Original Article

Adjuvant treatment can improve prognosis in patients with non-small cell lung cancer ≤3 cm after sublobectomy: a propensity score analysis

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Background: Numerous retrospective studies have reported that sublobectomy has a poorer prognosis than lobectomy in patients with early-stage lung cancer. The purpose of this study was to determine whether adjuvant treatment could improve the prognosis of patients with non-small cell lung cancer (NSCLC) ≤3 cm after sublobectomy.

Methods: We collected data from 17,763 patients with T1N0M0 NSCLC after surgery from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2015. Kaplan-Meier curves were generated to compare the overall survival (OS) rates and the lung cancer-specific survival (LCSS) rates. Cox proportional hazards regressions were performed to discover the independent risk factors for both the OS and LCSS rates.

Results: Lobectomy was performed in 12,428 cases and sublobectomy was performed in 5,335 cases. In the sublobectomy group, among the 394 patients treated with adjuvant therapy, larger tumor diameter, a lower number of lymph node dissections, and more wedge resections were observed in the patients treated with adjuvant therapy. In the subsequent survival analysis, the OS and LCSS rates of adjuvant therapy patients showed a significant survival advantage over those treated with sublobectomy alone (P<0.05). The survival analysis was performed again after propensity match scoring, generating similar results (P<0.05). There was still a significant difference in OS between adjuvant therapy and lobectomy alone (P<0.05).

Conclusions: Chemoradiotherapy can improve the OS of patients with NSCLC ≤3 cm after sublobectomy and reduce death caused by tumors. Therefore, when patients cannot tolerate lobectomy or are given inappropriate sublobectomy, adjuvant therapy can improve the prognosis of patients.

Keywords: Adjuvant treatment; sublobectomy; lobectomy; non-small cell lung cancer (NSCLC)

Submitted Nov 12, 2020. Accepted for publication Dec 29, 2020.
doi: 10.21037/jtd-20-3448
View this article at: http://dx.doi.org/10.21037/jtd-20-3448

Introduction

Lung cancer is one of the most common malignancies worldwide. With the application of low-dose spiral computed tomography (CT), an increasing number of small lung nodules have been detected, thus leading to an increase in the discovery of early-stage lung cancer (1). According to the current National Comprehensive Cancer Network (NCCN) guidelines, the recommended treatment for early-stage lung cancer is surgery, which includes lobectomy and sublobectomy. Because the prognosis of sublobectomy is poor, lobectomy with mediastinal lymph node dissection or sampling is preferred, while sublobectomy and segmentectomy can be chosen if the patient cannot tolerate lobectomy. Although adjuvant therapy is not recommended for early-stage lung cancer (2), sublobectomy cannot provide accurate staging, this part of patients which don't know accurate staging after sublobectomy cannot be considered as early lung cancer (3).

Since 1995, a series of studies have shown that the prognosis of sublobectomy is worse than lobectomy (4,5). In 1995, Ginsberg and Rubinstein conducted a study on the effects of lobectomy and sublobectomy on survival in early-stage lung cancer, reporting that sublobectomy led to worse outcomes in patients than lobectomy (4). The reasons behind this finding were not clearly explained, though it may be linked to insufficient lymph node dissection and insufficient distance from the resection margin. Furthermore, in many sublobectomies, the number of lymph nodes removed is insufficient or the lymph nodes are not removed (5). Liu *et al.* showed that more than half of the patients had less than 6 lymph nodes dissected during sublobectomy (3).

There are no clear criteria for the selection of suitable patients for sublobectomy, so some patients may have good prognosis after undergoing sublobectomy (6), whilst others may have poor prognosis. Additionally, there is no relevant research exploring how to improve the prognosis of patients. Hamada *et al.* showed that adjuvant chemotherapy significantly improves survival in patients with stage IA T1b non-small cell lung cancer (NSCLC) compared with surgery alone (7). Based on these considerations, we speculated that adjuvant therapy may improve the prognosis of these patients. Therefore, the purpose of this study was to determine whether radiotherapy and chemotherapy could improve the prognosis of patients undergoing sublobectomy.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3448).

