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Lymph node evaluation and nodal metastasis prediction in epithelial ovarian cancers: A retrospective study

Epitelyal over kanserlerinde lenf nodu değerlendirmesi ve nodal metastaz tahmini: Retrospektif bir çalışma

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Abstract

Objective: To identify consensus regarding lymph node (LN) evaluation in epithelial ovarian cancer (EOC). The objective of the present study was to evaluate surgico-pathological findings, LN involvement, and the prediction of LN metastasis via preoperative imaging and intraoperative assessment in women with EOC.

Materials and Methods: Women with EOC who underwent cytoreductive surgery (CRS) between Jan 2019 to June 2022 were included. The distribution of histology, stage, and LN metastasis was studied. The predictive value of serum cancer antigen (CA)-125, instead of and radiologically and surgically enlarged LNs with final LN histopathology was studied.

Results: A total of 96 women with EOCs underwent CRS. Fifty women (52%) underwent primary CRS and 46 women (48%) underwent interval CRS. Seventy-five women (78.13%) with EOC underwent pelvic and/or para-aortic lymphadenectomy, out of which 23 (30.67%) were histologically positive. High-grade serous carcinoma was the commonest (n=55, 73.33%) histology. The majority of women, 56 (74.67%) were stage III or IV at presentation. Complete cytoreduction was achieved in 59 (78.66%) patients. The receiver operating characteristics curve showed a cutoff for CA-125 of 1360 U/mL (area under the curve 0.702, p=0.002) for LN metastases. Both radiologically and surgically enlarged LNs significantly predicted LN metastasis on histopathology (p=0.02 and 0.006 respectively). The combined sensitivity, specificity, positive predictive value and negative predictive value of both contrast enhanced computed tomography (CECT) and surgically enlarged LNs were 78.26%, 57.69%, 45%, and 85.71%, respectively.

Conclusion: Serous histology, high-grade tumors, highCA-125 levels, and suspicious LNs on CECT or during surgery were significantly associated with LN metastasis. However, considering the false-negative rate of 21.74%, the combination of radiologically and surgically enlarged LNs cannot be used as the sole surrogate marker for lymphadenectomy.

Keywords: Epithelial ovarian cancer, lymph node metastasis, lymph node evaluation

PRECIS: Higher CA-125 levels (1360 U/mL) and suspicious LNs on CECT or during surgery are significantly associated with LN metastasis.

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Öz

Amaç: Epitelyal over kanserinde (EOC) lenf nodu (LN) değerlendirmesine ilişkin fikir birliği sağlamak amaçlanmıştır. Bu çalışmanın amacı, EOC'li kadınlarda cerrahi patolojik bulguları, LN tutulumunu ve preoperatif görüntüleme ve intraoperatif değerlendirme yoluyla LN metastazı tahminini değerlendirmektir.

Gereç ve Yöntemler: Ocak 2019 ile Haziran 2022 arasında sitoredüktif cerrahi (CRS) uygulanan EOC'li kadınlar dahil edildi. Histoloji, evre ve LN metastazının dağılımı incelendi. Serum kanser antijeni (CA)-125'in ve radyolojik ve cerrahi olarak gösterilen büyümüş LN'lerin ve son LN histopatolojisinin öngörücü değerleri araştırıldı.

Bulgular: EOC'li toplam 96 kadına CRS uygulandı. Elli kadına (%52) birincil CRS, 46 kadına (%48) aralıklı CRS uygulandı. EOC'li 75 kadına (%78,13) pelvik ve/veya para-aortik lenfadenektomi uygulandı, bunların 23'ü (%30,67) histolojik olarak pozitifti. Yüksek dereceli ayrılan karsinom en sık görülen histolojiydi (n=55, %73,33). Başvuru anında hastaların 56'sında (%74,67) hastalık evresi evre III veya IV idi. Hastaların 59'unda (%78,66) tam sitoredüksiyon sağlandı. Alıcı çalışma özellikleri eğrisi, LN metastazlarını öngörmede CA-125 için 1360 U/mL'lik (eğrinin altındaki alan 0,702, p=0,002) bir kesim değeri gösterdi. Hem radyolojik hem de cerrahi olarak gösterilen büyümüş LN'ler, histopatolojide LN metastazını anlamlı olarak öngördü (sırasıyla p=0,02 ve 0,006). Kontrastlı bilgisayarlı tomografi ile gösterilen LN'lerin birleşik duyarlılığı, özgüllüğü, pozitif tahmin değeri ve negatif tahmin değeri sırasıyla %78,26, %57,69, %45 ve %85,71 idi.

