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Survival impact of number of removed para-aortic lymph nodes in stage I epithelial ovarian cancer

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Abstract

Purpose The survival effect of presence or absence of lymphadenectomy in early-stage epithelial ovarian cancer (EOC) was priorly shown but the effect of number of removed lymph nodes kept in background. We aimed to evaluate the survival impact of number of removed lymph nodes and their localizations in stage I EOC.

Methods This study included 182 patients. The best cut-off levels for number of pelvic and para-aortic lymph nodes (PaLN) were 24 and 10, respectively. Univariate and multivariate survival analyses were performed for these cut-offs and other prognostic factors.

Results The median age of the patients was 49. The median number of removed pelvic and paraartic lymph nodes were 29 and 9, respectively. The median overall (OS) and progression-free survival (PFS) were 67 and 50 months, respectively. The 5-year OS rate was 89.6%. Recurrence occured in 24 (19.5%) patients. In univariate analyses tumor grade (p: 0.005), pelvic LN number (p: 0.041) and PaLN number (p: 0.004) were the factors that were significantly associated with PFS. Tumor grade and PaLN number were independently and significantly associated with PFS in multivariate analyses (p: 0.015 and p: 0.017, respectively). In OS analyses, age, tumor grade, presence of LVI, number of pelvic and PaLNs were the significantly associated factors ($p < 0.05$ for all). In multivariate analyses, age and PaLN number were independently and significantly associated with OS (p: 0.011 and p: 0.021, respectively).

Conclusions The number and localizations of removed lymph nodes may have a survival affect in stage I EOC. We also think that this study may constitute a kernel point for larger prospective series on lymph node number and lymphatic regions.

Keywords Early stage · Epithelial ovarian cancer · Lymph node number · Lymphadenectomy · Survival

Introduction

Lymphadenectomy is an important part of epithelial ovarian cancer (EOC) surgery because the lymph node status directly affects the prognosis and management. The role of lymphadenectomy in early-stage EOC surgery has been a longstanding discussion whether it is to stage the disease or has a survival effect itself. There are studies supporting both. It was reported that lymph node metastasis even in clinical stage Ia is about 6% [1], and about 14% in apparent early-stage EOC [2, 3]. This spread pattern which occurs out of vision, constitutes the back-up "adequate lymphadenectomy" and "identifying the occult metastases" concepts in the management of apparent early-stage EOC. Moreover, the positive survival effect of lymphadenectomy in apparent early-stage EOC was proven by multiple studies [4, 5]. Matsuo et al. showed that lymphadenectomy resulted in a reduction of

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cause specific mortality in apparent early-stage EOC [6]. In another recent study, Zhou et al. [7] presented remarkable results that in case of no gross residual tumor, higher number of removed lymph nodes was associated with a statistically significant lower mortality in women with advanced stage EOC. However, this effect was not priorly shown in early stage and it keeps in background whether number of collected lymph nodes and lymphadenectomy regions have a prognostic effect in women with negative node status. Starting with this point of view, we aimed to evaluate the survival impact of number of removed lymph nodes and their localizations (pelvic and para-aortic) in stage I EOC.

Materials and methods

This is a retrospective study which was conducted at Başkent University Ankara Hospital, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology in accordance with the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board (KA21/95).

We included 182 patients who underwent comprehensive surgical staging and diagnosed with stage I EOC between March 2007 and September 2019. Standard surgery included total hysterectomy, bilateral salphingooophorectomy (BSO), infracolic/total omentectomy, appendectomy and bilateral pelvic and paraaortic lymph node dissection. For fertility sparing surgery (FSS) approach, the uterus and at least one of the ovaries were preserved, and omentectomy, appendectomy and bilateral pelvic and paraaortic lymph node dissection were performed. Paraaortic lymph node dissection was performed up to the renal vessels [8].

