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Review Article

A meta-analysis of survival of patients with second primary non-small cell lung cancer after pulmonary lobectomy and partial pulmonary lobectomy

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Abstract: Objective: A meta-analysis of the screened data was performed to investigate the survival status of patients with second primary non-small cell lung cancer (SPNSCLC) after pulmonary lobectomy and partial pulmonary lobectomy, and assess the applicability of such option in the treatment of such disease. Methods: Based on the databases of PubMed, Ovid, and CNKI, relevant reports on postoperative survival of patients with SPNSCLC were obtained, and the information, including authors, publication year, research type, tumor staging, tumor diameter, surgical options, reasons for resection, and overall survival (OS), was extracted. The data were analyzed using Review Manager 5.3. Results: A total of 11 studies published from 2010 to 2017 were collected. Patients with SPNSCLC were mainly in stage Ia and Ib, 51.4% of whom underwent pulmonary lobectomy and 34.7% of whom underwent partial pulmonary lobectomy. The analysis results showed that after the second lobectomy, the mortality rate of the patients undergoing intensive surgery was 8%, the incidence of postoperative complications was 29%, and the 5-year OS rate was 53% after the second lobectomy for patients with SPNSCLC. Conclusion: The survival rate of patients with SPNSCLC is lower than that of patients with early lung cancer. In view of this, surgical resection is feasible. There are remarkable differences between pulmonary lobectomy and partial pulmonary lobectomy.

Keywords: Lung cancer, partial pulmonary lobectomy, meta-analysis

Introduction

Lung cancer is the malignant tumor with the highest mortality rate in the world. According to a 2012 report by the World Health Organization, about 1.82 million people are diagnosed with lung cancer every year, and 1.56 million people die from lung cancer [1]. With the continuous improvement of medical interventions, the long-term survival rate of lung cancer patients has been gradually increased through the early-stage screening techniques, which has led to a rise in the number of survivors, and caused the 5-year survival rate of lung cancer patients in some countries and regions to exceed 70% [2]. Meanwhile, lung cancer survivors are considered to have an increased risk of second primary cancer (SPC).

Generally, a second primary lung cancer (SPLC) refers to two primary cancer lesions occurring at the same time point or at different time points in the lung [2]. The annual incidence rate of SPLC is approximately 1% to 7% in patients with postoperative survival of NSCLC [3]. The 5-year OS rate of patients with heterochronous SPLC after surgical resection was 23-53% [4, 5]. Unlike the recurrence of primary lung cancer (PLC), SPNSCLC can be completely resected. For early-stage lung cancer, there is a controversy over the influences of surgical options on SPLC. Currently, there are studies on the comparison of the effects of partial pulmonary lobectomy (including segmentectomy and wedge resection of lung) and pulmonary lobectomy for SPLC. However, the treatment of heterochronous primary non-small cell lung cancer is based primarily on the retrospective data and a relatively small sample of patients, and there is a lack of high-quality evidence for the surgical treatment of SPNSCLC.

The purpose of this study was to determine the overall survival effect of patients with SPNSCLC

receiving different surgical treatments, and the long-term survival rate of patients with SPNSCLC developed from early lung cancer receiving surgical treatment.

Materials and methods

Literature retrieval strategy

As of June 20, 2019, the retrieval was performed based on the databases of PubMed, Scopus (Elsevier), Embase, Ovid, CNKI and Wanfang. Search strategy: "second primary" and "non-small cell lung cancer" and "segmentectomy" or "wedge resection of lung" or "pulmonary lobectomy" or "partial pulmonary lobectomy"; "limited" or "sublobectomy" or "sublobar" or "segmentectomy" or "wedge" or "segmental" or " conservative" with "lobectomy" and "death" or "mortality" or "survival" or "second primary lung cancer" or "NSCLC" or "second non-small cell lung cancer". The collected literatures included those in Chinese and English, and animal experiments were excluded. In addition, the references were also searched.

Criteria for literature selection

The eligibility criteria for inclusion in quantitative meta-analysis were: (1) published literature in Chinese or English; (2) with more than 30 patients receiving surgical treatment; (3) studies on the productivity of segmentectomy or wedge resection of lung; (4) provision of 5-year OS data as of the surgical treatment for the second primary tumor; (5) data were extractable. Exclusion criteria: (1) data were not extractable; (2) summary and case report; (3) the study subjects were without SPNSCLC.

