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Original Article

Lymphadenectomy in clinically early epithelial ovarian cancer and survival analysis (LILAC): a Gynecologic Oncology Research Investigators Collaboration (GORILLA-3002) retrospective study

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ABSTRACT

Objective: This study aimed to evaluate the therapeutic role of lymphadenectomy in patients surgically treated for clinically early-stage epithelial ovarian cancer (EOC).
Methods: This retrospective, multicenter study included patients with clinically early-stage EOC based on preoperative abdominal-pelvic computed tomography or magnetic resonance imaging findings between 2007 and 2021. Oncologic outcomes and perioperative complications were compared between the lymphadenectomy and non-lymphadenectomy groups. Independent prognostic factors were determined using Cox regression analysis. Disease-free survival (DFS) was the primary outcome. Overall survival (OS) and perioperative outcomes were the secondary outcomes.
Results: In total, 586 patients (lymphadenectomy group, n=453 [77.3%]; non-lymphadenectomy groups, n=133 [22.7%]) were eligible. After surgical staging, upstaging was identified based on the presence of lymph node metastasis in 14 (3.1%) of 453 patients. No significant difference was found in the 5-year DFS (88.9% vs. 83.4%, p=0.203) and 5-year OS (97.2% vs. 97.7%, p=0.895) between the two groups. Using multivariable analysis, lymphadenectomy was not significantly associated with DFS or OS. However, using subgroup analysis, the lymphadenectomy group with serous histology had higher 5-year DFS rates than did the non-lymphadenectomy group (86.5% vs. 74.4%, p=0.048; adjusted hazard ratio=0.281; 95% confidence interval=0.107–0.735; p=0.010). The lymphadenectomy group had longer operating time (p<0.001), higher estimated blood loss (p<0.001), and higher perioperative complication rate (p=0.004) than did the non-lymphadenectomy group.
Conclusion: In patients with clinically early-stage EOC with serous histology, lymphadenectomy was associated with survival benefits. Considering its potential harm,

JOURNAL OF GYNECOLOGIC ONCOLOGY

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

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lymphadenectomy should be performed according to histologic subtype and subsequent chemotherapy in patients with clinically early-stage EOC.

Trial Registration: Clinical Research Information Service Identifier: KCT0007309

Keywords: Ovarian Epithelial Carcinoma; Lymph Node Excision; Prognosis; Quality of Life

Synopsis

A study comparing the survival rates of patients with early-stage epithelial ovarian cancer with and without lymphadenectomy. The group that underwent lymphadenectomy had a survival advantage in serous histology compared to the group without lymphadenectomy. We suggest performing lymphadenectomy selectively according to histological subtype.

INTRODUCTION

Ovarian cancer is the most lethal gynecologic cancer [1]. In Korea, the age-standardized incidence rate was 7.2 per 100,000 in 2021, making it the third most common gynecologic cancer [2]. Most patients with epithelial ovarian cancer (EOC) were diagnosed with advanced International Federation of Gynecology and Obstetrics (FIGO) stage III/IV, whereas 25% were diagnosed with early-stage EOC [3].

The standard EOC treatment includes surgical resection of all visible tumors and systemic chemotherapy, depending on the stage and risk factors [4]. As part of surgical staging, pelvic and para-aortic lymphadenectomy is performed wherein lymph nodes are resected, and lymph node metastases are identified in a tissue sample. In clinically early-stage EOC diagnosed by preoperative imaging, the mean incidence of true lymph node metastasis after lymphadenectomy was approximately 14.2% (range, 6.1%–29.6%) [5]. Moreover, the lymph node metastasis rate reportedly differed according to the histologic subtype [6]. The frequency of lymph node involvement according to tumor histological subtype was 57% for serous, 13% for mucinous, and 28% for endometrioid tumors [6].

Lymphadenectomy in patients with early-stage EOC has been suggested to completely remove the occult tumor from the lymph node (therapeutic role) and define the disease stage, which influences the choice of systemic chemotherapy (diagnostic role) [7]. However, there are a few retrospective studies on the therapeutic role of lymphadenectomy in patients with early-stage EOC, with inconsistent results [8,9]. The recent phase 3 randomized Lymphadenectomy In Ovarian Neoplasms trial reported no survival benefit of lymphadenectomy in patients with advanced EOC with macroscopically complete resection and clinically negative lymph nodes [10]. Thus, the indication for lymphadenectomy in patients with advanced EOC is clearly rejected. This hypothesis could be adopted for early-stage EOC. In addition, with preoperative imaging modality development [11-16] and technical advances in surgery, research on the latest clinical data is warranted. Therefore, this multicenter retrospective cohort study aimed to evaluate the therapeutic role of lymphadenectomy in patients surgically treated for clinically early-stage EOC.

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JOURNAL OF GYNECOLOGIC ONCOLOGY

METHODS

1. Ethics statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. This multicenter, retrospective cohort study was conducted after obtaining ethical approval and waiver of informed consent from the Institutional Review Boards of 4 tertiary medical institutions: Konkuk University Medical Center (KUMC 2020-10-043), Seoul National University Hospital (2110-169-1266), Seoul National University Bundang Hospital (B-2112-728-401), and Ajou University Hospital (DB-2022-320). In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

2. Study population

From September 2007 to April 2021, the electronic medical records of all eligible patients in participating institutions were reviewed. The eligibility criteria were (**Fig. S1**): previously untreated primary EOC diagnosed with presumed FIGO stages I/II based on radiologic examinations, such as abdominal-pelvic computed tomography (CT) or magnetic resonance imaging (MRI), within 4 weeks before surgery, staging surgery for the treatment of EOC, and adequate performance status (Eastern Cooperative Oncology Group [ECOG] performance status, ≤2). The exclusion criteria were: short follow-up (<3 months); non-EOC; suspicious metastasis to the retroperitoneal lymph nodes or outside the pelvis preoperative imaging diagnosis; distant metastasis suspected by clinical and radiologic examinations or based on intraoperative findings from surgical records; neoadjuvant chemotherapy; and a history of another malignancy or underlying disease that could affect survival.