Patients with suspicion of ovarian cancer (postmenopausal mass, high Ca125 levels, presence of ascites, or suspicion in ultrasonography or MRI) were detected with thorax and whole abdominal computed tomography for evaluation of any distant, regional or lymphatic metastases. Lymphadenectomy was performed as a part of comprehensive surgical staging in all patients independently of the lymph node status in the pre-operative imaging results.

The stage of the disease was determined according to the FIGO 2014 classification system. Grade 1 tumor was defined as low grade and grade 2, 3 and clear cell histology was defined as high grade. Capsule integrity was determined as histopathologic tumor presence on the ovarian surface.

The decision about adjuvant chemotherapy was made individually according to the tumor grade, lymphovascular space invasion (LVSI), histology and capsule integrity. In selected patients (stage Ia and grade1 tumor), chemotherapy was avoided and all other patients received standard chemotherapy. The standard primary chemotherapy regimen included paclitaxel 175 mg/m^2 plus carboplatin dosed at an area under curve of 5 or 6 every 21 days for six cycles.

Patient data including age, gravidity, parity, histopathological results, and chemotherapy were obtained from the hospital database. All histopathological results were reviewed by the co-author pathologist.

Recurrence was diagnosed clinically (due to radiologic findings and/or CA-125 rise) or with histopathological evaluation of the suspicious lesion (excisional or guided biopsy). Diagnosis of recurrences was obtained from the patient records and progression free survival (PFS) analyses were performed in patients who continued their regular visits till the start of the study. Women with irregular follow-up and unknown recurrence status were excluded from PFS analyses. The final statuses of the patients were obtained from national social security database and overall survival (OS) analyses were performed for all patients.

Statistical analyses were performed using the statistical software package SPSS version 22.0 (SPSS, Inc. Chicago, IL). The data were expressed as median and range for continuous variables. Binary variables were reported as counts and percentages. A receiver operating characteristic (ROC) curve was used to assess the discriminative role of lymph node number (pelvic and para-aortic) on survival and area under the curve (AUC) was found significant for paraaortic lymph node (Pa-LN) numbers for OS and PFS and the best cut-off was 10 nodes (Fig. 1). ROC analysis was not significant for pelvic lymph node number and the best cut-off for number of pelvic lymph nodes for survival analyses was found as 24. The effect of pelvic and Pa-LN numbers were evaluated separately with both univariate and multivariate analyses. Kaplan–Meier and Cox regression analysis were used to analyze survival. Chi-square test was used to evaluate the association between risk factors for lymph node involvement (LNI) and number of Pa-LN numbers. The level of statistical significance was set at $p < 0.05$.

Results

The median age of the 182 patients included in the study was 49 (range 21–84). The most frequent histological types were endometrioid ($n = 50$, 27.5%), serous ($n = 47$, 25.8%), and clear cell ($n = 41$, 22.5%). Forty-one (22.5%) patients had high grade serous histology. The median number of removed pelvic and para-aortic lymph nodes were 29 (range 7–71) and 9 (range 0–33), respectively. The median PFS was 50 months (range 6–164) and the median OS was 67 months (range 13–164). The 5-year overall survival rate was 89.6%, and 19 (10.4%) patients died of disease. Twenty-four (19.5%) patients had recurrent disease. Chemotherapy was administered for 132 (72.3%) patients. Median hospital stay and chemotherapy start day were 6 days and 14 days,

