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Systematic lymphadenectomy in the treatment of epithelial ovarian cancer: a meta-analysis of multiple epidemiology studies

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Abstract

Objective: To evaluate the role of systematic lymphadenectomy in epithelial ovarian cancer by comparing 5-year overall survival rates between systematic and unsystematic lymphadenectomies.
Methods: A literature search of the Pubmed, Embase and Cochrane Library databases was performed up to 2014. Two authors independently determined the eligibility of the articles and extracted the available data. The role of systematic lymphadenectomy in epithelial ovarian cancer was analyzed by combining all qualified individual studies using a fixed-effect model. Then, subgroup analysis was performed by dividing articles according to type, cancer stage and residual tumor. Finally, heterogeneity and publication bias in all enrolled studies were assessed using Higgins I^2 statistics and funnel plots, respectively.
Results: Fourteen relevant studies including 3488 subjects were included in the analysis. The value of pooled relative ratios of all qualified studies revealed that the 5-year overall survival rate in the lymphadenectomy group was higher than that in the unsystematic lymphadenectomy group (relative ratio = 1.08; $P = 0.001$), which was duplicated in the subgroup analysis of observational studies (relative ratio = 1.07; $P = 0.002$) and advanced stage (relative ratio = 1.21; $P = 0.012$) epithelial ovarian cancer. No significant differences were observed in randomized controlled trials (relative ratio = 1.01; $P = 0.858$), early stage epithelial ovarian cancer (relative ratio = 1.06; $P = 0.064$) or patients with residual tumor $\leq$2 cm (relative ratio = 1.05; $P = 0.125$). The heterogeneity and publication bias in the enrolled studies were within acceptable thresholds.
Conclusions: Lymphadenectomy can improve the 5-year overall survival rate in advanced stage epithelial ovarian cancer but not in early stage epithelial ovarian cancer or in patients with residual tumor $\leq$2 cm.

Key words: systematic lymphadenectomy, epithelial ovarian cancer, 5-year overall survival rate, meta-analysis

Introduction

Ovarian cancer (OC) is the sixth most common cancer in women and the seventh most common cause of cancer death worldwide (1). Its occurrence is associated with a positive family history (2). Owing to the absence of effective measures for early detection, it is often diagnosed at an advanced stage, resulting in low long-term survival rates of OC patients at 30–40% (3).

Currently, the treatment of advanced OC is controversial (4). Based on retrospective studies, treatment consists of cytoreductive surgery and post-operative chemotherapy with platinum-containing

combination therapy, such as platinum with taxane (5). Although first-line chemotherapy is effective, >60% of patients at an advanced stage develop recurrent disease (6) and eventually die because of significant intraperitoneal and/or lymph node metastasis.

In recognition of the prognostic importance of lymphatic metastasis, the International Federation of Gynecology and Obstetrics (FIGO) staging classification was amended to include a substage for node involvement (7) and systematic lymphadenectomy (SL) was included in the guidelines. However, in our clinical work, the therapeutic efficacy of SL to improve survival remains controversial. Studies have shown that SL is associated with a risk of vascular injury, lymphocyst formation, pulmonary embolism and post-operative mortality even when performed by surgeons with extensive experience (8).

In 2010, Kim et al. (9) conducted a meta-analysis on SL for OC. However, several new studies have been conducted since then, and the efficacy of SL remains highly controversial. Therefore, further analysis including all qualified relevant studies performed to date is necessary to reevaluate the role of SL in OC. In the present study, we specifically focused on the analysis of epithelial OC (EOC).

Patients and methods

Literature search

Possible eligible articles were identified regularly in the Pubmed, Embase and Cochrane Library databases by two reviewers using the keywords: 'epithelial OC', 'epithelial ovarian tumor', 'epithelial ovarian carcinoma', 'epithelial ovarian neoplasm', 'lymphadenectomy' and 'lymph node dissection'. All terms were expanded to include all subcategories to identify all published studies that fit the selection criteria.

Study selection

Published studies were included if they (i) used a randomized controlled trial (RCT) or case–control or cohort study design; (ii) compared the 5-year overall survival (OS) rate between SL and unsystematic lymphadenectomy (USL) groups. The exclusion criteria were as follows: (i) patients with other diseases besides OC which may influence the survival rate; (ii) Other histological types; (iii) studies in which the comparison of OS was not performed between SL and USL; (iv) publications in the non-English literature due to a lack of accessibility and difficulty reading.

Quality assessment

For case–control or cohort studies, the Nine-star system of the Newcastle-Ottawa Quality Assessment Scale was used. The selection of study groups, comparability between groups and the exposure were judged, respectively. The full score was 9, and a high-quality study was defined as a study with quality scores ≥7 (10).