3. Data collection

Clinicopathologic data including age; ECOG performance status; Charlson Comorbidity Index; preoperative serum cancer antigen 125 (CA125); presumed clinical stage; final FIGO stage based on surgical-pathologic findings; operative time; estimated blood loss (EBL); and perioperative complications were collected from the electronic medical records. Treatment information, including surgery details and adjuvant chemotherapy types, was collected. All treatments were performed at the discretion of the attending physicians following the practice guidelines for ovarian cancer management in Korea [17]. All attending surgeons were gynecologic oncologists accredited by the Korean Society of Gynecologic Oncology. Basic surgical procedures included total abdominal hysterectomy; bilateral salpingo-oophorectomy; cytological evaluation of ascites or peritoneal washing; excision of suspicious peritoneal implants; omentectomy; and pelvic and para-aortic lymphadenectomy. However, completion of all these procedures was not mandatory [17].

Lymphadenectomy involved removal of all suspected and enlarged lymph nodes, including the pelvic and/or para-aortic lymph nodes. All patients who underwent lymphadenectomy, regardless of the number of lymph nodes collected, were allocated to the lymphadenectomy group. Operation time was defined as the time from skin incision to closure. The amount of EBL was determined based on the difference between the blood amount in suction bottles (considering the irrigation used at the surgical site) and the weight of blood-soaked sponges. Adjuvant chemotherapy after surgery in patients with early-stage EOC was considered an option in patients with stage I disease selected based on histological type and cancer substage. Regarding mucinous tumors, grade 1 endometrioid, and low-grade serous cases,

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the benefit of adjuvant systemic therapy has not been demonstrated and observation was optional [18]. The primary endpoint was disease-free survival (DFS). The secondary endpoints were overall survival (OS) and perioperative outcomes. DFS was defined as the period from primary surgery date to first recurrence or censoring date. Furthermore, OS was defined as the period from primary surgery date to death or censoring date.

4. Statistical analysis

Continuous variables were analyzed using the Mann–Whitney U test. Categorical variables were analyzed using the χ^2 test or Fisher's exact test. Propensity score matching was constructed using a multivariate logistic regression model, including variables significantly associated with treatment modality through univariate analysis and variables of significant clinical importance [19]. Inverse probability of treatment weighting (IPTW) used propensity scores to balance baseline patient characteristics in the lymphadenectomy and non-lymphadenectomy groups across patient groups in the analysis [20]. To balance basic clinicopathological factors, we constructed IPTW models. Analysis of survival according to lymphadenectomy before and after IPTW adjustment was performed using the Kaplan-Meier method. Additionally, the log-rank method was used for evaluating significance. A Cox regression model was used for analyzing the prognostic significance of lymphadenectomy. Variables with a p-value of <0.1 from univariable analysis and well-known prognostic variables were fitted into multivariable analysis. Forest plots were used for describing adjusted hazard ratios (HRs) for lymphadenectomy in different subgroups according to age (<65 and ≥65 years), histology (serous, mucinous, and clear cell), stage (I and II), and adjuvant chemotherapy (no and yes). All statistical analyses were performed using R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p<0.05$.

RESULTS

1. Patients

In total, 586 patients met the inclusion criteria: 453 (77.3%) underwent lymphadenectomy and 133 (22.7%) did not (**Fig. S1**). Based on the recommendations by the 2019 European Society of Oncology-European Society of Gynecological Oncology consensus conference, lymphadenectomy was considered the standard surgical staging method for clinically early-stage EOC. Consequently, a substantial cohort of patients underwent this procedure. Adjuvant chemotherapy was administered to 381 (84.1%) and 88 (66.1%) patients in the lymphadenectomy and non-lymphadenectomy groups, respectively. **Table 1** presents the patients' baseline characteristics. The median resected node number in the lymphadenectomy group was 21. Ten or more lymph nodes were harvested in 371 (81.9%) cases. The median preoperative serum CA125 level (64.25 vs. 52.35 U/mL, p=0.009) and histologic grade 2/3 frequency (80.6% vs. 70.7%, p=0.032) were significantly higher in the lymphadenectomy than in the non-lymphadenopathy group. In addition, histologic type and lymphadenectomy were significantly associated (p<0.001). The lymphadenectomy group had a significantly higher proportion of clear cell histology (27.8% vs. 18.0%, p=0.024) and a lower proportion of mucinous histology (15.0% vs. 39.1%, p<0.001) than did the non-lymphadenopathy group. **Table S1** presents the baseline characteristics of patients in the IPTW cohort based on propensity score. Moreover, no significant differences were found between the 2 groups.

