

Original Article



Lymphadenectomy for primary ovarian cancer: a systematic review and meta-analysis

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ABSTRACT

Objective: To assess the effectiveness of lymphadenectomy at primary debulking surgery (PDS) on the survival of patients with epithelial ovarian cancer (EOC).

Methods: We searched PubMed, Ichushi, and the Cochrane Library. Randomized controlled trials (RCTs) and retrospective cohort studies comparing survival of women with EOC undergoing lymphadenectomy at PDS with that of women without lymphadenectomy were included. We performed a meta-analysis of overall survival (OS), progression-free survival (PFS), and adverse events.

Results: For advanced-stage EOC, 2 RCTs including 1,074 women and 7 cohort studies comprising 3,161 women were evaluated. Meta-analysis revealed that lymphadenectomy was associated with improved OS (hazard ratio [HR]=0.80; 95% confidence interval [CI]=0.70–0.90). However, meta-analysis of 2 RCTs revealed no significant difference in OS between the lymphadenectomy and no-lymphadenectomy groups (OS: HR=1.02; 95% CI=0.85–1.22). For early-stage EOC, 1 RCT comprising 268 women and 4 cohort studies comprising 14,228 women were evaluated. Meta-analysis showed that lymphadenectomy was associated with improved OS (HR=0.75; 95% CI=0.68–0.82). A RCT of early-stage EOC reported that lymphadenectomy was not associated with improved OS (HR=0.85; 95% CI=0.49–1.47). Surgery-related deaths were similar in both groups (risk ratio [RR]=1.00; 95% CI=0.99–1.01); however, blood transfusion was required less frequently in the no-lymphadenectomy group (RR=0.74; 95% CI=0.63–0.86).

Conclusions: Meta-analysis of RCTs and observational studies suggest that lymphadenectomy was associated with improved OS in advanced- and early-stage EOC. However, results from RCTs demonstrate that lymphadenectomy was not associated with improved OS in advanced- and early-stage EOC.

Keywords: Ovarian Neoplasms; Lymph Node Excision; Meta-Analysis; Systematic Review

INTRODUCTION

Epithelial ovarian, fallopian tubal, and peritoneal cancer is one of the most common cancers in women, with over 295,000 new cases diagnosed worldwide each year [1]. About 70%–80%

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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 Data curation: C.T., S.M.; Formal analysis: C.T.,
 S.M.; Funding acquisition: M.M., K.H., A.D.;
 Investigation: C.T., S.M., S.T.; Methodology:
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 S.T., N.S., M.M.; Supervision: S.T., N.S., M.M.,
 K.H., A.D.; Writing - original draft: C.T., S.M.;
 Writing - review & editing: C.T., S.M., S.T.

of epithelial ovarian cancers (EOCs) are of a serous histologic type. The less common types include endometrioid (10%), clear cell (10%), mucinous (3%–4%), transitional (Brenner) (<1%), and undifferentiated carcinomas (2%) [2]. The primary treatment includes staging laparotomy with maximal cytoreduction and adjuvant platinum-based chemotherapy. In advanced-stage EOC, no visible disease achieved by maximal cytoreduction is the most favorable prognostic factor, and thus is the main goal of primary debulking surgery (PDS) [3-5]. Although pelvic or para-aortic lymph node metastasis is reported in approximately 14% of clinical stage I or II EOC [6], the efficacy of lymphadenectomy on improved overall survival (OS) has not been established. Observational retrospective studies suggested that lymphadenectomy may be a favorable prognostic factor for OS in advanced- and early-stage EOCs. Therefore, the aim of this current study was to evaluate the role of lymphadenectomy in advanced- and early-stage EOCs.

MATERIALS AND METHODS

1. Search strategy

We searched the following databases from January 1967 to September 2018: PubMed, Ichushi, and the Cochrane Library. We identified all relevant articles found on PubMed and used the “related articles” feature to conduct a further search for newly published articles. We sought articles in all languages. The search strategy is described in **Supplementary Table 1**.

2. Study selection

RCTs and retrospective studies were included. The study participants comprised women with advanced- or early-stage EOC who had a confirmed pathological diagnosis from surgery. The primary surgical procedures included standard surgical staging with or without lymphadenectomy. PDS, including the pelvic region only, or pelvic and para-aortic lymphadenectomy was defined as the treatment group, whereas PDS without systematic lymphadenectomy was defined as the control group. PDS with lymph node biopsy was also included in the control group. The primary outcome was OS, survival until death from any cause. The secondary outcomes included progression-free survival (PFS) and adverse events (AEs).

3. Data extraction

To select the studies, we downloaded all titles and abstracts retrieved by electronic searching to a reference management database, BunKan, where 2 review authors (C.T. and S.M.) independently examined the references. We excluded those studies which clearly did not meet the inclusion criteria and obtained full text copies of potentially relevant references. The 2 authors independently assessed the eligibility of all retrieved papers, resolving disagreements by discussion, and we collected the following data: authors, year of publication, journal citation, country, setting, inclusion and exclusion criteria, study design and methodology, study population (total number enrolled, participant characteristics, age, size of residual tumors after primary surgery, stage, histology, and number of lymph nodes removed), interventions (expertise of surgeons and type of chemotherapy), risk of bias, duration of follow-up, and outcomes (OS, PFS, and AEs).

We extracted outcome data as follows:

- For OS and PFS data, we extracted the hazard ratio (HR) and its standard error from trial reports.
- For dichotomous outcomes (AEs), we extracted the number of participants in each group

who experienced the outcome of interest and the number assessed at the end point, to estimate a risk ratio (RR).

