Meta-analysis of segmentectomy versus wedge resection in stage IA non-small-cell lung cancer

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Background: Although limited resection was once considered the surgical treatment for patients with Phase IA non-small-cell lung cancer (NSCLC), there has been an ongoing controversial surgical indication for wedge resection and segmentectomy in recent years. The objective of this study was to compare overall survival (OS) and disease-free survival (DFS) of segmentectomy and wedge resection for early stage NSCLC, using a meta-analysis.

Methods: Systematic research was conducted using four online databases to search for studies published before 2017. The DFS and OS for early stage NSCLC after segmentectomy and wedge resection were compared. The studies were selected according to rigorous predefined inclusion criteria, and meta-analyzed using the log (hazard ratio; ln[HR]) and its standard error (SE) calculations.

Results: Included in this meta-analysis were nine studies, published from 2006 to 2017, with a total of 7,272 patients. Survival outcome of segmentectomy was comparable to wedge resections for stage IA lung cancer because of OS (similar hazard ratio [HR]: 0.93, 95% confidence interval [CI]: 0.83–1.05, \( P = 0.26 \)) and DFS (similar HR: 0.81, 95% CI: 0.60–1.09, \( P = 0.17 \)).

Nevertheless, for stage IA NSCLC with tumor size \( \geq 2 \) cm, segmentectomy was superior to wedge resection (combined HR: 0.82, 95% CI: 0.70–0.97, \( P = 0.02 \)). However, there were no significant differences in OS rates, 1.07 (95% CI: 0.78–1.46, \( P = 0.68 \)), between segmentectomy and wedge resection for IA NSCLC with a tumor size of \( \leq 1 \) cm.

Conclusion: This study concluded that segmentectomy could achieve better OS than wedge resection for stage IA NSCLC with a tumor size of \( \leq 2 \) cm. However, surgeons could conduct segmentectomy and wedge resection for NSCLC \( \leq 1 \) cm according to patient profile and the location of tumor. These results should be confirmed by further randomized clinical trials.

Keywords: segmentectomy, wedge resection, IA NSCLC, meta-analysis

Introduction

With the wide use of low-dose helical computed tomography (LDCT) and high-resolution computed tomography (HRCT) screening in lung cancer, the number of patients with early stage lung cancer has been found to be increasing.\(^1\) The randomized trial by the Lung Cancer Study Group demonstrated that lobectomy was the standard surgical procedure for stage I non-small-cell lung cancer (NSCLC).\(^2\) In recent years, many studies indicated similar survival with sublobar resection and lobectomy for stage IA NSCLC.\(^3\)–\(^9\) Compared with those who underwent traditional lobectomy, patients who underwent sublobectomy had less lung tissue resected and more lung function preserved. The limited resection surgical approaches included wedge resection and segmentectomy. However, a few studies compared the effect between two types of limited resections;\(^10\) there was no effective evidence regarding
the selections between segmentectomy and wedge resections for early stage NSCLC. Hence, the controversial problem for many surgeons was how to make a decision between anatomic segmentectomy and extended non-anatomic wedge resection for stage IA NSCLC. This meta-analysis study aimed to compare the outcomes of overall survival (OS) and disease-free survival (DFS) for patients with stage IA NSCLC who underwent either wedge resection or segmentectomy. In addition, subgroup analysis including stage IA NSCLC, tumor size ≤2 cm and ≤1 cm and ground glass opacity (GGO) was performed.

**Methods**

**Literature search strategy**

A systematic search was performed, using Ovid, PubMed, Embase and Cochrane library databases for studies published before 2017, with the strategy of (limited resection [Title/Abstract]) OR (sublobar resection [Title/Abstract]) OR (segmentectomy [Title/Abstract]) OR (wedge resection [Title/Abstract]) AND (lung cancer [Title/Abstract]) OR pulmonary [Title/Abstract]) AND (cancer [Title/Abstract]) OR (carcinoma [Title/Abstract]). Potentially eligible articles were identified from citations of all retrieved articles.

