Survival Following Sublobar Resection Versus Lobectomy in Patients with Early-stage Non-small Cell Lung Cancer in Asia: A Meta-analysis

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Keywords: no-small lung cancer; sublobar resection; lobectomy; 5-year overall survival; Asia; meta-analysis.

Abstract: Background: Lobectomy is still the preferred treatment for patients with stage I NSCLC, but there is renewed interested in performing sublobar resection for 'intentional' selected patients with early-stage NSCLC (tumor size ≦ 2 cm). The objective of this study was comparing lobectomy and sublobectomy treatment to the early clinical stage NSCLC (tumor size ≦ 2 cm), 'intentional' selected program in the cohort of patients, in Asia. Methods: The searching strategy was developed in EMBASE, MEDLINE and Cochrane library from their earliest publication dates to May 2018. Our main endpoint was 5-year overall survival, used a fixed-effects model to evaluate aggregated data. Results: Of the 2,348 research literatures, 8 were eligible for inclusion and included in the analysis (N = 17817 participants). Compared with sublobar resection, lobectomy has no significant benefit for 5-year OS in patients with stage IA NSCLC with a tumor diameter of less than 2 cm HR, 0.88 (95% CI, 0.68 -1.13; P = 0.31). The combined OR for local recurrence was 0.87 (95% CI, 0.49 - 1.56; P = 0.65). Conclution: There was no significant difference in 5-year OS and local recurrence in early Asian NSCLC patients who were 'intentional' selected for sublobar resection compared with patients undergoing lobectomy. These results should be further confirmed through prospective randomized trials.

1. Introduction

The main cause of global cancer-related deaths is lung cancer, and about 85% of them are non-small cell lung cancer (NSCLC). With the widespread use of high-resolution computed tomography (CT) and low-dose spiral CT screening, the detection rate of early NSCLC has been significantly improved, making the more patients get treatment opportunities[1]. Currently, Surgery remains the primary treatment for early stage NSCLC[2].

In 1995, the Lung Cancer study Group (LCSG) published final results of a randomized controlled trial (RCT)[3], this trial analyzed the survival and local recurrence rates of early non-small cell patients(tumor size ≦3cm) who undergoing sublobar resection versus lobectomy, The results showed a higher local recurrence rate and poorer overall survival (OS) in sublobar resection. Some retrospective analyses and meta-analyses have reached similar conclusions[4, 5]. However, there also have some studies that give the opposite view.

A meta-analysis in 2005[6] collected 14 articles from 1980 to 2004 on the comparison of sublobar resection and lobectomy in patients with stage I NSCLC, the results showed there's no significant difference regarding 1-, 3-, or 5-year survival rate. Zhao Heng et al. retrospectively analyzed 666 patients > 65 years old with stage I NSCLC (tumor size ≤ 2cm), they concluded that when the tumor size ≤ 1cm, there is no OS advantages between the lobectomy group and the wedge resection group(DFS, P = 0.112; OS, P = 0.294), but when the tumor size was > 1 cm and ≤ 2 cm, the OS of the wedge resection group was significantly poorer than that of the lobectomy group (P = 0.041)[7]. Jian Hu et al. analyzed 16,819 patients with stage I NSCLC undergoing lobectomy or segment resection or wedge resection. They found that in the three treatment groups, the OS of the lobectomy group was

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significantly higher than the wedge resection group, but there was no significant difference in the lung cancer-specific survival rate (LCSS) between the three groups when the tumor diameter is less than 1cm. For tumors ranging from 1.1 to 2.0 cm, lobectomy group and segment resection group showed no statistical difference in LCSS rates, but both had better OS and LCSS rates than wedge resection group. For tumor size range from 2.1 to 3.0 cm, OS and LCSS rates were better for lobectomy group than sublobar resection group, but when segment resection group compared with wedge resection group, there was no difference in OS and LCSS[8].

The aim of this study was to determine whether there were differences in 5-year overall survival and local recurrence rates between patients with early-stage NSCLC (tumor size $\leq$ 2 cm) who underwent sublobar resection in the Asian population and those who underwent standard lobectomy.