Methods

The clinical data of patients who were pathologically diagnosed with NSCLC between 2004 and 2015 were extracted using the SEER*Stat software from the Surveillance, Epidemiology, and End Results (SEER) database. The eligibility criteria were as follows: 20 years of age or older, underwent sublobectomy, and NSCLC tumor ≤3 cm. The collected data included age, gender, pathological type, stage, tumor diameter, number of lymph node dissections, surgical methods, radiotherapy and chemotherapy, overall survival (OS), lung cancer-specific survival (LCSS). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Comparisons of the basic characteristics of tumors between groups were performed using a χ^2 test and *t*-test. The Kaplan-Meier method was used for univariate survival analysis. The Cox proportional hazards model was used for multivariate analysis. A P value of <0.05 was considered statistically significant.

Results

There were 17,763 eligible NSCLC cases found in the SEER database. Lobectomy was performed in 12,428 cases, and sublobectomy was performed in 5,335 cases. In the sublobectomy group, among the 394 patients treated with adjuvant therapy, 202 were treated with radiotherapy, 50 with chemoradiotherapy, and 142 with chemotherapy. The median follow-up time for lobectomy was 51.7 months, the median follow-up time for sublobectomy alone was 44.9 months, and the median follow-up time for sublobectomy with chemoradiotherapy was 45.4 months. Larger tumor diameter, lower number of lymph node dissections, and more wedge resections were observed in the patients treated with adjuvant therapy. No significant differences were found in regard to sex, ethnicity, and median (range) follow-up time between the two groups (*Table 1*).

After propensity score matching of the sublobectomy patients with and without adjuvant therapy using a ratio of 1:2, there were 394 patients in the adjuvant therapy group and 786 patients in the surgery group. The median follow-up time in the adjuvant therapy group was 45.4 months, and the median follow-up time in the surgery group was 46.1 months (*Table 1*).

In the subsequent survival analysis, the OS of adjuvant therapy patients showed a significant survival advantage over those treated with sublobectomy alone [hazard ratio (HR), 1.422; 95% CI, 1.218 to 1.660; P=0.000] (*Figure 1A*). In terms of LCSS, there were significant differences in survival between the adjuvant treatment group and the surgery-only group (P<0.05; *Figure 1B*). The survival analysis was performed again after the propensity match

Table 1 Baseline characteristics

Variable	CR + SUB *vs.* SUB			CR + SUB *vs.* LOB			CR + SUB *vs.* SUB (PSM)		
	CR + SUB	SUB	P	CR + SUB	LOB	P	CR + SUB *vs.* SUB	SUB	P
Sex			0.051			0.024*			0.106
Male	190 (48.2)	2,132 (43.1)		190 (48.2)	5,285 (42.5)		190 (48.2)	340 (43.3)	
Female	204 (51.8)	2,809 (54.9)		204 (51.8)	7,143 (57.5)		204 (51.8)	446 (56.7)	
Age, years	68.3±9.6	69.4±9.5	0.021*	68.3±9.6	67.2±9.2	0.026*	68.3±9.6	68.5±9.7	0.586
Lymph node			0.001*			0.000*			0.768
0	189 (48.0)	1,925 (39.0)		189 (48.0)	59 (0.5)		189 (48.0)	380 (48.3)	
1–3	104 (26.4)	1,325 (26.8)		104 (26.4)	1,567 (12.6)		104 (26.4)	196 (24.9)	
≥4	81 (20.6)	1,455 (29.4)		81 (20.6)	10,274 (82.7)		81 (20.6)	177 (22.5)	
Other	20 (5.1)	236 (4.8)		20 (5.1)	528 (4.2)		20 (5.1)	33 (4.2)	
Race/ethnicity			0.523			0.230			0.162
Hispanic	13 (3.3)	195 (3.9)		13 (3.3)	569 (4.6)		13 (3.3)	40 (5.1)	
Non-Hispanic	381 (96.7)	4,746 (96.1)		381 (96.7)	11,859 (95.4)		381 (96.7)	746 (94.9)	
Location			0.054			0.017*			0.086
Upper	272 (69.0)	3,111 (63.0)		272 (69.0)	7,874 (63.4)		272 (69.0)	495 (63.0)	
Middle	8 (2.0)	186 (3.8)		8 (2.0)	616 (5.0)		8 (2.0)	33 (4.2)	
Lower	112 (28.4)	1,597 (32.3)		112 (28.4)	3,816 (30.7)		112 (28.4)	251 (31.9)	
Other	2 (0.5)	47 (1.0)		2 (0.5)	122 (1.0)		2 (0.5)	7 (0.9)	
Size	18.4±6.4	16.6±6.2	0.000*	18.4±6.4	19.3±6.2	0.006*	18.4±6.4	18.1±6.3	0.408
WHO classification			0.004*			0.000*			0.888
Squamous cell carcinoma	143 (36.3)	1,453 (29.4)		143 (36.3)	3,144 (25.3)		143 (36.3)	282 (35.9)	
Adenocarcinoma	251 (63.7)	3,488 (70.6)		251 (63.7)	9,284 (74.7)		251 (63.7)	504 (64.1)	
Median (range) follow-up time	45.4±34.1	44.9±34.2	0.773	45.4±34.1	51.7±37.2	0.001*	45.4±34.1	46.1±34.8	0.773
Sublobectomy			0.000*			–			0.575
Segmentectomy	62 (15.7)	1,066 (21.6)					62 (15.7)	114 (14.5)	
Wedge resection	332 (84.3)	3,875 (78.4)					332 (84.3)	672 (85.5)	

