS before adjusting, and surgical resection was still a significant prognostic factor after PSM (log-rank P=0.010). Univariable analysis revealed gender (log-rank P=0.029), laterality (log-rank P=0.022)

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Table 1 Baseline characteristics of old	patients with stage I adenocard	inoma who underwent sublobar	resection or lobectomy, 2010–2014

Characteristics	Sublobar resection	Lobectomy	P value	Adjusted P ^a
Total (n=255)	N=112	N=143	_	_
Age			0.019	0.140
Mean ± SD	77.69±2.486	77.02±2.009		
Range	75–85	75–83		
Sex, No. (%)			0.209	0.593
Male	59 (52.7)	64 (44.8)		
Female	53 (47.3)	79 (55.2)		
Tumor size (cm)			0.007	0.335
≤1	10 (8.9)	4 (2.8)		
1–2	68 (60.7)	72 (50.3)		
2–3	34 (30.4)	67 (46.9)		
Tumor location, No. (%)			0.028	0.118
Upper	78 (69.6)	87 (60.8)		
Middle	2 (1.8)	14 (9.8)		
Lower	32 (28.6)	42 (29.4)		
Laterality, No. (%)			0.010	0.645
Left	62 (55.4)	56 (39.2)		
Right	50 (44.6)	87 (60.8)		
p-T stage, No. (%) ^b			0.006	-
1a	10	4		
1b	56	55		
1c	20	49		
2a	26	35		
Predominant histology subtype, No. (%) ^b			0.783	_
Lepidic	12	12		
Papillary + acinar	87	109		
Solid + micropapillary	9	16		
Variant	4	6		
Lymph nodes removed, No. (%) $^{^{\mathrm{b}}}$			<0.001	_
≤0	101	59		
>5	11	84		
VPI, No. (%) ^b			0.815	-
Yes	26	35		
No	86	108		
LVI, No. (%) ^b			0.606	_
Yes	4	7		
No	108	136		
Adjuvant therapy, No. (%) ^b			0.868	_
Yes	6	7		
No	106	136		

^a, adjusted for propensity scores; ^b, these factors were not preoperative characteristics (without adjusted P values), but were included in the Cox analysis for survival. SD, standard deviation.

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Variable	RFS	RFS		RFS ^ª	
	HR (95% CI)	P value	HR (95% CI)	P value	
Age, years	0.999 (0.880–1.133)	0.981	0.946 (0.798–1.122)	0.524	
Sex	2.301 (1.311–4.040)	0.004	1.417 (0.739–2.716)	0.294	
Tumor size	1.725 (1.032–2.883)	0.038	1.678 (0.914–3.079)	0.095	
Tumor location	0.890 (0.654–1.212)	0.460	0.879 (0.607–1.127)	0.494	
Laterality	0.899 (0.522–1.547)	0.700	0.955 (0.500–1.822)	0.889	
T stage	1.338 (0.974–1.838)	0.073	1.205 (0.834–1.741)	0.320	
Predominant histology subtype	1.407 (0.970–2.042)	0.072	1.718 (1.032–2.861)	0.037	
Lymph nodes removed	0.629 (0.353–1.120)	0.116	0.495 (0.231–1.061)	0.071	
Surgical resection	0.390 (0.217–0.703)	0.002	0.360 (0.177–0.730)	0.005	
VPI	1.422 (0.798–2.536)	0.232	1.149 (0.565–2.338)	0.701	
LVI	1.230 (0.383–3.950)	0.728	1.660 (0.509–5.411)	0.400	
Adjuvant therapy	0.644 (0.157–2.650)	0.542	0.588 (0.141–2.451)	0.466	

Table 2 Univariable analyses for RFS before and after adjusting for propensity scores

^a, these patients included in the Cox analysis for survival were selected using propensity score analysis. RFS, relapse-free survival; VPI, visceral pleural invasion; LVI, lymphatic invasion.

