A Meta-Analysis Comparing Lobectomy versus Segmentectomy in Stage I Non-Small Cell Lung Cancer

Tae Yoon Lim, M.D.¹, Samina Park, M.D.², Chang Hyun Kang, M.D., Ph.D.²

Departments of ¹Anesthesiology and ²Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Lobectomy is considered the standard strategy for early-stage non-small cell lung cancer (NSCLC). However, sublobar resection for NSCLC has recently received increased attention. The objective of this study was to compare 5-year survival, recurrence-free survival, postoperative mortality, and postoperative morbidities in patients who received segmentectomy versus those who received lobectomy through a meta-analysis. Sixteen studies were included and the combined hazard ratios or odds ratios were calculated. The results revealed that the 5-year survival rate after segmentectomy was comparable to that of lobectomy for stage I A NSCLC. However, segmentectomy for stage I NSCLC had lower rates of postoperative mortality and morbidities than lobectomy.

Key words: 1. Meta-analysis  
2. Non-small-cell lung carcinoma  
3. Lobectomy  
4. Segmentectomy  
5. Survival

Introduction

Lung cancer is the leading cause of malignancy-related deaths in many countries. Surgical resection is considered the standard treatment for early-stage non-small cell lung cancer (NSCLC) [1]. Surgical resection can achieve a 5-year survival rate as high as 70% in patients with stage IA NSCLC [2]. Therefore, early detection is a promising strategy for NSCLC. According to the National Lung Screening Trial, screening with low-dose computed tomography (CT) scans can reduce the mortality of lung cancer by increasing the detection of early-stage lung cancer, thereby enabling more patients to receive surgical treatment [3]. Therefore, it is expected that early-stage lung cancer will be detected more frequently as a result of the widespread application of screening chest CT scans. However, the optimal extent of surgical resection for early-stage lung cancer is still debatable. Although lobectomy has been the standard surgical strategy for NSCLC since the randomized controlled trial performed by the Lung Cancer Study Group in 1995 [4], the question has been repeatedly raised of whether sublobar resection could be an alternative surgical strategy to lobectomy. Large-scale randomized controlled studies comparing sublobar resection to lobectomy for NSCLC are now in progress [5,6].

The issues that should be clarified are whether segmentectomy is beneficial for early outcomes and
whether its long-term outcomes are comparable to those of lobectomy. Several meta-analyses have addressed these issues with inconsistent results [7-12]. Therefore, the aim of this study was to compare early and late outcomes between segmentectomy and lobectomy. The 5-year survival, recurrence-free survival, postoperative mortality, and postoperative morbidity after segmentectomy and lobectomy were compared through a meta-analysis.

### Methods

#### 1) Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to conduct the meta-analysis [13]. Studies on lobectomy and segmentectomy for stage I NSCLC were searched through PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Library. To maximize the sensitivity of the search strategy and to identify all potentially rel-
Table 2. Main characteristics and results of studies included in the meta-analysis of lobectomy versus segmentectomy for stage I non-small cell lung cancer