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Table 1. Baseline characteristics of enrolled patients and the surgical procedures

Characteristics	Non-lymphadenectomy (n=133)	Lymphadenectomy (n=453)	p
Age (yr)	52 (41.00–62.00)	52 (46.00–58.00)	0.673
Body mass index (kg/m^2)	22.81 (20.68–25.65)	23.19 (20.83–25.34)	0.684
ECOG			0.245
0	124 (93.2)	432 (95.4)	
1	6 (4.5)	18 (4.0)	
2	3 (2.3)	3 (0.7)	
CCI			0.234
0	92 (69.2)	339 (74.8)	
≥1	41 (30.8)	114 (25.2)	
Preoperative serum CA125 (U/mL)	52.35 (20.30–90.03)	64.25 (24.52–214.25)	0.009
BRCA mutation			0.554
Wild	25 (83.3)	135 (87.7)	
BRCA positive	5 (16.7)	19 (12.3)	
Presumed clinical stage*			0.884
I	121 (91.0)	408 (90.1)	
II	12 (9.0)	45 (9.9)	
Final FIGO stage†			0.179
IA	56 (42.1)	131 (28.9)	
IB	3 (2.3)	7 (1.5)	
IC	49 (36.8)	199 (43.9)	
IIA	5 (3.8)	35 (7.7)	
IIB	14 (10.5)	53 (11.7)	
IIIA	3 (2.3)	14 (3.1)	
IIIB	1 (0.8)	5 (1.1)	
IIIC	2 (1.5)	9 (2.0)	
Histologic grade			0.032
1	34 (25.6	77 (17.0)	
2–3	82 (61.7)	319 (70.4)	
Unknown	17 (12.8)	57 (12.6)	
Histologic type			<0.001
Serous	40 (30.1)	154 (34.0)	0.405
Mucinous	52 (39.1)	68 (15.0)	<0.001
Endometrioid	15 (11.3)	78 (17.2)	0.107
Clear cell	24 (18.0)	126 (27.8)	0.024
Miscellaneous	2 (1.5)	27 (6.0)	0.039
Re-staging surgery	16 (12.0)	42 (9.3)	0.408
Surgical procedures			
Hysterectomy	93 (69.9)	400 (88.3)	<0.001
Bilateral salpingo-oophorectomy	110 (82.7)	429 (94.7)	<0.001
Omentectomy	93 (69.9)	404 (89.2)	<0.001
Peritonectomy	34 (25.6)	111 (24.5)	0.820
LND type			
Not done	133 (100)		
PLND only		176 (38.9)	
PALND only		5 (1.1)	
PLND + PALND		272 (60.0)	
Number of harvested LN		21 (1–94)	

Values are presented as median (range) or number (%).
CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LND, lymph node dissection; PALND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection.
*Based on preoperative imaging studies.
†Based on final surgicopathological findings.

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2. Treatments

Table S2 reveals detailed information about the perioperative outcomes and postoperative management. The lymphadenectomy group showed a longer median operation time (200 vs. 135 minutes, p<0.001), higher median EBL (400 vs. 200 mL, p<0.001), more frequent perioperative adverse events (12.1% vs. 3.0%, p=0.004), and higher rate of adjuvant chemotherapy (84.1% vs. 66.2%, p<0.001) than did the non-lymphadenectomy group. Surgical staging resulted in upstaging in 28 patients (6.2%) in the lymphadenectomy group and 6 patients (4.5%) in the non-lymphadenectomy group. Upstaging was based on the finding of lymph node metastasis in 14 patients in the lymphadenectomy group (3.1%). Owing to metastasis to the peritoneum, omentum, and distal site, the stage was upstaged in 3 patients and 1 patient in 10 patients, respectively. In the non-lymphadenectomy group, peritoneum and omentum metastases were confirmed in 3 and 3 patients, respectively.

3. Survival outcomes

At a median follow-up period of 44 months (range, 3–143 months), 42 (9.3%) and 16 (12.0%) patients in the lymphadenectomy and non-lymphadenectomy groups, respectively, had recurrence. In the lymphadenectomy group, recurrence was confirmed in the pelvic cavity (n=19), retroperitoneal lymph node (n=4), and distant sites (n=19). In the non-lymphadenectomy group, recurrence was confirmed in the pelvic cavity (n=5), retroperitoneal lymph node (n=4), and distant sites (n=7). The 5-year DFS rates were 88.9% and 83.4% in the lymphadenectomy and non-lymphadenectomy groups, respectively; the median DFS was comparable (127 vs. 120 months, p=0.203, log-rank test) (**Fig. 1A**). As a result of adjusting for IPTW based on the propensity score, there was no difference in DFS between the lymphadenectomy and non-lymphadenectomy groups (p=0.10) (**Fig. S2A**). **Table 2** summarizes the results of Cox regression analysis of prognostic factors for DFS. Using multivariable analysis, histologic grade 2/3 was significantly associated with poor outcomes (adjusted HR=4.854; 95% confidence interval [CI]=1.084–21.742; p=0.039). After adjusting for age, preoperative serum CA125 level, histologic grade, and stage, no significant between-group difference was found regarding DFS (adjusted HR=0.667; 95% CI=0.326–1.367; p=0.269) (**Table 2**).

During the study period, 10/453 (2.2%) and 3/133 (2.3%) patients expired in the lymphadenectomy and non-lymphadenectomy groups, respectively, with 5-year OS rates of 97.7% and 97.2%, respectively. The median OS was not significantly different between groups