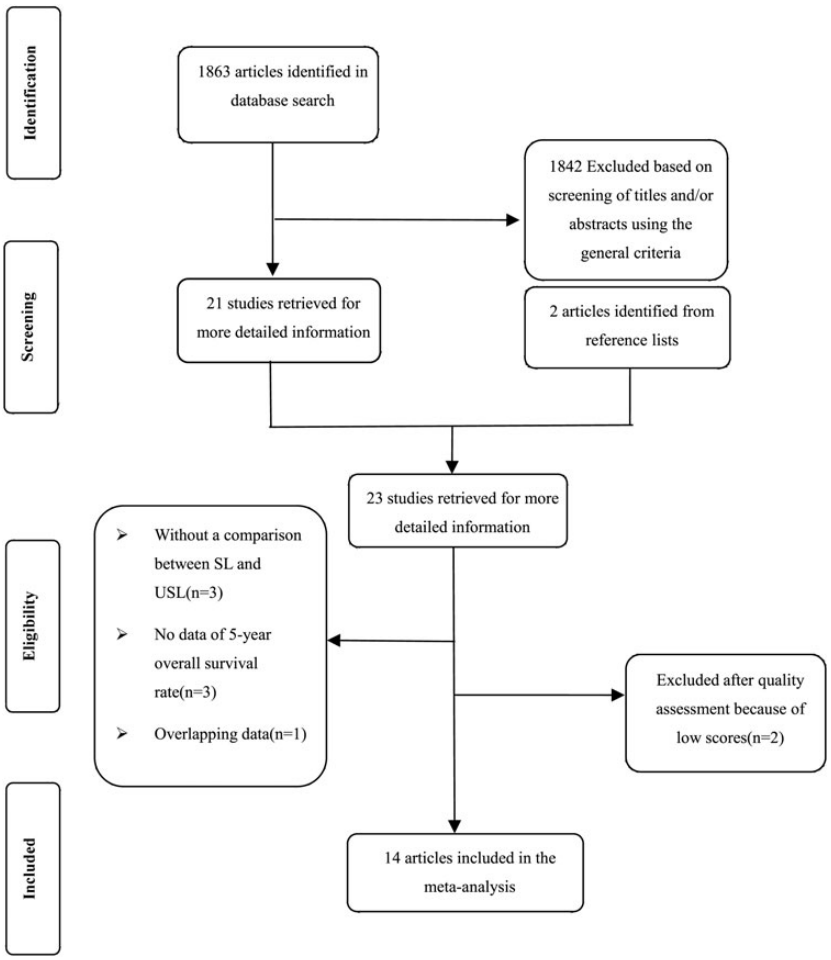

Figure 1. Flow diagram of the study selection process.

Table 1. Quality evaluation criteria for the observational study

Evaluation item								
Author	Selection				Comparability		Exposure		
	A	B	C	D	E		F	G	H
Burghard (14)	☆	☆	☆				☆	☆	☆
Saygili et al. (15)	☆	☆	☆		☆	☆	☆		
Kigawa et al. (16)	☆	☆	☆		☆	☆	☆	☆	☆
Kikkawa et al. (17)	☆	☆	☆		☆		☆	☆	☆
Di Re et al. (18)	☆	☆	☆		☆	☆	☆	☆	☆
Allen and Coulter (19)	☆	☆	☆		☆	☆	☆	☆	☆
Wang (20)	☆	☆	☆		☆		☆	☆	☆
Aletti et al. (23)	☆	☆	☆		☆		☆	☆	☆
Suzuki et al. (24)	☆	☆	☆		☆	☆	☆	☆	☆
Abe et al. (25)	☆	☆	☆	☆	☆		☆	☆	☆
Sakai et al. (27)	☆	☆	☆	☆	☆	☆	☆	☆	☆
Takafumi et al. (28)	☆	☆	☆	☆	☆	☆	☆	☆	☆
Svolgaard et al. (29)	☆	☆	☆	☆	☆	☆	☆	☆	☆

From A–H: (A) Representativeness of the exposed cohort: if they are truly representative of the average people in the community or somewhat representative of the average, one star was given. (B) Selection of the non exposed cohort: If they were drawn from the same community as the exposed cohort, one star was given. (C) Ascertainment of exposure: If they had secure record (e.g. surgical records) or structured interview, one star was given. (D) If it was demonstrated that outcome of interest was not present at start of study, one star was given. (E) Comparability of cohorts on the basis of the design or analysis: such as age, severity of disease or any other important factor which may affect results. A maximum of two stars could be given for this item. (F) Assessment of outcome: If they were independent blind assessed or had record linkage, one star was given. (G) If they were followed-up long enough for outcomes to occur, one star was given. (H) Adequacy of follow up of cohorts: If the study had complete follow up (all subjects were accounted for) or subjects lost to follow up were unlikely to introduce bias, one star was given.

Table 2. Quality evaluation criteria for the randomized controlled trials

Evaluation item								
Author	Randomizing method			Blinding method			Follow-up	
	A	B	C	D	E	F	G	H
Panici et al. (21)	2			2			1	
Maggioni et al. (22)	1			2			1	
Dell' Anna et al. (26)	2			2			1	

From A–H: (A) using computer to generate random number or similar appropriate methods (2 scores); (B) randomized method without description of the details (1 score); (C) non-randomized test (0 score); (D) use the same placebo or similar appropriate methods (2 scores); (E) blind trails without description of the details (1 score); (F) not a blind trail (0 score); (G) described the reasons for the lost (1 score); (H) without description of the reasons for the lost (0 score).

For RCTs, the JADAD assessments scale was used (11), by which a study was judged according to three broad aspects: randomizing method, blinding method and loss to follow-up. The full score was 5, and a high-quality study was defined as that with quality scores ≥4–5.

Quality assessment was independently performed by two investigators. In the case of disagreement, a third investigator was asked to reappraise until consensus was reached.

Data abstraction

The following data were independently extracted for the current study: first author, year of publication, study design, histology, disease status, number of patients, definition of SL and USL. Two reviewers compared the results of the abstraction for accuracy and in the case of disagreement, the third investigator served as the tiebreaker.

Statistical analysis

We pooled the relative ratios (RRs: the survival rate ratio of the SL group to USL group) from all the qualifying individual studies. Possible heterogeneity in the results across studies was examined by using Higgins I^2, which measures the percentage of the total variation across studies that is due to heterogeneity rather than chance (12). It usually ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity), and in the fixed-effect model, $I^2 \leq 50\%$ indicates no heterogeneity (13). A funnel plot, which is a scatter plot of standard error of the log RR of each study on the *X*-axis against log RR of individual studies on the *Y*-axis, was conducted to identify publication bias. If there was no publication bias, the funnel plot is symmetrical, otherwise it is asymmetrical (13).

This meta-analysis was performed using StataSE12 and a value of $P < 0.05$ was considered to be statistically significant.