**Selection criteria**

The eligible studies were evaluated by two authors based on the inclusion criteria as follows: 1) early stage NSCLC patients including those with stage IA, tumor size ≤1 cm and GGO; 2) sublobar resection or limited resection including wedge resection and segmentectomy; 3) outcome of studies comparing DFS and OS between segmentectomy and wedge resection and 4) when studies were from the same institution and the same period, the most informative study was selected. Letters to editors, case reports, non-English studies and reviews were excluded.

**Statistical analyses**

Combining the results of OS and DFS, meta-analysis was performed through hazard ratio (HR) and associated 95% confidence interval (CI) for each study. The data of HR and standard error (SE) of the selected studies, which were not provided, were extracted from the primary survival curve using the techniques described by Parmar et al.12 and Tierney et al.13 Two researchers independently calculated the data and read the Kaplan–Meier curves using Engauge Digitizer version 4.1 software. All statistical analyses were summarized using Review Manager version 5.3.0. Statistical heterogeneity was estimated by Higgins $I^2$, which represented the total variation percentage among the studies. A fixed-effect model (Mantel–Haenszel method) was used to pool homogeneous studies. If the $I^2$ statistic was less than 50%, the random-effect model (DerSimonian–Laird) was used. Begg’s funnel plot and Egger’s test14 were used to assess the publication bias.

**Results**

A total of 1,534 studies were obtained from the electronic databases. According to the selection criteria, papers were extracted from the databases as shown in Figure 1. There were finally nine articles published from 2006 to 2017 for this meta-analysis including 1,920 patients who underwent segmentectomy and 5,352 patients who underwent wedge resection. There were one prospective study and eight retrospective studies. The characteristics of the included studies are listed in Tables 1 and 2.

**Stage IA NSCLC**

There were 1,735 patients who underwent segmentectomy and 5,154 patients who underwent wedge resection for stage IA NSCLC. As there was no significant heterogeneity ($P=0.18$), the fixed-effect model was used for analysis. The combined HR of OS was 0.93 (95% CI: 0.83–1.05, $P=0.26$; Figure 2). The DFS data were detected from six eligible articles including 577 patients who underwent segmentectomy and 478 patients who underwent wedge resection. Pooled HR of DFS was 0.81 (95% CI: 0.60–1.09, $P=0.17$; Figure 3) using fixed-effect model for no heterogeneity. For tumor size ≤2 cm, there were six eligible papers. Combining the HR of OS using the fixed-effect model, the result was 0.82 (95% CI: 0.70–0.97, $P=0.02$; Figure 4). It showed that segmentectomy was superior to wedge resection for tumor size ≤2 cm. Two studies provided the data for patients in early stage NSCLC (tumor size ≤1 cm). As the study of Dai et al.24 used the same database as the research of Zhang et al.,23 Dai et al.’s study could not be included. However, it provided the research about the tumor size ≤1 cm. The pooled HR of OS was 1.07 (95% CI: 0.78–1.46, $P=0.68$; Figure 5). There were two studies about the GGO NSCLC. Analyzing the data of these studies, OS of combining HR was 1.79 (95% CI: 0.33–9.55, $P=0.50$; Figure 6). DFS of combining HR was 1.68 (95% CI: 0.20–13.94, $P=0.63$; Figure 7). There was no significant difference between segmentectomy and wedge resection for GGO NSCLC.
Records identified through database searching (n=1,534)  
Additional records through other sources (n=6)  
Records after removal of duplicates (n=980)  
Records screened (n=560)  
Records excluded as either conference abstracts, letters, case reports or irrelevant studies (n=510)  
Full-text eligible articles assessed (n=50)  
Full-text articles excluded due to failure to meet selection criteria (n=41)  
Studies included in meta-analysis (n=9)

Figure 1 Search strategy.