Where possible, all extracted data were relevant to an intention-to-treat analysis, in which participants were analyzed in the groups to which they were originally assigned.

4. Assessment of risk of bias in included studies

We assessed the risk of bias in the included RCTs using the Cochrane Collaboration's tool and the criteria specified in chapter 8 of the Cochrane Handbook [7]. This includes the following assessments: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases [7]. For observational studies, the sources of bias included selection bias, performance bias, detection bias, attrition bias, and others. Two review authors (C.T. and S.M.) independently applied the risk of bias tool, resolving differences by discussion. We interpreted the results of our meta-analysis in the light of the findings of the risk of bias assessments. We did not impute missing outcome data.

5. Assessment of heterogeneity and publication bias

We assessed heterogeneity between studies by visual inspection of forest plots and by estimation of the I^2 statistic. To evaluate the publication bias, we performed a funnel plot analysis. All studies were distributed evenly across the graph, indicating that no publication bias existed in the meta-analysis (**Supplementary Fig. 1**).

6. Data synthesis and analysis

We pooled the findings of the included studies into meta-analyses, using adjusted summary statistics when available and unadjusted results, otherwise. For time-to-event data, we produced and pooled HRs using the generic inverse variance facility of Review Manager 5. For dichotomous outcomes, we calculated the RR for each study and then pooled them. We used random-effects models for all meta-analyses.

RESULTS

1. Overview of the clinical trials included in the systematic review

We examined the titles and abstracts of 1,201 references identified by the original search (depicted in yellow cells, **Supplementary Table 1**) and determined that 45 studies were potentially relevant to this review. We obtained full text copies of the 45 studies, and 2 authors (C.T. and S.M.) assessed them independently for eligibility. Of the 45 studies, 33 were excluded during this process. The reasons for exclusion are presented in the characteristics of excluded studies table (**Supplementary Table 2**). We added an article from March 2019 which was already included in the Cochrane database [8] (**Fig. 1**). Ultimately, 3 randomized controlled trials (RCTs) and ten retrospective studies met all inclusion criteria (**Fig. 1, Table 1**).

2. Lymphadenectomy for advanced-stage ovarian cancer

For advanced-stage EOC, we identified 2 RCTs [8,9] and 7 observational studies, including one SEER database study [10-16] (**Table 1**). Two cohorts from the observational study of du Bois et al. [10] were selected: 1) no gross residual and 2) a residual tumor 1-10 mm. Regarding Panici et al.'s risk of bias [9], the selection bias of random sequence generation is high because more than two thirds of the included patients (61.8%) had residual postoperative

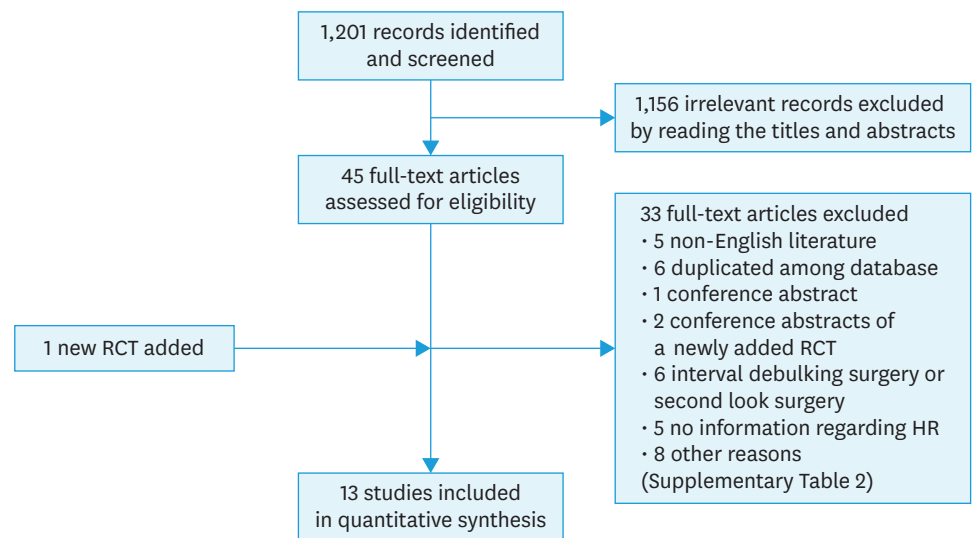


Fig. 1. Flow diagram of study selection. HR, hazard ratio; RCT, randomized controlled trial.

intraabdominal tumor which may have affected the prognosis, and resection of bulky lymph nodes was allowed in the control group. Another source of bias was that participating centers were not assessed for surgical quality (**Fig. 2, Supplementary Fig. 2**). The LION trial [8] has a low risk of bias since patients could undergo randomization only if macroscopically complete resection had been achieved, which is an appropriate design to compare the effectiveness of lymphadenectomy on survival. In addition, only patients with clinically negative lymph nodes were included in the study, and surgical quality was assured [8]. For observational studies, the overall risk of bias was generally considered unclear to high (**Fig. 2, Supplementary Fig. 2**). The meta-analysis of RCTs and observational studies using a random-effects model revealed that lymphadenectomy improved OS (HR=0.80; 95% CI=0.70–0.90) (**Fig. 3A**); however, the meta-analysis of RCTs alone showed that lymphadenectomy did not improve OS (HR=1.02; 95% CI=0.85–1.22) (**Fig. 3B**). The meta-analysis of observational studies showed that lymphadenectomy improved OS (HR=0.74; 95% CI=0.66–0.82) (**Fig. 3C**). Furthermore, the meta-analysis revealed that lymphadenectomy did not improve PFS (both RCT and observational studies: HR=0.77; 95% CI=0.54–1.10; RCTs: HR=0.92; 95% CI=0.63–1.35; and observational studies: HR=0.68; 95% CI=0.35–1.31) (**Fig. 3D–F**). In the meta-analysis of PFS including observational studies, heterogeneity was high ($I^2=87\%–90\%$) due to the results of Chang et al. [12]. It is not clear why the HR of lymphadenectomy on PFS was very low (HR=0.34), but lymphadenectomy was not a significant predictor of OS in their study [12].