*, P<0.05. CR, chemoradiotherapy; SUB, sublobectomy; LOB, lobectomy; PSM, propensity matching score.

scoring, generating similar results for OS (HR, 1.251; 95% CI, 1.047 to 1.494; P=0.014) (*Figure 1C*) and LCSS (P<0.05; *Figure 1D*).

There was still a significant difference in OS between adjuvant therapy and lobectomy alone (HR, 1.380; 95% CI, 1.186 to 1.606; P=0.000) (*Figure 2A*). In terms of LCSS, there were significant differences in survival between the adjuvant treatment group and the surgery-only group (P<0.05; *Figure 2B*). When chemotherapy, radiotherapy, and chemoradiotherapy were compared with sublobectomy alone, the survival benefit of adjuvant therapy was more obvious than that of surgery-only (P<0.05; *Figure 2C,D*), and chemotherapy was more beneficial than radiotherapy and chemoradiotherapy.

The Cox proportional hazards regression model showed that the factors that could affect OS in the sublobectomy

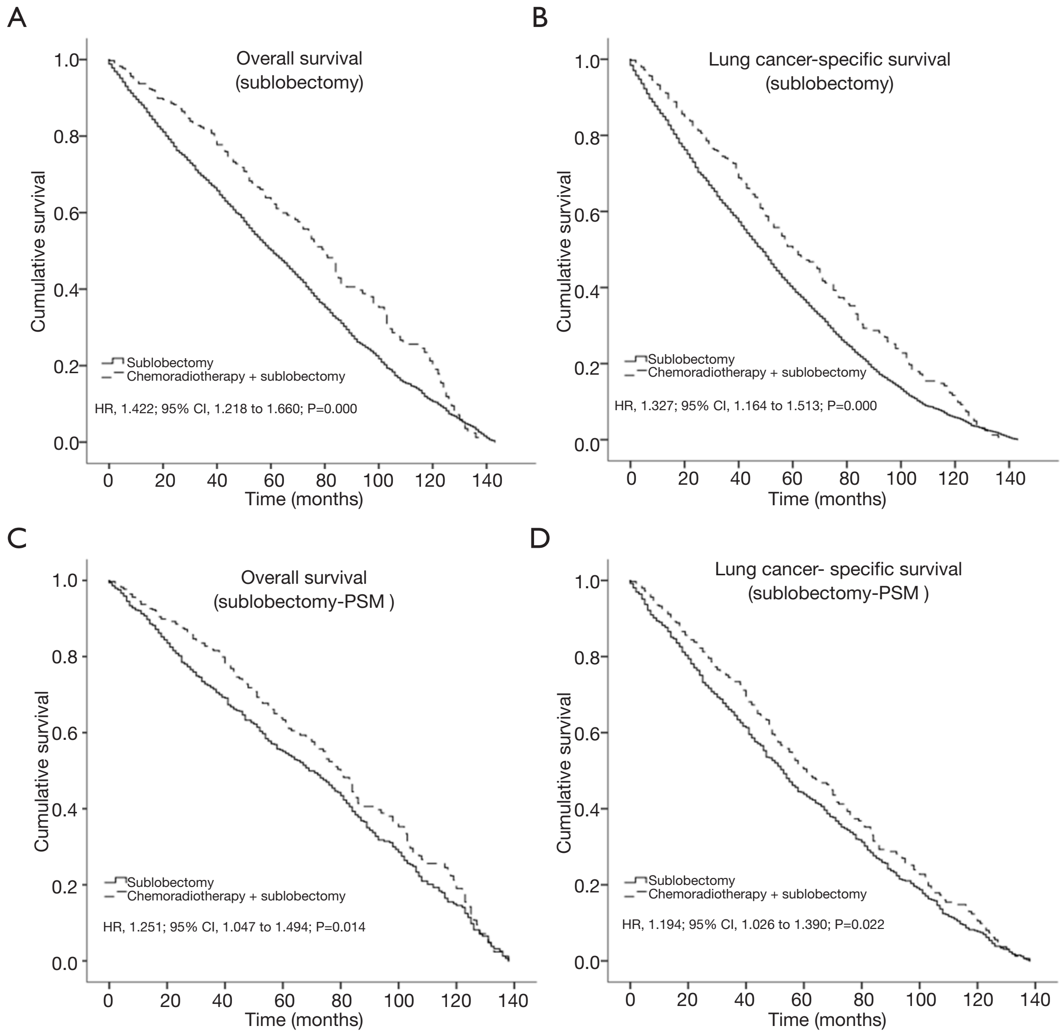

Figure 1 Survival comparison between sublobectomy and chemoradiotherapy + sublobectomy. (A) The overall survival of patients who underwent adjuvant therapy showed a clear survival advantage over sublobectomy alone; (B) similar results were found for lung cancer-specific survival; (C) the overall survival of patients who underwent adjuvant therapy after propensity score matching showed a clear survival advantage over sublobectomy alone; (D) similar results were found for lung cancer-specific survival. HR, hazard ratio; CI, confidence interval; PSM, propensity score matching.

versus chemoradiotherapy group were the number of lymph node dissections, tumor pathological types, and tumor size (P<0.05, *Table 2*). The correlation factors after propensity match scoring were the number of lymph node dissections and tumor size (P<0.05, *Table 3*). In the comparison between lobectomy and chemoradiotherapy, the factors influencing OS were the number of lymph node dissections, tumor pathological type, and tumor size (P<0.05, *Table 4*). In terms of LCSS, the factors affecting prognosis in the sublobectomy and chemoradiotherapy groups were age, number of lymph node dissections, and tumor size (P<0.05, *Table 2*). Age was also an influencing factor after propensity match scoring (P<0.05, *Table 3*). The relevant factors affecting prognosis in the lobectomy versus chemoradiotherapy groups were age, and number of lymph node dissections (P<0.05, *Table 4*).

Discussion

Half a century ago, the debate among surgeons for lung cancer patients was whether to choose lobectomy or pneumonectomy (8). Nowadays, the focus of debate among