| Study | Year | Institution | Study period | Segmentectomy (n) | Wedge resection (n) | Reasons for sublobar approach | Tumor size (cm) |
|-------|------|-------------|--------------|-------------------|---------------------|-----------------------------|----------------|
| Okada et al⁷ | 2006 | Department of Thoracic Surgery, Hyogo Medical Center for Adults, Akaishi City, Hyogo, Japan | 1992–2001 | 214 | 30 | Intentional | 2.0 |
| Sugi et al⁸ | 2010 | National Hospital Organization, Yamaguchi-Ube Medical Center, Japan | 2001–2004 | 33 | 15 | Intentional | 2.0 |
| Hamatake et al⁷ | 2012 | Breast and Paediatric Surgery, Fukuoka University School of Medicine, Fukuoka, Japan | 1995–2011 | 34 | 32 | Intentional | 1.0 |
| Siene⁴ et al⁸ | 2008 | Department of Thoracic Surgery, Albert-Ludwigs-University Freiburg, Freiburg, Germany | 1987–2003 | 56 | 31 | Unintentional for patients with cardiopulmonary impairment | 3.0 |
| Siene⁴ et al⁸ | 2008 | Department of Thoracic Surgery, Albert-Ludwigs-University Freiburg, Freiburg, Germany | 1987–2003 | 35 | 25 | Unintentional for patients with cardiopulmonary impairment | 2.0 |
| Yamato et al⁹ | 2008 | Chest Surgery, Niigata Cancer Center Hospital, Niigata, Japan | 1991–2004 | 153 | 93 | Unintentional for compromised patients | 2.0 |
| Altorki et al²⁰ | 2016 | Division of Thoracic Surgery, Department of Cardiothoracic Surgery, New York Presbyterian Hospital, Weill Cornell Medical College, New York, NY, USA | 2000–2014 | 129 | 160 | Unintentional and intentional: for smaller, pleural-based tumors; we prefer WR, poor performance status and debilitating comorbidities | 3.0 |

(Continued)
Table 1 (Continued)

| Study       | Year | Institution                                                                 | Study period     | Segmentectomy (n) | Wedge resection (n) | Reasons for sublobar approach                      | Tumor size (cm) |
|-------------|------|------------------------------------------------------------------------------|------------------|-------------------|---------------------|---------------------------------------------------|-----------------|
| Tsutani et al<sup>11</sup> | 2014 | Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan | 2005–2010        | 56                | 93                  | Intentional for GGO                                | 3.0             |
| Tamura et al<sup>22</sup> | 2014 | Department of General and Cardiothoracic Surgery, School of Medicine, Kanazawa University, Kanazawa, Japan | 1996–2009        | 89                | 149                 | Unintentional for high-risk status                 | 3.0             |
| Zhang et al<sup>23</sup> | 2016 | Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China | 1998–2012        | NR                | NR                  | NR: invasive adenocarcinoma                        | 2.0             |
| Zhang et al<sup>23</sup> | 2016 | Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China | 1998–2012        | NR                | NR                  | NR: squamous cell carcinoma                       | 2.0             |
| Zhang et al<sup>23</sup> | 2016 | Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China | 1998–2012        | 786               | 3,145               | NR: invasive adenocarcinoma                        | 3.0             |
| Zhang et al<sup>23</sup> | 2016 | Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China | 1998–2012        | 370               | 1,579               | NR: squamous cell carcinoma                       | 3.0             |
| Dai et al<sup>24</sup> | 2016 | Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China | 2000–2012        | 160               | 821                 | Intentional                                       | 1.0             |

Abbreviations: GGO, ground glass opacity; NR, not reported; WR, wedge resection.