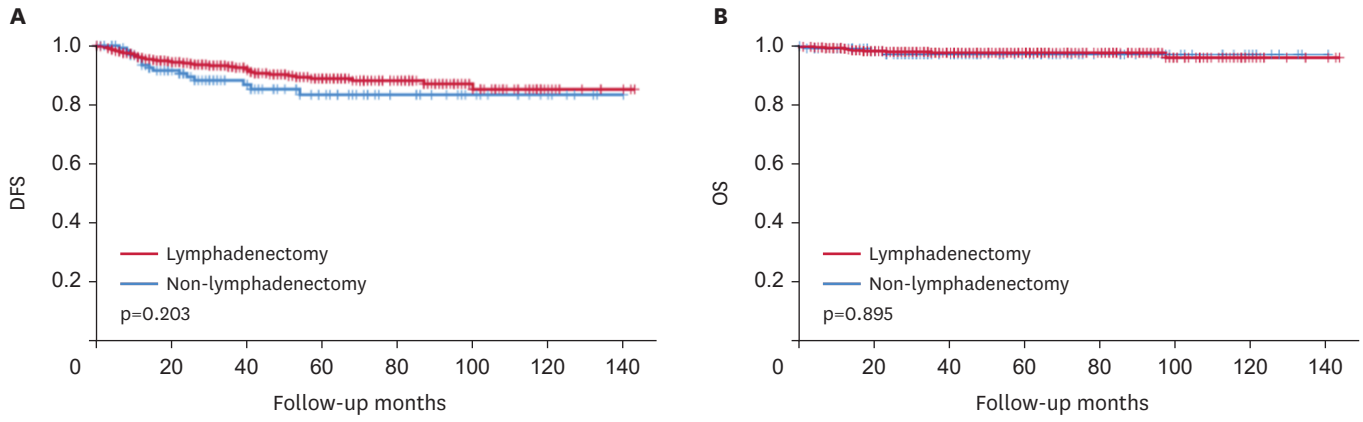

Fig. 1. Survival graph of patients with lymphadenectomy or non-lymphadenectomy. (A) DFS and (B) OS.
DFS, disease-free survival; OS, overall survival.

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Table 2. Cox regression analysis of disease-free survival and overall survival

Variables	Univariable analysis		Multivariable analysis (n=500)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Disease-free survival				
Age (yr)	1.004 (0.983–1.026)	0.703	0.974 (0.945–1.005)	0.101
Body mass index (kg/m²)	0.972 (0.901–1.047)	0.453		
ECOG				
0	1 (ref.)			
1	1.678 (0.524–5.374)	0.383		
2	1.742 (0.241–12.598)	0.583		
CCI				
0	1 (ref.)			
≥1	0.859 (0.471–1.568)	0.622		
Pre-op CA125 (U/mL)	1.000 (1.000–1.000)	0.084	1.000 (1.000–1.000)	0.052
BRCA mutation				
Wild	1 (ref.)			
BRCA mutation	0.637 (0.194–2.091)	0.457		
Histologic grade				
1	1 (ref.)		1 (ref.)	
2–3	4.343 (1.350–13.977)	0.014	4.854 (1.084–21.742)	0.039
Histologic type				
Serous	1 (ref.)		1 (ref.)	
Mucinous	0.721 (0.343–1.514)	0.387	0.711 (0.260–1.943)	0.506
Endometrioid	0.264 (0.079–0.878)	0.030	0.340 (0.099–1.168)	0.087
Clear cell	1.205 (0.667–2.178)	0.536	1.107 (0.550–2.227)	0.776
Miscellaneous	0.266 (0.036–1.974)	0.196	0 (0–Inf)	-
Stage				
I	1 (ref.)		1 (ref.)	
II	1.245 (0.565–2.744)	0.587	1.166 (0.478–2.844)	0.735
Fertility-sparing surgery	0.183 (0.025–1.321)	0.092	0 (0–Inf)	-
Chemotherapy	0.922 (0.488–1.741)	0.802	0.699 (0.270–1.809)	0.461
Lymphadenectomy	0.689 (0.387–1.226)	0.205	0.667 (0.326–1.367)	0.269
Overall survival				
Age (yr)	1.005 (0.960–1.051)	0.843	0.995 (0.948–1.044)	0.826
Body mass index (kg/m²)	0.999 (0.857–1.166)	0.994		
ECOG				
0	1 (ref.)		1 (ref.)	
1	5.287 (1.169–23.919)	0.031	4.532 (0.850–24.169)	0.077
2	0 (0–Inf)	-	0 (0–Inf)	-
CCI				
0	1 (ref.)			
≥1	2.388 (0.803–7.107)	0.118		
Pre-op CA125 (U/mL)	1.000 (0.999–1.001)	0.664	1.000 (0.999–1.001)	0.664
BRCA mutation				
Wild	1 (ref.)			
BRCA positive	0 (0–Inf)	-		
Histologic grade				
1	1 (ref.)			
2–3	0 (0–Inf)	-		
Histologic type				
Serous	1 (ref.)		1 (ref.)	
Mucinous	0.845 (0.211–3.383)	0.812	1.231 (0.247–6.128)	0.800
Endometrioid	0 (0–Inf)	-	0 (0–Inf)	-
Clear cell	0.894 (0.252–3.168)	0.862	1.008 (0.258–3.934)	0.990
Miscellaneous	0 (0–Inf)	-	0 (0–Inf)	-
Stage				
I	1 (ref.)		1 (ref.)	
II	1.565 (0.346–7.084)	0.561	1.641 (0.336–8.014)	0.540
Fertility-sparing surgery	0 (0–Inf)	-		
Chemotherapy	2.978 (0.387–22.909)	0.294	2.949 (0.333–26.105)	0.331
Lymphadenectomy	0.916 (0.252–3.332)	0.895	0.933 (0.234–3.714)	0.922

CA125, cancer antigen 125; CCI, Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