Table 3 Multivariable analyses for RFS before and after adjusting for propensity scores

Variable —	RFS		RFS ^ª	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	0.934 (0.822–1.062)	0.299	0.940 (0.789–1.120)	0.491
Sex	2.289 (1.276–4.108)	0.005	1.681 (0.811–3.485)	0.162
Tumor size	1.954 (0.695–5.494)	0.204	2.202 (0.612–7.923)	0.227
Tumor location	0.939 (0.678–1.300)	0.706	0.923 (0.615–1.384)	0.698
Laterality	1.003 (0.574–1.752)	0.992	0.934 (0.465–1.876)	0.848
T stage	0.877 (0.260–2.952)	0.832	0.781 (0.179–3.410)	0.742
Predominant histology subtype	1.414 (0.928–2.155)	0.107	1.768 (0.974–3.211)	0.061
Lymph nodes removed	1.053 (0.500–2.216)	0.892	0.910 (0.365–2.272)	0.840
Surgical resection	0.304 (0.143–0.645)	0.002	0.315 (0.131–0.756)	0.010
VPI	1.641 (0.268–10.062)	0.593	1.751 (0.170–17.976)	0.638
LVI	1.103 (0.327–3.716)	0.875	1.842 (0.533–6.364)	0.334
Adjuvant therapy	0.462 (0.104–2.045)	0.309	0.470 (0.101–2.192)	0.337

^a, these patients included in the Cox analysis for survival were selected using propensity score analysis. RFS, relapse-free survival; VPI, visceral pleural invasion; LVI, lymphatic invasion.

lymph nodes removed (log-rank P=0.043) and surgical resection (log-rank P<0.001) were all significant predictors of LCSS before adjusting while only tumor size (log-rank P=0.012) and surgical resection (log-rank P=0.002) were

the significant predictors after PSM (*Table 4*). Multivariable analysis revealed that tumor size (log-rank P=0.044) and surgical resection (log-rank P=0.002) were still significant prognostic factors for LCSS after PSM (*Table 5*).

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Variable	LCSS	LCSS		
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.993 (0.851–1.160)	0.934	0.968 (0.787–1.190)	0.756
Sex	2.062 (1.079–3.942)	0.029	1.146 (0.529–2.484)	0.729
Tumor size	1.590 (0.868–2.914)	0.134	4.686 (1.407–15.599)	0.012
Tumor location	0.870 (0.614–1.233)	0.433	1.010 (0.669–1.527)	0.961
Laterality	0.471 (0.248–0.896)	0.022	0.542 (0.245–1.201)	0.131
T stage	1.319 (0.899–1.936)	0.156	1.052 (0.673–1.643)	0.824
Predominant histology subtype	1.117 (0.706–1.769)	0.636	1.059 (0.505–2.220)	0.879
Lymph nodes removed	0.495 (0.251–0.977)	0.043	0.537 (0.224–1.286)	0.163
Surgical resection	0.260 (0.131–0.515)	<0.001	0.277 (0.121–0.635)	0.002
VPI	1.438 (0.736–2.809)	0.288	0.843 (0.351–2.021)	0.702
LVI	0.866 (0.208–3.603)	0.843	0.569 (0.077–4.213)	0.581
Adjuvant therapy	0.536 (0.574–2.785)	0.306	0.042 (0.000–14.594)	0.289

Table 4 Univariable analyses for LCSS before and after adjusting for propensity scores

^a, these patients included in the Cox analysis for survival were selected using propensity score analysis. LCSS, lung cancer special survival; VPI, visceral pleural invasion; LVI, lymphatic invasion.