2. Methods

2.1 Eligibility criteria.

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guideline[9]. Randomized clinical trial (RCT) and cohort studies, being published from 1966 to May 23, 2018, which reported comparisons of survival and local recurrence between lobectomy and sublobar resection in the early clinical stage NSCLC patients (tumor size $\leqq$ 2 cm), the study participants were patients with clinical early stage non-small cell lung cancer (tumor diameter $\leqq$ 2 cm). The studies focusing on Age greater than 80 or patients with poor cardiopulmonary function who cann't tolerate lobectomy would be excluded.

2.2 Search strategy.

An electronic search in PubMed, EMBASE, The Cochrane Library were conducted from 1966 to May 23, 2018 by two investigators (Zhe Sun and Xiaolu Fang). We were searched by using the strategy of (sublobar resection [Title/Abstract] OR (limited resection [Title/ Abstract]) OR (wide-wedge resection [Title/Abstract]) OR (segmentectomy [Title/Abstract]) OR (limited pulmonary resection [Title/Abstract]) OR (wedge resection [Title/Abstract]) AND (lung [Title/Abstract] OR pulmonary [Title/Abstract]) AND (carcinoma [Title/Abstract]) OR (cancer [Title/Abstract]) AND (lobectomy [Title/Abstract]) OR (lobar resection [Title/Abstract]). Only articles published in English are retrieved and included.

2.3 Quality assessment.

For RCT, use the five-point Jadad scale to assess methodological quality. Use the 9-star Newcastle-Ottawa Scale (NOS) to assess the risk of bias in cohort studies[10, 11]. The NOS scale is an eight-item tool used to assess patient numbers and choices, study comparability, follow-up and outcomes. NOS score of 5 or more were defined as a high-quality research and were included. Quality assessment is done independently by two researchers (Zhe Sun and Xiaolu Fang). Adopt a unified data extraction format. The study information was collected including the study year of each group, the author's name, the number of samples, the size of the tumor, and the number of positive events. Tatistical heterogeneity between studies was examined using the Cochrane Q test by calculating the I^2 value[12]. And $I^2 > 50\%$ or $p < 0.05$ were considered to have significant heterogeneity.

We calculated pooled estimates of the logrank Observed Minus Expected events (O-E) and logrank Variance (V) in 5-year overall survival between intervention groups by using a Fixed-effects model (O-E and Variance method). For categorical outcomes, we analyzed the number of effect events with a random-effects model. Cochran Q test was used to assess heterogeneity between studies [13]. Statistical analyses were performed using RevMan 5.3 software (the Cochrane Collaboration, Oxford, England).

3. Results

3.1 Study selection.

2348 possible related references were identified by search. Further 14 possible related literatures were identified by reviewing the list of references. After reading the headlines and Abstracts to exclude duplicate and irrelevant references, the number of articles that needed to be effectively read was 79. After reading the full text, 68 references were excluded due to the lack of valid data or due to “compromise“ grouping or because the patient was > 80 years old or because the tumor diameter was > 2cm. One article[14] is exhausted because the NOS score < 5. Finally, 8 studies[5, 7, 15-20] served as data sources for the present meta-analysis (Table 1). Figure 1 shows the flowchart of the search results.