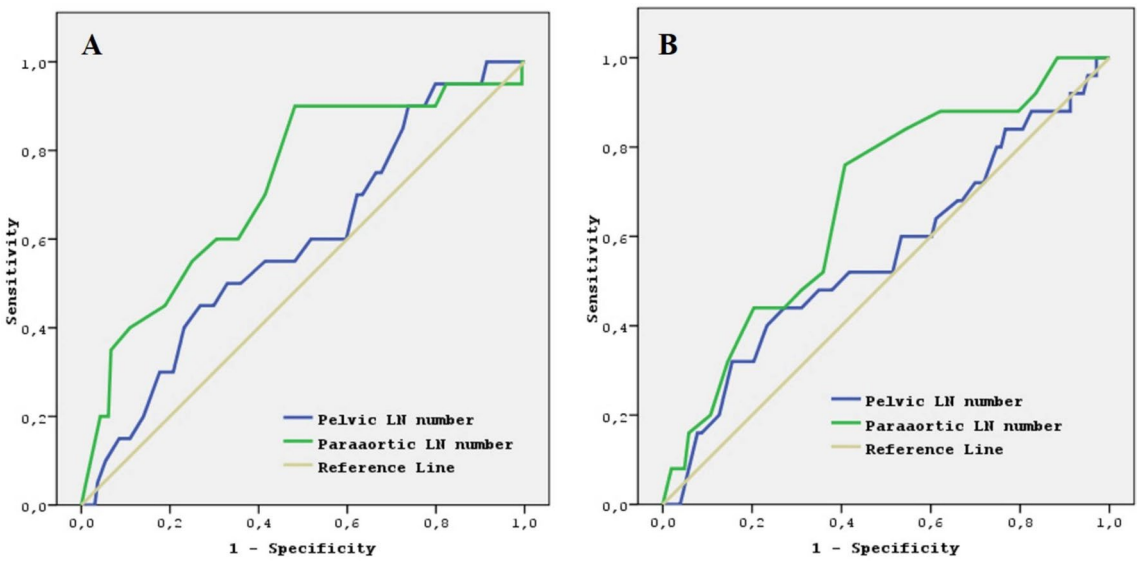

Fig. 1 Receiver operating characteristic (ROC) curve analysis of OS (**A**) and PFS (**B**). AUC was found significant for paraaortic lymph node numbers. AUC and *p* values and for OS: Pelvic (59.1%, *p*: 0.184), para-aortic (72.0%, *p*: 0.001). AUC and *p* values and for PFS: Pelvic (55.9%, *p*: 0.363), para-aortic (67.6.0%, *p*: 0.007)

Table 1 Clinical and surgical characteristics

	Mean ± std dev	Median (range)
Age (mean-range)	48.6 ± 1.0	49 (21–84)
Gravidity	2.0 ± 0.2	2 (0–8)
Parity	1.7 ± 0.2	2 (0–8)
Max. tumor diameter (cm)	10.9 ± 0.5	10.0 (0.5–33.0)
Total LN number	40.2 ± 1.0	38 (11–81)
Pelvic LN number	30.9 ± 0.9	29 (7–71)
Para-aotic LN number	9.4 ± 0.5	9 (0–33)
OS (months)	72.8 ± 2.9	67 (13–164)
PFS (months)	59.2 ± 3.4	50 (6–164)
Hospital stay (days)	6.9 ± 0.4	6 (3–20)
Chemotherapy start day	15.6 ± 1.1	14 (5–54)
	n	%
Death	19	10.4
Recurrence	24	13.2
Chemotherapy	132	72.5
Fertility sparing surgery	29	15.9

respectively. The general characteristics of patients were summarized in (Tables 1 and 2).

In univariate analyses, tumor grade ($p = 0.005$), pelvic LN number ($p = 0.041$) and PaLN number ($p = 0.004$) were the factors those were significantly associated with 5-year PFS. The number of pelvic lymph nodes was associated with a longer 5-year OS whereas this was not statistically significant in multivariate analyses. Tumor grade and PaLN number were independently and significantly associated with 5-year PFS [Hazard ratio (HR): 2.45, 95% Confidence

Table 2 Histopathological characteristics of patients

	n	%
Stage		
1a	88	48.4
1b	8	4.4
1c	86	47.3
Histology		
Serous	47	25.8
Mucinous	32	17.6
Endometrioid	50	27.5
Clear Cell	41	22.5
Mixed	12	6.6
Grade*		
Low	55	30.2
High	127	69.8
Capsule ıntegrity		
Intact	114	62.6
Not Intatct	68	37.4
LVI**		
Present	30	16.5
Absent	152	83.5
Tumor site		
Unilateral	163	89.6
Bilateral	19	10.4

*Low grade: grade 1, high grade: grade 2, 3 and clear cell

***LVI* Lymphovascular Invasion

Interval (CI): 1.18–5.08, $p = 0.015$ and HR 1.75, 95% CI 1.10–2.79, $p = 0.017$, respectively]. Patients who received and did not receive chemotherapy had similar estimated median PFS (51 (range 6–164) vs. 44 (range 10–126) months). The PFS analyses were shown in (Table 3).