Table 3. Demographic characteristics of fourteen eligible studies

Study	Year of publication	Design of study	Histology type	status (FIGO)	No. of patients		Definition of SL and USL
					SL	US	
Kigawa et al. (16)	1994	Observational	Epithelial ovarian cancer	III	29	24	SL: retroperitoneal lymphadenectomy USL: without retroperitoneal lymphadenectomy
Kikkawa et al. (17)	1995	Observational	Epithelial ovarian cancer	I–IV	61	89	SL: either pelvic or para-aortic or both lymphadenect-omy USL: without lymphadenectomy
Di Re et al. (18)	1996	Observational	Epithelial ovarian cancer	II–IV	214	36	SL: ≥20 resected pelvic and para-aortic lymphadenectomy USL: <20 resected pelvic and para-aortic lymphadenectomy
Allen and Coulter (19)	1999	Observational	Epithelial ovarian cancer	III	33	97	SL: retroperitoneal lymphadenectomy USL: without retroperitoneal Lymphadenectomy
Wang et al. (20)	2003	Observational	Epithelial ovarian cancer	I–IV	54	77	SL: retroperitoneal lymphadenectomy USL: without retroperitoneal Lymphadenectomy
Panici et al. (21)	2005	RCT	Epithelial ovarian cancer	III–IV	216	211	SL: pelvic and para-aortic lymphadenectomy USL: bulky nodes only
Maggioni et al. (22)	2006	RCT	Epithelial ovarian cancer	I–III	138	130	SL: pelvic (≥20) and para-aortic (≥15) resected LNs USL: random removal of pelvic and para-aortic LNs
Aletti (23)	2006	Observational	Epithelial ovarian cancer	III–IV	126	93	SL: retroperitoneal lymphadenectomy USL: without retroperitoneal Lymphadenectomy or bulky nodes only
Suzuki et al. (24)	2008	Observational	Epithelial ovarian cancer	I–II	104	101	SL: pelvic and para-aortic lymphadenectomy USL: exploration or sampling
Abe et al. (25)	2010	Observational	Epithelial ovarian cancer	I–IV	68	50	SL: retroperitoneal lymphadenectomy USL: without retroperitoneal Lymphadenectomy
Dell' Anna et al. (26)	2012	RCT	Epithelial ovarian cancer	I–IV	158	150	SL: pelvic and aortic lymphadenectomy USL: bulky nodes only
Sakai et al. (27)	2012	Observational	Epithelial ovarian cancer	III–IV	87	93	SL: pelvic and aortic lymphadenectomy USL: without lymphadenectomy or bulky nodes only
Takafumi et al. (28)	2013	Observational	Epithelial ovarian cancer	Not mentioned	284	138	SL: retroperitoneal lymphadenectomy USL: without retroperitoneal Lymphadenectomy
Svolgaard et al. (29)	2013	Observational	Epithelial ovarian cancer	I	211	416	SL: retroperitoneal lymphadenectomy USL: without retroperitoneal Lymphadenectomy

Results

Literature search and quality assessment

A total of 1863 potentially relevant articles were found in the three databases in our initial search. After the first screening based on the abstract or title, 21 articles were included for full text review. Two additional articles were added from the references; therefore, the full text review included 23 articles. Seven articles were excluded because: (i) they described the benefit of lymphadenectomy without a comparison between SL and USL ($n = 3$); (ii) no data of 5-year OS rate ($n = 3$); (iii) one overview ($n = 1$) with overlapping data. The remaining 16 studies were included for quality assessment. After review of these studies, two were excluded because of low quality: (i) Burghard et al. (14): without declaring the conflict of interest; mixed the OC of all stage; had no information about the age of objects. (ii). Saygili et al. (15): had no conflict of interest statement; without long enough follow-up time; high rate of defaulters.

The remaining 11 observational studies whose scores ranged from 7 to 9 with a median score of 8 (16–20,23–25,27–29) and three RCTs (21–22,26) with scores from 4 to 5 were finally included in our analyses. Figure 1 shows an overview of the process of selection. Tables 1 and 2 show the details of quality assessment.

Study characteristics

The characteristics of the 14 included articles are shown in Table 3. These articles, including 1783 cases and 1705 controls, were published between 1994 and 2013 and consisted of 11 observational studies (16–20,23–25,27–29) and three RCTs (21–22,26). Among the included studies, SL was defined as follows: (i) either pelvic or para-aortic lymphadenectomy or both (16–17,19–20,21,23–29); (ii) >20 resected pelvic and para-aortic lymph nodes (18,22). On the other hand, USL was defined as follows: not performed or no lymphadenectomy other than suspicious lymph nodes and the removal number was <20.

Comparisons of survival rates and heterogeneity

We pooled all the studies using a fixed-effect model. Since Wang et al. (20) compared the OS of patients with residual tumor >2 cm and ≤2 cm, respectively, and Abe et al. (25) compared the OS of Stages I–II and III–IV separately, the sets of data increased to 16. The average RR was 1.08 ($P = 0.001$, 95%CI: 1.03–1.13). This indicated that SL can improve the 5-year OS rate compared with USL (Fig. 2).

Because of differences in the proof strength between observational studies and RCTs, we performed further analysis based on