Sonuç: Seröz histoloji, yüksek dereceli tümörler, yüksek CA-125 düzeyleri ve kontrastlı bilgisayarlı tomografide veya ameliyat sırasında şüphe edilen LN'ler LN metastazı ile anlamlı derecede ilişkiliydi. Ancak %21,74'lük yanlış negatiflik oranı dikkate alındığında, radyolojik ve cerrahi olarak gösterilen büyümüş LN'lerin kombinasyonu, lenfadenektomi için tek belirteç olarak kullanılamaz.

Anahtar Kelimeler: Epitelyal over kanseri, lenf nodu metastazı, lenf nodu değerlendirmesi

Introduction

Determination of various histological patterns using comprehensive surgical staging and lymph node (LN) evaluation is crucial for the management and prognosis of epithelial ovarian cancers (EOCs). Thorough research into various factors predicting LN metastasis is required. The present study aimed to evaluate LN involvement in various histotype and predict LN metastasis using preoperative imaging and intraoperative assessment among women with EOC.

The incidence of LN involvement by EOC varies widely. The diagnosis depends mainly on the clinical stage of the disease, histological subtype, and extent of lymphatic dissection[1]. The reported rate of microscopic lymphatic involvement is 13-20% among women with tumors clinically confined to ovary[2]. However, lymphatic involvement is detected in 13-74% of stage III ovarian cancer (OC) and in 33-88% of stage IV OC women[3]. The role of systematic lymphadenectomy remains controversial. For patients with presumed early-stage OC, systematic lymphadenectomy is recommended due to improved overall survival[4]. However, few prospective studies have revealed the survival advantage of routine lymphadenectomy[5]. The lymphadenectomy in ovarian neoplasms (LION) trial showed no advantage of systematic lymphadenectomy in primary debulking surgery in advanced OCs (stage IIB-IV) with clinically negative LNs in terms of overall survival[6]. The National Comprehensive Cancer Network recommended resection of all suspicious or enlarged nodes along with the removal of LNs to have potential metastasis at the time of initial diagnosis, which is selective LN removal[7]. Various imaging methods are frequently employed in the preoperative assessment. Positron emission tomography (PET) has good sensitivity (73.2%) and specificity (96.7%) for detecting metastatic LNs[8]. However, PET is not always feasible as a routine test because of its non-availability and high cost. Computed tomography (CT) scan remains the most widely used preoperative imaging tool in women with ovarian cancer, but its utility is limited considering the varied sensitivity in various studies[8]. Additionally, cancer antigen (CA)-125 was found to be an independent predictor of LN involvement[9,10].

Herein, the primary objective of the study was to evaluate LN metastasis among various histotype of EOC along with the prediction of LN metastasis with enlarged LNs observed on preoperative imaging workup and during surgery on intraoperative clinical examination. The secondary objective of the study was to predict LN metastasis with preoperative CA-125 levels in women with EOC.

Material and Methods

Study Design, Setting, Participants

The present study is an observational retrospective study; conducted in the department of Obstetrics & Gynecology and Surgical Oncology at All India Institute of Medical Sciences (AIIMS), Rishikesh, India, from January 2019 to June 2022. The study protocol was approved by the AIIMS Institutional Ethics Committee (approval number: AIIMS/IEC/21/704, date: December 24, 2021). Women with EOCs aged 18 years or older who underwent cytoreductive surgery (CRS); both primary and interval CRS, with Eastern Cooperative Oncology Group (ECOG) status 0-2 at the time of surgery, were included in the study after providing written informed consent. The exclusion criteria of the study were women who were treated with palliative intent, diagnosed with non-epithelial or borderline tumors, or with recurrent OC or synchronous malignancy.

Data Collection

Demographic characteristics, detailed clinical history, CA-125 level, and preoperative contrast-enhanced computed tomography (CECT) findings were recorded. CRS included sampling of ascitic fluid or peritoneal washing, careful exploration of the pelvic and abdominal cavity, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsy from suspected areas, pelvic and/or para-aortic

lymphadenectomy, and removal of all gross disease with the goal of R0 resection. In case of advanced OC, where the tumor is not amenable to R0 resection (patients with diffuse deep infiltration of small bowel mesentery, diffuse and confluent carcinomatosis of stomach and/or small bowel, involvement of superior mesenteric artery, multiple liver/brain/lung metastasis) or patients who are poor surgical candidates (ECOG 3) or more, low serum albumin <3 gm/dL, multiple comorbidities, neoadjuvant chemotherapy (NACT) followed by interval CRS was performed.

