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## Original Article

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# The impact of lymph node dissection on survival in patients with clinical early-stage ovarian cancer

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## ABSTRACT

**Objective:** To estimate the impact of lymph node dissection on survival in patients with apparent early-stage epithelial ovarian cancer (EOC).

**Methods:** We conducted a retrospective review of patients with clinical stage I–II EOC. All patients underwent primary surgery at Sun Yat-sen University Cancer Center between January 2003 and December 2015. Demographic features and clinicopathological information as well as perioperative adverse events were investigated, and survival analyses were performed.

**Results:** A total of 400 ovarian cancer patients were enrolled, and patients were divided into 2 groups: 81 patients did not undergo lymph node resection (group A), and 319 patients underwent lymph node dissection (group B). In group B, the median number of removed nodes per patient was 25 (21 pelvic and 4 para-aortic nodes). In groups A and B, respectively, the 5-year progression-free survival (PFS) rates were 83.3% and 82.1% (p=0.305), and the 5-year overall survival (OS) rates were 93.1% and 90.9% (p=0.645). The recurrence rate in the retroperitoneal lymph nodes was not associated with lymph node dissection (p=0.121). The median operating time was markedly longer in group B than in group A (220 minutes vs. 155 minutes, p<0.001), and group B had a significantly higher incidence of lymph cysts at discharge (32.9% vs. 0.0%, p<0.001).

**Conclusion:** In patients with early-stage ovarian cancer, lymph node dissection was not associated with a gain in OS or PFS and was associated with an increased incidence of perioperative adverse events.

**Keywords:** Lymph Node Dissection; Ovarian Cancer; Survival

## INTRODUCTION

Epithelial ovarian cancer (EOC) causes the most fatalities of any gynecological cancer [1]. Although ovarian cancer is usually diagnosed at an advanced stage, approximately 30% of patients present at an early stage [1,2].

The standard surgery for early-stage ovarian cancer is comprehensive staging surgery that includes systematic pelvic and para-aortic lymphadenectomy. The value of lymphadenectomy is primarily to define the stage accurately, which will have clinical implications for future

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

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adjuvant management. By the International Federation of Gynecology and Obstetrics (FIGO) classification (2014), patients who are initially presumed to have early-stage disease (clinical stage I or II) but have histologically proven positive nodes are upstaged to IIIA. Previous studies found that the rate of affected lymph nodes in patients with apparent early-stage ovarian cancer was 5.1%–20% [3-6], resulting in at least 80% overtreatment. Systematic pelvic and para-aortic lymphadenectomy is challenging and might be associated with a high risk of both intraoperative and postoperative adverse events [7].

The Lymphadenectomy in Ovarian Neoplasms (LION) trial demonstrated that systematic pelvic and para-aortic lymphadenectomy was not associated with longer survival in patients with advanced ovarian cancer who had undergone intra-abdominal macroscopically complete resection and had normal lymph nodes both before and during surgery [8]. However, the survival value of lymph node dissection in early-stage ovarian cancer patients is not clear. Although a few retrospective studies have analyzed the association between lymphadenectomy and survival in early-stage ovarian cancer patients, no consensus has been reached due to the inconsistent results of different studies [9-12]. Moreover, the only prospective randomized study that examined the potential therapeutic value of systematic lymphadenectomy in apparent early ovarian cancer did not have the statistical power to detect a difference in survival due to the low number of cases [13].

In this study, we aimed to estimate the impact of lymph node dissection on survival and perioperative adverse events in women diagnosed with clinical stage I and II EOC.

