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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

Conceptualization: C.T., S.M., S.T., N.S., M.M.; 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: C.T., S.M.; Project administration: C.T., S.M., 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 I² 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 (I²=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;

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Control: <12 resected pelvic LNs Details of ly.									Control: <12 resected pelvic LNs	Details of lymphadenectomy not clear





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 advancedand 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

Study or subgroup		<u>сг</u>	Lymphodonootomy	Control	Weight	HR	Voor		H	3	
study of subgroup	гобіцкі	SE	Lymphadenectomy	Control	(%)	IV, Random, 95% CI	rear		IV, Randon	n, 95% Cl	
Panici et al. [9]	-0.0305	0.1381	216	211	12.5	0.97 (0.74–1.27)	2005		-	-	
du Bois et al. [10] No gross residual	-0.3425	0.1303	387	338	13.3	0.71 (0.55-0.92)	2010				
Abe et al. [11]	-0.0408	0.2936	28	28	4.1	0.96 (0.54-1.71)	2010				
du Bois et al. [10] Residual tumor 1-10 mm	-0.2231	0.0982	223	556	17.5	0.80 (0.66-0.97)	2010		-		
Sakai et al. [13]	-0.1031	0.2505	87	93	5.3	0.90 (0.55-1.47)	2012			_	
Chang et al. [12]	-0.3147	0.2139	135	54	6.9	0.73 (0.48-1.11)	2012			-	
Pereira et al. [14]	-0.6539	0.2979	30	53	4.0	0.52 (0.29-0.93)	2012				
Paik et al. [15]	-0.5276	0.1869	135	126	8.4	0.59 (0.41-0.85)	2016				
Zhou et al. [16]	-0.3243	0.1240	367	521	14.1	0.72 (0.57-0.92)	2018				
Harter et al. [8]	0.0583	0.1248	323	324	14.0	1.06 (0.83-1.35)	2019		-	-	
Total (95% CI)			1,931	2,304	100.0	0.80 (0.70-0.90)			•		
Heterogeneity: τ^2 =0.01; χ^2 =14.0	06, df=9 (p=	0.12); I ² =36	i%					0.01	0.1	1 10	100

Heterogeneity: τ^2 =0.01; χ^2 =14.06, df=9 (p=0.12); I²=36% Test for overall effect: Z=3.52 (p=0.0004)

B OS: RCT

Study or subgroup	Log[HR]	SE	Lymphadenectomy	Control	Weight (%)	HR IV, Random, 95% CI	Year		IV, Ran	HR dom,	95% CI	
Panici et al. [9]	-0.0305	0.1381	216	211	45.0	0.97 (0.74–1.27)	2005			+		
Harter et al. [8]	0.0583	0.1248	323	324	55.0	1.06 (0.83-1.35)	2019			+		
Total (95% CI)			539	535	100.0	1.02 (0.85–1.22)				•		
Heterogeneity: τ^2 =0.00; χ^2 = Test for overall effect: Z=0.2	0.23, df=1 (p=0 20 (p=0.84)	0.63); l ² =0 ⁴	%					0.01 Favours	0.1 ymphadened	1 tomy	10 Favours cont	100 rol

C OS: Observational studies

Otudu ar aubgraup		05	Lumphadanastamu	Control	Weight	HR	Veer	HR	
Study of subgroup	LOG[HK]	SE	Lymphadenectomy	Control	(%)	IV, Random, 95% CI	rear	IV, Random, 95%	o CI
Abe et al. [11]	-0.0408	0.2936	28	28	3.7	0.96 (0.54-1.71)	2010		
du Bois et al. [10] Residual tumor 1-10 mm	-0.2231	0.0982	223	556	32.7	0.80 (0.66-0.97)	2010	-	
du Bois et al. [10] No gross residual	-0.3425	0.1303	387	338	18.6	0.71 (0.55-0.92)	2010	-	
Chang et al. [12]	-0.3147	0.2139	135	54	6.9	0.73 (0.48-1.11)	2012		
Sakai et al. [13]	-0.1031	0.2505	87	93	5.0	0.90 (0.55-1.47)	2012		
Pereira et al. [14]	-0.6539	0.2979	30	53	3.6	0.52 (0.29-0.93)	2012		
Paik et al. [15]	-0.5276	0.1869	135	126	9.0	0.59 (0.41-0.85)	2016		
Zhou et al. [16]	-0.3243	0.1240	367	521	20.5	0.72 (0.57–0.92)	2018	+	
Total (95% CI)			1,392	1,769	100.0	0.74 (0.66-0.82)		•	
Heterogeneity: τ^2 =0.00; χ^2 =5.0 Test for overall effect: Z=5.39 (05, df=7 (p=0 (p<0.00001)	0.65); l ² =0 ⁰	%					0.01 0.1 1 Favours lymphadenectomy Fav	10 100 vours control

