

# 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  $\leq 2$  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.<sup>1</sup> 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).<sup>2</sup> In recent years, many studies indicated similar survival with sublobar resection and lobectomy for stage IA NSCLC.<sup>3–9</sup> 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;<sup>10,11</sup> there was no effective evidence regarding

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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  $\leq 2$  cm and  $\leq 1$  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  $\leq 1$  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

Combing 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<sup>12</sup> and Tierney et al.<sup>13</sup> 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 test<sup>14</sup> 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  $\leq 2$  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  $\leq 2$  cm. Two studies provided the data for patients in early stage NSCLC (tumor size  $\leq 1$  cm). As the study of Dai et al<sup>24</sup> used the same database as the research of Zhang et al,<sup>23</sup> Dai et al’s study could not be included. However, it provided the research about the tumor size  $\leq 1$  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.

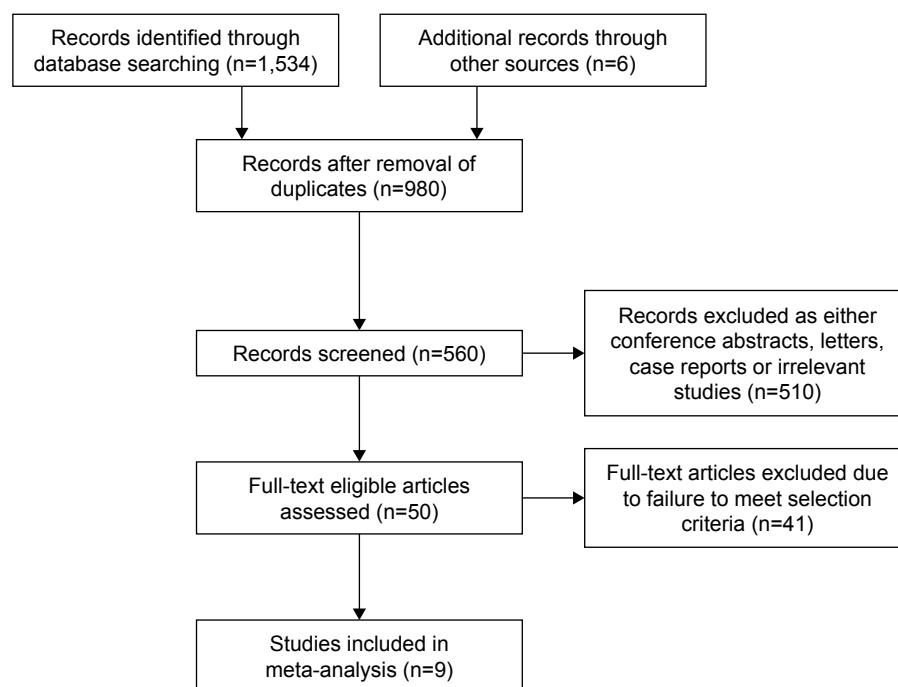


Figure 1 Search strategy.

Table 1 Characteristics of the included studies

Study	Year	Institution	Study period	Segmentectomy (n)	Wedge resection (n)	Reasons for sublobar approach	Tumor size (cm)
Okada et al <sup>7</sup>	2006	Department of Thoracic Surgery, Hyogo Medical Center for Adults, Akashi City, Hyogo, Japan	1992–2001	214	30	Intentional	2.0
Sugi et al <sup>8</sup>	2010	National Hospital Organization, Yamaguchi-Ube Medical Center, Japan	2001–2004	33	15	Intentional	2.0
Hamatake et al <sup>17</sup>	2012	Breast and Paediatric Surgery, Fukuoka University School of Medicine, Fukuoka, Japan	1995–2011	34	32	Intentional	1.0
Sienel et al <sup>18</sup>	2008	Department of Thoracic Surgery, Albert-Ludwigs-University Freiburg, Freiburg, Germany	1987–2003	56	31	Unintentional for patients with cardiopulmonary impairment	3.0
Sienel et al <sup>18</sup>	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 al <sup>19</sup>	2008	Chest Surgery, Niigata Cancer Center Hospital, Niigata, Japan	1991–2004	153	93	Unintentional for compromised patients	2.0
Altorki et al <sup>20</sup>	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>21</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	63	NR (54.8)	NR (54.8)
Sugi et al <sup>8</sup>	61.6±9.4	62.5±13.4	19 (30.6)	13 (38.2)
Hamatake et al <sup>17</sup>	64.0 (M)	64.0 (M)	62 (43.4)	62 (43.4)
Sienei et al <sup>18</sup>	67±9	63±8	NR (64)	NR (81)
Sienei et al <sup>18</sup>	67±9	63±8	NR (64)	NR (81)
Yamato et al <sup>19</sup>	65.2	65.2	NR (50)	NR (50)
Altorki et al <sup>20</sup>	71.0 (M)	74.0 (M)	53 (43.4)	68 (42.5)
Tsutani et al <sup>21</sup>	65	65	94 (39.3)	94 (39.3)
Tamura et al <sup>22</sup>	67	67.7	90 (60.4)	57 (64.0)
Zhang et al <sup>23</sup>	69	69.1	296 (37.7)	1,374 (43.7)
Zhang et al <sup>23</sup>	71.3	71.7	185 (50)	811 (51.4)
Zhang et al <sup>23</sup>	69	69.1	296 (37.7)	1,374 (43.7)
Zhang et al <sup>23</sup>	71.3	71.7	185 (50)	811 (51.4)
Dai et al <sup>24</sup>	>65 (62%)	>65 (65%)	218 (36)	1,017 (41)