## MATERIALS AND METHODS

### 1. Patient population

A retrospective review of 429 patients with clinical stage I–II primary EOC who underwent primary surgery at Sun Yat-sen University Cancer Center between January 2003 and December 2015 was conducted. Inclusion criteria were: (a) primary diagnosis of EOC clinical stage I–II; (b) received comprehensive staging surgery or restaging surgery with or without lymph node dissection; (c) diagnosed with new FIGO stage I–IIIA1 after surgery. The intra-peritoneal staging surgery included peritoneal washing (or peritoneal fluid) cytology, hysterectomy, bilateral salpingo-oophorectomy, omentectomy and suspicious peritoneal biopsy; fertility-sparing patients preserved uterus and one ovary. All patients received imaging (plain and enhanced computer tomography/magnetic resonance scan of abdomen and pelvic, or whole body positron emission tomography/computer tomography) before surgery, patients who had suspicious pelvic or paraaortic nodes at preoperative imaging evaluation, were excluded. Twenty-nine patients who were lost to follow-up or had missing details regarding surgery or pathological assessment were excluded from the study. The remaining 400 patients were eligible for analysis in the study. None of the patients had residual tumors after surgery. After surgery, adjuvant chemotherapy was carried out in most cases (89.8%, 359/400), with a median of 4 cycles (range 1–8); the exceptions were those with both FIGO stage IA and grade 1 status and those who refused adjuvant chemotherapy. Information on demographics, clinicopathological features, treatment, survival, and perioperative adverse events was analyzed and reported. The study protocol conformed to the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (GZR2019-220). Written informed consent was obtained from each patient before treatment.

### 2. Patient groups

Patients were divided into 2 groups according to whether lymph node dissection was performed. Eighty-one patients underwent surgery with no lymph node resection (group A), and 319 patients underwent lymph node dissection (group B). In group B, 289 patients underwent systematic lymphadenectomy, and 30 patients underwent lymph node sampling alone. Group B was subdivided according to the number of lymph nodes removed, with 25 (the median number of nodes resected) serving as the cutoff; the 2 subgroups were defined as ≤25 and >25. Additionally, patients were grouped according to the regions where lymph node dissection was performed: either the pelvic region only or both the pelvic and para-aortic regions.

### 3. Statistical analysis

Various clinical and pathological factors were compared using Pearson $\chi^2$ tests for categorical data and independent-sample t-tests for normally distributed continuous data. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. Prognostic factors were compared using the log-rank test for univariate analysis and Cox proportional-hazards modeling for multivariable analyses. A 2-tailed p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, NY, USA) and the R statistical package (R software version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria) [14].

## RESULTS

### 1. Patient characteristics

The median age of the patients was 47 years (range 17–85), the median PFS was 62 months, and the median OS was 69 months. The median follow-up duration was 69 months (range 4–195). The demographic and pathological characteristics are shown in **Table 1**. Lymph node dissection was significantly correlated with histological grade (p<0.001), histological type (p<0.001), fertility sparing (p=0.02) and time period of surgery (p<0.001). The rates of clear cell histology and grade 3 were significantly higher in group B than in group A. The rate of fertility-sparing surgery was higher in group A than in group B. Over the 3 time periods of the study (2003–2006, 2007–2010, and 2011–2015), the percentage of women receiving lymph node dissection increased from 30.6% to 87.9% to 95.7%, respectively.

Adjuvant chemotherapy was administered to 70 (86.4%) group A patients and 289 (90.6%) group B patients. There was no correlation between lymph node dissection and chemotherapy (p=0.268). The most common chemotherapy regimens were platinum+paclitaxel (194/359; 54.0%), platinum+liposomal paclitaxel (64/359; 17.8%) and platinum+docetaxel (60/359; 16.7%). Forty-one patients (11.5%) received other platinum-based chemotherapy, such as cisplatin+bleomycin+cyclophosphamide.

### 2. Analysis of prognosis

In group B, the median number of nodes resected was 25 (range 1–64), comprising 21 in the pelvic region and 4 in the para-aortic region. Ten (3.1%) patients had lymph node metastasis, of which 6 patients had metastatic nodes in the pelvic region only, 3 in the para-aortic region only, and one in both regions. There was no difference in lymph node metastasis according to stage, histological grade or histological subtype in group B patients.