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 I² value.

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SE, standard error. (continued to the next page)

^{0.01} 01 1 Favours lymphadenectomy Favours control



D PFS: RCT + Observational studies

	[Weight	HR				HR		
Study or subgroup	LOG[HR]	SE	Lymphadenectomy	Control	(%)	IV, Random, 95% CI	Year		IV, Ra	ndom,	95% CI	
Panici et al. [9]	-0.2877	0.1224	216	211	21.3	0.75 (0.59-0.95)	2005					
Chang et al. [12]	-1.0788	0.1994	135	54	18.4	0.34 (0.23-0.50)	2012		-	-		
Sakai et al. [13]	-0.1009	0.2108	87	93	17.9	0.90 (0.60-1.37)	2012			_		
Paik et al. [15]	-0.0111	0.1535	135	126	20.2	0.99 (0.73-1.34)	2016			-		
Harter et al. [8]	0.1044	0.0958	323	324	22.2	1.11 (0.92–1.34)	2019			-		
Total (95% CI)			896	808	100.0	0.77 (0.54–1.10)						
Heterogeneity: τ^2 =0.14; χ^2 =	=30.87, df=4 (p<0	0.00001);	² =87%					0.01	0.1	1	10	100
Test for overall effect: Z=1.	42 (p=0.16)							Favours	lymphadene	ectomv	Favours con	trol

E PES: RCT

Study or subgroup	Log[HR]	SE	Lymphadenectomy	Control	Weight (%)	HR IV. Random, 95% CI	Year		IV. Ra	HR ndom.	95% CI	
Panici et al. [9]	-0.2877	0.1224	216	211	48.1	0.75 (0.59-0.95)	2005		,			
Harter et al. [8]	0.1044	0.0958	323	324	51.9	1.11 (0.92–1.34)	2019			-		
Total (95% CI)			539	535	100.0	0.92 (0.63-1.35)				•		
Heterogeneity: τ^2 =0.06; χ^2 =0 Test for overall effect: Z=0.4	6.36, df=1 (p=0 3 (p=0.67)	0.01); l²=84	%					0.01 Favours	0.1 lymphadene	1 ectomy	10 Favours contr	100 ol

F PFS: Observational studies

Ctudu ar aubgraup		0.5	Lumanhadanaatamu	Control	Weight	HR	Veer			HR		
study of subgroup	LOG[HK]	SE	Lymphadenectomy	Control	(%)	IV, Random, 95% CI	rear		IV, F	andom,	95% CI	
Sakai et al. [13]	-0.1009	0.2108	87	93	32.5	0.90 (0.60–1.37)	2012					
Chang et al. [12]	-1.0788	0.1994	135	54	32.9	0.34 (0.23-0.50)	2012					
Paik et al. [15]	-0.0111	0.1535	135	126	34.6	0.99 (0.73–1.34)	2016			+		
Total (95% CI)			357	273	100.0	0.68 (0.35–1.31)						
Heterogeneity: τ^2 =0.31; χ^2 = Test for overall effect: Z=1.	19.60, df=2 (p<0 16 (p=0.25)	0.0001); l ^{2,}	=90%					0.01 Favours	0.1 lymphade	1 nectomy	10 Favours cor	100 htrol

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 I² 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