Data extraction and quality assessment

Two cardiothoracic surgeons (Shaofeng Xia and Xueyu Zhu) independently assessed the literatures and extracted the data. The extracted information included: authors, publication year, research type, tumor staging, tumor diameter, surgical options, reasons for resection, OS and disease-free survival. In case of disagreement, the third researcher was asked for advice. The methodological quality assessment on randomized controlled study was conducted according to Jadad-61 criteria, and the literature with more than 3 points was considered to be of high-quality. The methodological quality assessment on included non-randomized controlled studies was performed in accordance with STROBE statement.

Statistical method

The data were analyzed using Review Manager 5.3. The included studies were input using Random Effect Summaries. Logarithmic standard error was only used in subgroup comparative analysis. I^2 value less than 25, between 25 to 50, and greater than 50% indicated low, medium, and high heterogeneity, respectively. The accuracy of funnel plot was used to assess the publication bias, and the analysis results were represented by the forest plot.

Results

Basic characteristics included in this study

A total of 334 literatures were preliminarily retrieved (**Figure 1**). A total of 117 literatures were preliminarily included through reading the titles and abstracts. After reading the full text, a total of 40 literatures that did not meet the inclusion criteria were excluded. Finally, 11 literatures were included [6-16]. All the studies were retrospective, with 30 to 161 patients included in each study. There were 1008 patients totally (**Table 1**).

Patient characteristics

The results revealed the clinical features of the patients undergoing the resection of SPNSCLC. In the five studies, heterochronous SPLC was defined based on Martini's definition [17]: (1) different histologies; (2) same histology, at least 2-year interval between the two cancers, originated from carcinoma in situ or the second cancer was located in different pulmonary lobes or cancer-free lung tissues. Lymphoma and extra-pulmonary metastasis were common at diagnosis. The modified criteria of Martini were used in the other six studies. Regarding the same histology, a 2-year interval was not strictly required in the three studies [7, 9, 11], and the different pulmonary lobes or lungs were not strictly required in one study [12]. The mean age of patients with SPNSCLC was 65 years. Males accounted for 67.7% of the patients with SPNSCLC. The mean interval for the progression of SPNSCLC was 46.6 months.