**Table 1.** Characteristics of the patients grouped by treatment modality

| Characteristics | Total | Group A | Group B | p-value |
|---|---|---|---|---|
| Age (yr) | | | | 0.955 |
|    Median (range) | | 47 (20–85) | 47 (17–76) | |
| Presumed stage | | | | 0.768 |
|    IA | 93 | 23 (28.4) | 70 (21.9) | |
|    IB | 9 | 1 (1.2) | 8 (2.6) | |
|    IC | 164 | 31 (38.3) | 133 (41.6) | |
|    IIA | 27 | 3 (3.7) | 24 (7.6) | |
|    IIB | 107 | 23 (28.4) | 84 (26.3) | |
| Histological grade | | | | <0.001 |
|    1 | 85 | 28 (34.6) | 57 (17.9) | |
|    2 | 100 | 21 (25.9) | 79 (24.8) | |
|    3 | 193 | 21 (25.9) | 172 (53.9) | |
|    Unclassified | 22 | 11 (13.6) | 11 (3.4) | |
| Histological type | | | | <0.001 |
|    Serous | 166 | 37 (45.7) | 129 (40.4) | |
|    Mucinous | 60 | 20 (24.7) | 40 (12.5) | |
|    Clear cell | 63 | 3 (3.7) | 60 (18.8) | |
|    Endometrioid | 65 | 8 (9.9) | 57 (17.9) | |
|    Other* | 46 | 13 (16.0) | 33 (10.4) | |
| Surgery | | | | 0.022 |
|    Standard surgery | 366 | 69 (85.2) | 297 (93.1) | |
|    Fertility-sparing surgery | 34 | 12 (14.8) | 22 (6.9) | |
| Time period | | | | <0.001 |
|    2003–2006 | 85 | 59 (72.8) | 26 (8.2) | |
|    2007–2010 | 107 | 13 (16.1) | 94 (29.4) | |
|    2011–2015 | 208 | 9 (11.1) | 199 (62.4) | |

Values are presented as number (%).
*Included: malignant brenner tumour, seromucinous carcinoma, undifferentiated carcinoma and unclassified epithelial carcinoma.

On Kaplan-Meier analysis, no significant differences in PFS (p=0.305) or OS (p=0.645) were observed between the treatment groups (**Fig. 1**). The 5-year PFS rates were 83.3% and 82.1% in group A and group B, respectively. The 5-year OS rates were 93.1% and 90.9% in group A and group B, respectively. In group B, the number of removed lymph nodes (fewer than 25 or 25, more than 25) had no significant relationship with survival. The location of
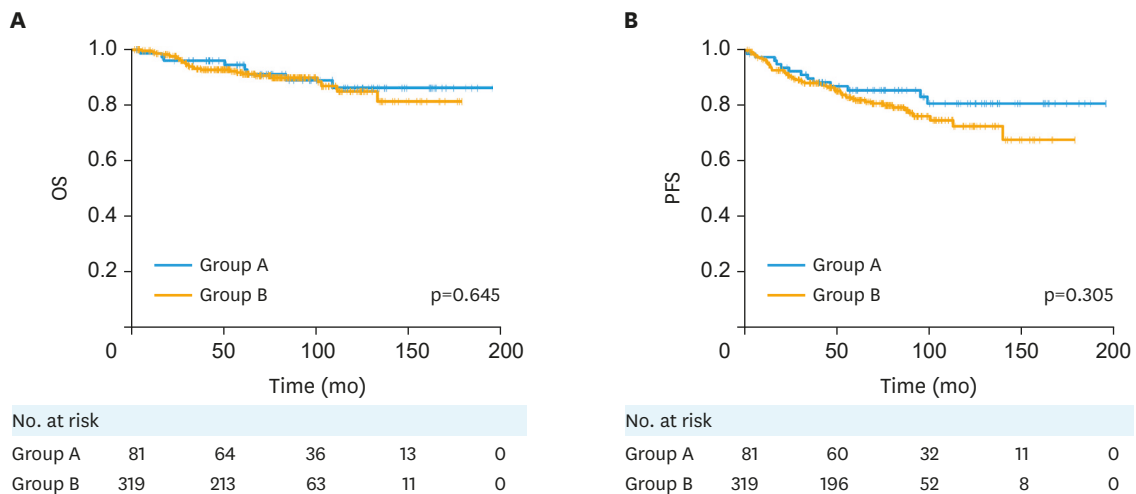