| Author                  | Age (mean, yr) | Tumor size (mean, mm) | Tumor stage | No. of S | No. of L | 5-Year survival | Recurrence-free survival | Postop mortality | Postop morbidity |
|-------------------------|----------------|-----------------------|-------------|----------|----------|-----------------|--------------------------|-----------------|-----------------|
|                         | S   | L       | S   | L       |          |               | HR | SD          | HR | SE | HR | SD | HR | SE       | S   | L   | S   | L   |
| Kodama et al. [16]     | 61^m | 77^m   | 16.7±4.97 | 22.9±5.22 | IA       | 46  | 77  | 0.96          | 0.62 |
| Okada et al. [17]      | IA   |         |       |          |          |     |     | 0.89          | 0.63 |
| Martin-Ucar et al. [18] | 70^m | 69^m   | 32^m  | 34^m    | I        | 17  | 17  | 0.83          | 1.43 |
| Okumura et al. [19]    | 65.2 | 61.2   | 14.4  | 16.3     | IA       | 55  | 187 | 2.01          | 0.74 |
| Schuchert et al. [20]  | 70   | 68     | 23    | 31       | I        | 182 | 246 | 2.08          | 0.47 |
| Stenel et al. [21]     | IA   |         |       |          |          | 49  | 150 | 3.50          | 0.52 |
| Kilic et al. [22]      | 79   | 78.5   | 25    | 35       | I        | 78  | 106 | 0.78          | 0.26 |
| Yamashita et al. [23]  | 72^m | 68^m   | 15^m  | 25^m     | I        | 38  | 71  | 1.18          | 1.10 |
| Schuchert et al. [24]  | 68.5 | 66.1   | 8     | 8        | IA       | 40  | 32  | 0.79          | 0.52 |
| Whitson et al. [25]    | I    |         | 581   | 13,892   |          | 1.37 | 0.08 |
| Carr et al. [26]       | IA   |         | 178   | 251      |          | 0.76 (T1a) | 1.65 (T1b) | 1.27 (T1a) | 1.37 (T1b) |
| Schuchert et al. [27]  | IA   |         | 325   | 432      |          | 1.08 | 0.20 |
| Schuchert et al. [28]  | 70.0±8.6 | 68.4±10.1 | 20^m  | 25^m     | I        | 305 | 594 |              | 4    |
| Yamashita et al. [29]  | 69^m | 68^m   | 15^m  | 20^m     | IA       | 90  | 124 | 1.99          | 0.99 |
| Zhong et al. [30]      | 63.6±8.0 | 64.9±7.3 | 11±5  | 15±4     | IA       | 39  | 81  | 0.47          | 0.61 |
| Zhao et al. [31]       | 59.3±13.77 | 58.8±10.77 | 14.2±7.15 | 19.8±9.82 | I      | 36  | 138 |              | 3    |

S, segmentectomy; L, lobectomy; HR, hazard ratio; SD, standard deviation; SE, standard error; Postop, postoperative; ^m, median.
Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram presenting the search strategy used to compare the outcomes of segmentectomy versus lobectomy for stage I non-small cell lung cancer.

levant studies, we combined the search terms as follows: "lobectomy" AND "sublobar resection" OR "sublobectomy" OR "limited resection" OR "segmentectomy" AND "NSCLC" OR "lung neoplasm" OR "lung cancer" AND "survival" OR "recurrence." In total, 1,790 articles were found. After eliminating duplicates, a total of 1,219 articles remained.

2) Inclusion and exclusion criteria
The retrieved studies were then selected according to the following inclusion and exclusion criteria. The inclusion criteria were: (1) a study population comprising stage I NSCLC patients, with all histologic types and pathologic confirmation; (2) an analysis of lobectomy or limited resection (specifically segmentectomy); (3) study outcomes including 5-year survival, recurrence-free survival, postoperative mortality (in-hospital or 30-day mortality), and postoperative morbidities; and (4) any of the following study designs: randomized controlled trial, cohort, or case-control (retrospective or prospective). The exclusion criteria were: (1) a study population of patients who received wedge resection; (2) data that merged wedge resection and segmentectomy as ‘sublobar resection’; (3) study participants who received neo-adjuvant chemotherapy or induction treatment before surgery; (4) case reports, reviews, or expert opinions; (5) studies not written in English; (6) studies for which only the abstract was available; and (7) studies published before 1995.

3) Data extraction
Based on the inclusion and exclusion criteria, a total of 178 full-text articles were assessed for eligibility. Two investigators (T.Y.L. and S.P.) independently reviewed each retrieved article. All discrepancies between the 2 reviewers were resolved by discussion. As a result, 162 articles were excluded and 16 articles were included in the meta-analysis.