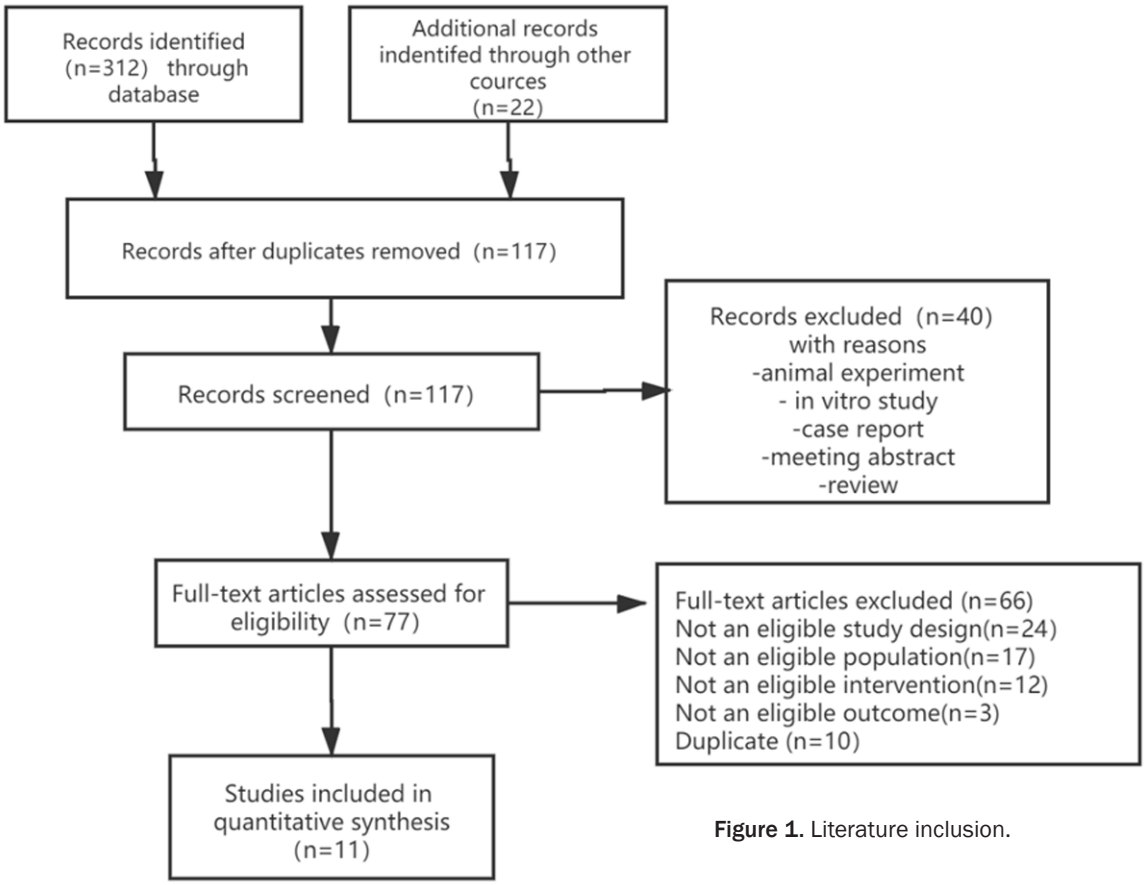

Figure 1. Literature inclusion.

Tumor characteristics

Seven studies reported the histological features of patients with lung cancer undergoing the initial surgery. Among them, adenocarcinoma was the most common histological feature (mean: 54.2%). Eight studies reported the histologies of patients with the second primary tumor. Among them, adenocarcinoma was the most common histology (mean: 50.4%). Seven studies reported the pathological grading of the primary tumors. The fifth edition of AJCC grading system was primarily used. The mean pathological grade was stage Ia (42.3%), followed by stage Ib (31.7%). All studies reported the pathological stages of the second primary tumor. Among them, the most common pathological stage was stage Ia (52.3%), followed by stage Ib (26.4%) (**Table 2**).

Therapeutic method for SPNSCLC

Most of the patients with SPNSCLC (51.4%) underwent pulmonary lobectomy, and pulmonary lobectomy accounted for 34.7%. Only two studies reported the surgical methods (thoracoscopic surgery and thoracotomy), indicating that thoracoscopic surgery was performed in the two studies (21.7% and 27.3%). The two studies suggested that thoracoscopic surgery was not an important factor affecting the OS of the patients undergoing the resection of SPNSCLC. Four studies reported the information on adjuvant treatment after resection of SPNSCLC. In the four studies, 21%, 11.2%, 4.7%, and 2.4% of the patients received adjuvant treatment.

Surgical mortality and morbidity after resection of SPNSCLC

Seven studies reported the surgical mortality after resection of SPNSCLC. The meta-analysis results in the seven studies (**Figure 2**) showed a mortality rate of 8% for combined surgery (95% CI: 5% to 13%). Five studies reported the surgical morbidity after resection of SPNSCLC (**Figure 3**), and the incidence rate was 29% for combined surgery (95% CI: 22% to 36%).

Table 1. Information on included literatures

Author	Year	Range	Number of case	Age, Median (range)	Male (%)	Months from first NSCLC median (range)	Extent of resection
Yang	2014	2006-2011	143	60 (35-81)	74.1	34 (3-186)	CP 23.1%; L 35%; S 4.2%; W 37.7%
Zuin	2013	1995-2010	98	NI	NI	66 (8-402)	NI
Hamaji	2013	2000-2009	161	70 (34-80)	54.7	42.7 (7-205)	CP 0.6%; L 22.4%; S 16.8%; W 60.2%
Haraguchi	2010	1982-2008	30	64 (34-82)	60	55.2 (9.6-162)	CP 17%; L 30%; S 20%; W 33%
Lee	2009	1995-2008	58	67 (47-86)	39.7	42 (8-312)	L 40%; S 24%; W 36%
Riquet	2008	1983-2005	116	64.2±7.9	77.9	NI	CP 31%; L 38.8%; S + W 30.2%
Battafarano	2004	1988-2002	69	67.5±8.9	52	28.8±30	CP 6%; L 45%; S 7%; W 42%
Van Rens	2001	1970-1997	127	66.8	91.3	44.4	CP 29.9%; L 40.2%; S + W 29.9%
Doddoli	2001	1985-1999	38	63±8	92.1	60±52	P 2.6%; CP 39.5%; L 26.3%; S 13.2%; W 18.4%
Zhao	2017	2001-2014	115	60.0 (36-78)	47.8	28	CP 0.9%; L 48.7%; W 32.2%; S 18.3%
Yusuke	2017	2006-2013	53	71.0 (43-84)	66	42.0 (8.6-141.4)	CP 90.6%; S 7.5%; W 1.9%

Note: CP = lobar lobectomy; L = pulmonary lobectomy; NI = no information; P = pneumonectomy; S = segmentectomy; W = wedge resection of lung.