Table 2 Component ratio of included studies

| Study       | Age (mean), years | Male gender, n (%) |
|-------------|-------------------|--------------------|
|             | S                 | W                  | S                  | W                  |
| Okada et al<sup>7</sup> | 63                | NR (54.8)          | 63                 | NR (54.8)          |
| Sugi et al<sup>8</sup>  | 61.6±9.4          | 19 (30.6)          | 62.5±13.4          | 13 (38.2)          |
| Hamatake et al<sup>17</sup> | 64.0 (M)         | 62 (43.4)          | 64.0 (M)           | 62 (43.4)          |
| Sienel et al<sup>18</sup> | 67±9              | NR (64)            | 63±8               | NR (81)            |
| Sienel et al<sup>18</sup> | 67±9              | NR (64)            | 63±8               | NR (81)            |
| Yamato et al<sup>19</sup> | 65.2              | NR (50)            | 65.2               | NR (50)            |
| Altorki et al<sup>21</sup> | 71.0 (M)         | 53 (43.4)          | 74.0 (M)           | 68 (42.5)          |
| Tsutani et al<sup>21</sup> | 65                | 94 (39.3)          | 65                 | 94 (39.3)          |
| Tamura et al<sup>22</sup> | 67                | 90 (60.4)          | 67.7               | 57 (64.0)          |
| Zhang et al<sup>22</sup> | 69                | 296 (37.7)         | 69.1               | 1,374 (43.7)       |
| Zhang et al<sup>22</sup> | 71.3              | 185 (50)           | 71.7               | 811 (51.4)         |
| Zhang et al<sup>22</sup> | 69                | 296 (37.7)         | 69.1               | 1,374 (43.7)       |
| Zhang et al<sup>23</sup> | 71.3              | 185 (50)           | 71.7               | 811 (51.4)         |
| Dai et al<sup>24</sup> | >65 (62%)         | 218 (36)           | >65 (65%)          | 1.017 (41)         |

Abbreviations: NR, number not reported; M, median; variance; S, patients who underwent segmentectomy; W, patients who underwent wedge resection.
Segmentectomy versus wedge resection in stage IA NSCLC

| Study or subgroup | Log [HR] | SE | S Total | W Total | Weight (%) | HR IV, fixed, 95% CI |
|-------------------|----------|----|---------|---------|------------|----------------------|
| Hamatake et al (2012) | −0.6162 | 2.04 | 34 | 32 | 0.1 | 0.54 (0.91, 0.29) |
| Sugi et al (2010) | 0.5134 | 0.9493 | 33 | 15 | 0.4 | 0.67 (0.26, 1.74) |
| Zhang et al (2016) | 0.001 | 0.103 | 370 | 1597 | 34.7 | 1.00 (0.82, 1.22) |
| Zhang et al (2016) | −0.1381 | 0.079 | 786 | 3145 | 58.9 | 0.87 (0.75, 1.02) |
| Tsutani et al (2014) | 0.8671 | 1.9709 | 56 | 93 | 0.1 | 2.38 (0.05, 113.29) |
| Tamaura et al (2014) | 0.5922 | 0.2941 | 89 | 149 | 4.3 | 1.81 (1.02, 3.22) |
| Okada et al (2006) | −0.5108 | 1.5285 | 214 | 30 | 0.2 | 0.60 (0.03, 12.00) |
| Yamato et al (2008) | −0.9676 | 0.5095 | 153 | 93 | 1.4 | 0.38 (0.14, 1.03) |

Total (95% CI) 1.735, 5.154 100 0.93 (0.83, 1.05)

Heterogeneity: \(\chi^2=10.15, df=7 (P=0.18); I^2=31\%

Test for overall effect: \(Z=1.12 (P=0.28)\)

Figure 2 OS of segmentectomy versus wedge resection for stage IA NSCLC.

Abbreviations: OS, overall survival; NSCLC, non-small-cell lung cancer; HR, hazard ratio; IV, inverse variance; SE, standard error; CI, confidence interval; S, patients who underwent segmentectomy; W, patients who underwent wedge resection.

| Study or subgroup | Log [HR] | SE | S Total | W Total | Weight (%) | HR IV, fixed, 95% CI |
|-------------------|----------|----|---------|---------|------------|----------------------|
| Tamura et al (2014) | −0.3711 | 0.318 | 89 | 149 | 22.6 | 0.69 (0.37, 1.32) |
| Okada et al (2006) | 0.0583 | 1.1559 | 214 | 30 | 1.7 | 1.06 (0.11, 10.21) |
| Atorki et al (2016) | −0.0726 | 0.1907 | 129 | 160 | 62.8 | 0.93 (0.64, 1.35) |
| Sienel et al (2008) | −0.821 | 0.456 | 56 | 31 | 11.0 | 0.44 (0.18, 1.08) |
| Sugi et al (2010) | 0.4187 | 1.6491 | 33 | 15 | 0.8 | 1.52 (0.06, 38.51) |
| Tsutani et al (2014) | 0.5933 | 1.4289 | 56 | 93 | 1.1 | 1.81 (0.11, 29.78) |

Total (95% CI) 577, 478 100 0.81 (0.60, 1.09)

Heterogeneity: \(\chi^2=3.09, df=5 (P=0.69); I^2=0\%

Test for overall effect: \(Z=1.38 (P=0.17)\)

Figure 3 DFS of segmentectomy versus wedge resection for stage IA NSCLC.