Detailed examination of retroperitoneal LNs in CECT scan (performed within 4 weeks prior to surgery) was performed. LNs were considered suspect if they were larger than 1 cm or if their shape deviated from the normal. Intraoperative details included the presence of ascites, largest tumor dimension, laterality, clinical examination of retroperitoneal LNs, including grossly enlarged (more than 1 cm) LN site and size, peritoneal cancer index (PCI) scores, lymphadenectomy details, surgical complexity score (SCS), residual disease, operative time, and blood loss, including any complications. Regarding intra-operative clinical examination of LNs, the opinion of two surgeons was taken; in case of a difference in opinion, evaluation by a third senior gynecology surgeon was sought. Systematic pelvic lymphadenectomy involved the removal of external iliac, internal iliac, and obturator LNs, and para-aortic lymphadenectomy included the removal of common iliac LNs and LNs related to the aorta and vena cava up to the level of the renal vein. Histopathological details, including tumor grade, histological type, number and sites of LN involvement, and final surgicopathological stage, were recorded. The rate of patients with positive LNs according to different histotype was identified, and the possible association between CA-125, radiological and intraoperative clinical examination of LNs with positive LNs (histopathologically proven) was evaluated.

Outcome Measures

Primary outcome measures included histopathological types and LN positivity rate, number (%) of women with LN metastasis among various histotype, positive LNs in women with preoperatively enlarged LNs on imaging, and LN positivity rate among surgically enlarged LNs. Secondary outcome measures included various International Federation of Gynecology and Obstetrics (FIGO) staging of disease and CA-125 levels among all women with EOC and LN metastasis.

Statistical Analysis

Categorical variables are presented as numbers and percentages (%). Quantitative data with normal distribution are presented as mean ± standard deviation and the data with non-normal distribution are presented as median (25^{th} and 75^{th} percentiles). The association of the variables which were quantitative and not normally distributed were analyzed using Mann-Whitney test (two groups) and Kruskal-Wallis test (more than two groups). The optimal cut-off value for CA-125 in patients with LN metastasis was determined using receiver operating characteristics (ROC) curve. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of radiologically enlarged LNs and surgically enlarged LNs were calculated alone and in combination to predict positive LNs. The final analysis was performed using the Statistical Package for Social Sciences (SPSS) software (IBM, Chicago, USA; version 21.0.

Results

A total of 167 women with OC underwent CRS between January 2019 and June 2022. Among them, 71 women were excluded from the study (54 with non-epithelial/borderline tumor, 12 with recurrent OC and 5 with synchronous cancer of endometrium). In total, 96 women underwent CRS. Among the 96 women with EOC, only 75 underwent pelvic and/or para-aortic lymphadenectomy. Out of 75 women with EOC, 35 (47%) underwent primary CRS and 40 (53%) underwent interval CRS. Thus, the final data analysis was done in n=75 women (Supplemental Figure 1).

The mean age of the participants was 48.42±11.6 years. The mean body mass index was 24.06±3.96 kg/m^2. The majority of them, 40 out of 75 (53.33%) were P2-P3 followed by 25 women (33.33%) higher than P3. Eight women (10.67%) were nulliparous. Forty-one women (54.67%) were postmenopausal. The mean duration of menopause was 8.81±5.79 years. Only seven out of 75 (9.33%) had a history of infertility/ovulation induction (Table 1).

The mean initial CA-125 value among women with EOC was 2861.72±11208.85 U/mL with a median (25^{th}-75^{th} percentile) of 894 (312.55-1907.2) U/mL. Most women with EOC had an advanced stage at the time of diagnosis. The most common stage was stage III C (53.3%, 40 out of 75 women) (Supplemental Figure 2). The mean PCI, CC, and SCS of women was 4.71±5.8, 0.36±0.77, and 4.08±1.97, with a range of 0-30, 0-3, and 2-11, respectively. Complete cytoreduction was achieved in 78.66% of women.