Table 5 Multivariable analyses for LCSS before and after adjusting for propensity scores

Variable	LCSS	LCSS		LCSS ^ª	
	HR (95% CI)	P value	HR (95% CI)	P value	
Age	0.936 (0.796–1.100)	0.421	1.013 (0.810–1.267)	0.912	
Sex	2.203 (1.108–4.378)	0.024	1.819 (0.777–4.262)	0.168	
Tumor size	1.777 (0.545–5.793)	0.340	1.422 (1.182–2.978)	0.044	
Tumor location	0.866 (0.593–1.267)	0.460	1.028 (0.647–1.633)	0.906	
Laterality	0.511 (0.263–0.992)	0.047	1.267 (0.241–6.664)	0.780	
T stage	1.194 (0.285–5.007)	0.808	1.597 (0.239–10.695)	0.629	
Predominant histology subtype	1.160 (0.684–1.969)	0.581	1.101 (0.459–2.640)	0.829	
Lymph nodes removed	1.037 (0.430–2.505)	0.935	0.891 (0.324–2.447)	0.823	
Surgical resection	0.156 (0.063–0.386)	<0.001	0.184 (0.063–0.532)	0.002	
VPI	1.536 (0.174–13.541)	0.699	0.709 (0.032–15.497)	0.827	
LVI	0.816 (0.171–3.892)	0.798	0.690 (0.077–6.179)	0.740	
Adjuvant therapy	0.862 (0.287–2.046)	0.879	0.943 (0.810–1.099)	0.545	

^a, these patients included in the Cox analysis for survival were selected using propensity score analysis. LCSS, lung cancer special survival; VPI, visceral pleural invasion; LVI, lymphatic invasion.

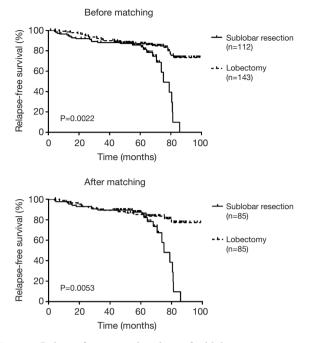


Figure 1 Relapse-free survival analysis of sublobar resection versus lobectomy before and after adjusting for propensity scores.

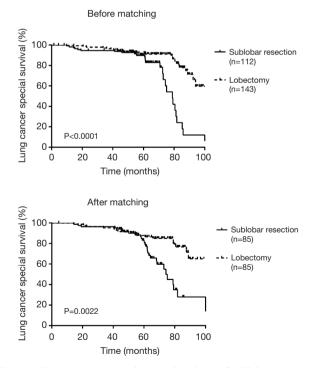


Figure 2 Lung cancer special survival analysis of sublobar resection versus lobectomy before and after adjusting for propensity scores.

There was a significant difference in RFS and LCSS between sublobectomy versus lobectomy before (RFS log-rank P=0.0022; LCSS log-rank P<0.001) and after (RFS log-rank P=0.0053; LCSS log-rank P=0.0022) adjusting of PSM (*Figures 1,2*).

A subgroup analysis of tumor size and the number of harvested lymph nodes was also conducted to further research prognosis between these two groups. Unsurprisingly, we still identify significant difference in RFS or LCSS among those stratified tumor size groups or harvested lymph node groups after PSM (*Figures 3,4*) except for the RFS in the group of harvested lymph nodes ≤ 5 (logrank P=0.0681).

Discussion

For the elderly patients with early-staged lung adenocarcinoma, the debate still persisted over whether sublobectomy could achieve considerable tumor prognosis compared with lobectomy. Razi et al. (13) suggested that sublobectomy should be considered for these specific populations based on the SEER database. De Zoysa et al. (14) also revealed that equivalent survival was observed between sublobectomy and lobectomy for elder patients with stage IA NSCLC and sublobectomy could be considered in high-risk patients. However, another SEER-based analysis showed that patients aged ≥ 70 years who underwent segmentectomy had significantly worse OS and LCSS than patients who underwent lobectomy, indicating poorer reservation of cardiopulmonary function and a limited life expectancy, thus, limited resections could be recommended for reducing surgery-related morbidity and reserving more pulmonary function (15). Above, it was undefined whether elderly patients with stage I NSCLC were eligible for sublobectomy. In the current study of stage I lung adenocarcinoma with age ≥ 75 years old, we analyzed the prognosis of patients who underwent sublobectomy and lobectomy, the results showed lobectomy was superior to sublobar resection.