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

Study or subgroup		<u>сг</u>	Lumphadapaatamu	Control	Weight	HR	Voor	HR	
study of subgroup	LOG[HK]	SE	Lymphadenectomy	Control	(%)	IV, Random, 95% CI	rear	IV, Random, 95% CI	
Maggioni et al. [17]	-0.1625	0.2810	138	130	2.9	0.85 (0.49–1.47)	2006	;	
Oshita et al. [18]	-0.3486	0.3185	284	138	2.3	0.71 (0.38-1.32)	2013	3	
Svolgaard et al. [19]	-0.5310	0.2901	216	411	2.7	0.59 (0.33-1.04)	2014	1	
Matsuo et al. [20]	-0.2877	0.0500	8,489	4,628	92.1	0.75 (0.68-0.83)	2018	3	
Total (95% CI)			9,127	5,307	100.0	0.75 (0.68-0.82)		•	
Heterogeneity: τ^2 =0.00; χ^2 =	0.93, df=3 (p=0	0.82); I ² =0	%					0.01 0.1 1 10 1	100
Test for overall effect: Z=6.0	09 (p<0.00001)	1						Favours lymphadenectomy Favours control	

Test for overall effect: Z=6.09 (p<0.00001)

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

Study or subgroup	Log[HR]	SE	Lymphadenectomy	Control	Weight (%)	HR IV, Random, 95% CI	Year		⊢ IV, Rando	IR m, 95% CI	
Maggioni et al. [17]	-0.1625	0.2810	138	130	36.8	0.85 (0.49-1.47)	2006			-	
Oshita et al. [18]	-0.3486	0.3185	284	138	28.7	0.71 (0.38–1.32)	2013			+	
Svolgaard et al. [19]	-0.5310	0.2901	216	411	34.5	0.59 (0.33-1.04)	2014			-	
Total (95% CI)			638	679	100.0	0.71 (0.51–0.99)			•		
Heterogeneity: $\tau^2=0.00$; $\chi^2=0$ Test for overall effect: Z=2.0	0.83, df=2 (p=0 1 (p=0.04)	0.66); l ² =0	%					0.01 Favours	0.1 lymphadenector	1 10 ny Favours cor	100 trol

C OS: RCT

Study or subgroup		\$F	Lymphadenectomy	Control	Weight	HR	Voar			HR		
Study of Subgroup	Log[IIII]	32	Lymphadenectomy	Control	(%)	IV, Random, 95% CI	ieai		IV, Ra	ndom,	95% CI	
Maggioni et al. [17]	-0.1625	0.2810	138	130	100.0	0.85 (0.49-1.47)	2006					
Total (95% CI)			138	130	100.0	0.85 (0.49-1.47)				-		
Heterogeneity: Not applicable Test for overall effect: Z=0.58	e (p=0.56)							0.01 Favours l	0.1 ymphadene	1 ectomy	10 Favours contr	100 rol

D OS: Observational studies

					Weight	HR				HR	
Study or subgroup	Log[HR]	SE	Lymphadenectomy	Control	(%)	IV, Random, 95% CI	Year		IV, Rand	om, 95% CI	
Oshita et al. [18]	-0.3486	0.3185	284	138	2.3	0.71 (0.38-1.32)	2013			•	
Svolgaard et al. [19]	-0.5310	0.2901	216	411	2.8	0.59 (0.33-1.04)	2014			_	
Matsuo et al. [20]	-0.2877	0.0500	8,489	4,628	94.8	0.75 (0.68-0.83)	2018				
Total (95% CI)			8,989	5,177	100.0	0.74 (0.68-0.82)				•	
Heterogeneity: τ^2 =0.00; χ^2 =	=0.71, df=2 (p=0	0.70); l ² =0º	/o					0.01	0.1	1 10	100
Test for overall effect: Z=6.	08 (p<0.00001)	0.0001) Favours lymphadenectomy Fav					omy Favours o	ontrol			

E OS: Observational studies (without SEER study)

Study or subgroup	Log[HR]	SE	Lymphadenectomy	Control	Weight (%)	HR IV, Random, 95% CI	Year		IV, Rand	HR lom, 9	95% CI	
Oshita et al. [18]	-0.3486	0.3185	284	138	45.3	0.71 (0.38-1.32)	2013		_	•+		
Svolgaard et al. [19]	-0.5310	0.2901	216	411	54.7	0.59 (0.33-1.04)	2014			-		
Total (95% CI)			500	549	100.0	0.64 (0.42-0.97)			•			
Heterogeneity: τ²=0.00; χ²=0.18, df=1 (p=0.67); l²=0% Test for overall effect: Z=2.09 (p=0.04)								0.01 Favours	0.1 ymphadenect	1 omy	10 Favours conti	100 ol

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 I² value.