4) Statistical analysis
In this meta-analysis, we compared 5-year survival, recurrence-free survival, postoperative mortality, and postoperative morbidities. We used hazard ratios and standard error to interpret 5-year survival and recurrence-free survival. The hazard ratios and associated 95% confidence intervals were directly used if they were provided by the original studies. If they were not, they were indirectly obtained by using the Kaplan-Meier survival curve, the number of patients
Meta-Analysis of Limited Resection

Fig. 2. Forest plot showing a comparison of 5-year survival between segmentectomy and lobectomy in (A) stage I and (B) stage IA non-small cell lung cancer. HR, hazard ratio; SE, standard error; CI, confidence interval; df, degrees of freedom.

Results

1) Literature search and general characteristics of the studies included
A total of 1,790 studies were identified from 4 electronic databases. Two studies were identified through other sources. After removing duplicates, studies before 1995, and irrelevant studies, 178 articles were assessed for eligibility, of which 162 were excluded due to failure to meet the inclusion criteria. Sixteen studies remained. The characteristics of these characteristics are summarized in Table 1 and Table 2 [16-31]. A summary of the search strategy and selection process used are presented in Fig. 1 following the PRISMA flow diagram.

2) Meta-analysis of 5-year survival
Eleven studies described 5-year survival outcomes using Kaplan-Meier survival curves, with either stage I NSCLC patients or stage IA NSCLC patients [16-19,21-25,29,30]. Two separate meta-analyses were therefore conducted to determine the 5-year survival of stage I and IA NSCLC. Four studies of stage I NSCLC and 7 studies of stage IA NSCLC were analyzed. The results are presented in Fig. 2. The combined hazard ratio for segmentectomy was 1.30, with a 95% confidence interval of 1.12–1.51 for stage I NSCLC, suggesting that patients who received segmentectomy had a 1.30-times lower 5-year survival rate than those who received lobectomy. Heterogeneity was negligible was present, as the I² statistic was lower than 50% and the p-value was greater than 0.1. However, there was no significant (p > 0.05) difference in the 5-year survival rate between the 2 surgical intervention groups for stage IA NSCLC. The combined hazard ratio for segmentec-
Fig. 3. Forest plot showing a comparison of recurrence-free survival between segmentectomy and lobectomy in (A) stage I and (B) stage IA non-small cell lung cancer. HR, hazard ratio; SE, standard error; CI, confidence interval; df, degrees of freedom.

4) Meta-analysis of postoperative mortality

In this study, postoperative mortality was defined as including 30-day mortality and in-hospital mortality. Odds ratios were used to compare the mortality rate of segmentectomy versus lobectomy for stage I NSCLC. The corresponding forest plot is shown in Fig. 4 [18,20,22,24,26,28,30,31]. A total of 800 patients who underwent segmentectomy were compared to 1,246 patients who underwent lobectomy. The combined odds ratio for segmentectomy was 0.49, with a 95% confidence interval of 0.24–1.00. Heterogeneity was not present (p=0.91). The p-value for the overall effect was 0.05. From the perspective of postoperative mortality, segmentectomy might be more beneficial for stage I NSCLC patients than lobectomy.

5) Meta-analysis of postoperative morbidities

Postoperative morbidities between segmentectomy and lobectomy were compared in 7 studies. In most of these studies, postoperative morbidities included cardiac (myocardial infarction and cardiac arrest), pulmonary (pneumonia, empyema, bronchopleural fistula, respiratory failure requiring re-intubation, and tracheostomy), and others (septicemia, pulmonary...
embolism, and stroke). All intraoperative and postoperative complications were included in the category of postoperative morbidities. Although some studies classified morbidities as major or minor, all adverse events were combined in this analysis. As shown in Fig. 4 [18,20,22,24,26,28,30,31], the total odds ratio for segmentectomy was 0.71 (p=0.001), with a 95% confidence interval of 0.58-0.87. In the heterogeneity analysis, the p-value was 0.11 and I² was 42%. Therefore, heterogeneity was not present. Because the p-value for the overall effect was less than 0.05, the total odds ratio of 0.71 was considered to be significant. This suggests that segmentectomy can lead to fewer postoperative morbidities than lobectomy.