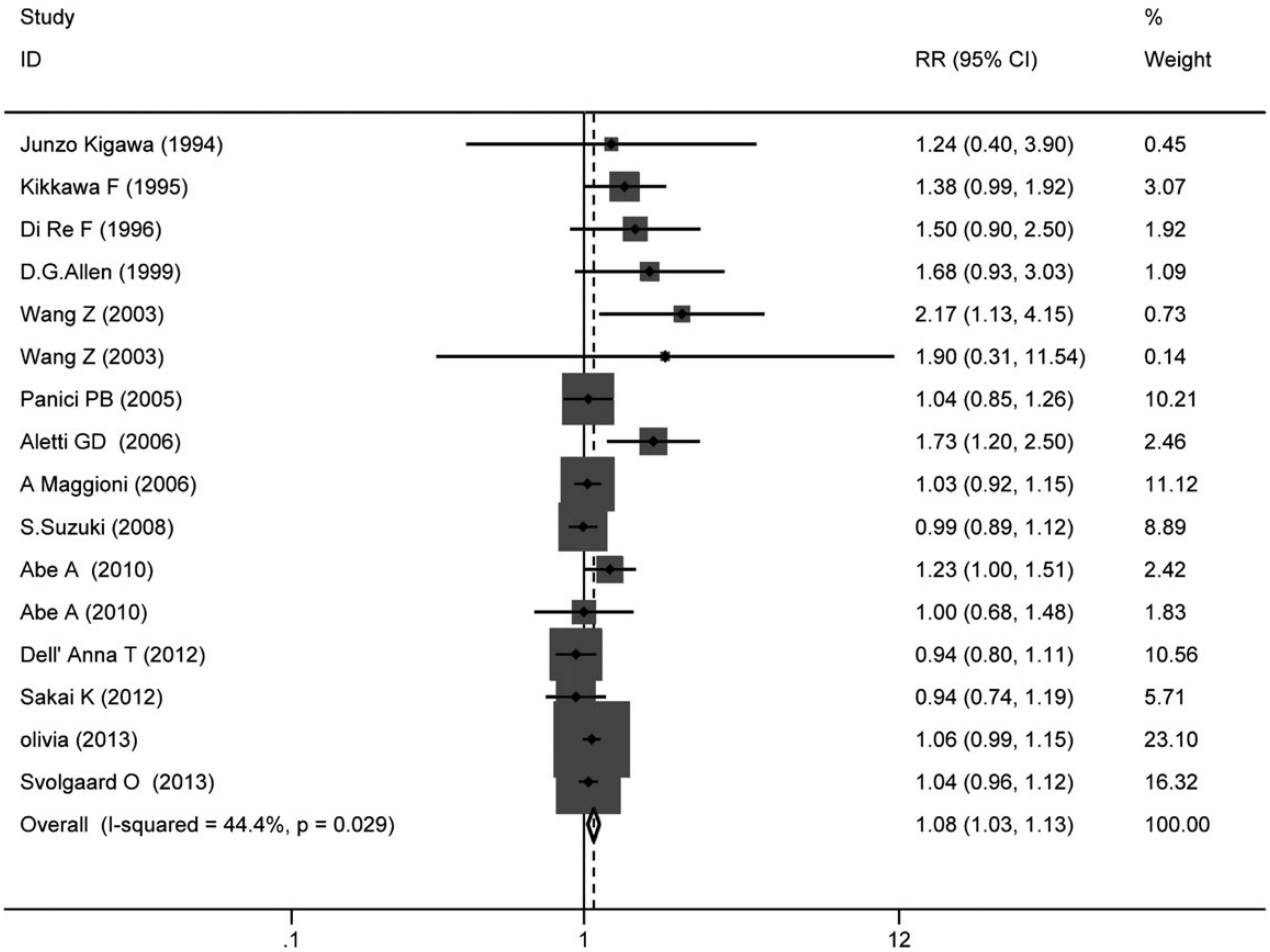

Figure 2. Comparison of 5-year overall survival rates between systematic and unsystematic lymphadenectomies in all studies. Since Wang et al. (20) compared the overall survival rate of patients with residual tumor >2 cm and ≤2 cm respectively, and Abe et al. (25) compared the overall survival rate of stage I–II and III–IV separately, the sets of data increased to 16 ($P = 0.001$).

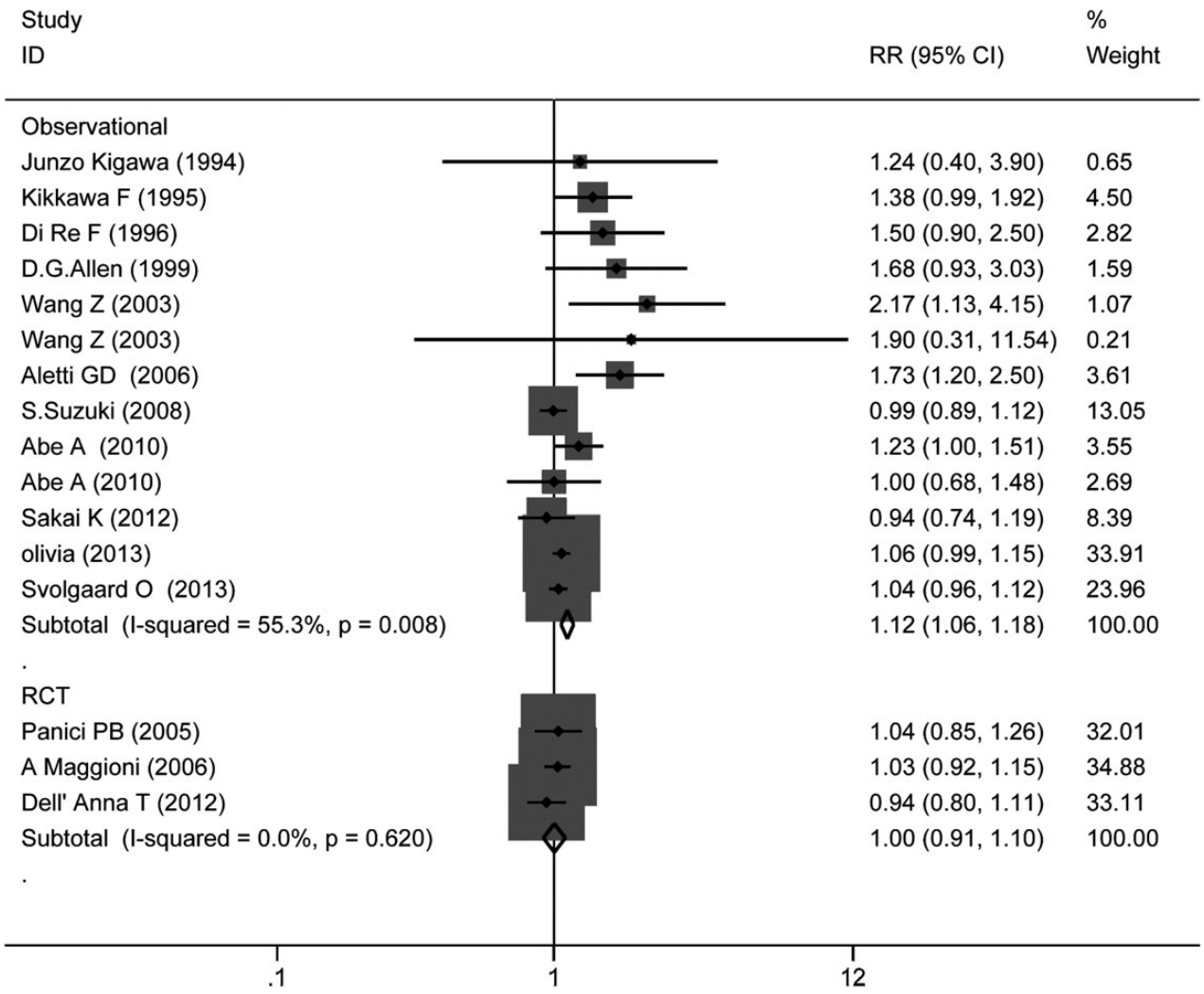

Figure 3. Comparison of 5-year overall survival rates between systematic and unsystematic lymphadenectomies based on research type. Observational studies: $P = 0.001$; randomized controlled trial: $P = 0.858$.

the research type. The summary RR of the 5-year OS rate between the SL and USL groups in these 11 observational studies was 1.12 ($P = 0.001$, 95%CI: 1.06–1.18), which confirms the improvement of OS in the SL group. In three RCTs, the value of SL was not observed, since $P > 0.05$ ($P = 0.858$), indicating that the difference was not statistically significant (Fig. 3). In further study, we discovered that slight heterogeneity was seen in observational studies ($I^2 = 55.3\%$). In order to find its origin, we used deduction to test each research (Fig. 4). It was easy to detect that Sakai's study brought about the heterology of the whole research. In further investigation, we found the age span in this study was too large (from 18 to 84) and the year of the surgery conducted for those patients was significantly different (from 1986 to 2009). As we all know, the extent of optimal cytoreductive surgery often has a great influence on survival rate. Too large spans of year often accompanied with leaps and bounds of surgical skills, which may reduce the comparability between objects as well as leading to the heterogeneity between studies. For this consideration, we deleted this research in our following analyses. New figure was shown as follows, though the conclusion was similar to Fig. 3 except for the heterogeneity (Fig. 5).