Table 2. Pathological staging and histological types

Author	Histology n (%)	AJCC Edition	Ia n (%)	Ib n (%)	IIa n (%)	IIb n (%)	IIIa n (%)	IIIb n (%)	IV n (%)
Yang	Ad 64 (44.8); Sq 54 (37.8); AdSq 11 (7.6)	7th	87 (60.8)	54 (37.8)	8 (5.6)	8 (5.6)	11 (7.7)	1 (0.7)	3 (2.1)
Zuin	NI	7th	NI	NI	NI	NI	NI	NI	NI
Hamaji	Ad 98 (60.9); Sq 41 (25.5); other 22 (13.6)	6th or 7th	111 (68.9)	13 (8.1)	3 (1.9)	13 (8.1)	6 (3.7)	9 (5.6)	8 (4.9)
Haraguchi	Ad 23 (76.7); Sq 6 (20); AdSq 1 (3.3)	5th	19 (66.7)	4 (13.3)	0	3 (10)	2 (6.7)	2 (6.7)	0
Lee	Ad 48 (82.8); Sq 6 (10.3); large 4 (6.9)	NI	43 (74)	13 (22)	1 (1.7)	0	1 (1.7)	0	0
Riquet	Ad 51 (44); Sq 51 (44); other 14 (12)	NI	42 (36.3)	33 (28.4)	9 (7.7)	11 (9.5)	16 (13.8)	3 (2.6)	2 (1.7)
Battafarano	Ad 20 (29.0); Sq 32 (46.4)	5th	34 (49.3)	16 (23.2)	3 (4.3)	3 (4.3)	4 (5.8)	8 (11.6)	1 (1.4)
van Rens	Ad 36 (28.3); Sq 81 (63.8); AdSq 7 (5.5)	5th	50 (39.4)	40 (31.5)	5 (3.9)	22 (17.3)	10 (7.9)	0	0
Doddoli	Ad 14 (36.9); Sq 17 (44.7)	5th	9 (23.7)	18 (47.4)	1 (2.6)	3 (7.9)	3 (7.9)	4 (10.5)	0
Zhao	Ad 19 (16.5); Sq 9 (7.8); AdSq 38 (33.0); other 43 (37.3)	7th	54 (47.0)	13 (11.3)	44 (38.3)	2 (1.7)	2 (1.7)	0	
Yusuke	AD 39 (73.6); Other (26.4)	7th	34 (65.4)	0	8 (15.4)	0	4 (7.7)	0	0

Note: Ad = adenocarcinoma; AdSq = adenosquamous cell carcinoma; NI = no information; Sq = Squamous-cell carcinoma.

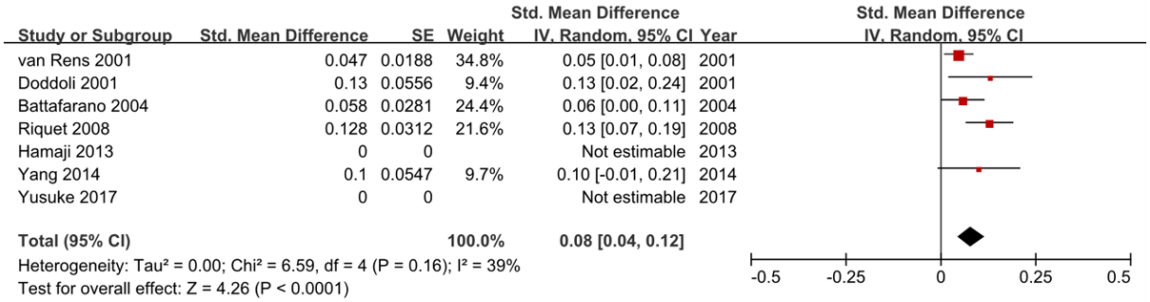

Figure 2. Forest plot for surgical mortality of patients.