Abbreviations: DFS, disease-free survival; NSCLC, non-small-cell lung cancer; HR, hazard ratio; IV, inverse variance; SE, standard error; CI, confidence interval; S, patients who underwent segmentectomy; W, patients who underwent wedge resection.

| Study or subgroup | Log [HR] | SE | S Total | W Total | Weight (%) | HR IV, fixed, 95% CI |
|-------------------|----------|----|---------|---------|------------|----------------------|
| Hamatake et al (2012) | 0.5134 | 0.9493 | 0.8 | 1.67 (0.26, 10.74) |
| Okada et al (2006) | −0.6162 | 2.04 | 0.2 | 0.54 (0.01, 29.43) |
| Sugi et al (2010) | −0.5108 | 1.5285 | 0.3 | 0.60 (0.03, 12.00) |
| Yamato et al (2008) | −0.9676 | 0.5095 | 2.7 | 0.38 (0.14, 1.03) |
| Zhang et al (2016) (2) | −0.2065 | 0.1005 | 70.6 | 0.81 (0.67, 0.99) |
| Zhang et al (2016) (2) | −0.0888 | 0.1875 | 26.4 | 0.92 (0.66, 1.27) |

Total (95% CI) 100 0.82 (0.70, 0.97)

Heterogeneity: \(\chi^2=3.36, df=5 (P=0.64); I^2=0\%

Test for overall effect: \(Z=2.32 (P=0.02)\)

Figure 4 OS of segmentectomy versus wedge resection for NSCLC with tumor size ≤2 cm.

Abbreviations: OS, overall survival; NSCLC, non-small-cell lung cancer; HR, hazard ratio; IV, inverse variance; SE, standard error; CI, confidence interval.

| Study or subgroup | Log [HR] | SE | S Total | W Total | Weight (%) | HR IV, fixed, 95% CI |
|-------------------|----------|----|---------|---------|------------|----------------------|
| Hamatake et al (2012) | −0.6162 | 2.04 | 34 | 32 | 0.6 | 0.54 (0.01, 29.43) |
| Dai et al (2016) | 0.07 | 0.1595 | 160 | 821 | 99.4 | 1.07 (0.78, 1.47) |

Total (95% CI) 194 853 100 1.07 (0.78, 1.46)

Heterogeneity: \(\chi^2=0.11, df=1 (P=0.74); I^2=0\%

Test for overall effect: \(Z=0.41 (P=0.68)\)

Figure 5 OS of segmentectomy versus wedge resection for NSCLC with tumor size ≤1 cm.

Abbreviations: OS, overall survival; NSCLC, non-small-cell lung cancer; HR, hazard ratio; IV, inverse variance; SE, standard error; CI, confidence interval; S, patients who underwent segmentectomy; W, patients who underwent wedge resection.
## Sensitivity analysis and publication bias

The outcomes were similar whether fixed-effects models or random-effects models were used. A funnel plot estimating the precision of the trials (plots of the logarithm of the HR for efficacy against sample size) was examined for asymmetry to determine publication bias.