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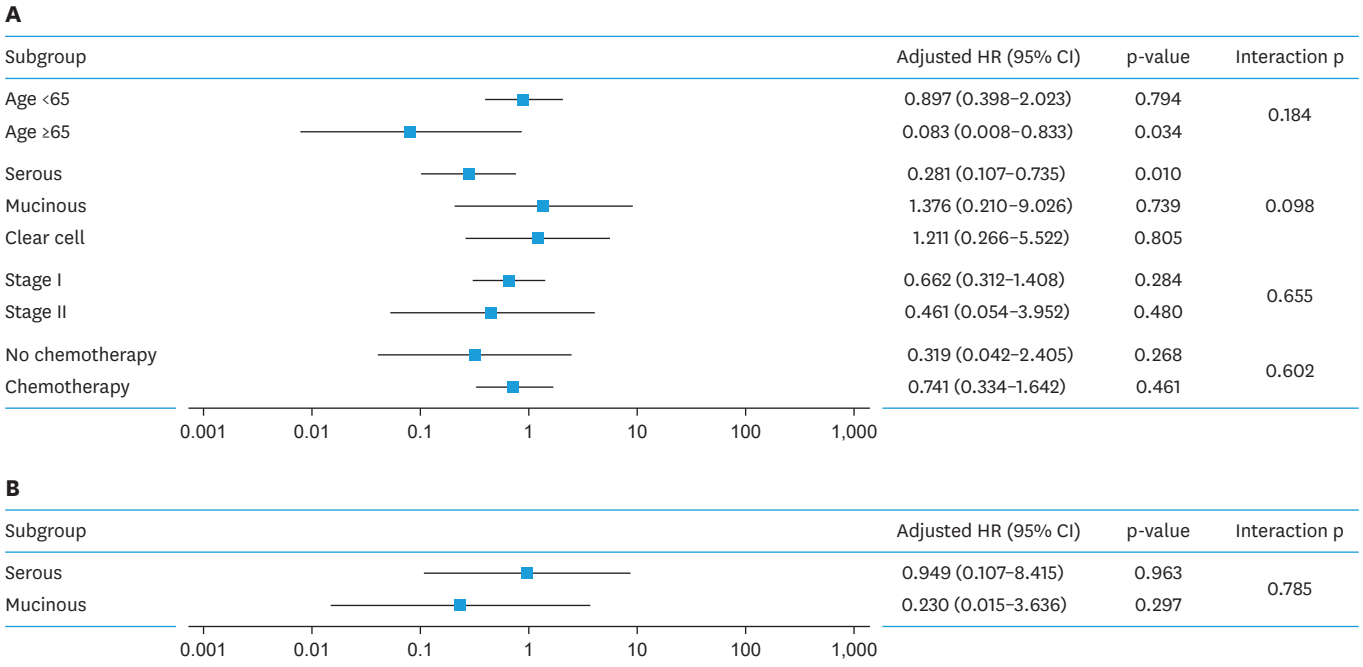

Fig. 2. Subgroup analyses of adjusted HR* for DFS (A) and OS (B) between the lymphadenectomy and non-lymphadenectomy groups according to age, histology, stage, and adjuvant chemotherapy.
CA125, cancer antigen 125; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.
*Adjusted for age, preoperative serum CA125 level, histologic grade, and stage.

(139 vs. 136 months, p=0.895, log-rank test) (**Fig. 1B**). There was no significant difference in OS between the lymphadenectomy and non-lymphadenectomy groups after adjusting for IPTW (p=0.95) (**Fig. S2B**). After adjusting for age, ECOG status, preoperative serum CA125 level, histologic type, and stage, no significant between-group difference was found in OS (adjusted HR=0.933; 95% CI=0.234–3.714; p=0.922).

We sub-analyzed DFS between the 2 groups according to age, histology, stage, and adjuvant chemotherapy. However, lymphadenectomy remained an independent prognostic factor for longer DFS in patients with serous histology (adjusted HR=0.281; 95% CI=0.107–0.735; p=0.010) and those aged 65 years (adjusted HR=0.083; 95% CI=0.008–0.833; p=0.034) (**Fig. 2A**). Subgroup analysis of OS according to age, stage, and adjuvant chemotherapy could not be performed because of the small number of events. Using subgroup analysis by histology, lymphadenectomy was not associated with OS in patients with serous histology or mucinous histology (**Fig. 2B**).

Kaplan–Meier curves for DFS and OS by lymphadenectomy according to histologic type are shown in **Fig. 3**. Among patients with serous histology, those who underwent lymphadenectomy showed better 5-year DFS than did those who did not (86.5% vs. 74.4%, p=0.048) (**Fig. 3A**). However, no significant differences were observed in patients with mucinous (p=0.674) (**Fig. 3B**), endometrioid (p=0.412) (**Fig. 3C**), and clear cell (p=0.894) histologies (**Fig. 3D**). OS was not significantly different between the groups of all histologic types. When the survival rate in the lymphadenectomy group was further stratified according to the presence or absence of lymph node metastasis, the lymph node metastasis group showed worse DFS (p=0.000) and OS (p=0.000) (**Fig. S3**). In the patients, excluding those who were upstaged, the 5-year DFS rates were 90.5% and 85.5% in the lymphadenectomy and

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non-lymphadenectomy groups, respectively (p=0.281, log-rank test) (**Fig. S4A**). In the patients, excluding upstaging cases, the 5-year OS rates were 98.8% and 98.9% in the lymphadenectomy and non-lymphadenectomy groups, respectively (p=0.605, log-rank test) (**Fig. S4B**). In patients who did not receive postoperative chemotherapy, the 5-year DFS rates were 94.6% and 76.7% in the lymphadenectomy and non-lymphadenectomy groups, respectively, suggesting significant improvements in the lymphadenectomy group (p=0.020, log-rank test) (**Fig. S5**). When the survival rate was analyzed according to the removed lymph node number, there