**Abbreviations:** NR, number not reported; M, median±variance; S, patients who underwent segmentectomy; W, patients who underwent wedge resection.

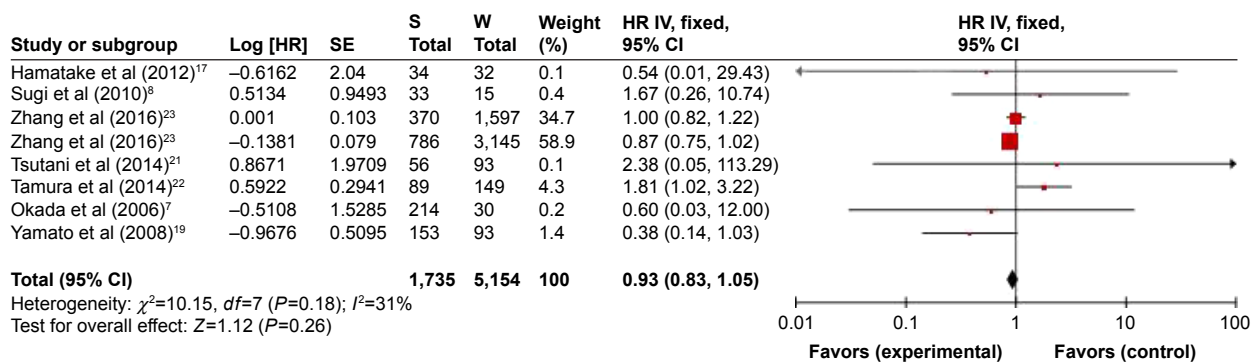


Figure 2 OS of segmentectomy versus wedge resection for stage IA NSCLC.

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.

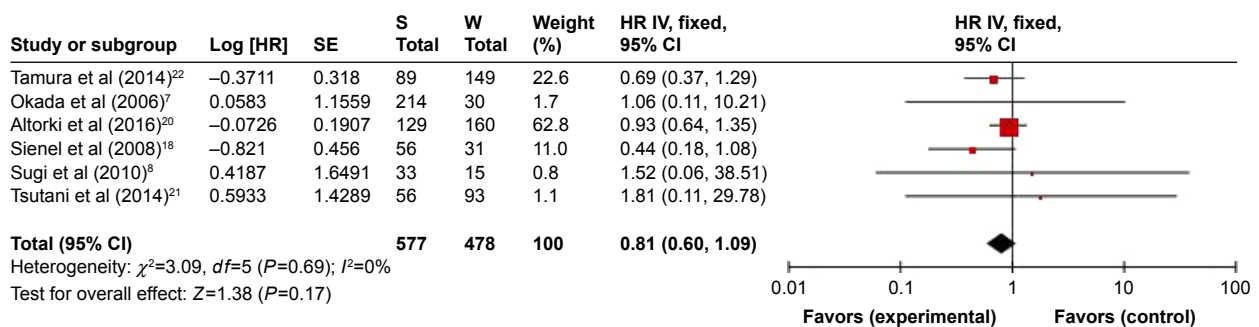


Figure 3 DFS of segmentectomy versus wedge resection for stage IA NSCLC.

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.