3. Lymphadenectomy for early-stage ovarian cancer

For early-stage EOC, one RCT [17] and 4 observational studies, including one SEER database study [11,18–20], were included in the systematic review (**Table 1**). In the RCT [17], biases resulted because participating centers were not assessed for surgical quality, unilateral lymphadenectomy was allowed in unilateral tumors, and the primary endpoint of the study was the prevalence of patients with positive retroperitoneal nodes (**Fig. 2A**). Overall risk of bias in all 4 observational studies was not considered low (**Fig. 2B**). A meta-analysis of the RCT and retrospective early-stage EOC studies revealed that lymphadenectomy was associated with favorable OS (HR=0.75; 95% CI=0.68–0.82, without SEER study; HR=0.71; 95% CI=0.51–0.99) (**Fig. 4A and B**). The RCT of early-stage EOC reported no significant effects of lymphadenectomy on OS (HR=0.85;

Table 1. Clinical characteristics of RCTs and observational studies included in the systematic review

Stages	Author	Design of study	Clinical stage	Histology	Debulking status	No. of patients		Definition of SL and control	Quality	
						SL	Control			
Advanced-stage	Panici et al. [9]	RCT	IIIB-IV	Various	Optimal or residual tumors <2 cm	216	211	SL: pelvic and para-aortic SL Control: removal of ≥1 cm LN	62.1% had residual postoperative intraabdominal tumor (RO SL: 37.0%, Control: 37.4%) Resection of bulky lymph nodes allowed in control Surgical quality not assessed	
	Harter et al. [8]	RCT	IIB-IV	Various	Complete	323	324	SL: pelvic and para-aortic SL Control: not performed	All data available to study question (RO SL: 99.4%, Control: 99.4%) Exploratory analysis of 3 RCTs	
	du Bois et al. [10]	Observational	IIB-IV	Various	Optimal	610	894	SL: pelvic and para-aortic SL Control: not performed	Surgical quality not clear SL by discretion of surgeon	
	Abe et al. [11]	Observational	III-IV	Various	Optimal or residual tumors <2 cm	28	28	SL: pelvic and/or para-aortic SL Control: not performed	Small sample size Surgical quality unclear	
	Chang et al. [12]	Observational	IIIC (node metastasis only excluded)	Various	Optimal or suboptimal	135	54	SL: pelvic and/or para-aortic SL Control: not performed	Single center 22% of SL were pelvic only	
	Sakai et al. [13]	Observational	III-IV	Various	Optimal	87	93	SL: pelvic and para-aortic SL Control: removal of ≥1 cm LNs	Patient characteristics was balanced Surgical quality unclear	
	Pereira et al. [14]	Observational	IIIC-IV (peritoneal implants ≥2 cm with positive nodes)	Various	Optimal or suboptimal	30	53	SL: >40 resected pelvic and para-aortic LNs Control: ≤40 resected pelvic and para-aortic LNs	Single center Selection bias Control underwent lymphadenectomy	
	Paik et al. [15]	Observational	III (node metastasis only excluded)-IV	Various	Optimal or suboptimal	135	126	SL: pelvic and/or para-aortic SL Control: not performed	Single center Selection bias SL group younger than control	
	Zhou et al. [16]	Observational	IIIC-IV	Various	Optimal or suboptimal	367	521	SL: >20 resected LNs Control: not performed	SEER study Age and residual tumor different between SL and control	
	Early-stage	Maggiorni et al. [17]	RCT	I-II	Various	Optimal	138	130	SL: pelvic and para-aortic SL (unilateral pelvic lymphadenectomy allowed in unilateral tumors) Control: random sampling	Surgical quality not assessed Unilateral lymphadenectomy allowed
		Abe et al. [11]	Observational	I-II	Various	Optimal or residual tumors <2 cm	40	22	SL: pelvic and/or para-aortic SL Control: not performed	Small sample size Residual tumor different between SL and control
		Oshita et al. [18]	Observational	I-II	Various	Unknown	284	138	SL: pelvic and para-aortic SL Control: not performed	Selection bias Surgical quality unclear
		Svolgaard et al. [19]	Observational	I	Various	Unknown	216	411	SL: pelvic SL or para-aortic SL or both Control: not performed	Selection bias No background information of each group
		Matsuo et al. [20]	Observational	I-II	Various	Unknown	8,489	4,628	SL: ≥12 resected pelvic LNs Control: <12 resected pelvic LNs	Pelvic SL 44%, para-aortic SL 7%, both 48% SEER study Details of lymphadenectomy not clear

LN, lymph node; RO, no residual disease; RCT, randomized controlled trial; SL, systematic lymphadenectomy.

A RCT

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall risk of bias
Harter et al. [8]	+	+	?	?	+	?	?	+
Maggioni et al. [17]	+	+	?	?	+	?	-	?
Panici et al. [9]	-	+	?	?	+	?	-	?