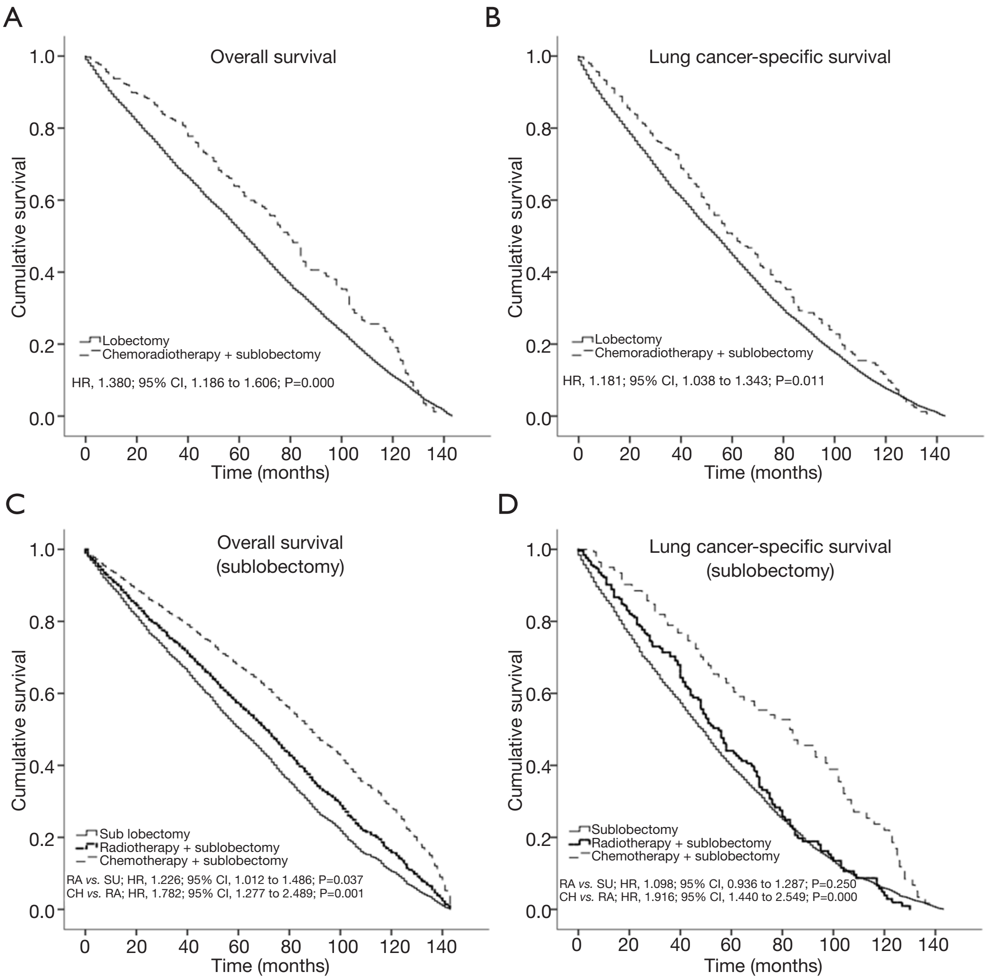

Figure 2 Survival comparison between lobectomy and chemoradiotherapy + sublobectomy. (A) There was a significant difference in total survival between adjuvant therapy and lobectomy; (B) similar results were found for lung cancer-specific survival; The effect of different treatments on survival after sublobectomy (C,D) when chemotherapy and radiotherapy were compared with sublobectomy alone, the survival benefit of adjuvant therapy was more obvious than that of surgery-only. HR, hazard ratio; CI, confidence interval.

surgeons for patients with operable clinical stage I NSCLC is whether to choose lobectomy or sublobectomy. The factors influencing prognosis are surgical method, margin, tumor diameter, number of lymph node dissections, and pathological type for operable NSCLC. In order to find a suitable standard for sublobectomy, some studies have explored the diameter of the tumor (9), the number of lymph nodes dissected (3), and the pathological type (10).

Despite the increased detection rate of pulmonary nodules, the choice of surgical method for patients with stage I NSCLC is controversial in the field of thoracic surgery. The current NCCN guidelines recommend lobectomy for stage Ia NSCLC, however, sublobectomy should still be recommended for patients with stage I NSCLC who cannot tolerate lobectomy (2). Consequently, there are no clear criteria for the selection of patients suitable for sublobectomy, which may lead to poor prognosis in some patients due to inappropriate surgical methods.