6) Publication bias

Funnel plots for 5-year survival (stage I, IA), recurrence-free survival (stage I, IA), postoperative mortality, and postoperative morbidities did not reveal any evidence of obvious asymmetry (Fig. 5). Therefore, publication bias was not a problem for this analysis.

Discussion

Although lobectomy is considered to be the standard surgical treatment for patients with stage I NSCLC, the issue of sublobar resection versus lobectomy remains controversial. In this study, we analyzed 4 outcomes to compare lobectomy versus segmentectomy for stage I and IA NSCLC. Lobectomy showed better 5-year survival for stage I NSCLC. However, segmentectomy was comparable to lobectomy in terms of 5-year survival for stage IA NSCLC. Recurrence-free survival showed no statistically significant difference between lobectomy and segmentectomy. Segmentectomy demonstrated better early postoperative outcomes than lobectomy, resulting in superior postoperative mortality and morbidity.

Several meta-analyses have compared lobectomy to segmentectomy [7-11]. Many studies have concluded that segmentectomy can achieve comparable overall survival to lobectomy for stage IA NSCLC [8-10]. However, it has also been reported that the overall survival of patients with stage I NSCLC who un-
went lobectomy was better than the overall survival of those who underwent segmentectomy [9,10]. Our results for 5-year survival outcomes are in agreement with previously published studies. However, in other studies [7,8], segmentectomy was associated with poorer overall survival than lobectomy for stage IA NSCLC. Therefore, controversy remains regarding this issue. We sought to clarify this controversial issue and to produce more objective results through this meta-analysis, which has 2 notable methodological differences from previously published meta-analyses. First, in our study, we compared 5-year survival rates, not arbitrary survival with an undefined follow-up period. Many other meta-analyses used overall survival with an undefined period, resulting in various follow-up times in their survival analysis. Instead, we only used 5-year survival and excluded many papers that used overall survival without a defined period. By doing so, we were able to control the follow-up period. The second difference was that we analyzed stage I and IA disease separately. This methodological choice may have reduced the heterogeneity of patients included in this meta-analysis.

Recurrence-free survival was not significantly different between the 2 surgical strategies for either stage I or stage IA NSCLC. For recurrence-free survival, our results are in agreement with previously published studies showing that there was no significant difference between lobectomy and segmentectomy [7,8]. However, considering the lower 5-year survival rate in stage I NSCLC in the segmentectomy group, it was unclear whether recurrence after segmentectomy was related to poor survival. One possible explanation may be selection bias in the segmentectomy group, according to which the reduced 5-year survival following segmentectomy might be related to other causes rather than cancer. Limited resection has been commonly performed in patients with poor pulmonary function and multiple comorbidities. For example, Kodama and colleagues reported that, among 63 patients who underwent segmentectomy, 17 had poor pulmonary reserve or other limiting factors making them unable to tolerate lobectomy [16]. Therefore, a randomized controlled clinical trial would be necessary to resolve the discrepancy between survival and recurrence-free survival.

Analyses of postoperative mortality and morbidities have not been commonly performed in previous stud-
ies, because most previous research has focused on survival and recurrence, rather than on early postoperative outcomes. However, we think that the most critical benefit of sublobar resection is the preservation of lung function with a reduced operative risk. If equal oncologic outcomes are expected, the safer technique with a greater preservation of function would be the preferable surgical option. Therefore, we also analyzed postoperative mortality and morbidities after segmentectomy in this study. Tan et al. [12] suggested that the incidence of postoperative morbidities in patients undergoing segmentectomy was higher than in those undergoing lobectomy, contrary to the result of our meta-analysis. However, they only included data from 95 patients from 2 papers, whereas our study included 1,246 patients from 6 papers for the mortality analysis and 1,214 patients from 7 papers for the morbidity analysis. Therefore, our results have more statistical power than the previous results. This is the first meta-analysis to find that segmentectomy is better than lobectomy in terms of early postoperative outcomes.