B Observational studies

	Selection of participants (selection bias)	Deviations from intended interventions (performance bias)	Measurement of outcomes (detection bias)	Missing outcome data (attrition bias)	Other bias	Overall risk of bias
Abe et al. [11]	?	-	?	?	+	?
Chang et al. [12]	-	?	?	?	+	-
du Bois et al. [10]	+	?	+	+	+	+
Matsuo et al. [20]	+	?	?	?	+	?
Oshita et al. [18]	-	?	+	?	+	?
Paik et al. [15]	?	-	+	+	+	?
Pereira et al. [14]	-	-	?	+	+	-
Sakai et al. [13]	+	?	?	+	+	?
Svolgaard et al. [19]	-	-	?	?	+	-
Zhou et al. [16]	-	-	?	?	+	-

Fig. 2. Methodological quality summary: Review authors' judgements about each methodological quality item for each RCT (A) and observational studies (B). Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias. RCT, randomized controlled trial.

95% CI=0.49–1.47) [17] (**Fig. 4C**). A meta-analysis of the observational studies showed that lymphadenectomy was associated with favorable OS (HR=0.74; 95% CI=0.68–0.82, without SEER study; HR=0.64; 95% CI=0.42–0.97) (**Fig. 4D and E**). Meta-analysis of the RCT and retrospective early-stage EOC studies revealed that lymphadenectomy was not associated with favorable PFS (HR=0.71; 95% CI=0.47–1.07) (**Fig. 4F**). The RCT reported no significant effects of lymphadenectomy on PFS (HR=0.72; 95% CI=0.46–1.13) [17] (**Fig. 4G**).

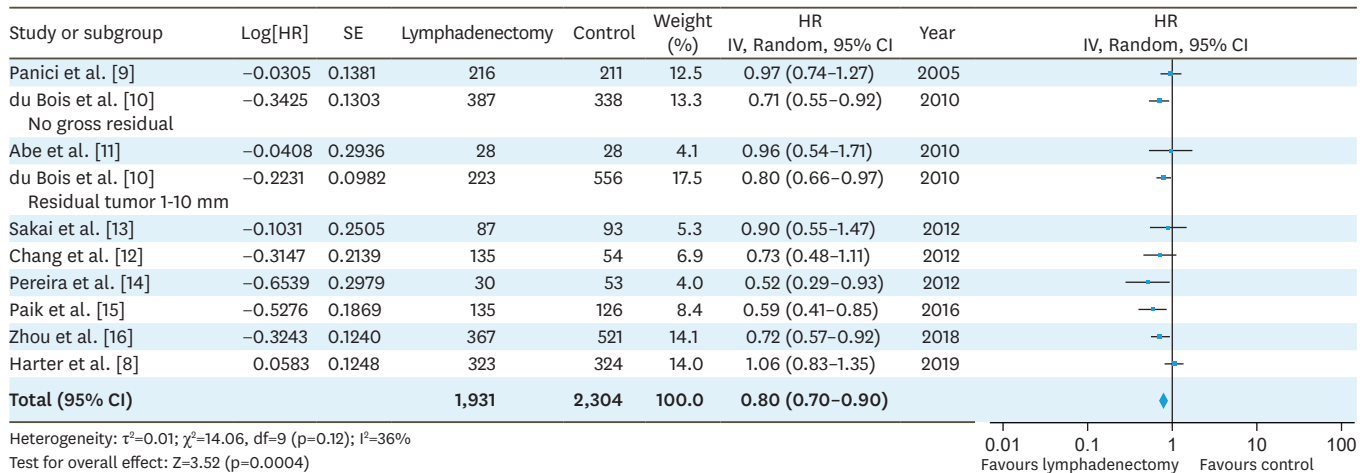
4. Risk of AEs

Using 3 RCTs and one observational study, AEs associated with lymphadenectomy were analyzed [8,9,17,18]. Lymphadenectomy was not associated with mortality related to surgery (RR=1.00; 95% CI=0.99–1.01) (**Fig. 5A**), although the LION trial reported that lymphadenectomy was significantly associated with mortality within 60 days following surgery [8]. Patients without lymphadenectomy required blood transfusion less frequently than the lymphadenectomy group (RR=0.74; 95% CI=0.63–0.86) (**Fig. 5B**).

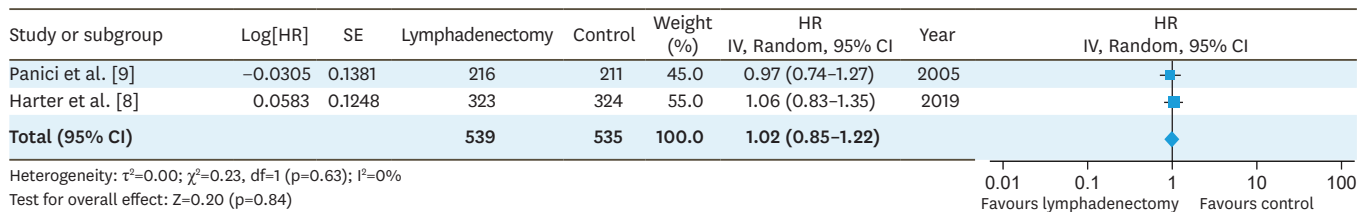
DISCUSSION

Pelvic and para-aortic lymphadenectomy has been routinely performed at PDS in both advanced- and early-stage EOCs relying on data from retrospective studies. In advanced-stage EOC, pelvic and para-aortic lymphadenectomy, which can contribute to maximal cytoreduction, has been performed as an important surgical procedure [3-5]. One RCT [9], which did not exhibit an advantage to lymphadenectomy, has been criticized on several points: surgical quality was not