In a randomized controlled study on sublobectomy and lobectomy from 1995, lobectomy was superior to sublobectomy in terms of survival and local recurrence (4). However, some thoracic surgeons believe this study has many shortcomings, such as an insufficient margin, erroneous pathological classification, and lymph nodes that were not dissected. The margin is also an essential factor that should be taken into consideration after sublobectomy

Table 2 Cox proportional hazards regression model for overall survival and lung cancer-specific survival (chemoradiotherapy + sublobectomy *vs.* sublobectomy)

Variable	Overall survival		Lung cancer-specific survival	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age, years	1.001 (0.997 to 1.005)	0.529	1.010 (1.007 to 1.014)	0.000*
Lymph node		0.000*		0.020*
0	1.00 (reference)		1.00 (reference)	
1–3	0.913 (0.770 to 1.082)	0.293	0.975 (0.842 to 1.128)	0.732
≥4	1.071 (0.902 to 1.271)	0.433	1.020 (0.879 to 1.184)	0.790
Other	1.226 (1.036 to 1.452)	0.018*	1.100 (0.949 to 1.275)	0.208
Size	0.982 (0.976 to 0.987)	0.000*	0.992 (0.987 to 0.997)	0.001*
WHO classification				
AD	1.00 (reference)		1.00 (reference)	
SQ	1.120 (1.031 to 1.217)	0.007*	0.936 (0.874 to 1.003)	0.059*
Sublobectomy				
WR	1.00 (reference)		1.00 (reference)	
SE	0.977 (0.898 to 1.063)	0.590	1.026 (0.951 to 1.106)	0.505

*, P<0.05. CI, confidence interval; AD, adenocarcinoma; SQ, squamous cell carcinoma; WR, wedge resection; SE, segmentectomy.