**Fig. 1.** Kaplan-Meier analysis of OS (A) and PFS (B) according to treatment modality.
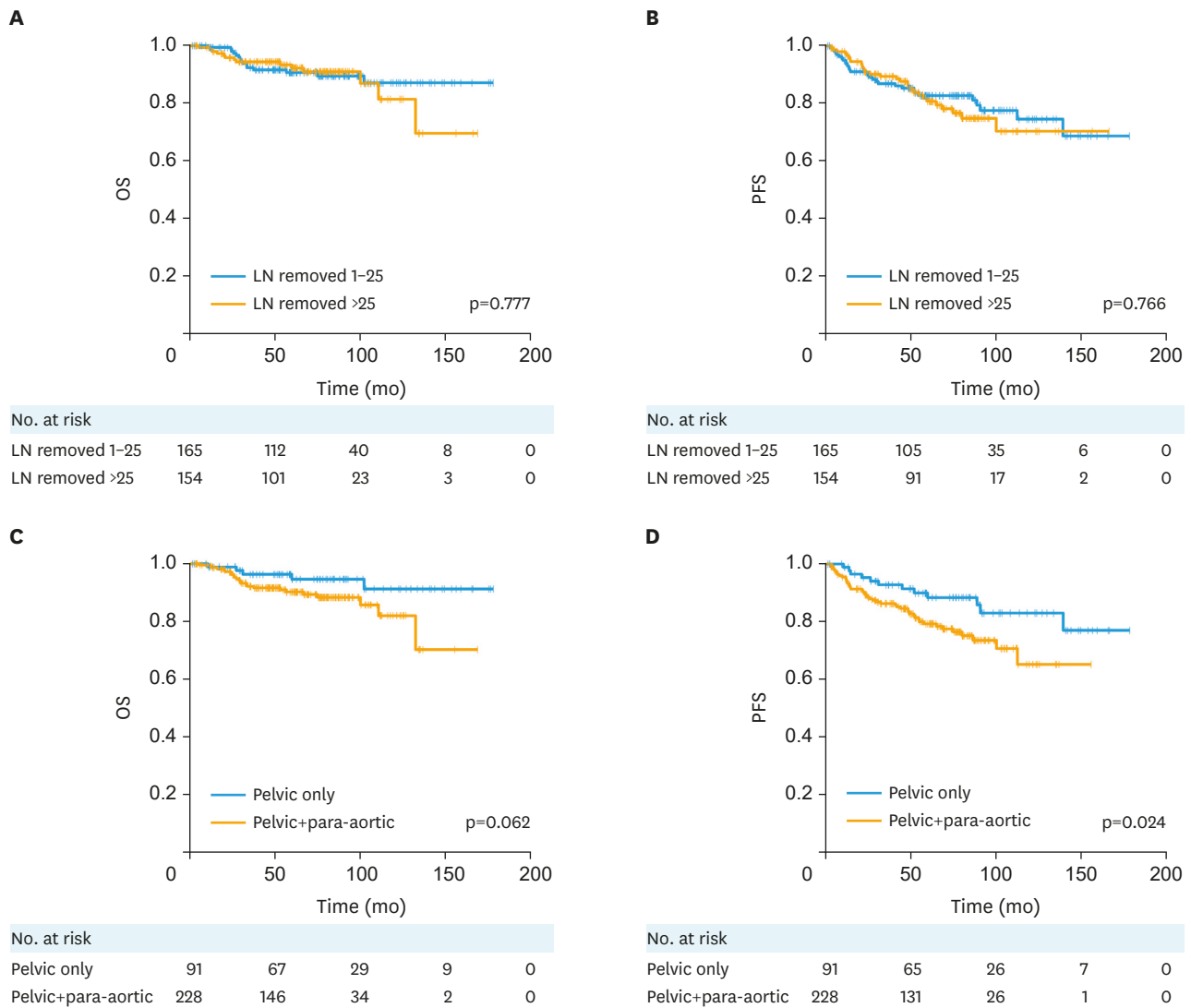OS, overall survival; PFS, progression-free survival.

**Fig. 2.** Kaplan-Meier analysis of OS (A) and PFS (B) in patients who underwent LND, grouped according to the number of LNs removed. Kaplan-Meier analysis of OS (C) and PFS (D) in patients who underwent LND, grouped according to location from which LNs were removed.
LN, lymph node; LND, lymph node dissection; OS, overall survival; PFS, progression-free survival.

node resection (pelvic region only or pelvic+para-aortic regions) was associated with PFS in univariate analysis (p=0.024) (**Fig. 2**).