As shown in Table 2, the majority of women (55, 73.33%) had high-grade serous carcinoma (HGSC), followed by mucinous (8, 10.67%), endometrioid (4, 5.33%), low-grade serous carcinoma (LGSC) (3, 4.0%), and carcinosarcoma (2, 2.67%). Clear cell carcinoma, mixed carcinoma, and squamous carcinoma comprised one each (1.3%). Among 75 women with EOC who underwent lymphadenectomy along with CRS, 23 (30.67%) had pelvic or para-aortic LN metastasis. Para-aortic LNs were detected in only 16 out of 75 women (21.33%). Pelvic LNs were detected in only 17 out of 75 (22.67%) women. A median of 12 (range 1-60) LNs were removed, with a median of 8 pelvic LNs (range 1-32) and 3 para-aortic LNs (range 1-28) (Supplementary Table 1). Of 23 women with positive retroperitoneal LNs, 20 women (87%) were of HGSC; however, only 1 (infiltrative variety) case out of 8 women with mucinous carcinoma was positive, one woman with LGSC and

Table 1. Baseline characteristics of women with EOC (n=75)

Baseline characteristics	Frequency	Percentage
Age (years)		
20-30	5	6.67%
31-40	16	21.33%
41-50	17	22.67%
51-60	27	36.00%
>60	10	13.33%
Mean ± SD	48.42±11.6	
Median (25^{th}-75^{th} percentile)	50 (40-57.25)	
Range	20-73	
Body mass index (BMI) kg/m²		
18.5-22.99 kg/m² (Normal BMI)	34	45.34%
23-24.99 kg/m² (Overweight)	16	21.33%
>25 kg/m² (Obese)	25	33.33%
Mean ± SD	24.06±3.96	
Median (25^{th}-75^{th} percentile)	23.4 (21.175-25.625)	
Range	18.6-40.3	
Socioeconomic status (Modified Kuppuswamy scale)		
Upper	6	8.00%
Upper middle	23	30.67%
Lower middle	38	50.66%
Lower	8	10.67%
Parity		
P0	8	10.67%
P1	2	2.67%
P2-P3	40	53.33%
>P3	25	33.33%
Mean ± SD	3.01±1.61	
Median (25^{th}-75^{th} percentile)	3 (2-4)	
Range	0-8	
Prior menstrual history		
Irregular	12	16.00%
Regular	63	84.00%
H/0 infertility/ovulation induction	7	9.33%
Menopausal status	41	54.67
Duration of menopause (years)		
Mean ± SD	8.81±5.79	
Median (25^{th}-75^{th} percentile)	9 (4.75-10.25)	
Range	1-20	
Family history of cancer		
No	69	92.00%
Yes	6	8.00%
Contraception		
No	35	46.67%
Barrier	18	24.00%
IUCD	6	8.00%
OCP	3	4.00%
Tubal ligation	13	17.33%

EOC: Epithelial ovarian cancer, SD: Standard deviation

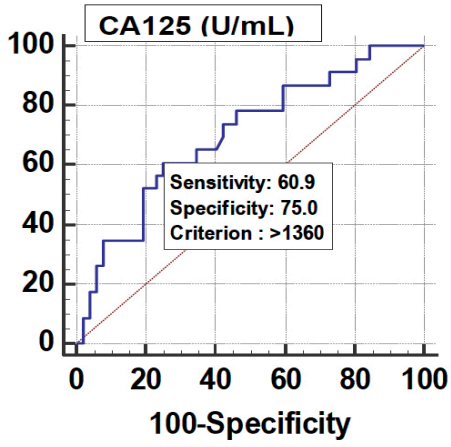

Figure 1. Receiver operating characteristic curve of CA-125 (U/mL) for predicting positive lymph nodes

CA: Cancer antigen

carcinosarcoma was positive each. The numbers of positive LNs among the various histotypes are shown in Table 2.

The median (25^{th}-75^{th} percentile) CA-125 level in positive LNs was 1913.8 (897.1-5048.5) U/mL, which was significantly higher than that in negative LNs (p-value 0.006) (Supplementary Table 2). The discriminatory power of CA125 (U/mL) [area under the curve (AUC) 0.702; 95% confidence interval: 0.585 to 0.802] was acceptable. CA-125 was a significant predictor of positive LNs at a cut-off point of >1360 U/mL with a 70.20% chance of correctly predicting positive LNs and a sensitivity of 60.87%. If CA-125 ≤1360 U/mL, then there was an 81.20% chance of normal LNs (Figure 1, Supplementary Table 3).