Table 3 Cox proportional hazards regression model for overall survival and lung cancer-specific survival after propensity score matching (chemoradiotherapy + sublobectomy *vs.* sublobectomy)

Variable	Overall survival		Lung cancer-specific survival	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age, years	1.003 (0.994 to 1.012)	0.509	1.013 (1.005 to 1.021)	0.001*
Lymph node		0.001*		0.181
0	1.00 (reference)		1.00 (reference)	
1–3	0.868 (0.578 to 1.304)	0.496	0.938 (0.653 to 1.348)	0.731
≥4	1.052 (0.692 to 1.597)	0.814	1.026 (0.707 to 1.488)	0.894
Other	1.329 (0.877 to 2.014)	0.180	1.147 (0.789 to 1.667)	0.471
Size	0.977 (0.964 to 0.990)	0.001*	0.990 (0.978 to 1.001)	0.076
WHO classification				
AD	1.00 (reference)		1.00 (reference)	
SQ	1.077 (0.898 to 1.292)	0.422	0.949 (0.816 to 1.106)	0.498
Sublobectomy				
WR	1.00 (reference)		1.00 (reference)	
SE	0.931 (0.745 to 1.163)	0.528	1.076 (0.881 to 1.313)	0.474

*, P<0.05. CI, confidence interval; AD, adenocarcinoma; SQ, squamous cell carcinoma; WR, wedge resection; SE, segmentectomy.

Table 4 Cox proportional hazards regression model for overall survival and lung cancer-specific survival (chemoradiotherapy + sublobectomy *vs.* lobectomy)

Variable	Overall survival		Lung cancer-specific survival	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age, years	1.000 (0.998 to 1.002)	0.946	1.008 (1.006 to 1.011)	0.000*
Lymph node		0.000*		0.000*
0	1.00 (reference)		1.00 (reference)	
1–3	0.989 (0.801 to 1.222)	0.919	1.068 (0.891 to 1.280)	0.476
≥4	1.116 (0.989 to 1.258)	0.074	1.079 (0.969 to 1.201)	0.166
Other	1.306 (1.173 to 1.453)	0.000*	1.206 (1.097 to 1.327)	0.000*
Size	0.994 (0.991 to 0.997)	0.000*	0.997 (0.994 to 1.000)	0.051
WHO classification				
AD	1.00 (reference)		1.00 (reference)	
SQ	1.094 (1.041 to 1.151)	0.000*	0.968 (0.926 to 1.012)	0.149

*, P<0.05. CI, confidence interval; AD, adenocarcinoma; SQ, squamous cell carcinoma.

of NSCLC. The adequate margin of wedge resection should ideally be >2 cm or at least 1 cm to reduce local recurrence. However, it has been reported that wedge resection is frequently associated with margins less than 1 cm (48–61%). Even in segmentectomy, 23% to 27% of presented margins are less than 1 cm (11,12). Insufficient margin has been associated with a high risk of locoregional recurrence, which may partially account for sublobectomy failure. Nowadays, surgical methods are much better than before. Although there are still no randomized controlled studies, numerous retrospective studies have reported inconsistent results (13). In particular, segmentectomy can be used to successfully achieve anatomic resection. However, the results of previous studies may not necessarily be applicable today, and sublobectomy, which is similar to lobectomy, can be performed in some patients, especially on ground-glass opacity (GGO) nodules (6,14). Although many studies have reported good prognosis after sublobectomy for GGO nodules (15,16), Moon *et al.* reported that sublobectomy in clinical N0 solid-predominant nodules could actually increase recurrence due to the marginal factors (13).