On multivariable analysis, lymph node metastasis, advanced stage, and high grade were significant independent prognostic factors for poor PFS. The results showed that lymph node dissection was not a prognostic factor (hazard ratio=0.01; 95% confidence interval=0.01–1.12; p=0.931); additionally, the extent and location of node resection were not prognostic factors (**Table 2**).

Tumors recurred in 69 patients: 13 in group A and 56 in group B. The primary sites of disease recurrence are summarized in **Supplementary Table 1**. There were no significant differences in sites of recurrence between the 2 groups. The most common sites were the pelvis and the abdominal cavity. Recurrence in retroperitoneal lymph nodes occurred in 3 cases in group A and 22 cases in group B, despite the resection of some lymph nodes in group B.

**Table 2.** Univariate and multivariate analyses for factors associated with PFS

| Characteristics | No. (%) | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Age | | | | | |
| ≤Median | 206/400 (51.5) | 1.00 | | 1.00 | |
| >Median | 194/400 (48.5) | 1.58 (0.99–2.53) | 0.055 | 1.34 (0.81–2.22) | 0.249 |
| Stage | | | | | |
| I | 266/400 (66.5) | 1.00 | | 1.00 | |
| II | 134/400 (33.5) | 2.98 (1.86–4.76) | <0.001 | 2.33 (1.37–3.98) | 0.002 |
| Histological grade | | | | | |
| 1 | 85/400 (21.3) | 1.00 | | 1.00 | |
| 2 | 100/400 (25.0) | 2.00 (0.82–4.87) | 0.125 | 1.71 (0.67–4.42) | 0.265 |
| 3 | 193/400 (48.3) | 3.66 (1.65–8.12) | 0.001 | 2.65 (1.05–6.66) | 0.038 |
| Histological type | | | | | |
| Serous | 166/400 (41.5) | 1.00 | | 1.00 | |
| Mucinous | 60/400 (15.0) | 0.48 (0.20–1.14) | 0.094 | 1.29 (0.47–3.59) | 0.622 |
| Clear cell | 63/400 (15.8) | 0.71 (0.33–1.54) | 0.389 | 0.81 (0.36–1.87) | 0.629 |
| Endometrioid | 65/400 (16.3) | 0.66 (0.32–1.37) | 0.259 | 0.88 (0.38–2.03) | 0.766 |
| Other | 46/400 (11.4) | 1.40 (0.74–2.64) | 0.300 | 1.42 (0.74–2.73) | 0.297 |
| Lymphadenectomy | | | | | |
| No | 81/400 (20.3) | 1.00 | | 1.00 | |
| Yes | 319/400 (79.7) | 1.46 (0.80–2.67) | 0.222 | 0.01 (0.01–1.12) | 0.931 |
| Number of nodes resected | | | | | |
| 0 | 81/400 (20.3) | 1.00 | | 1.00 | |
| ≤25 | 165/400 (41.3) | 1.39 (0.72–2.66) | 0.328 | 2.14 (0.01–12.80) | 0.916 |
| >25 | 154/400 (38.4) | 1.55 (0.80–3.00) | 0.197 | 1.69 (0.01–10.07) | 0.918 |
| Region of lymphadenectomy | | | | | |
| Pelvic only | 101/319 (31.7) | 1.00 | | 1.00 | |
| Pelvic+para-aortic | 218/319 (68.3) | 2.18 (1.15–4.13) | 0.017 | 0.52 (0.07–4.05) | 0.532 |
| Lymph node metastasis | | | | | |
| Negative | 309/319 (96.8) | 1.00 | | 1.00 | |
| Positive | 10/319 (3.2) | 3.15 (1.15–8.66) | 0.026 | 3.11 (1.09–8.86) | 0.033 |

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

The recurrence rate in the retroperitoneal lymph nodes was not associated with lymph node dissection (p=0.121).

### 3. Analysis of perioperative adverse events

**Table 3** shows the impact of lymph node dissection on surgical parameters such as median operative time, the volume of blood loss, median length of hospitalization and proportion of patients undergoing blood transfusions. The median operative time was significantly longer in group B than in group A (220 minutes vs. 155 minutes, p<0.001). In 297 patients who had available data from the assessment of lymphatic cysts, we found that group B had a significantly higher prevalence of lymphatic cysts at discharge than group A (32.9% [76 of 231] vs. 0.0% [0 of 66], p<0.001). There was no significant intergroup difference in the volume of blood loss, median length of hospitalization or proportion of patients undergoing blood transfusions.