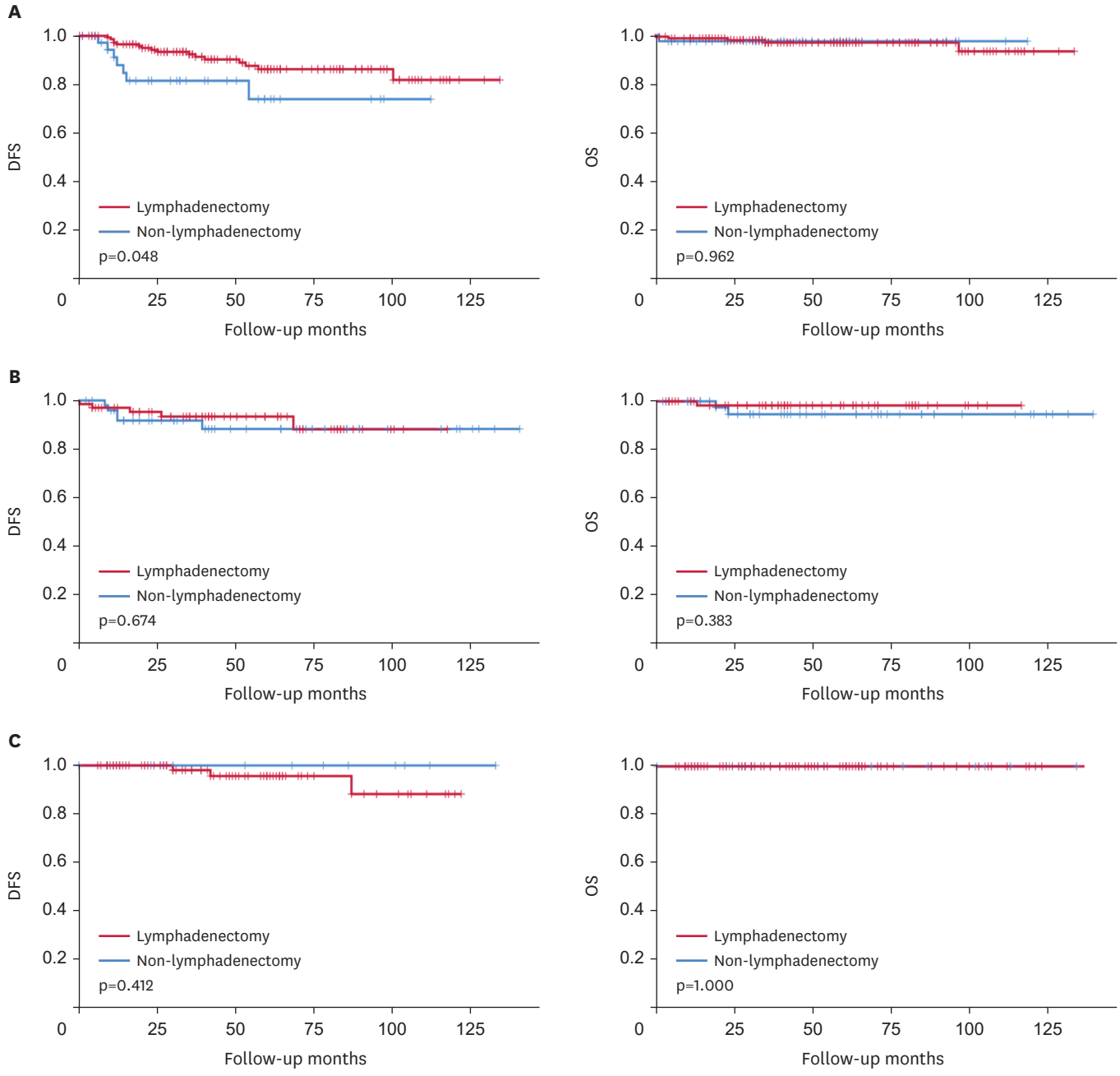

Fig. 3. DFS and OS between the lymphadenectomy and non-lymphadenectomy groups according to histologic subtypes: (A) serous, (B) mucinous, (C) endometrioid, and (D) clear cell.
DFS, disease-free survival; OS, overall survival.

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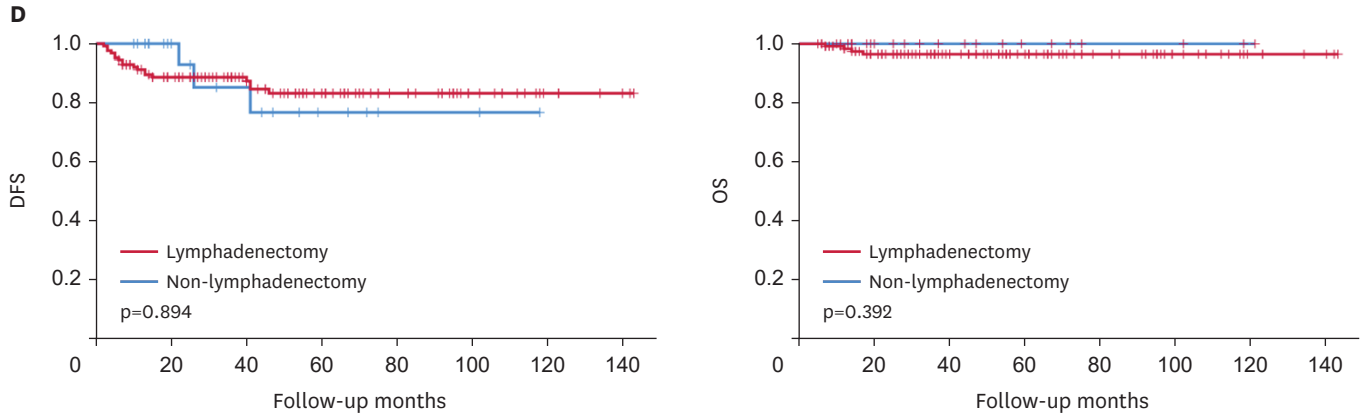