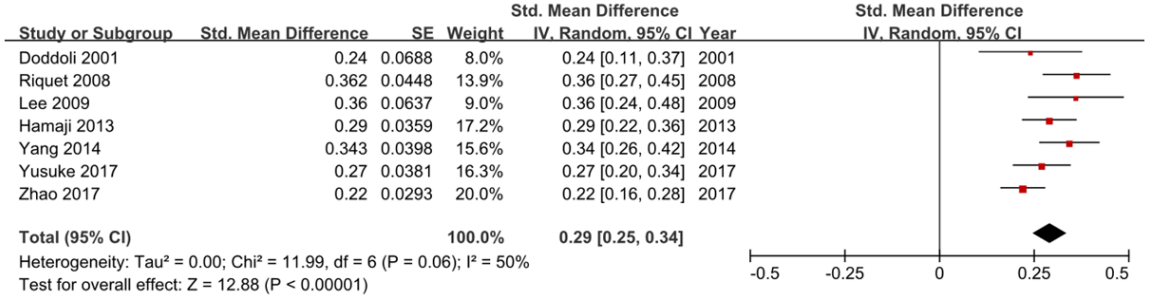

Figure 3. Forest plot for incidence rate of surgical complications.

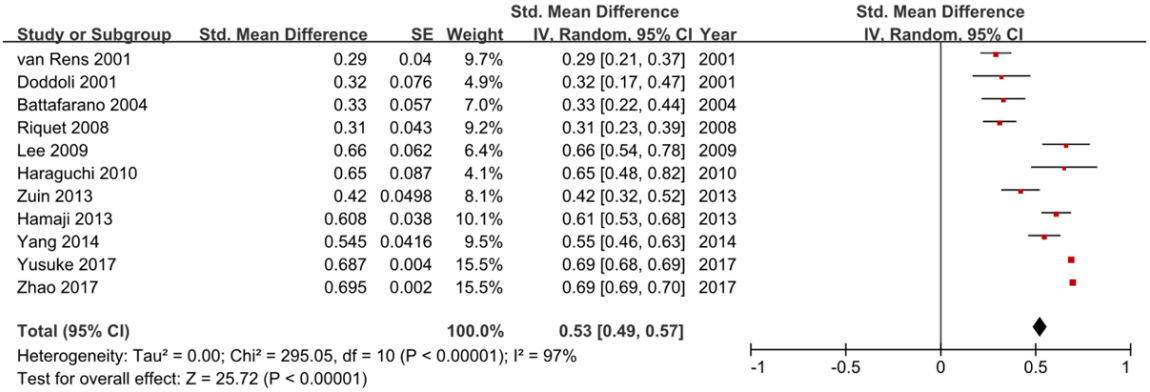

Figure 4. Forest plot for 5-year survival rate after surgery.

OS rates after resection of SPNSCLC and FPNSCLC

Seven studies reported the 5-year OS after resection of SPNSCLC. The combined rate of the 5-year OS was 53% (95% CI: 0.31-0.69), and there was a high degree of heterogeneity among studies (**Figure 4**). Only two studies reported the 10-year OS, which was not included in the meta-analysis (**Table 3**).

Analysis of different surgical options

The present study investigated the same or different histologies between the patients with second primary tumor undergoing pulmonary lobectomy and partial pulmonary lobectomy and the influences of disease-free interval ≥2 years on the 5-year OS. Four individual studies reported the 5-year OS rate of pulmonary lobectomy and partial pulmonary lobectomy. Based on the random model, the combined risk difference in the 5-year OS was 7% (95% CI: -0.17-0.30, P = 0.59), with a high degree of heterogeneity among studies. Five independent studies reported the 5-year OS incidence rates of patients with the less than 2-year interval after the initial surgery and patients with an abnormal surgical interval of more than 2

Table 3. Long-term survival rate of patients with the second primary lung cancer

Author	5-Year OS (%)	10-Year OS (%)
Yang	54.5	NI
Zuin	42	NI
Hamaji	60.8	20
Haraguchi	65	45.3
Lee	66	NI
Riquet	31	NI
Battafarano	33.4	NI
van Rens	26	NI
Doddoli	32	NI
Zhao	69.5	NI
Yusuke	68.7	NI

years. Based on the random model, the combined risk difference in the 5-year OS was 10% (95% CI: 0.00-0.20, P = 0.06), with a high degree of heterogeneity among studies.