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SE, standard error. (continued to the next page)



F PFS: RCT + Observational studies

Study or subgroup	Log[HR]	SE	Lymphadenectomy	Control	Weight (%)	HR IV, Random, 95% CI	Year		HR IV, Random,	95% CI	
Maggioni et al. [17]	-0.3285	0.2286	138	130	84.3	0.72 (0.46-1.13)	2006		+		
Abe et al. [11]	-0.4308	0.5301	40	22	15.7	0.65 (0.23-1.84)	2010			_	
Total (95% CI)			178	152	100.0	0.71 (0.47–1.07)			•		
Heterogeneity: $\tau^2=0.00$; $\chi^2=0$ Test for overall effect: Z=1.64	.03, df=1 (p=0 (p=0.10)	//o					0.01 Favours lym	0.1 1 phadenectomy	10 Favours cont	100 rol	

G PFS: RCT

Study or subgroup	l og[HB]	SE	Lymphadenectomy	Control	Weight	HR	Vear			HR			
Study of Subgroup	Log[IIII]			controt	(%)	IV, Random, 95% CI	icai		IV, Ra	ndom,	95% CI		
Maggioni et al. [17]	-0.3285	0.2286	138	130	100.0	0.72 (0.46-1.13)	2006			-			
Total (95% CI)			138	130	100.0	0.72 (0.46-1.13)							
Heterogeneity: Not applicable Test for overall effect: Z=1.44 (p=0.15)								0.01 Favours	0.1 lymphadene	1 ectomy	10 Favours co	ontrol	100

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 I² 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

Ctudu or oulogroup	Lymphade	enectomy	Control		Weight	RR (Non-event)	Veer	RR (Non-event)					
study of subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% Cl	rear		RR (Non-event) M-H, Random, 95% CI	CI			
Panici et al. [9]	0	216	0	211	32.2	1.00 (0.99–1.01)	2005			•			
Maggioni et al. [17]	0	138	0	130	23.7	1.00 (0.99–1.01)	2006			+			
Oshita et al. [18]	0	284	0	138	29.0	1.00 (0.99–1.01)	2012			4			
Harter et al. [8]	10	323	3	324	15.1	0.98 (0.96-1.00)	2019						
Total events	10		3										
Total (95% CI)		961		803	100.0	1.00 (0.99–1.01)							
Heterogeneity: τ^2 =0.00; χ^2 =7.98, df=3 (p=0.05); I ² =62% Test for overall effect: Z=0.61 (p=0.54)								0.01 Fa	0.1 vours control	1 Favours lyn	10 1phadei	100 nectomy	

B Blood transfusion

Study or subgroup	Lymphade	enectomy	Control		Weight	RR (Non-event)	Voor	RR (Non-event)					
Study of Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% CI	fear		RR (Non-event) M-H, Random, 95% Cl	% CI			
Panici et al. [9]	155	216	125	211	17.5	0.69 (0.53-0.91)	2005						
Maggioni et al. [17]	49	138	28	130	27.5	0.82 (0.71-0.96)	2006			-			
Oshita et al. [18]	124	284	16	138	31.0	0.64 (0.57-0.72)	2012						
Harter et al. [8]	205	322	181	323	24.0	0.83 (0.68-1.00)	2019			-			
Total events	533		350										
Total (95% CI)		960		802	100.0	0.74 (0.63-0.86)				•			
Heterogeneity: τ ² =0.02; χ ² =9.41, df=3 (p=0.02); I ² =68%								0.01	0.1	1	10	100	
Test for overall effect: Z=3.90 (p<0.0001)								Favours control Favours lymp			lymphader	nectomy	

Fig. 5. RR of adverse events. Mortality related to surgery (A) and blood transfusion (B). Cl, 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).

Click here to view

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