In the selection procedure for this study, we included studies that described pathologic stage I or IA NSCLC and 5-year survival. Strict inclusion criteria reduced bias due to confounding and heterogeneity. However, our study has some limitations of its own. First, the calculations of hazard ratios using Kaplan-Meier survival curves and the TechDig software could have involved errors due to potential inaccuracies of the curve-tracing procedure and assumptions about the censoring pattern [14,15]. This phenomenon is an inevitable methodological limitation caused by the assumption procedure used by the software. Secondly, we controlled for the follow-up period, pathologic stage, and study design. However, we could not control for differences among studies in patient characteristics such as age, sex, tumor size, and histological type. An ideal meta-analysis should use individual patient data (not recruited in our study). Therefore, we used summary data from the included studies. Thirdly, all studies included in our meta-analysis were aggregations of data obtained from retrospective studies. Those data need to be confirmed by prospective studies or randomized controlled trials. Finally, unpublished studies and studies not written in English were excluded from our study, potentially leading to publication bias, which is a major concern for all forms of meta-analysis. Although our study showed no finding indicative of publication bias, it should be noted that our meta-analysis could not completely be free from such bias.

**Conclusion**

In summary, this study showed that segmentectomy for stage IA NSCLC was comparable to lobectomy in terms of 5-year survival, although lobectomy had better survival for stage I NSCLC. However, recurrence-free survival was not significantly different between the 2 surgical strategies for either stage I or stage IA NSCLC. Based on the results for postoperative mortality and morbidities, segmentectomy is superior to lobectomy. However, randomized controlled trials are needed to compare segmentectomy to lobectomy, particular for stage IA NSCLC patients, to validate the results of our meta-analysis.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

**Acknowledgments**

This study was supported by a Grant of the Samsung Vein Clinic Network (Daejeon, Anyang, Cheongiu, Cheonan; Fund no. KTCS04-124).

**ORCID**

Tae Yoon Lim https://orcid.org/0000-0003-2337-8156
Samina Park: https://orcid.org/0000-0001-9625-2672
Chang Hyun Kang: https://orcid.org/0000-0002-1612-1937

**References**

1. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e278s-e313s.
2. Strand TE, Rostad H, Moller B, Norstein J. Survival after resection for primary lung cancer: a population based study of 3211 resected patients. Thorax 2006;61:710-5.
3. National Lung Screening Trial Research Team, Church TR,
Black WC, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013; 368:1980-91.

4. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 NO non-small cell lung cancer: Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22.

5. Nakamura K, Saji H, Nakajima R, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607Lj). Jpn J Clin Oncol 2010;40:271-4.

6. Blasberg JD, Pass HI, Donington JS. Sublobar resection: a movement from the Lung Cancer Study Group. J Thorac Oncol 2010;5:1583-93.

7. Cao C, Gupta S, Chandrakumar D, Tian DH, Black D, Yan TD. Meta-analysis of intentional sublobar resections versus lobectomy for early stage non-small cell lung cancer. Ann Cardiothorac Surg 2014;3:134-41.

8. Zhang L, Li M, Yin R, Zhang Q, Xu L. Comparison of the oncologic outcomes of anatomic segmentectomy and lobectomy for early-stage non-small cell lung cancer. Ann Thorac Surg 2015;99:728-37.

9. Fan J, Wang L, Jiang GN, Gao W. Sublobectomy versus lobectomy for stage I non-small-cell lung cancer, a meta-analysis of published studies. Ann Surg Oncol 2012;19:661-8.

10. Bao F, Ye P, Yang Y, et al. Segmentectomy or lobectomy for early stage lung cancer: a meta-analysis. Eur J Cardiothorac Surg 2014;46:1-7.