Publication bias or heterogeneity analysis

The funnel plot for each meta-analysis is shown in **Figure 5**. In all funnel plots, each study appeared symmetrically, with most of them centered on the center axis, showing relatively low levels of publication bias.

Sensitivity analysis

The literature that did not strictly comply with the requirements was excluded to test the stability of the results. It was not much different from that before exclusion, indicating that the results showed good stability (**Figures 6**-**8**).

Discussion

Standardized treatment for heterochronous SPNSCLC has not been established. Currently, SPNSCLC can be treated with multiple options. Unlike the recurrence of PLC, SPNSCLC can be completely resected [14]. To date, the understanding of survival outcomes after resection of the heterochronous NSCLC has been based on the level-3 evidence from a retrospective case series, and no prospective studies have been conducted in such patients. Therefore, this study was conducted to comprehensively assess the 5-year survival outcomes of recent cohort patients with primary NSCLC who had previously undergone surgical resection of SPNSCLC.

A total of 9 retrospective studies published from 2000 to 2017 were included in this study, and 840 patients undergoing the surgery for the heterochronous SPNSCLC were selected. The study results showed that the combined 5-year OS rate of patients undergoing the surgery for SPNSCLC was 44%. The 5-year OS rate in recent studies was 60.8-66% [7, 9, 14]. In these reports, stage Ia tumors accounted for more than 60% of SPNSCLC, and stage Ia tumors with a 5-year OS amounted for 68% of SPNSCLC. Similarly, the independent predictive factors for the long-term survival after resection of the second primary lesion included early stage in four studies [8, 12-14]; there were relatively small tumors in two studies [7, 14], and there was a N0 stage in one study [16]. In summary, the above-mentioned findings indicate that early diagnosis of SPNSCLC by monitoring procedures may be conducive to improving the clinical efficacy.

Recently, the US National Lung Cancer Screening Test (NLCST) has confirmed the benefits of lung cancer screening. The test showed that the specific mortality rate of lung cancer was reduced by 20% in a screened high-risk population. This survival advantage has led to the extensive studies on postoperative monitoring of lung cancer survivors. It is fair to say that lung cancer survivors have a higher risk of lung cancer than those screened for NLCST in the US. Like most early lung cancer, SPLC is usually asymptomatic. Therefore, the monitoring procedure is crucial for detection. In our study, the mean duration from treatment of FPNSCLC to progression to SPNSCLC was 46.6 months. However, the interval was usually wider (205, 312 and 402 months) in each individual study [6, 7, 9], indicating that SPNSCLC may progress more than 30 years after resection of the primitive tumor. Similarly, the lung cancer research group reported that for NSCLC with T1 or N0 stage, the incidence rate of SPLC occurring more than 5 years after resection of the first primary tumor was twice as high as that over the past 5 years. In a study of 2151 patients undergoing surgical resection of primary non-small cell lung cancer, the 10-year cumulative incidence rate of SPLC was 18.2-20.3% [1]. Based on these data, the American Association for Thoracic Surgery recently recommended that the low-dose computed tomography (CT) should be performed annually to