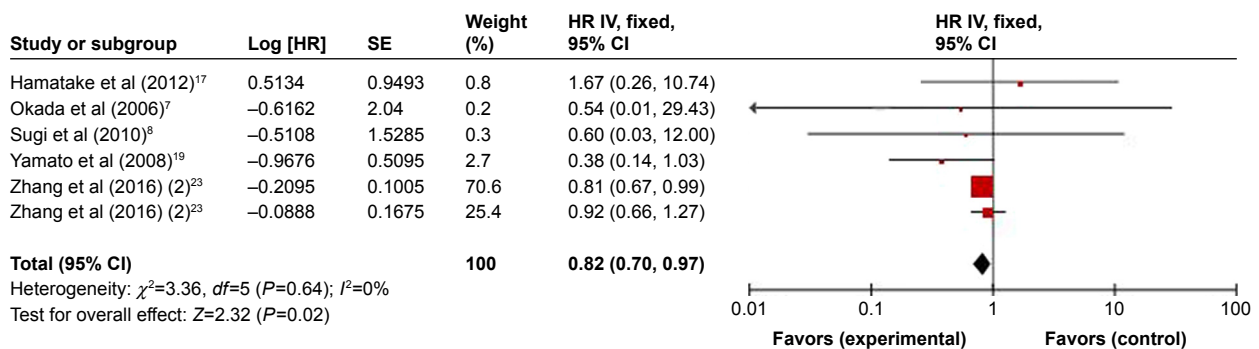


Figure 4 OS of segmentectomy versus wedge resection for NSCLC with tumor size  $\leq 2$  cm.

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

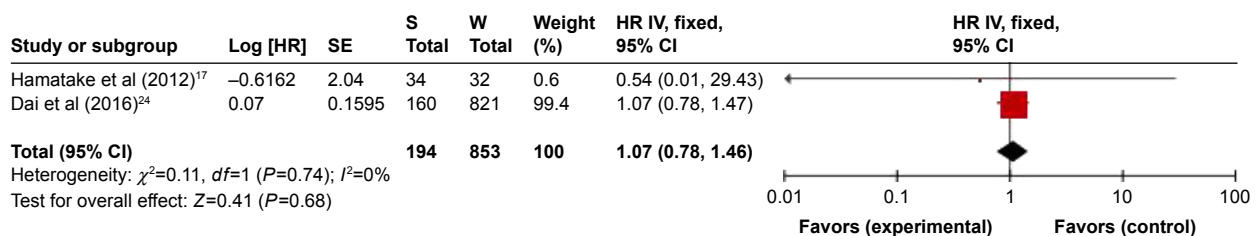
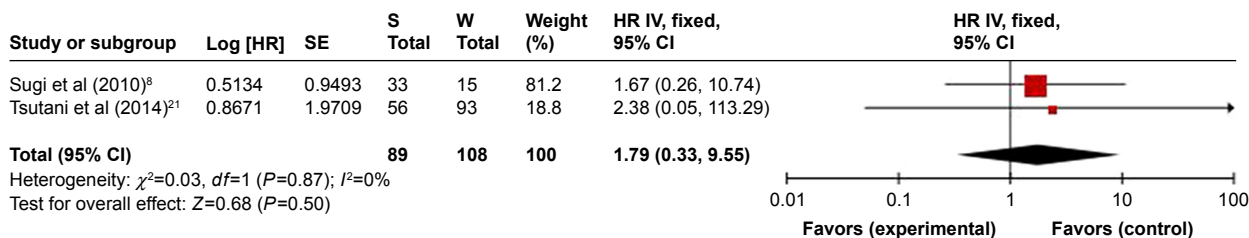


Figure 5 OS of segmentectomy versus wedge resection for NSCLC with tumor size  $\leq 1$  cm.

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.



**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.

### 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.

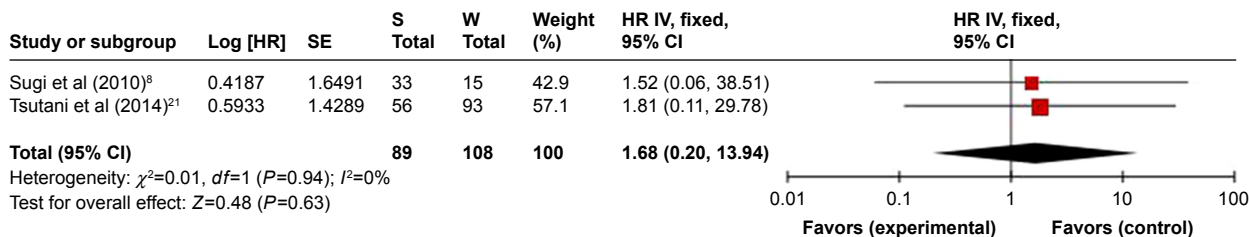
### Discussion

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<sup>2</sup> 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.<sup>9,15,16</sup> 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<sup>10</sup> 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 0.81 (95% CI: 0.60–1.09,  $P=0.17$ ) showed that segmentectomy was not superior to wedge resection. While for tumor size  $\leq 2$  cm, it was in favor of segmentectomy for the better OS of combined HR 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  $\leq 2$  cm NSCLC. For tumor size  $\leq 1$  cm and GGO



**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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