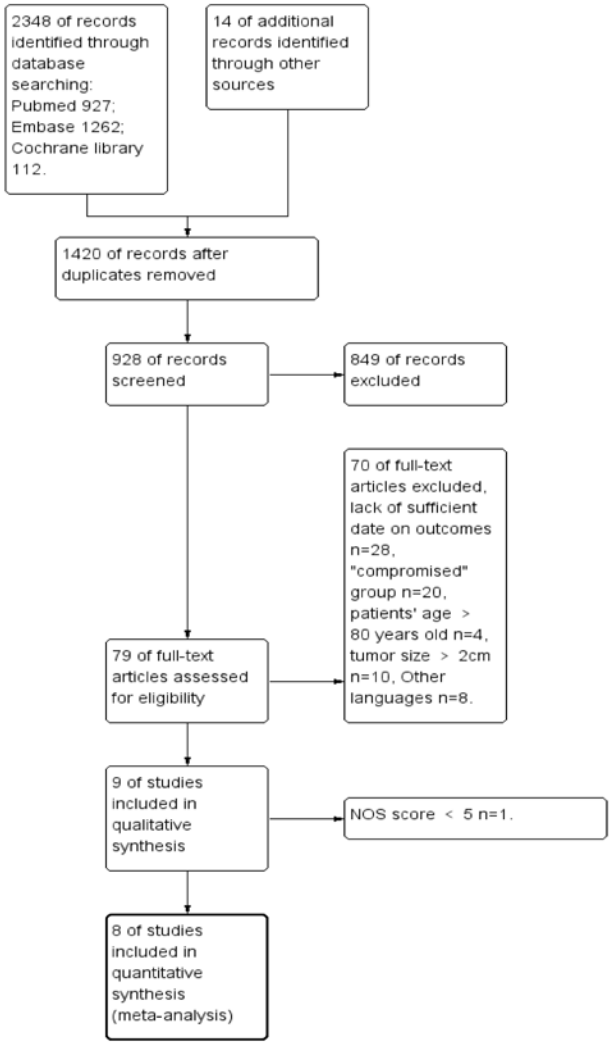

Figure 1. Flowchart of the process for the identification of relevant studies.

3.2 Characteristics of included Studies.

Based on search results, their designs were retrospective in 7, and RCT in one. sublobar resection, include segment resection and wedge resection, was performed for a total of 5119 patients, while comparable standard lobectomy was performed for 12698 patients, they were all from Asia (China and Japan). The quality of the study included in this meta-analysis was scored 5 to 8 stars. The characteristics of the included studies are listed in Table 1.

Table 1. Studies included in the present meta-analysis

Authors	Year	Study design	Tumor size	Countries	Sub (n)	Lob (n)	Reasion for limited resection	Survival difference	Quality score
Dai C.	2016	RS	≤2cm	China	4260	11520	intention	lob better	5
Noriaki Tsubota	2001	RS	≤2cm	Japan	70	139	intention	NS	8
Akinori Iwasaki	2012	RS	≤1cm	Japan	66	77	intention	NS	5
Teruaki Koike	2003	RS	≤2cm	Japan	74	159	intention	NS	6
Masanori Tsuchida	2016	RS	≤2cm	Japan	87	87	intention	NS	6
Morihito Okada	2006	RS	≤2cm	Japan	305	262	intention	NS	7
Teruaki Koike	2016	RCT	≤2cm	Japan	33	32	intention	NS	8
Heng Zhao	2018	RS	≤2cm	China	224	442	intention	NS	6

Sub = sublobar resection; Lob = lobectomy; NS = not significant; RCT = randomized controlled trial; RS = retrospective study.

3.3 Year overall survival.

Only one research reported the OS for lobectomy was superior to that of sublobar resection, and another showed there is no difference. The combined HR of 5-year OS was 0.88 (95% CI, 0.68 to 1.13; P = 0.31). The lobectomy group and sublobar resection group showed no statistical difference in the 5-year OS rate. The Cochran tests for heterogeneity showed that $chi^2 = 11.32$, df =7 (P = 0.13); I^2 = 38%, which showed that there is no significant inconsistency (Figure 2). Significant publication bias was found in the Asian group (Figure 3).