A OS: RCT + Observational studies



B OS: RCT



C OS: Observational studies

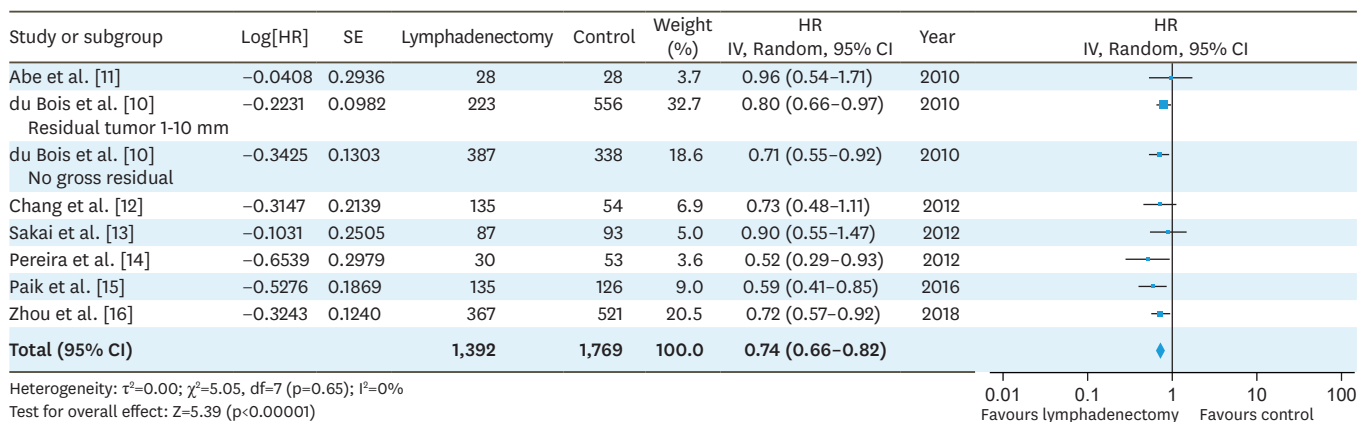


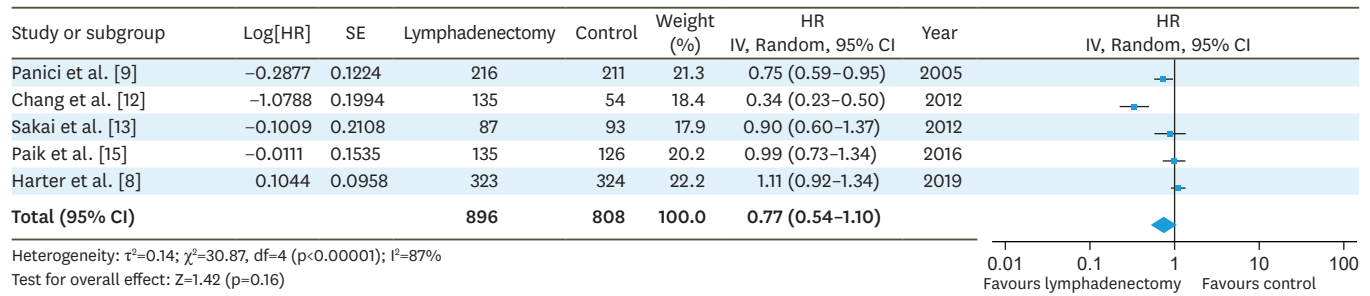
Fig. 3. Forest plots for the lymphadenectomy vs. control studies of the OS (A-C) and PFS (D-F) in advanced-stage ovarian cancer. The test for heterogeneity is indicated with the I^2 value.

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SE, standard error.

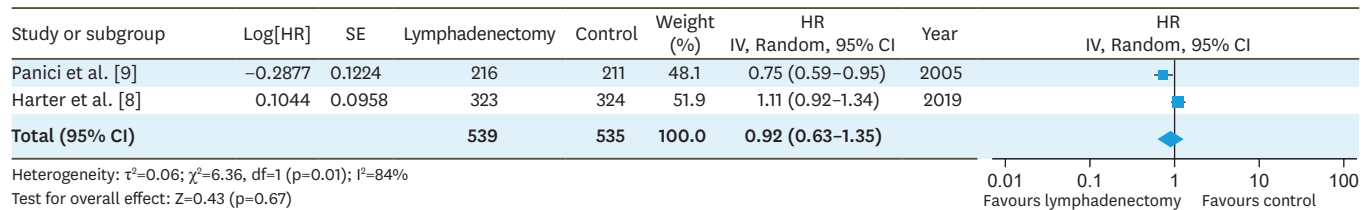
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Ovarian cancer lymphadenectomy meta-analysis

D PFS: RCT + Observational studies



E PFS: RCT



F PFS: Observational studies

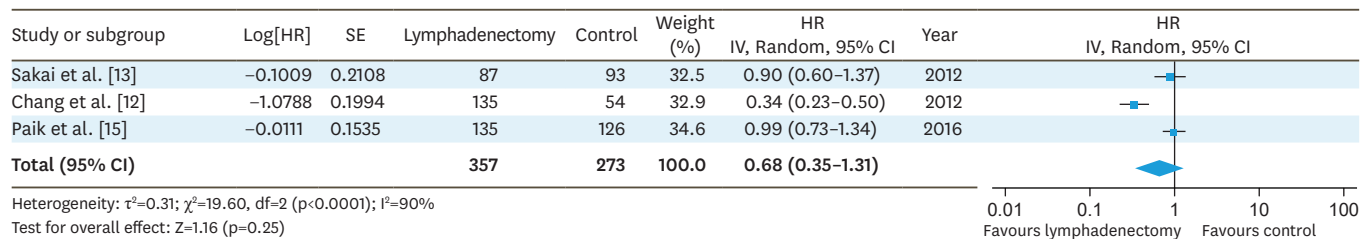


Fig. 3. (Continued) Forest plots for the lymphadenectomy vs. control studies of the OS (A-C) and PFS (D-F) in advanced-stage ovarian cancer. The test for heterogeneity is indicated with the I^2 value.