Table 3 shows a significant correlation between radiologically enlarged LNs and final histopathological findings (p-value 0.006) and surgically enlarged LNs (p-value 0.020).

Table 4 shows that the sensitivity, specificity, PPV, NPV, and accuracy of detecting LN metastasis with CECT were 56.52%, 78.85%, 54.17%, 80.39%, and 72%, respectively, and those with intraoperative LN assessment alone were 69.57%, 59.62%, 43.24%, 81.58%, and 62.67%, respectively. The combined sensitivity, specificity, PPV, and NPV of both CECT and surgically enlarged LNs were 78.26%, 57.69%, 45%, and 85.71%, respectively.

Combined (radiological + surgical) assessment had a sensitivity of 78.26%, followed by intra-op (69.57%) and radiological (56.52%) assessments in the prediction of positive LNs. Radiological assessment had the lowest sensitivity (56.52%) but higher specificity for predicting positive LN. Women who had positive LNs, 78.26% had enlarged LNs on radiologically or intraoperatively. If an enlarged LN was seen in either radiological or intra-op assessment, there was a 45% probability of a positive LN. If an enlarged LN is not seen on both CECT and intraoperatively, there is an 85.71% chance of no LN metastasis.

Discussion

This study analyzed the pattern of LN metastasis among EOC and evaluated whether CA-125, preoperative CT scan, and intraoperative LN gross examination could reliably predict LN metastasis, in order to decide whether women with EOC could be identified in whom lymphadenectomy could be omitted.

Regarding the spectrum of LN involvement, a significant percentage (23 out of 75, 30.67%) of EOC women were found to have pelvic or para-aortic LN metastasis, whereas in 22.67% of women, pelvic LNs and in 28% of women, para-aortic LN involvement were found. The majority of women (87%) with positive LN metastasis were HGSC. The optimum cut-off

Table 2. Association of positive lymph nodes with histological type

Lymph node status	High grade serous (n=55)	Low grade serous (n=3)	Mucinous (n=8)	Endometrioid (n=4)	Clear cell (n=1)	Squamous cell (n=1)	Mixed (n=1)	Carcinosarcoma (n=2)	Total (n=75)
Total lymph nodes positive									
Negative	35	2	7	4	1	1	1	1	52 (69.33%)
Positive	20	1	1	0	0	0	0	1	23 (30.67%)
Para-aortic lymph nodes positive									
Negative	40	3	8	4	1	1	1	1	59 (78.67%)
Positive	15	0	0	0	0	0	0	1	16 (21.33%)
Pelvic lymph nodes positive									
Negative	41	2	7	4	1	1	1	1	58 (77.33%)
Positive	14	1	1	0	0	0	0	1	17 (22.67%)

Table 3. Association of enlarged LNs with histopathologically positive LNs

Enlarged LNs	Negative (n=52)	Positive (n=23)	Total	p-value
Radiologically enlarged lymph nodes				
No	41 (78.84%)	10 (43.47%)	51 (68%)	0.006†
Yes	11 (21.15%)	13 (56.52%)	24 (32%)	
Surgically enlarged lymph nodes on intra op clinical examination				
No	31 (59.61%)	7 (30.43%)	38 (50.67%)	0.020†
Yes	21 (40.38%)	16 (69.57%)	37 (49.33%)	
Combined radiological + Surgically enlarged LN on intra-op examination				
No	30 (57.69)	5 (21.74%)	35	0.006†
Yes	22 (42.31%)	18 (78.26%)	40	

†: Chi-square test, LN: Lymph node

Table 4. Sensitivity, specificity, positive predictive value and negative predictive value of radiologically enlarged lymph nodes and intra op clinically enlarged lymph nodes for predicting positive lymph nodes

Variables	Radiologically enlarged LNs	Surgically (Intra-op) enlarged LNs	Combined (radiological + surgical assessment)
Sensitivity (95% CI)	56.52% (34.49% to 76.81%)	69.57% (47.08% to 86.79%)	78.26% (56.30% to 92.54%)
Specificity (95% CI)	78.85% (65.30% to 88.94%)	59.62% (45.10% to 72.99%)	57.69% (43.20% to 71.27%)
AUC (95% CI)	0.68 (0.56 to 0.78)	0.65 (0.53 to 0.75)	0.68 (0.56 to 0.78)
Positive predictive value (95% CI)	54.17% (32.82% to 74.45%)	43.24% (27.10% to 60.51%)	45% (29.26% to 61.51%)
Negative predictive value (95% CI)	80.39% (66.88% to 90.18%)	81.58% (65.67% to 92.26%)	85.71% (69.74% to 95.19%)
Diagnostic accuracy	72.00%	62.67%	64.00%