In univariate analyses, age, tumor grade, presence of LVSI, pelvic and Pa LN numbers were significantly associated with 5-year OS ($p < 0.05$ for all). In multivariate analyses, age and Pa LN number were independently and significantly associated with 5-year OS (HR 1.84, 95% CI 1.14–2.96, $p = 0.011$ and HR 2.39, 95% CI 1.14–5.03, $p = 0.021$, respectively). Patients who received chemotherapy had similar estimated median OS when compared to who did not (68 (range 16–147) vs. 67 (range 13–164) months). The overall survival rate in patients who underwent FSS was 93.1% (27/29). The OS analyses were summarized in (Table 4).

Patient groups according to the removed para-aortic lymph node numbers had similar histology, grade, capsule integrity, bilaterality and LVSI rates ($p > 0.05$ for all) (Table 5).

When the women were grouped according to the number of total lymph nodes harvested, the hospital stay was similar between patients with < 40 nodes harvested and those

Table 3 Progression free survival—univariate and multivariate analyses

	Univariate analyses				Multivariate analyses			
	Months (estimate)	95% CI		*p*	HR	95% CI		*p*
Age (year)								
< 60	134.9 ± 6.1	122.9	147.0	**0.668**				
≥ 60	108.5 ± 13.6	81.9	135.1					
Pelvic LN number								
< 24	78.1 ± 7.6	63.1	93.1	**0.041**				**0.067**
≥ 24	140.4 ± 6.0	128.6	152.2					
PaLN number								
< 10	97.0 ± 7.4	82.6	111.5	**0.004**	1.75	1.10	2.79	**0.017**
≥ 10	149.6 ± 5.6	138.6	160.6					
Histology								
Serous	122.3 ± 12.4	97.9	146.6	**0.340**				
Others	134.2 ± 5.8	122.8	145.7					
Grade								
Low	156.4 ± 5.2	146.2	166.7	**0.005**	2.45	1.18	5.08	**0.015**
High	118.6 ± 7.5	103.8	133.4					
Capsule int								
Intact	136.6 ± 6.9	123.1	150.1	**0.386**				
Not intact	106.5 ± 7.4	91.9	121.2					
LVI								
Present	89.6 ± 7.9	74.0	105.3	**0.783**				
Absent	134.1 ± 6.1	122.1	146.2					
Tumor site								
Unilateral	136.1 ± 5.6	125.0	147.1	**0.319**				
Bilateral	112.1 ± 19.4	74.1	150.1					
Surgery								
Standard	118.4 ± 5.5	107.6	129.2	**0.793**				
FSS***	130.3 ± 13.3	104.2	156.3					
Chemotherapy								
Absent	122.1 ± 3.8	114.7	129.6	**0.023**				
Present	126.0 ± 6.8	112.6	139.5					