Furthermore, we conducted a subgroup analysis based on cancer stage. Since Stage I–II OC is considered early phase and Stage III–IV is recognized as advanced stage, we divided these articles into two groups based on this standard. There were seven sets of data analyzing the role of SL in advanced stage OC. A forest plot proved its efficiency (RR: 1.21, $P = 0.012$, 95%CI: 1.04–1.40) but the same result was not observed in three groups of early stage patients (RR: 1.06, $P = 0.064$, 95%CI: 0.99–1.15) (Fig. 6).

The last but not the least, we conducted a subanalysis based on residual tumor, since the completeness of surgery also had great impact on survival. There were nine sets of data analyzing the role of SL in patients with residual tumor ≤2 cm but only one set of data on residual tumor >2 cm could be picked out. So we pooled the former together. It seemed that SL was unnecessary for them (RR: 1.05, $P = 0.125$, 95%CI: 0.99–1.11) (Fig. 7).

Heterogeneity and publication bias

Tests for heterogeneity demonstrated that there was no significant difference between study variations. The Begg's test for publication bias showed that all studies were distributed evenly across the graph, suggesting no publication bias in this meta-analysis (Fig. 8).

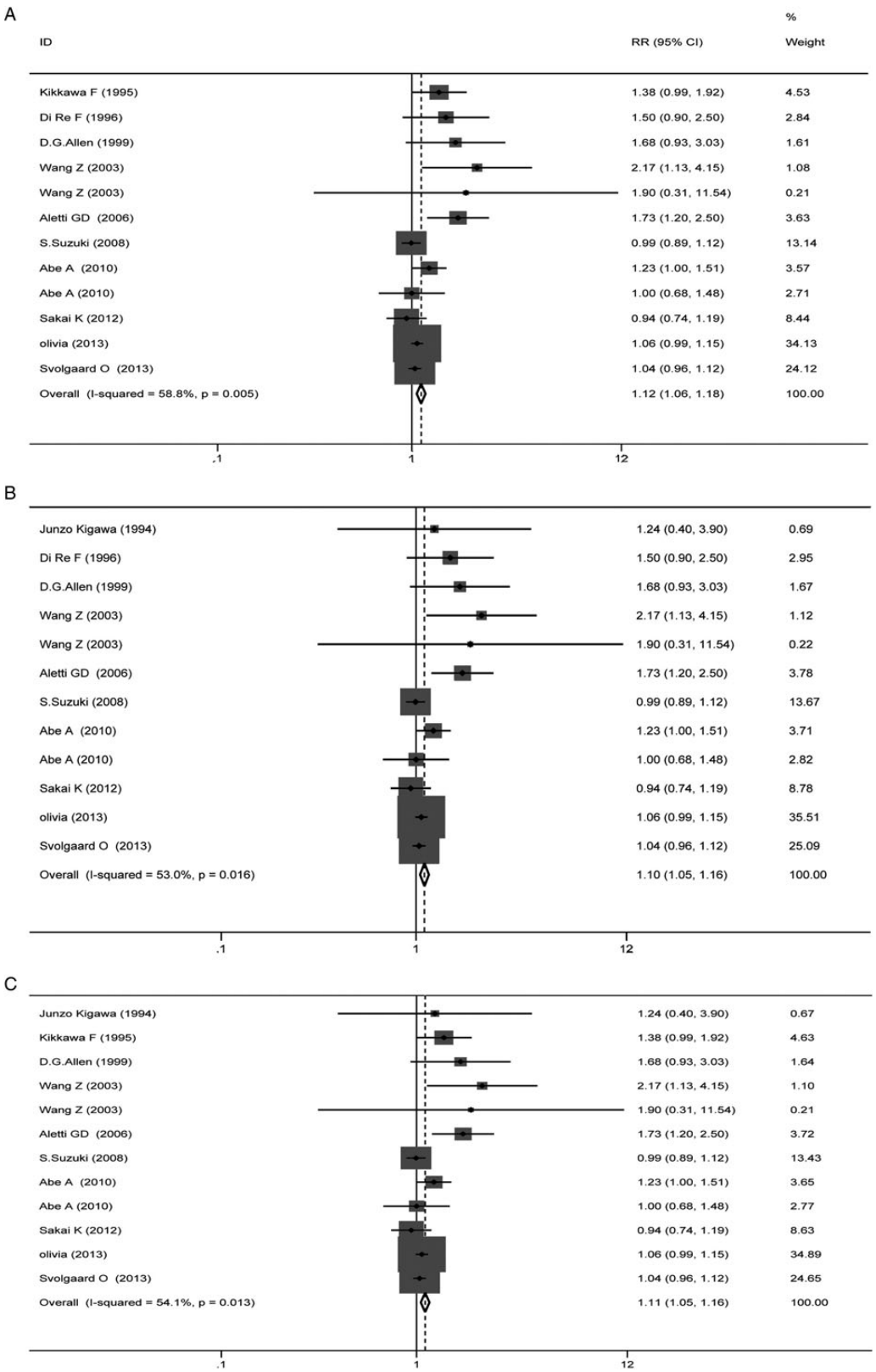

Figure 4. The exploration of heterogeneous sources. From A to F: (A) Remove the article of Junzo Kigawa ($I^2 > 50\%$); (B) Remove the article of Kikkawa F ($I^2 > 50\%$); (C) Remove the article of Di Re F ($I^2 > 50\%$); (D) Remove the article of D.G.Allen ($I^2 > 50\%$); (E) Remove the article of Abe A ($I^2 > 50\%$); (F) Remove the article of Sakai K ($I^2 < 50\%$).