**Table 3.** Surgical parameters according to treatment modality

| Variables | Group A (n=81) | Group B (n=319) | p-value |
|---|---|---|---|
| Operating time (min) | 155 (70–330) | 220 (75–480) | <0.001 |
| Blood loss (mL) | 150 (20–350) | 200 (10–1,600) | 0.690 |
| Patients receiving transfusions (%) | 14 (17.3) | 41 (12.9) | 0.301 |
| Hospital stay (day) | 14 (6–32) | 13 (6–43) | 0.637 |

Values are presented as median (range) or number (%).

# DISCUSSION

Lymphatic metastasis and lymphadenectomy have been the most analyzed issues in EOC during the last 2 decades [15,16]. The present study investigated the outcomes in women with apparent early-stage EOC who underwent primary surgery with or without lymph node dissection at a single center. We found that patients with apparent early-stage EOC did not benefit from lymph node dissection. In contrast, lymph node dissection significantly extended operative time and increased the incidence of lymph cysts. Moreover, we showed that the extent of node resection (fewer than 25 or 25, and more than 25) also had no effect on survival. The location of lymph node dissection (pelvic region only or pelvic+para-aortic regions) was associated with PFS in univariate analysis (p=0.024) but not in multivariable analysis (p=0.532). Our data also showed no difference between the treatment groups concerning the recurrence rate in the retroperitoneal lymph nodes.

There are 3 meta-analyses in the literature that report the effect of lymphadenectomy on survival [17-19]. In the first 2 of these meta-analyses [18,19], lymphadenectomy was shown to increase 5-year patient OS in advanced-stage cancer but not early-stage cancer. More recently, Ercelep et al. [9] conducted a retrospective analysis to estimate the impact of lymphadenectomy on survival in EOC and reported that systematic lymphadenectomy had no effect on either PFS or OS in clinical stage I–II patients; they also found no correlation between the number of lymph nodes removed and the number of metastatic lymph nodes. Using the Surveillance, Epidemiology, and End Results database, Cheng et al. [20] showed that the number of removed lymph nodes was not significantly associated with survival prognosis in apparent early-stage ovarian cancer patients. Similarly, we observed no significant differences in survival or recurrence between the treatment groups. **Table 4** shows the comparison of current study and previous studies analyzed the association between lymphadenectomy and survival in early-stage EOC.

There are several possible reasons for the lack of significant survival benefits from lymphadenectomy. First, the rate of lymph node metastasis in early-stage ovarian cancer was low in our study; we found a rate of only 3.1%, which was lower than in other reports [6]. Second, although lymphadenectomy can remove latent microscopic lymphatic metastasis, this practice makes only a minor contribution compared to platinum-based adjuvant chemotherapy.

**Table 4.** Comparison of current study and previous studies analyzed the association between lymphadenectomy and survival in early-stage EOC

| Author | Year | Study design | FIGO stage | Group | No. of patients | No. of resected lymph nodes | Results |
|---|---|---|---|---|---|---|---|
| Present study | - | Retrospective | IA–IIIA1 | LND | 391 | Median 25 (range 1–64) | Negative |
| | | | | No-LND | 81 | | |
| Cheng et al. [20] | 2020 | Based on SEER database | IA–IIIA1 | LND | 3,459 | NA | Negative |
| | | | | No-LND | 1,086 | | |
| Ercelep et al. [9] | 2019 | Retrospective | I–II | LND | 100 | NA | Negative |
| | | | | No-LND | 77 | | |
| Oshita et al. [10] | 2013 | Retrospective | I–II | LA | 284 | Median 34 (10th–90th percentile: 20–52) | Negative |
| | | | | No-LA | 138 | | |
| Abe et al. [11] | 2010 | Retrospective | IA–IIIA1 | LA | 40 | Mean 66 (range 9–80) | Positive |
| | | | | No-LA | 22 | | |
| Chan et al. [12] | 2007 | Based on SEER database | I | LND | 2,862 | Median 9 (range 1–84) | Positive |
| | | | | No-LND | 3,824 | | |
| Maggioni et al. [13] | 2006 | RCT | I–II | LA | 138 | Median 47 (25th–75th percentile: 33–65) | Underpower* |
| | | | | Sampling | 130 | Median 5.5 (25th–75th percentile: 0–12) | |

Negative: There were no significant differences between the treatment groups for PFS or OS; Positive: Lymphadenectomy was associated with better PFS and OS.
EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; LA, lymphadenectomy; LND, lymph node dissection; NA, not available; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results.
*The study did not have the statistical power to detect a difference in survival due to the low number of cases.