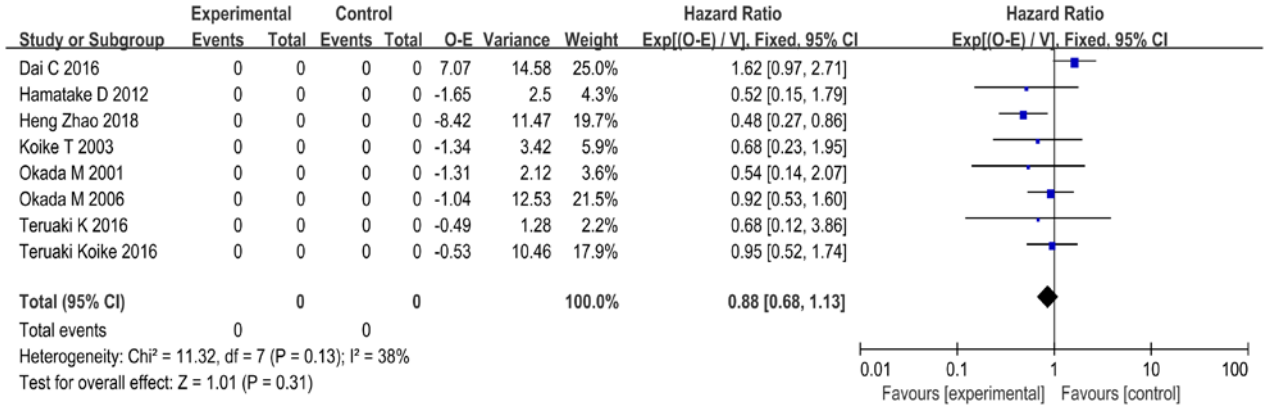

Figure 2. Forest plot of HR for 5-year OS impact of operative approach (sublobar resection versus lobectomy) of stage IA NSCLC patients. The combined HR displayed in this figure when compared with sublobar resection suggested that there was no significant benefit of lobectomy on 5-year OS of stage IA patients with tumors no larger than 2 cm, HR 0.88 (95% CI, 0.68 to 1.13; P = 0.31). CI, confidence interval; HR, hazard ratio, 5-year OS, 5-year overall survival, NSCLC, non-small cell lung cancer.

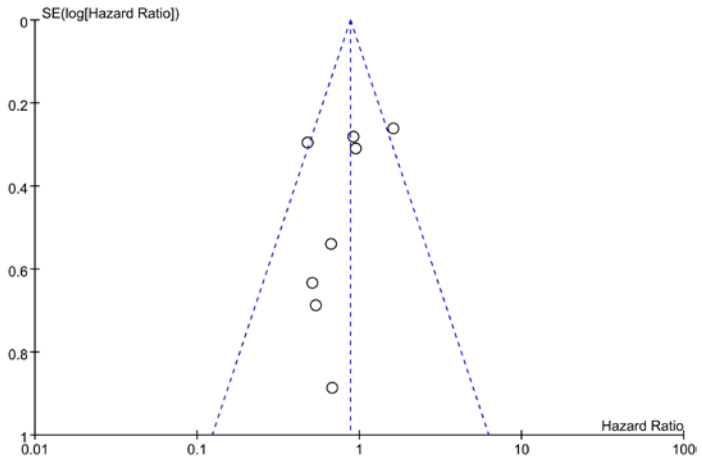

Figure 3. Funnel plot of this analysis. The crossed two lines in the figure represent the 95% CI. This figure presents the impact of operative approach sublobar resection versus lobectomy) on OS of stage IA NSCLC patients with a tumor size of 2 cm or less.

3.4 Local recurrence.

Five studies reported the local recurrence between sublobar resection group and lobectomy group, but two of these studies[17, 20] reported there were no local recurrences during follow-up. Finally 3 studies were selected in the analysis [16, 18, 19]. The combined OR for local recurrence was 0.84 (95% CI, 0.37 – 1.86; P = 0.66), the combined OR displayed in this figure when Compared with sublobar resection, lobectomy has no significant benefit in local recurrence in patients with tumors size ≦ 2 cm (Figure 4). The Cochran tests for heterogeneity suggested that $chi^2 = 1.47$, df =2 (P = 0.48); $I^2 = 0\%$, there is no significant inconsistency.