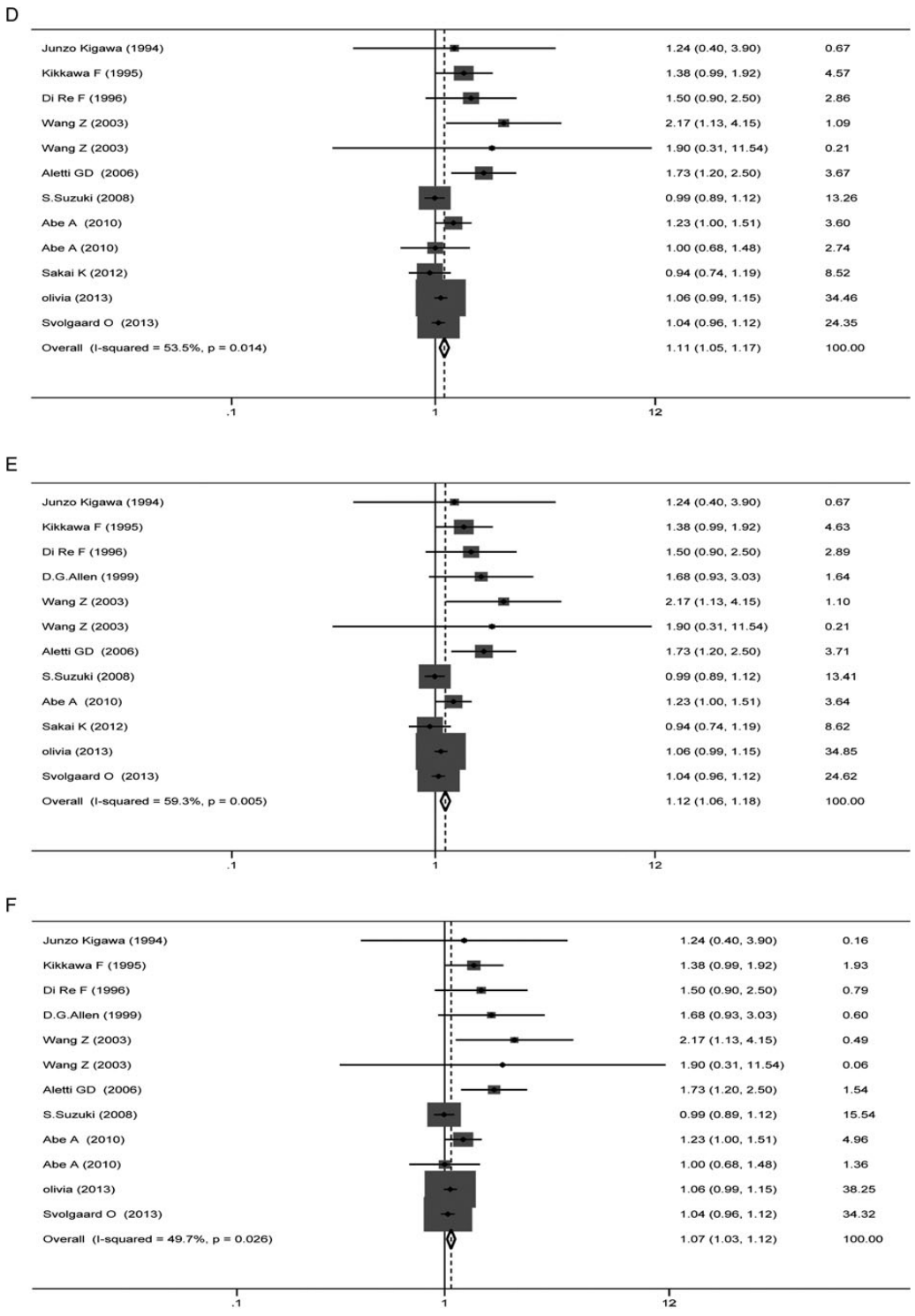

Figure 4. Continued

Discussion

Although the relationship between the retroperitoneal spread of lymph nodes and patient prognosis has been demonstrated in several studies (30,31), lymphadenectomy, as a routine treatment procedure in gynecological oncology, remains controversial (32–34). To the best of our knowledge, there are three major reasons as follows.

First, the main method used to evaluate lymphatic infiltration in our clinical work is magnetic resonance imaging (MRI). Some studies have reported that its accuracy is not ideal (35) because lymph nodes believed to be metastatic based on their large diameter on MRI can be finally proved to be lymphedema, which can also have an enlarged appearance. The lymph nodes without metastasis retain their function.