In our study, adjuvant chemotherapy was carried out in most cases (89.8%, 359/400) after surgery, and all the regimens were based on platinum. Third, retroperitoneal surgery would have an impact on the postoperative course and long-term complications [8]. Moreover, previous studies suggested that lymph node metastasis had an indolent evolution [20].

Several retrospective and prospective studies found that systematic lymphadenectomy increased surgical morbidity [8,13,21-24]. The data from the LION trial showed that the addition of open lymphadenectomy to a debulking surgery had a significant effect on the median duration of surgery, median blood loss, the percentage of patients receiving transfusions or fresh-frozen plasma and the percentage of patients admitted postoperatively to an intermediate or intensive care unit, all in favor of the non-lymphadenectomy group. The lymphadenectomy group also had higher rates of infections treated with antibiotics, lymphatic cysts at discharge, symptomatic cysts, and repeat laparotomies for complications, as well as a significantly higher 60-day mortality [8]. Another prospective randomized study, which examined the potential therapeutic value of systematic lymphadenectomy in presumed early ovarian cancer, also found that systematic lymphadenectomy had a significant impact on surgical parameters such as median operative time, blood loss, and proportion of patients undergoing blood transfusions [13]. Indeed, we observed a significantly extended operation time in patients who underwent lymph node dissection, and postoperative lymphatic cysts were also observed only in the lymph node dissection group.

One of the strengths of this study is the fact that this is a large single-center study evaluating the effect of lymph node dissection on survival on stage I–II ovarian cancer. However, the current study has a number of limitations because it is a retrospective survey. On the one hand, in our study, patients who underwent lymph node dissection had higher rates of clear cell histology, grade 3 cancer, and fertility-sparing surgery than those who did not have lymph node dissection. Surgeons were more likely to perform lymph node dissection in patients with high grade cancer and clear cell cancer which considered as poorly differentiated carcinoma and tended to avoid lymphadenectomy in unmarried young patients; the survival data may have been affected by these patient characteristics. Moreover, the surgical strategy regarding lymphadenectomy changed with time period, most (88.9%, 72/81) surgeries without lymph node dissection were performed before 2010, and 72.8% (59/81) before 2007. Because in our center, the administration criteria for lymph node dissection in early-stage EOC was not unified before 2010, especially before 2007. After 2010, the procedure of complete staging surgery in early-stage EOC was standardized according clinical guidelines, the unified surgical procedure included completing exploration of abdomen and pelvic cavity, peritoneal washing (or peritoneal fluid) cytological examination, hysterectomy, bilateral salpingo-oophorectomy (preservation of uterus and one ovary for fertility-sparing patients), omentectomy, peritoneal biopsy and systematic pelvic and para-aortic lymphadenectomy up to the level of the renal vessel or inferior mesenteric artery. On the other hand, the extent of lymph node dissection was variant; some clinicians performed lymph node sampling alone or resected lymph node only in pelvic region. Even the quality of a systematic lymphadenectomy may be slightly different depending on the gynecologist who performed the surgery and the number of resected nodes can hardly indicate the quality of the lymphadenectomy, as nodal counts may depend on various factors, such as comprehensiveness of pathological analysis, surgical expertise, and anatomical variants among patients.

In summary, our study suggested that lymph node dissection in patients with early-stage ovarian cancer was associated with a higher incidence of perioperative adverse events and was

not associated with longer OS or PFS compared with no lymph node resection. Therefore, we conclude that lymph node dissection may not have therapeutic value in patients with early-stage EOC. However, this study had limited power because of its retrospective nature. In the future, a large-scale, prospective randomized study may provide clearer answers.

## SUPPLEMENTARY MATERIAL

### Supplementary Table 1
Sites of recurrence according to treatment modality

**Click here to view**

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