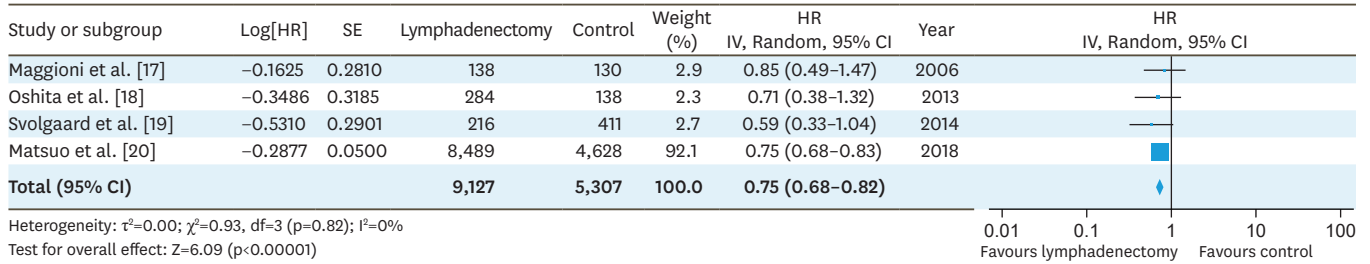
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SE, standard error.

assessed, bulky lymph node dissection was allowed in the control group, and approximately 60% of the cases with lymphadenectomy had residual intraabdominal tumor. The LION study is considered to be a well-designed trial to measure the benefit of lymphadenectomy, because randomization was performed only after complete surgical resection of intraabdominal lesions has been achieved, surgical quality was assured, and cases with only clinically negative lymph node metastasis were included in the study. The trial revealed that 55.7% of the cases in the lymphadenectomy group had lymph node metastasis pathologically, and lymphadenectomy did not provide any survival benefit [8]. This may indicate that adjuvant chemotherapy can eliminate the effect of micro-metastases in the lymph nodes on survival. Meta-analysis of advanced-stage EOC including observational studies showed that lymphadenectomy improved OS (RCT and observational studies: HR=0.80; observational studies: HR=0.74) (Fig. 3A and C). However, a meta-analysis of 2 RCTs revealed that lymphadenectomy did not improve OS (HR=1.02) (Fig. 3B). The heterogeneity of the retrospective studies was low ($I^2=0\%$) (Fig. 3C). The difference between the result of retrospective studies and RCTs may be attributed to several biases, including selection bias for patients with older age, low performance status, or preexisting disorders who did not undergo lymphadenectomy. A meta-analysis of RCTs and observational studies did not reveal a benefit of lymphadenectomy on PFS in advanced-stage EOC (Fig. 3D-F). It is not known

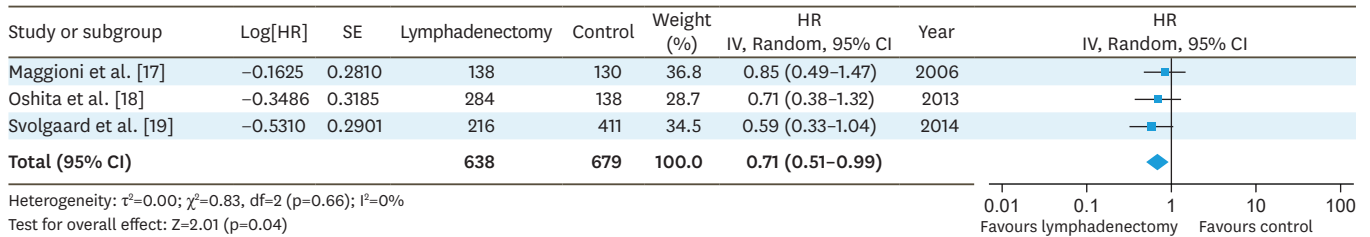
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whether chemotherapy would be effective in the case of grossly apparent lymph node metastasis. At present, removing apparently clinically metastatic lymph nodes may be the most realistic