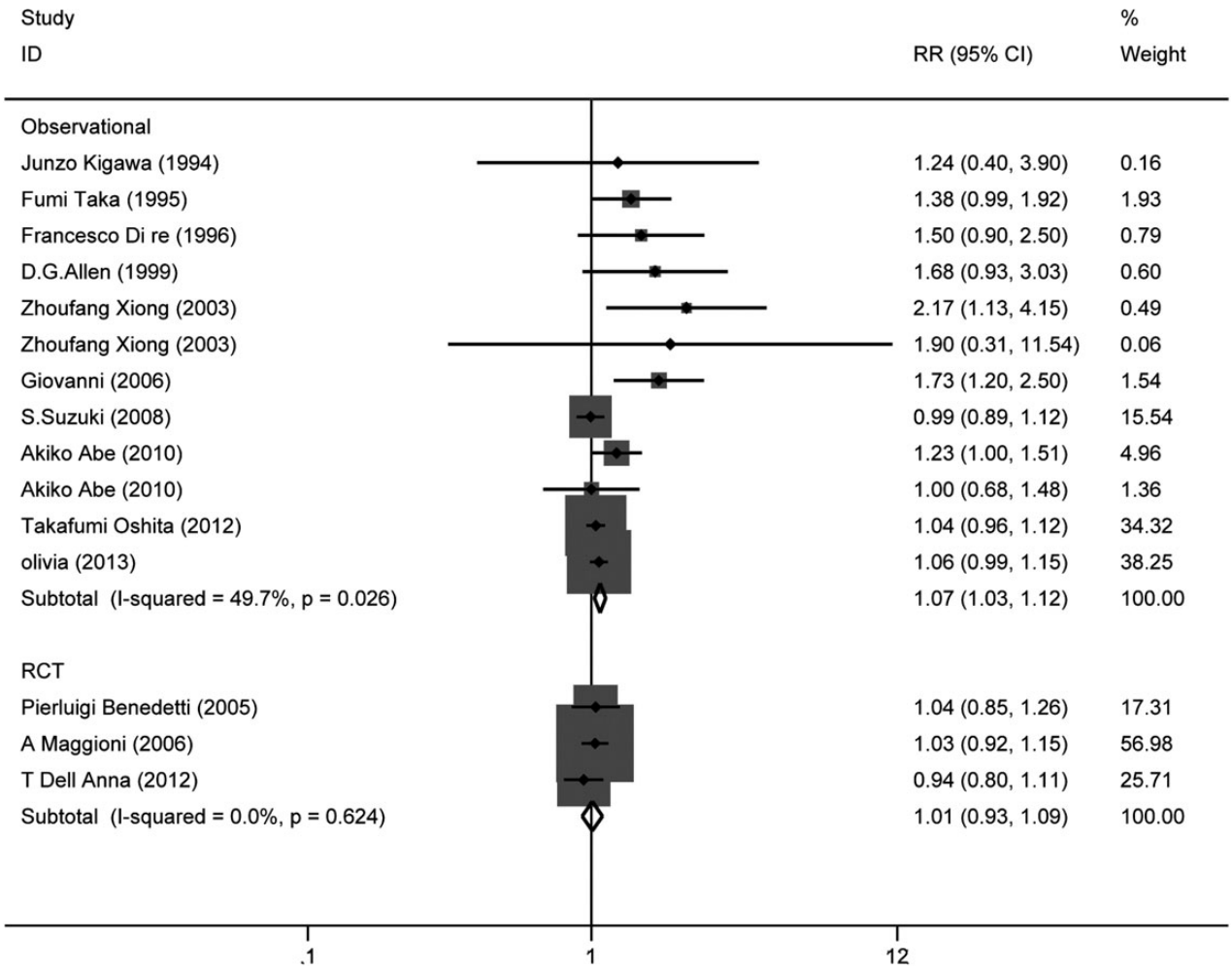

Figure 5. Comparison of 5-year overall survival rates between systematic and unsystematic lymphadenectomies based on research type. Observational studies: $P = 0.002$; randomized controlled trial: $P = 0.858$.

SL may remove normal lymph nodes by mistake. Second, because lymphadenectomy is performed in close proximity to larger vascular structures, the threat of intraoperative hemorrhage is always present (8). Moreover, SL often prolongs operation times, which may result in additional surgical complications such as lymphocele, lymphatic obstruction and nerve injury (36).

The debate regarding the efficacy of systematic lymphadenectomy led to the design of this meta-analysis. We pooled the relative risks from individual studies using a fixed-effect model and found that SL improved the 5-year OS in all 16 sets of data (RR = 1.08; $P = 0.001$, 95%CI: 1.03–1.13) (16–29). Because of differences in the experimental design, we combined observational studies and RCTs, respectively, as the latter are more convincing than the former. The outcome of the 13 observational sets of data (RR = 1.12; $P = 0.001$, 95%CI: 1.06–1.18) was the same as that above (SL improved the 5-year OS), but a similar result was not observed in three RCTs (RR = 1; $P = 0.858$, 95%CI: 0.91–1.10). The main reason for this controversial finding was the inclusion of only three RCTs, and the number of subjects in these studies was not large, which is not sufficient to describe the role of SL in patients with OC.

Furthermore, we conducted a subgroup analysis based on cancer stage and residual tumor. The results showed that SL was necessary for patients with EOC in an advanced stage. However, its effectiveness was not observed in early stage patients or in patients with residual tumor ≤2 cm. This can be explained as follows: the pharmacologic sanctuary hypothesis suggests that nodal metastases of OC may be less sensitive to systemic chemotherapy because of diminished blood supply; therefore, lymphadenectomy in advanced EOC is therapeutic with the purpose of removing as much tumor as possible (8). On the other hand, in early stage patients or in patients with optimal cytoreduction, its complications may counteract its functions.

Finally, we performed heterogeneity and publication bias analyses. The latter was within acceptable thresholds. However, there was slight heterogeneity between observational studies at first. We used deduction to explore the heterogeneous sources and detected that Sakai's study brought about the heterology of the whole research. So in the following analyses, we deleted this research. Since then, no other heterogeneity could be seen in our study.

Our analysis included almost all available epidemiological evidences supporting an association between SL and 5-year OS rates in EOC. Combining individual data from multiple studies has the advantage of increasing statistical power. Single studies do not have sufficient power to examine these associations in detail.

The present study also had several limitations. Firstly, there were only 14 relevant studies, although we attempted to perform an extensive literature search to obtain all published studies. For this reason,