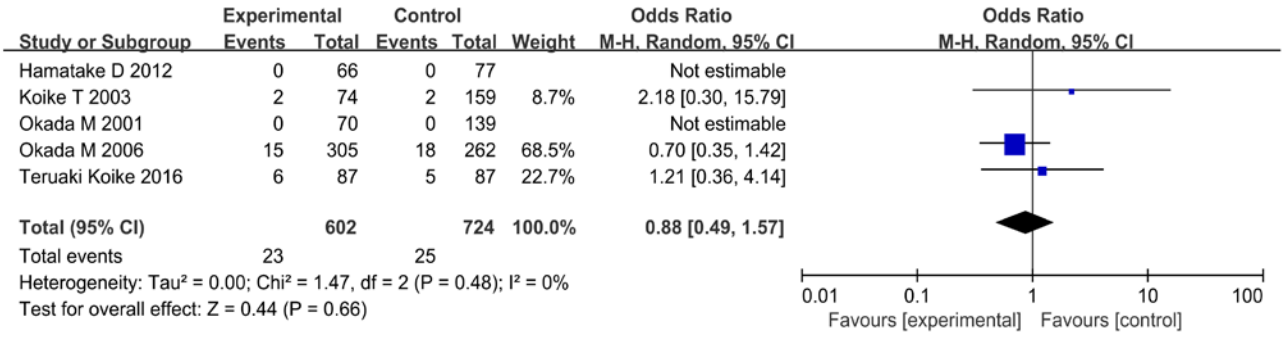

Figure 4. Forest plot of local recurrence. The combined OR for local recurrence was 0.84 (95% CI, 0.37 – 1.86; P = 0.66), The combined OR displayed in this figure when compared with sublobar resection suggested that there was no significant benefit of lobectomy on local recurrence of patients with tumors no larger than 2 cm. CI, confidence interval; OR, odds ratio.

4. Discussion

Lobectomy and systemic lymph nodes dissection are considered the standard surgical treatments for patients with early clinical stage NSCLC. However, sublobar resection is another alternative treatment for early stage NSCLC with complication or high risk of death due to lobectomy[21]. Although sublobar resection is considered reasonable for patients with cardiopulmonary insufficiency or age > 80 years, intentional sublobar resection for patients who are expected to undergo lobectomy has not been established. Two meta-analysis[22, 23] mentioned that there was no

significant difference in disease-free survival between the “intentional“ group compared with lobectomy. Therefore, we combined the relevant research and conducted a meta-analysis to draw conclusions on the topic. This analysis was used to study patients with early clinical stage NSCLC (tumor size ≤ 2 cm) who were 'intention' selected for sublobar resection. As far as we know, there is no analysis of Asian population.

Result of this meta-analysis demonstrated that patients who intentionally selected for sublober resection to treat early-stage NSCLC, tumor size ≦ 2 cm, had 5-year OS that was not different to those who performed lobectomies. We only analyzed local recurrence of two different surgical procedures (lobectomy and lobectomy), and the results showed that there was no significant difference between the two surgical procedures. Regarding the problem of distant metastasis after sublobar resection, some studies[18, 19] suggested no significant difference between the two groups. However, there are few literatures available for meta-analysis, and most of them are retrospective cohort analysis, lacking randomized controlled trials, so the reliability of this conclusion remains to be discussed.

There also have some limitations of this meta-analysis. I, we can not collect and analyze data about the radiotherapy and chemotherapy which affect the survival of the patients. II, We were unable to collect data on patients' lymph node dissection, and could not rule out the effects of systemic lymph node dissection or lymph node sampling on 5-year survival rate and local recurrence.III, Comparison of sublobar resection and lobectomy for tumor diameter ≤ 2 cm NSCLC did not take into account the appearance of CT (pure solid, pure ground grass opacity (GGO), and part solid + GGO), which seriously affect the long-term survival of patients. IV, our research population is Asian, and the articles collected are published by Asians, so there is a publication bias.

5. Conclusions

In conclusion, our analysis seems to support that for patients with early stage non-small cell lung cancer in Asia, there was no significant difference in 5-year OS and local recurrence between patients who had ‘intentional’ selected sublobar resection compared with who had lobectomy. Although we need more randomized controlled trials to verify the accuracy of this conclusion, our findings seem to have solved this problem.

6. Abbreviations

NSCLC: no-small lung cancer; CT: computed tomography; LCSG: Lung Cancer study Group; RCT: randomized controlled trial; OS: overall survival; LCSS: lung cancer-spesific survival; Lob: lobectomy; NS: not significant; RS: retrospective study; OR: odds ratio; HR: hazard ratio.

7. Availability of data and materials

The datasets analyzed during the current study are not publicly available due to further publications pending but are available from the corresponding author on reasonable request.

8. Authors’ contributions

Hong Yu reviewed the manuscript. Zhe Sun analyzed the data and wrote the manuscript. Xiaolu Fang analyzed the data and wrote the manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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