Bold values indicate the level of statistical significance $p < 0.05$

*Low grade: grade 1, high grade: grade 2, 3 and clear cell

***LVI* Lymphovascular Invasion

****FSS* Fertility Sparing Surgery

Table 4 Overall survival—univariate and multivariate analyses

	Univariate analyses				Multivariate analyses			
	Months (estimate)	95% CI		*p*	HR	95% CI		*p*
Age (years)								
< 60	152.3 ± 3.5	145.3	159.3	**0.001**	1.84	1.14	2.96	**0.011**
≥ 60	112.7 ± 9.0	94.9	130.4					
Pelvic LN number								
< 24	132.9 ± 9.4	114.5	151.5	**0.018**				**0.144**
≥ 24	151.4 ± 3.8	144.0	158.8					
PaLN number								
< 10	136.4 ± 5.9	124.6	148.1	**0.001**	2.39	1.14	5.03	**0.021**
≥ 10	159.4 ± 3.1	153.2	165.6					
Histology								
Serous	143.8 ± 7.5	128.9	158.6	**0.815**				
Others	147.9 ± 4.1	139.7	156.2					
Grade								
Low	158.4 ± 3.8	150.9	165.9	**0.036**				**0.116**
High	140.7 ± 5.1	130.6	150.8					
Capsule int								
Intact	149.4 ± 4.3	140.8	157.9	**0.227**				
Not intact	140.7 ± 6.5	127.8	153.5					
LVI								
Present	94.6 ± 7.1	80.7	108.6	**0.004**				**0.315**
Absent	151.1 ± 3.5	144.1	158.0					
Tumor site								
Unilateral	147.7 ± 3.8	140.2	155.3	**0.449**				
Bilateral	137.7 ± 13.2	111.8	163.6					
Surgery								
Standard	144.7 ± 4.3	136.2	1532	**0.384**				
FSS***	154.4 ± 6.5	141.5	167.2					
Chemotherapy								
Absent	141.2 ± 3.7	133.5	149.0	**0.101**				
Present	142.6 ± 4.7	133.3	151.9					

Bold values indicate the level of statistical significance $p < 0.05$

*Low grade: grade 1, high grade: grade 2, 3 and clear cell

***LVI* Lymphovascular Invasion

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with ≥ 40 nodes harvested (7.2 vs. 6.6 days, $p = 0.366$). On the other hand, the interval between surgery and chemotherapy start was longer in women with ≥ 40 nodes harvested when compared to those with < 40 nodes harvested (18.2 vs. 13.0 days, respectively, $p = 0.018$). Operative complications (bladder injury and external iliac vein injury) occurred in only two patients (1.1%). Postoperative complications occurred in 12 patients (6.6%) and the most common complication was ileus ($n = 4$, 2.2%). Re-laparatomy was required only in one patient due to bleeding from the vaginal cuff. Lymphocel occurred in one patient (0.5%).

Discussion

In this study, we discussed the prognostic impact of number of removed lymph nodes in stage I EOC and the results were remarkable. First, removal of ≥ 10 para-aortic lymph nodes was significantly and independently associated with better 5-year OS and 5-year PFS. Besides this some well-accepted prognostic factors such as age, tumor grade were also independently and significantly associated with 5-year OS. The median number of collected lymph nodes was 38. Removal of ≥ 40 nodes was not associated with an increase in hospital stay but resulted in a chemotherapy delay.

Table 5 The association between para-aortic lymph node number and histopathologic risk factors

	Para-aortic LN number				*p* value
	< 10		≥ 10		
	n	%	*n*	%	
Histology					
Serous	28	59.6	19	40.4	0.240
Others	67	49.6	68	50.4	
Grade					
Low	24	43.6	31	56.4	0.128
High	71	55.9	56	44.1	
Capsule integrity					
Intact	57	50.0	57	50.0	0.442
Not intact	38	55.9	30	44.1	
LVI					
Present	19	63.3	11	36.7	0.182
Absent	76	50	76	50	
Tumor site					
Unilateral	84	51.5	79	48.5	**0.599**
Biateral	11	57.9	8	42.1	

Bold value indicates the level of statistical significance $p < 0.05$

Prior studies on lymphadenectomy in apparent early-stage EOC have focused on the effect of absence or presence of lymphadenectomy [4] and the rate of upstaging in clinical early-stage disease [2]. The underlying reason of the benefit of lymphadenectomy was kept in background. This constituted the kernel point of our study. As a tertiary ovarian cancer center which routinely performs lymphadenectomy during ovarian cancer surgery, we evaluated our experience whether this approach results in a survival benefit or not. A homogenous patient group with histologically proven Stage I disease was evaluated for a better understanding for the role of lymphadenectomy. Firstly, we have targeted to evaluate the total lymph node number and we found statistically significant results. Thereafter, we evaluated pelvic and paraaortic lymph node numbers separately to specify the underlying cause of this significancy and found that paraaortic lymph node number was independently and significantly associated with both 5-year (and median) PFS and OS in multivariate analyses. This finding is important because it emphasizes the importance of comprehensive lymphadenectomy even in FIGO stage I EOC and is reported for the first time in the literature.