In terms of tumor size, some previous studies have demonstrated equivalent prognosis with sublobectomy for tumor size ≤ 1 cm, even ≤ 2 or 3 cm (8,13,16). Varlotto *et al.* (17) conducted a study of 93 patients with stage I NSCLC who underwent sublobectomy and found tumor size ≥ 2 cm was a significant indicator for local recurrence.

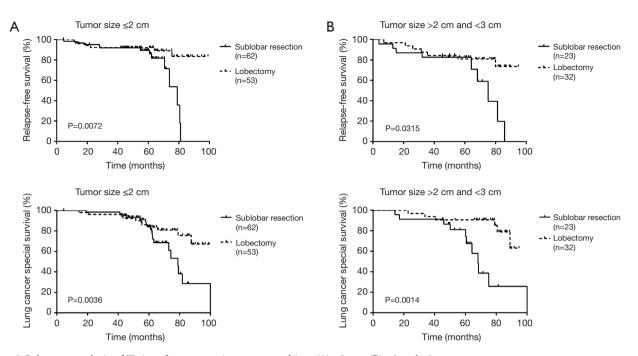


Figure 3 Subgroup analysis of T size after propensity score matching. (A) ≤ 2 cm; (B) >2 and ≤ 3 cm.

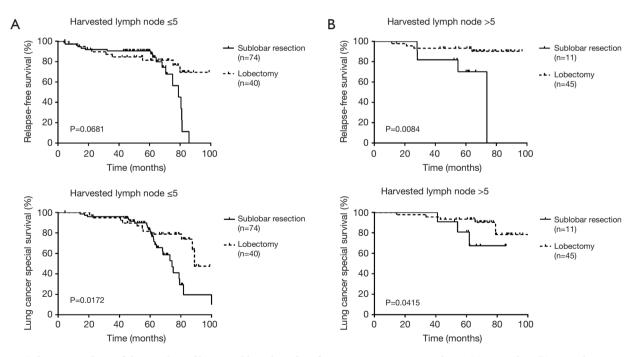


Figure 4 Subgroup analysis of the number of harvested lymph nodes after propensity score matching. (A) \leq 5 nodes; (B) >5 nodes.

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In current study, the RFS and LCSS in elder patient with stage I lung adenocarcinoma was both difference between the two surgical resections in subgroups of tumor size (≤ 2 , >2 and ≤ 3 cm) after adjusting for propensity scores.

A SEER database analyse of Osarogiagbon and colleagues (18) shown that a continues decline in mortality risk was obtained when the increased number of lymph nodes examined, and the lowest mortality rate was observed when 18–21 lymph nodes were harvested, while the median number of lymph nodes in their study was only 6. In our research, the median number of lymph nodes examined was 2 nodes (0–18 nodes) after PSM, we still identified significant difference in RFS or LCSS among those stratified tumor size groups or harvested lymph node groups after PSM. Conversely, Zhao *et al.* (19) did not even observe any survival advantages in those patients who underwent lobectomy. Of course, further studies were needed to be done.

There are some limitations of this study. First, many patients had their further therapies in local hospitals and the specific treatments were unknown. Second, we could not further compare the survival difference between lobectomy and wedge resection and segmentectomy because of the relatively small sample size in this study. Third, the shortcoming of our retrospective analysis was unavoidable, hence, the prospective analysis especially randomized clinical trials for sublobectomy and lobectomy for elder patients with stage I lung invasive adenocarcinoma was necessary to be investigated in future.

In summary, this study showed that prognosis of elderly patients (\geq 75 years) with stage I lung adenocarcinoma \leq 3 cm treated with sublobectomy were worse than lobectomy. Lobectomy could be preferable for the treatment of elderly patients with stage I lung adenocarcinoma. However, prospective randomized trials were still needed to be done for further investigation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tcr.2019.03.18). The authors have no 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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all patients. The study was approved by the Institutional Review Board of our hospital [ID: KS(Y)1668].

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