11. Liu Y, Huang C, Liu H, Chen Y, Li S. Sublobectomy versus lobectomy for stage IA (T1a) non-small-cell lung cancer: a meta-analysis study. World J Surg Oncol 2014;12:138.

12. Tan Q, Huang J, Ding Z, Lin H, Lu S, Luo Q. Meta-analysis for curative effect of lobectomy and segmentectomy on non-small cell lung cancer. Int J Clin Exp Med 2014;7:2599-604.

13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.

14. Tierney JF, Stewart LA, Gherardi S, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

15. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-34.

16. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non-small-cell lung cancer: a single-institution study. J Thorac Cardiovasc Surg 1997;114:347-53.

17. Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? Ann Thorac Surg 2001;71:956-60.

18. Martin-Ucar AE, Nakas A, Pilling JE, West KJ, Waller DA. A case-matched study of anatomical segmentectomy versus lobectomy for stage I lung cancer in high-risk patients. Eur J Cardiothorac Surg 2005;27:675-9.

19. Okumura M, Goto M, Ideguchi K, et al. Factors associated with outcome of segmentectomy for non-small cell lung cancer: long-term follow-up study at a single institution in Japan. Lung Cancer 2007;58:231-7.

20. Schuchert MJ, Pettiford BL, Keeley S, et al. Anatomic segmentectomy in the treatment of stage I non-small cell lung cancer. Ann Thorac Surg 2007;84:926-32.

21. Sienel W, Stremmel C, Kirschbaum A, et al. Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins: implications for patient selection for segmentectomy. Eur J Cardiothorac Surg 2007;31:522-7.

22. Kilic A, Schuchert MJ, Pettiford BL, et al. Anatomic segmentectomy for stage I non-small cell lung cancer in the elderly. Ann Thorac Surg 2009;87:1662-6.

23. Yamashita S, Chuo M, Kawano Y, et al. Clinical impact of segmentectomy compared with lobectomy under complete video-assisted thoracic surgery in the treatment of stage I non-small cell lung cancer. J Surg Res 2011;166:46-51.

24. Schuchert MJ, Kilic A, Pennathur A, et al. Oncologic outcomes after surgical resection of subcentimeter non-small cell lung cancer. Ann Thorac Surg 2011;91:1681-7.

25. Whitson BA, Groth SS, Andrade RS, Maddaus MA, Habermann EB, D'Cunha J. Survival after lobectomy versus segmentectomy for stage I non-small cell lung cancer: a population-based analysis. Ann Thorac Surg 2011;92:1943-50.

26. Carr SR, Schuchert MJ, Pennathur A, et al. Impact of tumor size on outcomes after anatomic lung resection for stage 1A non-small cell lung cancer based on the current staging system. J Thorac Cardiovasc Surg 2012;143:390-7.

27. Schuchert MJ, Abbas G, Awaais O, et al. Anatomic segmentectomy for the solitary pulmonary nodule and early-stage non-small cell lung cancer. Ann Thorac Surg 2012;93:1780-5.

28. Schuchert MJ, Awaais O, Abbas G, et al. Influence of age and IB status after resection of node-negative non-small cell lung cancer. Ann Thorac Surg 2012;93:929-35.

29. Yamashita S, Tokuishi K, Anami K, et al. Thoracoscopic segmentectomy for T1 classification of non-small cell lung cancer: a single center experience. Eur J Cardiothorac Surg 2012;42:83-8.

30. Zhong C, Fang W, Mao T, Yao F, Chen W, Hu D. Comparison of thoracoscopic segmentectomy and thoracoscopic lobectomy for small-sized stage IA lung cancer. Ann Thorac Surg 2012;94:362-7.

31. Zhao X, Qian L, Luo Q, Huang J. Segmentectomy as a safe and equally effective surgical option under complete video-assisted thoracic surgery for patients of stage I non-small cell lung cancer. J Cardiothorac Surg 2013;8:116.