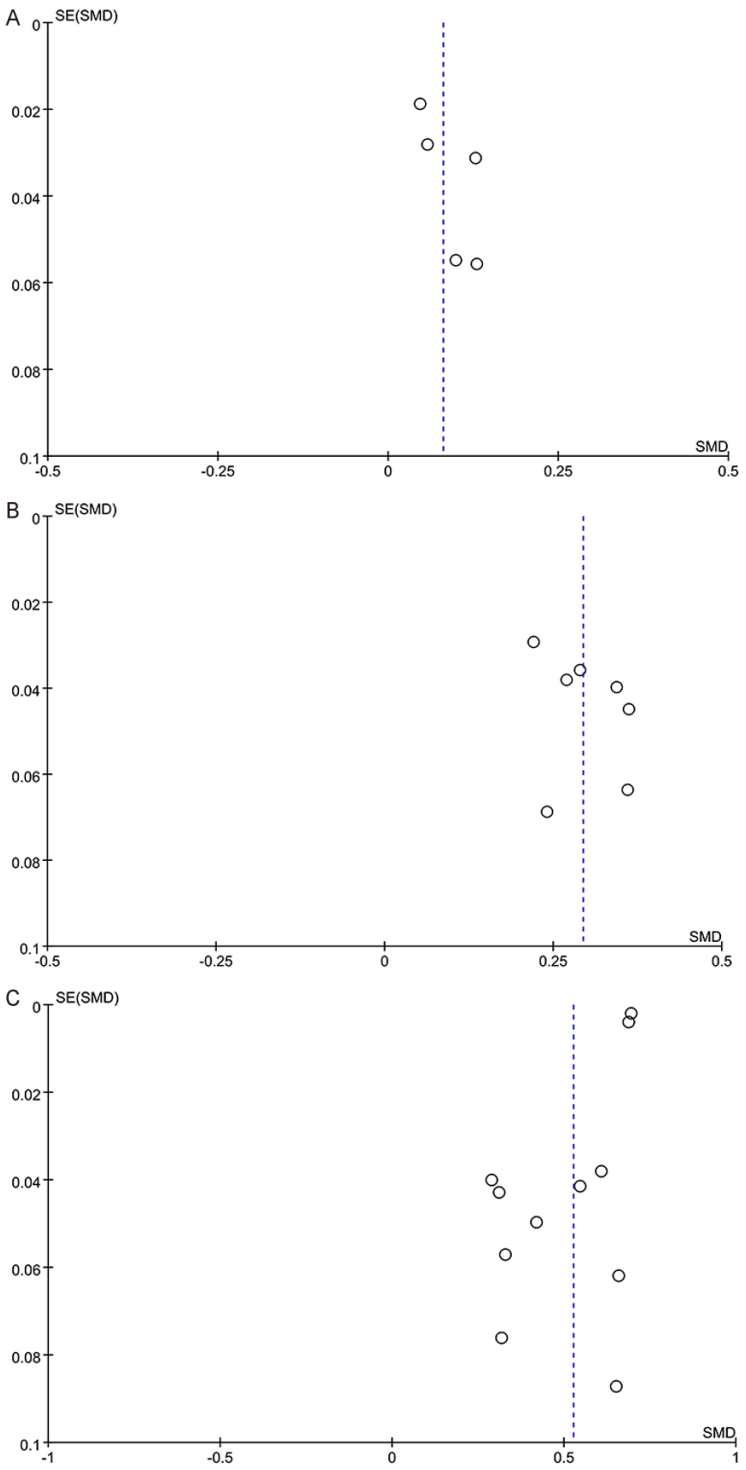

Figure 5. Publication bias. All studies were symmetrical, indicating low publication bias.

detect SPLC in patients with IIIA NSCLC undergoing surgical resection at stage IA, and the patients should have the functional status and pulmonary reserve function necessary to the treatment of the new lung cancer.

The anatomic pulmonary lobectomy should be considered for patients with primary non-small cell lung cancer. However, the surgical options have not been determined yet for the treatment of patients with SPLC. These patients may have insufficient pulmonary function. Therefore, they cannot undergo an additional pulmonary lobectomy. Many studies have reported the safety and effectiveness of surgical resection of SPNSCLC, and some have reported that the OS and cancer-specific survival (CSS) for partial pulmonary lobectomy may be the same as for pulmonary lobectomy [8, 15, 18-24]. The meta-analysis showed no marked difference between partial pulmonary lobectomy and pulmonary lobectomy. However, these results must be accommodated by the significant degree of heterogeneity between the studies in this subgroup analysis and the relatively few patients in the two groups.

Of 11 literatures in this study, 5 literatures were from Martini and Melamed [12], and the modified criteria of Martini and Melamed were implemented in other studies. If the histology of the second non-small cell lung cancer is the same as that of the first non-small cell lung cancer, it will be considered as the heterochronous tumor if the interval from the initial non-small cell lung cancer is over 2 years as required by the initial criteria. The subgroup analysis showed no remarkable difference in OS between patients with the same and different histologies, or between patients with disease-free interval ≤2 years

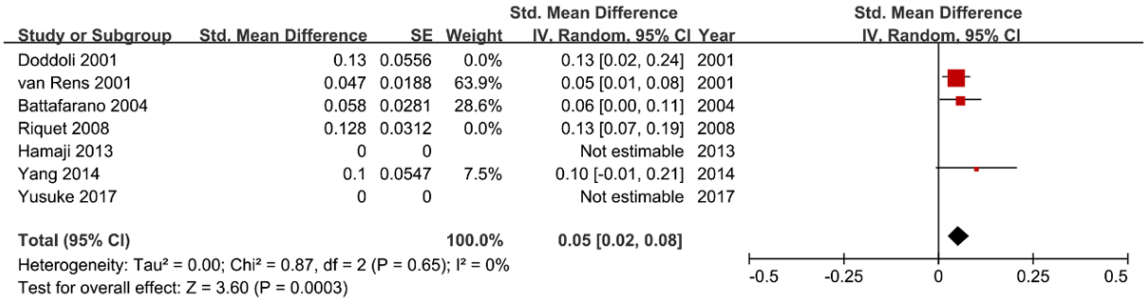

Figure 6. Sensitivity analysis of surgical mortality of patients.