CI: Confidence interval, AUC: Area under the curve, LN: Lymph node

value of serum CA125 in the ROC curve for LN metastasis was 1.360 U/mL with AUC of 0.702 (p-value 0.002) and 60.87% sensitivity and specificity of 75%. Both radiologically and surgically enlarged LNs significantly predicted LN metastasis on histopathology (p=0.02 and 0.006 respectively). Combined (radiological + surgical) assessment had a sensitivity of 78.26%, followed by intra-op (69.57%) and radiological (56.52%) assessments for predicting positive LNs. Radiological assessment had the lowest sensitivity (56.52%) but higher specificity for predicting positive LN. Women who had positive LNs, 78.26% had enlarged LNs on CECT or intraoperatively. If an enlarged LN was seen in either radiological or intra-op assessment, there was a 45% probability of a positive LN. If an enlarged LN is not seen radiologically and intraoperatively, there is an 85.71% chance of no LN metastasis.

Regarding the spectrum of LN metastasis in EOCs, similar to our results, Zhou et al.[11] found LN metastasis in 32.8% women in a retrospective analysis of 256 patients with EOC; majority were HGSC. Similarly, a cross-sectional study of 55 patients with EOC by Andrijono et al.[12] showed an LN positivity rate of 42.9% in serous carcinoma. The discrepancy in the total number of positive LNs between HGSC and LGSC may be attributed to differences in the incidence of different histotypes of EOC in the present study. The LN positivity rate could not be calculated because the present study was underpowered to evaluate subtype-specific associations, particularly for rare histotype. In contrast to the present study, Widschwendter et al.[13] found that 51.8% of women had LN metastasis (pelvic and/or para aortic) in a retrospective analysis of 114 women with EOC. The reason could be higher LN retrieval and the non-inclusion of NACT cases.

Various other studies also showed a correlation between CA-125 and LN metastasis. Sudolmus et al.[14] concluded that the cut-off value for LN metastases was 7192 U/mL in the ROC curve, which was significant in logistic regression analysis (p=0.005) but associated with a high rate of false positivity in the Turkish population. Zhang et al.[15] concluded that serum CA-125 combined with D-dimer had good predictive value for LN metastasis in EOC.

Regarding the prediction of LN metastasis by CT scan, Uysal et al.[16] found the sensitivity, specificity, PPV, NPV, and accuracy of 62%, 52%, 57%, 57%, and 57%, respectively, in a retrospective analysis of 89 women with EOC. Concordance with our results, another retrospective analysis done by Widschwendter et al.[11] concluded that CT scan has a sensitivity of 40.7%, specificity of 89.1%, PPV of 80%, and NPV of 58.3% in the prediction of LN metastasis in EOC patients.

Regarding the prediction of LN metastasis by LN palpation during surgery, Arango et al.[17] found a sensitivity, specificity, PPV, and NPV of 72%, 81%, 56%, and 89%, respectively, in a prospective study of 126 women with EOC. Khunnarong et al.[18] analyzed 124 women with EOC and concluded that 81% had sensitivity, 91% specificity, 65% PPV, 96% NPV, and 90% accuracy. Harter et al.[19] performed a retrospective analysis of 195 women with EOC and inferred similar results. A meta-analysis of 89 women with EOC performed by Mimoun et al.[20] concluded that intra-op clinical examination for the prediction of LN metastasis has a sensitivity of 79%, specificity of 85%, and accuracy of 86%. Hailing Xiang et al. constructed a nomogram integrating CT-reported LN status, child-bearing status, tumor laterality, and stage, which showed good calibration and discrimination with an AUC of 0.775, significantly improving performance over the CT results (0.699, p=0.0002)[21]. Recently, a prospective multicentric study conducted by the FRANCOGYN group evaluated the utility of a new diagnostic tool, consisting of pelvic and/or para-aortic LN metastasis on CT and/or PET/CT scan, initial PCI ≥10 and/or diaphragmatic carcinosis, and initial CA-125 ≥500 U/mL, in predicting LN metastasis in women with advanced EOC. The group at a high risk of LN metastasis had 83.5% sensitivity, 2.73% LR+, and 79.3% observed probability of LN metastasis[10].