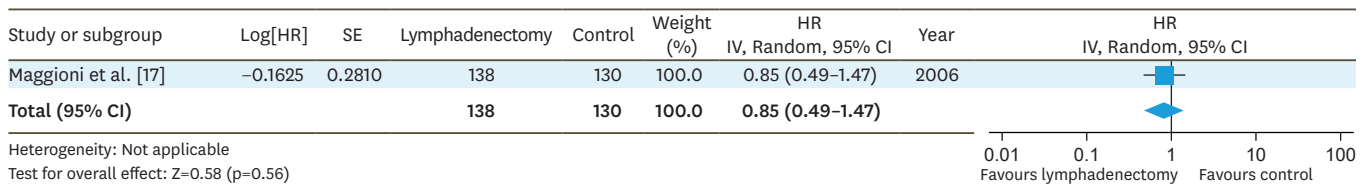
A OS: RCT + Observational studies



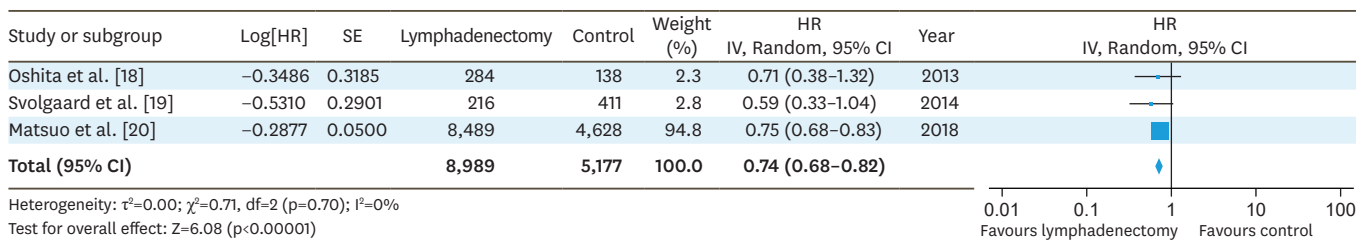
B OS: RCT + Observational studies (without SEER study)



C OS: RCT



D OS: Observational studies



E OS: Observational studies (without SEER study)

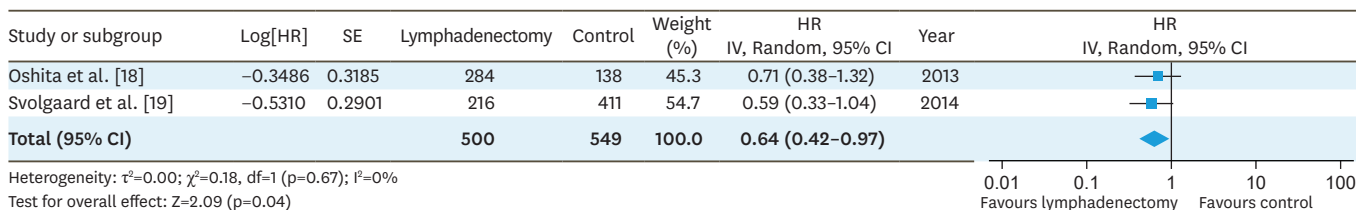


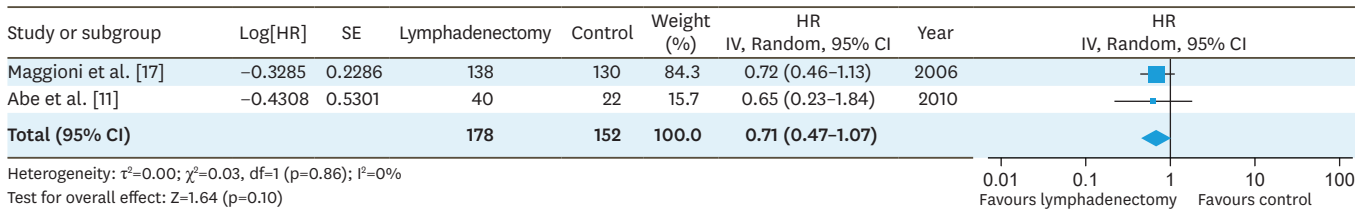
Fig. 4. Forest plots for the lymphadenectomy vs. control studies of the OS (A-E) and PFS (F, G) in early-stage ovarian cancer. The test for heterogeneity is indicated with the I^2 value.

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SE, standard error.

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F PFS: RCT + Observational studies



G PFS: RCT

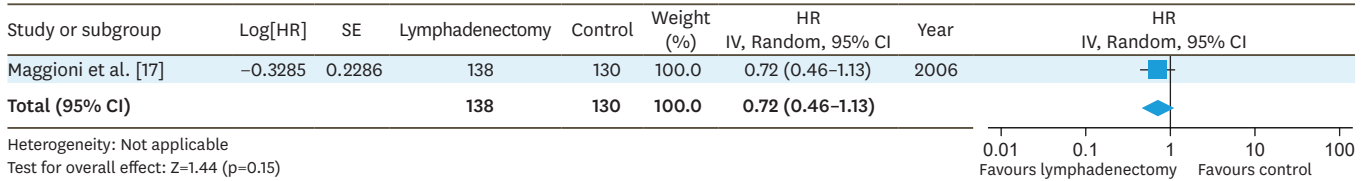
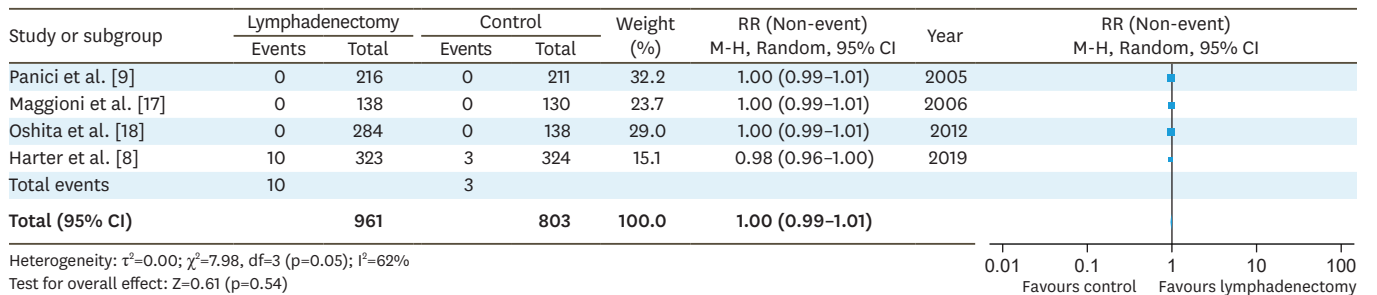


Fig. 4. (Continued) Forest plots for the lymphadenectomy vs. control studies of the OS (A-E) and PFS (F, G) in early-stage ovarian cancer. The test for heterogeneity is indicated with the I^2 value. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SE, standard error.