Fig. 3. (Continued) DFS and OS between the lymphadenectomy and non-lymphadenectomy groups according to histologic subtypes: (A) serous, (B) mucinous, (C) endometrioid, and (D) clear cell.
DFS, disease-free survival; OS, overall survival.

was no significant difference in DFS (p=0.233) and OS (p=0.174) between <10 and >10 lymph node groups (**Fig. S6**). We allocated the patients to groups according to whether or not they underwent lymphadenectomy. Furthermore, we compared the survival curves of the patient group that received adjuvant chemotherapy with that of the patient group that did not (Figs. S7 and S8). In the group that underwent lymphadenectomy, there was no significant improvement in survival rate depending on whether chemotherapy was administered. However, the non-lymphadenectomy group, the group that received chemotherapy, tended to experience less recurrence, despite showing no statistical significance.

DISCUSSION

In the present study, lymphadenectomy was not an independent prognostic factor in patients surgically treated for early-stage EOC after adjusting for other well-known prognostic variables. However, the histologic subtype was associated with a survival benefit after lymphadenectomy. Lymphadenectomy resulted in improved DFS in patients with serous ovarian cancer. Considering the potential risk of lymphadenectomy, it should be selectively performed according to the different histologic subtypes and adjuvant chemotherapy in patients with clinically early-stage EOC.

No phase 3 randomized trials have primarily evaluated the therapeutic role of lymphadenectomy in early-stage EOC. Per the recommendations of the 2019 European Society for Medical Oncology–European Society of Gynaecological Oncology consensus conference on ovarian cancer, lymphadenectomy was considered a standard surgical staging method for clinically early-stage EOC. However, the level of evidence was IV (based on retrospective studies), and 22.5% (9/40) experts did not reach a consensus [21]. These findings highlight physicians' concerns regarding the uncertainty of lymphadenectomy in the treatment of early-stage EOC. Although a randomized controlled trial compared the prevalence of lymph node metastasis between lymphadenectomy and non-lymphadenectomy groups in patients with early-stage EOC, survival data were used as secondary endpoints [22]. Although this trial had an imbalance regarding adjuvant chemotherapy and lacked the power to detect clinically meaningful effects of lymphadenectomy, 5-year DFS (71.3% vs. 78.3%) and 5-year OS (81.3% vs. 84.2%) were comparable between the two groups. These results were consistent with ours.

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The lymph node metastasis rate in patients with clinically early-stage EOC varies by histologic subtype [6]. Although the serous histology rate rises above 10% [23], the rate in patients with low-grade endometrioid or mucinous histology is <2% [24,25]. The results of the present study are in the same context, as the lymph node metastasis rates were 5.2% for serous, 4.0% for clear cell, 0% for mucinous, and 1.3% for endometrioid histologies. These findings further indicated that lymphadenectomy did not improve survival in patients with mucinous and endometrioid ovarian cancer. Thus, lymphadenectomy should be used as a diagnostic tool in patients with an elevated risk for lymph node metastases, but not in those with a very low incidence of lymph node metastasis, because it plays a very limited role in determining adjuvant chemotherapy requirements in such cases.

Another suggested function of lymphadenectomy is complete removal of the occult tumor from the lymph node. However, as suggested by the former two meta-analyses [8,26], the effect of lymphadenectomy on survival in patients with clinically early-stage EOC remains unknown. According to the recent phase 3 LION trial, no therapeutic role of lymphadenectomy was confirmed in patients with completely resected advanced EOC treated with adjuvant systemic chemotherapy who had clinically negative lymph node [10]. Based on the results of this study, the effects of occult lymph node metastasis could be reversed by adjuvant chemotherapy. This finding can be extrapolated to early stage EOC. The EORTC-ACTION trial is a phase 3 randomized trial to test the efficacy of adjuvant chemotherapy in patients with early-stage EOC [27]. Regarding observation, patients who were optimally staged had significantly better OS and recurrence-free survival than did those who were non-optimally staged. However, regarding chemotherapy, no such association was observed, indicating that the poor prognosis of non-optimally staged patients could be improved by adjuvant chemotherapy.

Our study also showed similar results. In the subgroup that did not receive adjuvant chemotherapy, although not statistically significant, the lymphadenectomy group (adjusted HR=0.319; 95% CI=0.042–2.405) was favored compared with the non-lymphadenectomy group. However, the effect size (adjusted HR=0.741) was reduced in the subgroup that received adjuvant chemotherapy. In the present study, the adjuvant chemotherapy rates for serous histology in the lymphadenectomy and non-lymphadenectomy groups were 88.3% and 37.5%, respectively, whereas most patients (98.6%) with clear cell histology received adjuvant chemotherapy. This imbalance probably explains the difference in prognosis according to lymphadenectomy for serous, but not clear cell, histology.