However, comparisons across studies should be made with utmost caution because of differences in study design and study populations. The sensitivity, specificity, PPV, and NPV of the combination of radiological + surgically enlarged LN for detecting LN metastasis were 78.26%, 57.69%, 45%, and 85.71%, respectively, in the present analysis. The assessment of retroperitoneal LNs by a combination of CECT+ intraoperative clinical evaluation is not sufficient to preclude lymphadenectomy in the case of normal-appearing LNs; the probable reason could be the presence of microscopic tumor metastasis without a visible bulky LN in the present study.

Our study showed that positive radiological findings combined with surgical assessment triage women into a group at high risk of LN metastases, with a clear indication for pelvic and para-aortic lymphadenectomy, as described in the literature and particularly in the LION trial[6].

Negative radiological and intraoperative assessment triage women into groups at low risk of LN metastases. However, it does not appear sufficient to conclusively rule them out in view of the considerable number of false-negative (21.74%) in the combined assessment in the present study. Nonetheless, it must be noted that in the LION trial, despite the 55.7% false-negative rate, no survival difference was observed between the "lymphadenectomy" and "no lymphadenectomy" groups in advanced ovarian cancer.

Strengths and Limitations of the Study

Our study evaluated the prediction of LN metastasis with the combined assessment of preoperative CECT scan and intraoperative gross examination of LNs, along with CA-125 levels. To date, no study has evaluated LN involvement in consideration of the above-mentioned factors in combination. To reduce observational bias, the opinions of at least two surgeons were obtained during the intraoperative clinical evaluation of retroperitoneal LNs.

In this study, patients were enrolled retrospectively, which has

the inherent potential to introduce selection bias. Our institution is a tertiary referral oncology center; therefore, most patients were primarily referred with low-performance status and advanced stage. The present study identified a high percentage of interval debulking surgery (IDS) cases due to poor ECOG status at presentation and the COVID-19 pandemic. Depending on these factors, the number of removed pelvic and para-aortic LNs was less than the minimum number described in the literature. The present study was underpowered to evaluate subtype-specific associations, particularly for rare histotype.

Conclusion

Serous histology, higher CA-125 levels (1360 U/mL, AUC 0.702, p=0.002), and suspicious LNs on CECT and during surgery were significantly associated with LN metastasis. However, normal LNs both in size and morphology, as assessed by the combination of CECT and intraoperative findings, were positive in 21.74% of women in the present study, suggesting that a combination of radiologically and surgically enlarged LNs cannot be used as sole surrogate markers for lymphadenectomy. A pragmatic approach to complete surgical staging with systematic lymphadenectomy for ovarian cancer is needed. However, the effect of this is yet to be known; since the present study did not evaluate overall survival and progression-free survival in women. Further prospective randomized trials in a larger population are needed to confirm these findings.

Ethics

Ethics Committee Approval: The study protocol was approved by the AIIMS Institutional Ethics Committee (approval number: AIIMS/IEC/21/704, date: December 24, 2021).
Informed Consent: All participants provided informed consent before entering the study.

Authorship Contributions

Surgical and Medical Practices: A.B., S.R., R.K.S., J.C., R.M., S.R., Concept: P.V., A.B., S.R., R.K.S., Design: P.V., A.B., S.R., R.K.S., Data Collection or Processing: P.V., I.S., A.H., Analysis or Interpretation: R.K.S., A.G., S.R., Literature Search: P.V., J.C., R.M., Writing: P.V., A.B.
Conflict of Interest: No conflict of interest was declared by the authors.
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Supplementary Table 1. Lymph node yield of all EOC women with LND on histopathology

Lymph node yield	Mean ± SD	Median (25^{th}-75^{th} percentile)	Range
Total LN yield	13.61±12.5	12 (1-22)	0-60
LN yield (para-aortic)	4.33±5.89	2.5 (0-7)	0-28
LN yield (pelvic)	9.28±8.21	8 (1-15.25)	0-32

SD: Standard deviation, EOC: Epithelial ovarian cancer, LN: Lymph node, LND: Lymph node dissection

Supplementary Table 2. Association of CA-125 (U/mL) with histopathologically positive LNs