Some studies have suggested that tumor diameter is related to the type of surgery, meaning that sublobectomy could be performed on tumors smaller than 20 mm in diameter (17,18). Chen *et al.* demonstrated that the difference in survival between sublobectomy and lobectomy was not statistically significant when the diameter was less than 2 cm (5). Several retrospective studies have shown that limited resection may be equally as effective for the treatment of stage Ia patients with tumors ≤2 cm compared with lobectomy, particularly among elderly patients (4,6,19). Kates *et al.* analyzed the outcomes of patients with NSCLC ≤1 cm, and concluded that lobectomy conferred no OS benefit (20). However, other studies have found that tumor diameter cannot be used as a criterion for choosing surgical methods because lymph node metastasis can occur even if the tumor diameter is very small (9). For example, when the tumor diameter is less than 20 mm, the rate of N1 and N2 lymph node metastasis can be as high as 5.3% and 6.6% (21). It is well known that sublobectomy may understage lung cancer because of inadequate lymphadenectomy for hilar (N1) lymph nodes compared with lobectomy (22). Yendamuri *et al.* demonstrated that the survival advantage offered by lobectomy over sublobectomy in NSCLC patients with tumor size ≤2 cm has incrementally decreased over the past 2 decades with advancements in surgical methods, however, the prognosis of lobectomy is still better than sublobectomy (23). Therefore, for many NSCLC cases, although the tumor is less than 3 cm in size, it cannot be identified as stage I lung cancer as the lymph node is not guaranteed to be negative after sublobectomy. In order to obtain accurate staging, intraoperative systemic lymph node dissection is required. In the current study, lung adenocarcinoma was the main pathological type in the sublobectomy group. According to the newly revised classification of pulmonary adenocarcinoma by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/ European Respiratory Society (ERS), adenocarcinoma is divided into adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma (24). There is no lymph node metastasis in the presence of adenocarcinoma *in situ* or minimally invasive adenocarcinoma, resulting in 100% 5-year disease-free survival (10), whereas those with invasive adenocarcinoma have 76–84% 5-year disease-free survival (25). Many thoracic surgeons believe that sublobectomy can be performed for adenocarcinoma *in situ* and minimally invasive adenocarcinoma. Nonetheless, lobectomy should be performed for invasive adenocarcinoma (25,26). At present, preoperative examinations, such as bronchoscopy and CT-guided percutaneous lung biopsy, can only be recommended for patients with pathological types and cannot be further classified due to the small number of samples. While intraoperative freezing can obtain enough tissue to quickly determine the pathological type, there is a certain error in intraoperative freezing pathology, which may lead to the erroneous diagnosis of some invasive adenocarcinoma such as adenocarcinoma in situ, thus leading to inappropriate surgical treatment (27).

This study showed that sublobectomy had worse prognosis than lobectomy, hence, sublobectomy is not recommended for all ≤3 cm NSCLC. We verified that sublobectomy may not perform adequate lymph node dissection, and some lung cancers with longer diameters also received sublobectomy. Therefore, we believe that the poor prognosis of some patients is due to not being given the correct surgery. Although the SEER database does not explain why adjuvant therapy was given, the present study showed that the prognosis of these patients significantly improved after adjuvant therapy, reaching even more optimal results than lobectomy. Moreover, other studies have also confirmed that radiotherapy and chemotherapy demonstrate efficacy in stage I patients (28,29).

The present study has some limitations that need to be addressed. First, the SEER database does not provide specific chemotherapy regimens and radiation doses. Second, this study is a retrospective study. Although the propensity score matching analysis was performed, there is still a possibility of some bias. Finally, due to the low number of chemotherapy, radiotherapy, and chemoradiotherapy cases, they were all grouped into the 1 same group to reduce bias, which could not be analyzed in more detail.

In summary, the results of this study show that chemoradiotherapy can improve the OS of patients after sublobectomy and reduce death caused by tumors. Therefore, when patients cannot tolerate lobectomy or are given inappropriate surgery, adjuvant therapy can improve the prognosis of patients. Our conclusion still needs to be verified using prospective randomized controlled trials.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-3448

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-3448). 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).

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(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Ma H, Cheng J, Yu Y, Liu B, Qin J, Xing W, Luo S. Adjuvant treatment can improve prognosis in patients with non-small cell lung cancer ≤3 cm after sublobectomy: a propensity score analysis. J Thorac Dis 2021;13(1):312-321. doi: 10.21037/jtd-20-3448