A Mortality related to surgery



B Blood transfusion

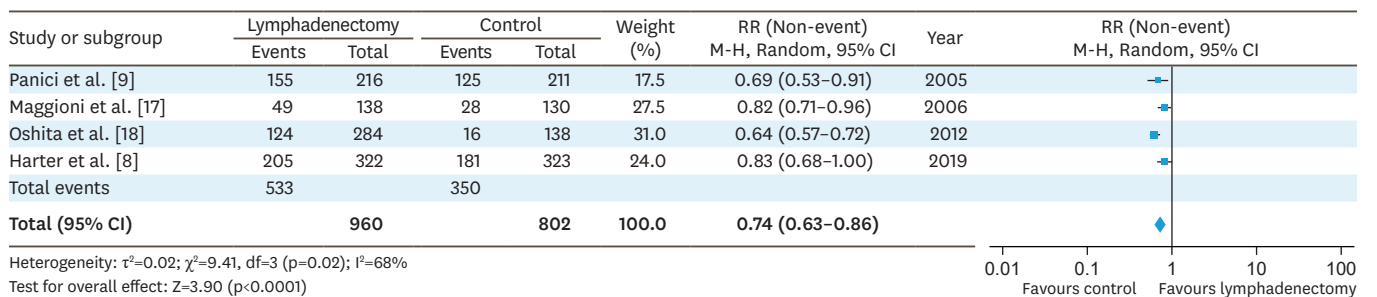


Fig. 5. RR of adverse events. Mortality related to surgery (A) and blood transfusion (B). CI, confidence interval; RR, risk ratio.

approach; however, whether it is necessary to remove grossly apparent metastatic lymph nodes has not been elucidated yet.

In early-stage EOC, lymphadenectomy is believed to be an important procedure to remove micrometastases which may contribute to improved survival and to find cases in which adjuvant chemotherapy can be omitted. In fact, a review of 14 retrospective studies of pT1 or pT2 EOC showed lymph node metastases were found in an average of 14.2% (range 6.1%–29.6%) of

cases, 2.9% in only a pelvic lymph node, 7.1% in only a para-aortic lymph node, and 4.3% in both pelvic and para-aortic lymph nodes [6]. One RCT of early-stage EOC, which did not exhibit any survival benefit to lymphadenectomy, has been criticized for its small number of cases and the allowance of lymph node biopsy in the control group [17]. In that study, 18% of the lymphadenectomy group and 4% of the control group with stage I disease at randomization had lymph node metastasis. Moreover, 31% of the lymphadenectomy group and 20% of the control group with stage II disease had lymph node metastasis. Although many more lymph nodes with metastasis had been removed in the lymphadenectomy group, lymphadenectomy did not exhibit a benefit in either OS or PFS [17]. A meta-analysis of RCTs and observational studies showed that lymphadenectomy improved OS but did not improve PFS in early-stage EOC (**Fig. 4**). The risk of bias of the RCT and observational studies of early-stage EOC ranged from unclear to high (**Fig. 2**). Thus, as suggested by the former meta-analysis [21], the efficacy of lymphadenectomy on survival is still unknown because of the lack of a well-designed RCT in early-stage ovarian cancer. Based on the LION study of advanced-stage EOC [8], the effects of occult lymph node metastasis can be reversed by adjuvant chemotherapy. Thus, it can be said that the main purpose of systematic lymphadenectomy in early-stage EOC is to identify the patients who can avoid adjuvant chemotherapy. Lymphadenectomy can be possibly omitted with improvements in diagnostic imaging or with sentinel lymph node biopsy.

Regarding the histologic subtypes, clear cell ovarian cancer is more chemoresistant than serous histologic-type cancer [22]. The study of Panici et al. [9] includes only 16 cases (3.7%), and the LION trial only includes 14 cases (2.2%) of clear cell histologic type. The SEER database study of early-stage EOC showed that an effective lymphadenectomy was associated with a survival benefit for serous, endometrioid, and clear cell but not for mucinous tumors [20]. In a retrospective cohort study of 240 patients with clear cell ovarian cancer, lymphadenectomy was a strong prognostic factor [23]. Therefore, it may be too early to conclude that lymphadenectomy has no impact on survival for clear cell ovarian cancer. A RCT of adequate clear cell EOC cases is necessary to provide evidence that lymphadenectomy improves the survival of clear cell ovarian cancer patients.

In conclusion, this systematic review and meta-analysis suggest that pelvic and para-aortic lymphadenectomy at PDS has no additional effect on survival and appears to increase the rate of AEs.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Search strategies for the PubMed, Ichushi, and Cochrane Library

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Supplementary Table 2

Characteristics of excluded studies

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Supplementary Fig. 1

The funnel plot for 10 cohorts (9 studies) of advanced-stage ovarian cancer (A) and 5 studies of early-stage ovarian cancer (B).

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Supplementary Fig. 2

Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included RCTs (A) and observational studies (B).

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