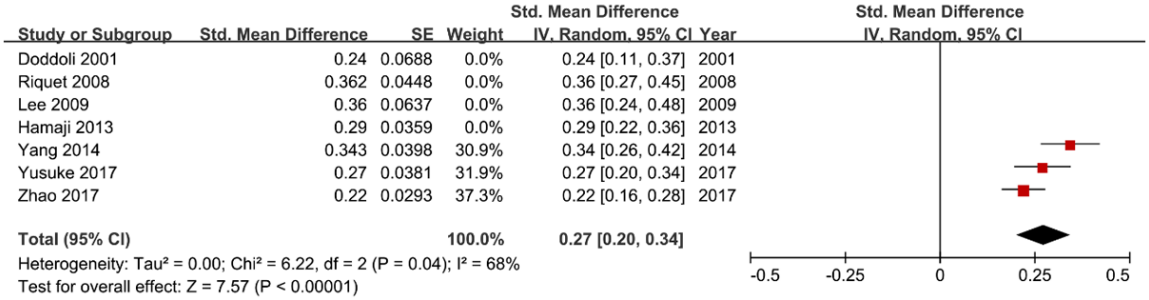

Figure 7. Sensitivity analysis of incidence rate of surgical complications.

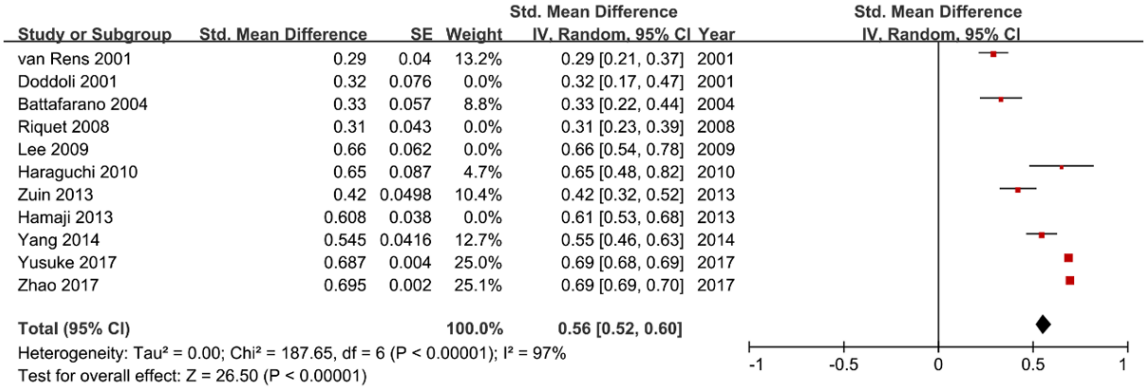

Figure 8. Sensitivity analysis of 5-year survival rate after surgery.

and patients with disease-free interval ≥2 years, indicating that the above factors may not be the most important determining factors for long-term survival in lung cancer.

Although the meta-analysis is an effective tool for assessing rare populations, it is essentially restricted by the limitations of the original study. The analysis of funnel plot did not show a significant relationship between therapeutic effects and study scale. Therefore, there was no significant publication bias. However, our meta-analysis was limited by the relatively small sample size and the quality of evidence in these studies, and no prospective or random data were available. In addition, the selection bias in the original study may affect our analysis. For example, the data pertaining to the pulmonary function and functional status were rarely provided in the original study, and the data regarding patients who performed well after surgical resection were not presented. Moreover, the preoperative staging data on SPNSCLC were largely lacking.

In summary, this study confirms the acceptable rate of long-term OS of patients with heterochronous SPNSCLC receiving surgical treatment.

It is recommended to implement the surgical treatment for patients with heterochronous SPNSCLC, and to continue the long-term follow-up after the initial resection of primary lung cancer.

Disclosure of conflict of interest

None.

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