Age, tumor factors (grade, histologic type, presence of LVSI or molecular factors such as abnormal oncogene expressions or gene mutations) and surgical factors such as execution of lymphadenectomy have been reported to determine the prognosis of stage I EOC [2, 4, 9–11]. Of those, only the surgical factors can be changed and improved. Although the quality of lymphadenectomy has improved with the experience of surgeons and improvement of surgical techniques by years, lymphadenectomy is absolutely associated with increased risk of complications [4, 6] and this leads to some concerns about performing or canceling this approach. However, lymphadenectomy is an absolute component of EOC surgery and is particularly important in early-stage EOC when compared to advanced stage disease [12]. Lymphadenectomy is not only to stage the disease but also improves survival when performed [4]. This points the importance of lymphadenectomy that in case of detection of lymphatic involvement, cancer upstages to FIGO stage III and on the contrary, when adequate lymphadenectomy performed, patients with low-risk disease may avoid adjuvant treatment due to the absence of lymphatic metastasis. Quality of lymphadenectomy is generally based on the number of removed lymph nodes and there are published studies indicating that collecting around ten lymph nodes may be sufficient to catch a metastatic node in EOC [5, 6]. Bizzarri et al. defined comprehensive lymphadenectomy as ≥ 20 lymph nodes and also presented a survival benefit of comprehensive lymphadenectomy when compared to no lymphadenectomy [4]. In our study, minimum and median numbers of removed lymph nodes were 11 and 38 fulfilling the required lymph node numbers for adequate staging. Additionally, we found a positive survival effect of lymphadenectomy for patients with stage I EOC. Apart from previous studies, all patients underwent lymphadenectomy and statistical analyses were performed on lymphatic region basis in the current study and importantly, we found that this positive effect was dependent on the number of removed para-aortic lymph nodes.

Para-aortic lymphatic region is especially important for EOC rather than other gynecological cancers because during embryologic development ovaries develop in the upper abdomen and migrate to pelvis with their blood, nerve and lymphatic supplies and their lymph vessels continue to drain to the para-aortic region [13]. Thus, paraaortic region is the primary location for lymph node metastasis for ovarian cancer [2, 14]. Isolated para-aortic lymph node involvement constitutes about 50% of lymph node metastasis in clinical early-stage disease [3]. Based on this information, we investigated whether there is an association between the histopathologic properties and the number of para-aortic lymph node removed. We evaluated previously presented risk factors for lymph node involvement such as LVSI, tumor grade, bilaterality, tumor histology, tumor diameter, and capsule invasion [2, 3, 15, 16]. This analysis showed that the histopathological properties of the groups were similar and was not capable to build a hypothesis on these results. However, there are unclear points about ultra-low-volume disease or isolated tumor cells [17] and we think that there

may be different patterns in molecular or cellular basis, those we could not show with routine histopathologic evaluation.

Another finding of the study was that age and grade were the other independent factors associated with survival and this finding was in agreement with the prior related literature [2, 3, 15, 16].

The strengths of the study were thought as the standard surgical and histopathological management of the same gynecologic oncology team and remarkable number of stage I EOC patients from a single institution. The main limitation of the current study was its retrospective design.

In conclusion, the importance of lymphadenectomy is a crystal-clear fact in early-stage EOC. In this study, we showed that the number and localizations of removed lymph nodes may have a survival effect in stage I EOC. Larger prospective series on lymph node number and lymphatic regions are needed to verify our findings.

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Declarations

Conflict of interest The authors declare there are no conflicts of interest—financial or otherwise—related to the material presented herein. The authors declare there are no ethical considerations for the case.

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki. Study was approved by the Institutional Review Board (KA21/95).

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