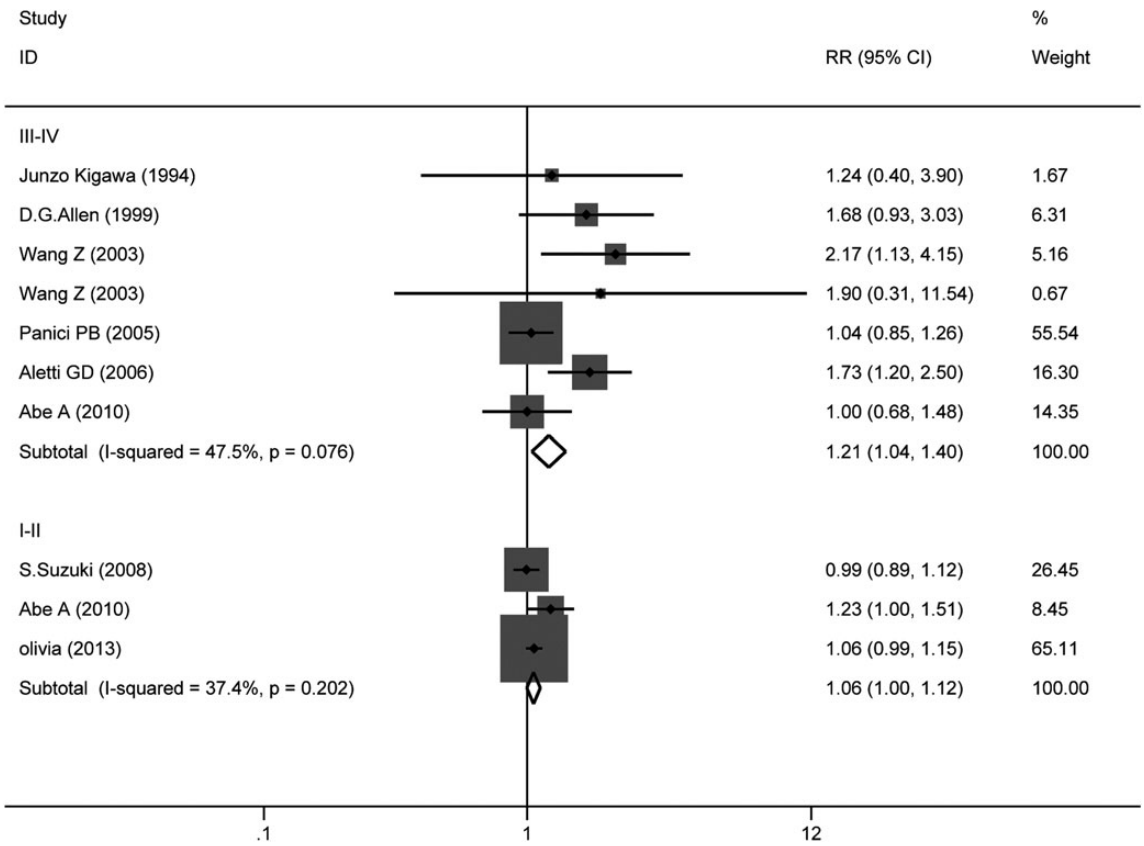

Figure 6. Subgroup analysis based on cancer stage. The value of *P* was 0.012 and 0.064 in advanced stage epithelial ovarian cancer and early stage epithelial ovarian cancer, respectively.

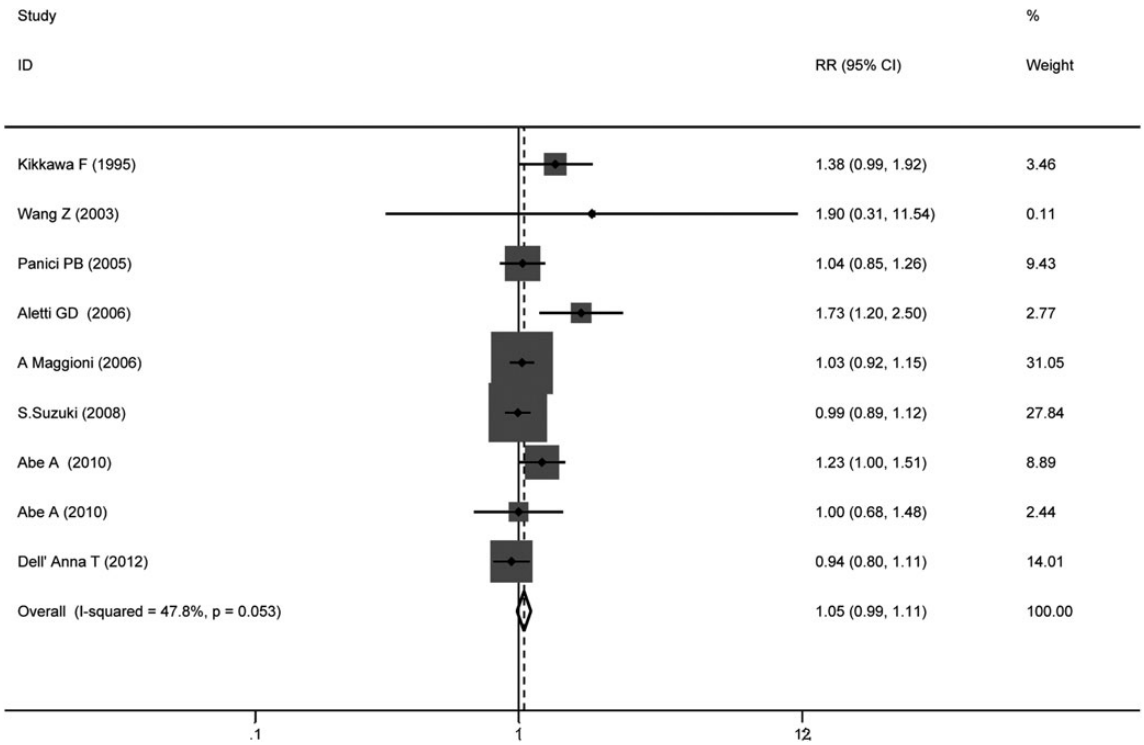

Figure 7. Subgroup analysis based on residual tumor (≤2 cm).

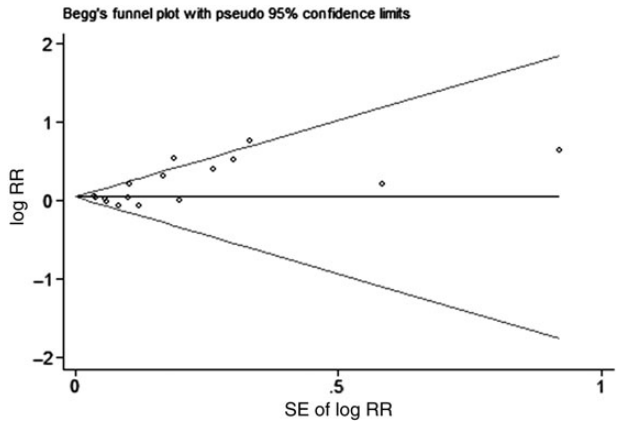

Figure 8. The funnel plot for all eligible studies in the meta-analysis.

we were unable to conduct a more detailed analysis, such as combining studies according to patient age or country of origin. Secondly, most of the studies included in the analysis were observational ones, which have lower inferential strength than RCTs. However, the German AGO group has taken the initiative and is starting an RCT that will hopefully provide more accurate answers (8). Thirdly, in our article, we used 5-year OS to evaluate the role of SL in EOC. Certainly, it can describe the efficiency of SL well, but the limit exists, since it does not take time-point into consideration when conducting analyses. Though Greenland (37) once believed OS was similar to hazard ratio in the COX model, it would be much better to calculate them both.

Conflict of interest statement

None declared.

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