## Discussion

Lobectomy has been considered as the standardized surgical approach of early stage NSCLC in the last few decades. Only the randomized clinical trial by the Lung Cancer Study Group\(^2\) showed the superiority of lobectomy. However, 30% of sublobar resection was wedge resection and not segmentectomy in this trial. Most studies supported lobectomy, without considering the factors affecting survival such as tumor size, differences in limited resections, the age of patients, patients combining with comorbidities and the type of lymph node dissection. The intentional sublobectomy can receive equivalent survival to lobectomy for early stage NSCLC.\(^9,15,16\) Hence, the limited resection was considered the surgical method for the early stage NSCLC as far as the preservation of lung function was concerned. The study by Smith et al\(^10\) through the Surveillance, Epidemiology and End Results (SEER)-Medicare registry indicated that segmentectomy should be the preferred technique for limited resection of patients with stage IA NSCLC. However, the subsequent Japanese studies demonstrated that only tumors up to 2 cm are indication for segmentectomy. In this study, for stage IA NSCLC, the HR of OS of 0.93 (95% CI: 0.83–1.05, \(P=0.26\)) and HR of DFS of 0.82 (95% CI: 0.70–0.97, \(P=0.02\), Figure 4). Moreover, the GGO of early stage NSCLC was detected by HRCT; combining the HR of OS of 1.79 (95% CI: 0.33–9.55, \(P=0.50\)) and HR of DFS of 1.68 (95% CI: 0.20–13.94, \(P=0.63\)) demonstrated that wedge resection received the similar survival rate compared to segmentectomy. Since there were only two studies in this comparison and the ratio of GGO was the independent factor of OS and DFS, we could not draw a definite conclusion. In this study, there were three studies that underwent sublobar approach for patients with cardiopulmonary impairment. It was also the important factor leading to the heterogeneity between studies. Because of the highly selected patients according to the accurate criteria and all retrospective studies with no randomized controlled trial (RCT) test, the level of evidence was low. Because systematic lymph node resection for the early stage NSCLC is still controversial the, number of included literature was only 9.

## Conclusion

This meta-analysis suggests that segmentectomy compared with wedge resection may lead to better survival rate for tumor size \(\geq 2\) cm NSCLC. For tumor size \(\leq 1\) cm and GGO

### Table 6: OS of segmentectomy versus wedge resection for GGO NSCLC.

| Study or subgroup | Log [HR] | SE | S Total | W Total | Weight (%) | HR IV, fixed, 95% CI |
|------------------|----------|----|---------|---------|------------|---------------------|
| Sugi et al (2010)\(^1\) | 0.5134 | 0.9493 | 33 | 15 | 81.2 | 1.67 (0.26, 10.74) |
| Tsutani et al (2014)\(^2\) | 0.8671 | 1.9709 | 56 | 93 | 18.8 | 2.38 (0.05, 113.29) |
| Total (95% CI) | 89 | 108 | 100 | 1.79 (0.33, 9.55) |

### Figure 6: OS of segmentectomy versus wedge resection for GGO NSCLC.

**Abbreviations:** OS, overall survival; GGO, ground glass opacity; NSCLC, non-small-cell lung cancer; HR, hazard ratio; IV, inverse variance; SE, standard error; CI, confidence interval; S, patients who underwent segmentectomy; W, patients who underwent wedge resection.

### Table 7: DFS of segmentectomy versus wedge resection for GGO NSCLC.

| Study or subgroup | Log [HR] | SE | S Total | W Total | Weight (%) | HR IV, fixed, 95% CI |
|------------------|----------|----|---------|---------|------------|---------------------|
| Sugi et al (2010)\(^1\) | 0.4187 | 1.6491 | 33 | 15 | 42.9 | 1.52 (0.06, 38.51) |
| Tsutani et al (2014)\(^2\) | 0.5933 | 1.4289 | 56 | 93 | 57.1 | 1.81 (0.11, 29.78) |
| Total (95% CI) | 89 | 108 | 100 | 1.68 (0.20, 13.94) |

### Figure 7: DFS of segmentectomy versus wedge resection for GGO NSCLC.

**Abbreviations:** DFS, disease-free survival; GGO, ground glass opacity; NSCLC, non-small-cell lung cancer; HR, hazard ratio; SE, standard error; IV, inverse variance; CI, confidence interval; S, patients who underwent segmentectomy; W, patients who underwent wedge resection.
NSCLC, patients who received wedge resection achieved comparable survival to those who underwent segmentectomy. The results and conclusion should be confirmed by a large, randomized, prospective study (ACOSOG4032) and the Cancer and Lymphoma Group B (CALGB 140503).

Disclosure
The authors report no conflicts of interest in this work.

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