Our results did not suggest that routine omission of lymphadenectomy was beneficial in patients with early-stage EOC. Rather, lymphadenectomy should be considered based on the histologic subtype, patient performance, and influence of the results of staging lymphadenectomy for subsequent treatment. Lymphadenectomy has little diagnostic role in high-risk patients for whom adjuvant chemotherapy is planned regardless of information on lymph node metastases. However, lymphadenectomy should be considered for its diagnostic role in patients for whom adjuvant chemotherapy has not yet been determined. Considering these, lymphadenectomy appears to be the most beneficial in patients with early-stage serous ovarian cancer, where it has the potential to impact the choice of stage-adapted adjuvant chemotherapy [28]. If patients are sub-optimally staged during the initial surgery, we can choose restaging with lymphadenectomy followed by tailored adjuvant chemotherapy or blind administration of chemotherapy without staging lymphadenectomy. Although this is a debatable concept, future clinical trials focusing on quality-of-life issues are required

for confirmation. A prospective, randomized, multicenter trial comparing the treatment outcomes of staging surgery with and without lymphadenectomy in patients with stage I and II EOC with indications for adjuvant chemotherapy is ongoing at Sun Yat-sen University Cancer Center [29].

To our knowledge, this is one of the largest studies to evaluate the therapeutic role of lymphadenectomy in patients with clinically early-stage EOC. Moreover, the study period and sites represent recent clinical practice in a real-world setting, with an adequate follow-up period for survival analysis.

The present study has some limitations. First, inherent selection bias owing to the retrospective cohort study design might have existed. Although all consecutive patients with clinically early-stage EOC from four tertiary medical centers were screened, several relevant prognostic factors could have been adjusted to minimize this risk. Unmeasured confounding factors could not have been completely ruled out. Second, the surgical procedure for lymphadenectomy was not as detailed as an a priori protocol, and a quality issue may have existed. Moreover, para-aortic lymphadenectomy was not performed in 38.9% of the patients in the lymphadenectomy group. Therefore, the true lymph node involvement rates might be unclear. The harvested lymph node number is a surrogate marker of lymphadenectomy quality and influences false-negative rates [30]. Adequate dissection of at least 10 lymph nodes is the standard procedure for early-stage EOC staging [31]. In this study, the harvested lymph node number was >10 (81.9%). Thus, the surgical procedure quality was considered appropriate. Third, the mucinous histology subclassification, including expansile and infiltrative types, could not be further considered because of limited information. A recent study reported a distinct pattern of lymph node metastasis according to this classification. The expansile type was associated with rare events of lymph node metastasis and excellent prognosis, whereas the infiltrative type was associated with a higher prevalence (17%) of lymph node metastasis [32]. Nonetheless, it is reasonable that our results were minimally affected by this missing information, considering the very low recurrence or death in cases of mucinous histology, regardless of lymphadenectomy.

Fourth, regarding treatment of ovarian cancer, targeted therapy such as vascular endothelial growth factor (VEGF) inhibitors and poly (ADP-ribose) polymerase inhibitors (PARPi) may affect survival rates. A subgroup analysis of the GOG 218 showed that bevacizumab maintenance improved progression-free survival (PFS) in patients with ascites [33] and in those with stage IV disease (43 vs. 33 months, HR=0.75; 95% CI=0.59–0.95) [34]. In addition, in a subgroup of the ICON7 study, bevacizumab maintenance treatment reported an improvement in PFS in women at high risk of progression (stage 3 with residual disease greater than 1.0 cm at the end of surgery, inoperable stage 3 or 4) [35]. In the lymphadenectomy group included in this study, upstage cases were stage 3 or higher 28/453 (6.1%). Among these, there were very few high-risk cases that could be administered VEGF inhibitors as a high-risk group. Therefore, it is expected that there will be very few cases that could benefit from VEGF inhibitors. Additionally, this study mainly comprised a cohort before PARPi was clinically applied as front-line maintenance, with few patients receiving PARPi, the effect of PARPi was expected to be minimal.

Considering the potential risk of lymphadenectomy, it should be selectively performed based on the histologic subtype, patient's medical condition, and influence of the results of lymphadenectomy on adjuvant chemotherapy. To verify this hypothesis, well-designed randomized trials are warranted. Concurrently, our results may be useful for counseling

patients and deciding the addition of lymphadenectomy for early-stage EOC cases during initial staging as well as restaging in clinical practice.

In conclusion, this large-scale retrospective multicenter cohort study showed that lymphadenectomy was not associated with a survival benefit in patients surgically treated for clinically early-stage EOC, after adjusting for prognostic variables. However, for a serous histology, lymphadenectomy may have a survival benefit from stage-adapted adjuvant chemotherapy, not from surgical excision of lymph nodes per se.

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SUPPLEMENTARY MATERIALS

Table S1
Baseline characteristics after inverse probability treatment weighting

Table S2
Perioperative outcomes and postoperative treatments

Fig. S1
Flowchart of the study population.

Fig. S2
DFS and OS in patients with lymphadenectomy or non-lymphadenectomy after IPTW. (A) DFS and (B) OS.

Fig. S3
DFS and OS according to presence or absence of metastases in the lymphadenectomy group. (A) DFS and (B) OS.

Fig. S4
DFS and OS in patients who underwent lymphadenectomy or non-lymphadenectomy, excluding upstaging cases. (A) DFS and (B) OS.

Fig. S5
DFS and OS after lymphadenectomy or non-lymphadenectomy in patients who did not receive chemotherapy. (A) DFS and (B) OS.

Fig. S6
DFS and OS between the lymphadenectomy and non-lymphadenectomy groups according to the number of harvested lymph nodes. (A) DFS and (B) OS.

Fig. S7
DFS and OS in patients who underwent lymphadenectomy with or without chemotherapy. (A) DFS and (B) OS.

Fig. S8

DFS and OS in patients without lymphadenectomy with or without chemotherapy. (A) DFS and (B) OS.

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