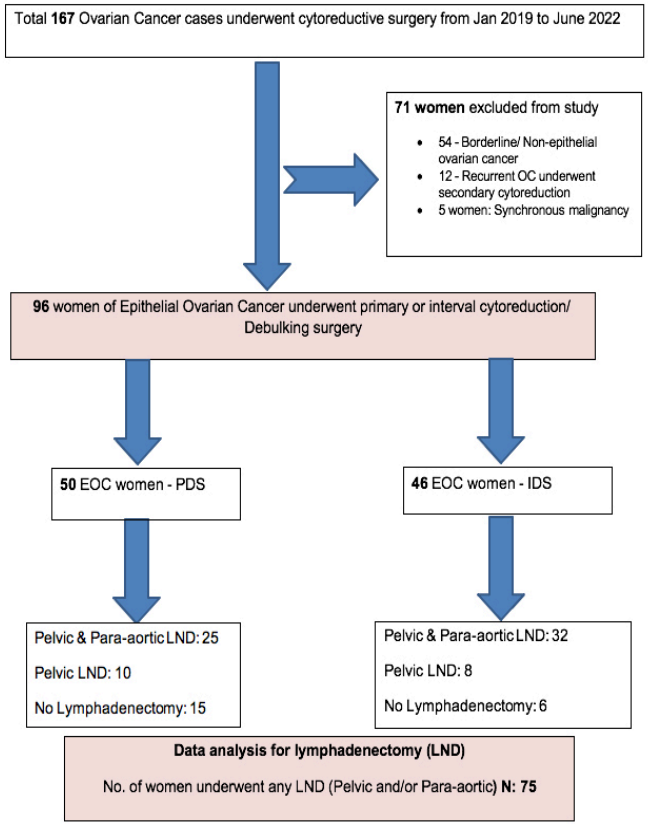
CA125 (U/mL)	Negative (n=52)	Positive (n=23)	Total	p-value
0-35 IU/L	4 (7.69%)	0 (0%)	4 (5.33%)	0.306*
>35 IU/L	48 (92.31%)	23 (100%)	71 (94.67%)	
Mean ± SD	3407.23±14966.95	3519.01±4076.48	3441.51±12622.52	0.006‡
Median (25^{th}-75^{th} percentile)	665.35 (344.85-1395)	1913.8 (897.1-5048.5)	946 (363.05-2268.5)	
Range	4.2-108.290	117.4-14.507	4.2-108.290	

‡: Mann-Whitney test, *: Fisher's exact test, SD: Standard deviation, LN: Lymph node, CA: Cancer antigen

Supplementary Table 3. Receiver operating characteristic curve of CA-125 (U/mL) for predicting positive lymph nodes

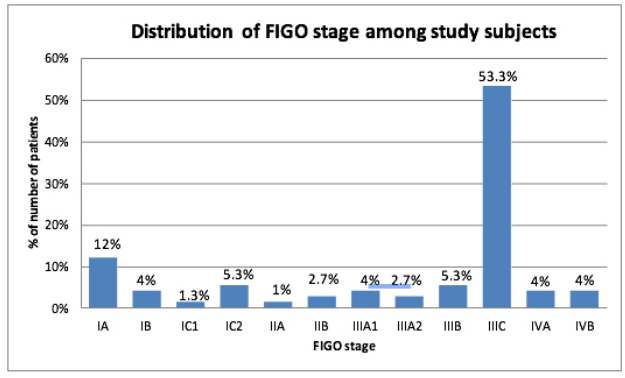
Variables	Value
Area under the ROC curve (AUC)	0.702
Standard error	0.066
95% confidence interval (CI)	0.585 to 0.802
P-value	0.0022
Cut-off	>1360 U/mL
Sensitivity (95% CI)	60.87% (38.5-80.3%)
Specificity (95% CI)	75% (61.1-86.0%)
PPV (95% CI)	51.9% (31.9-71.3%)
NPV (95% CI)	81.2% (67.4-91.1%)
Diagnostic accuracy	70.67%

ROC: Receiver operating characteristics, CA: Cancer antigen, PPV: Positive predictive value, NPV: Negative predictive value



Supplemental Figure 1. Flow-chart for analysis of all women with EOC under study

EOC: Epithelial ovarian cancer, LND: Lymph node dissection



Supplemental Figure 2. Distribution of FIGO stage among women with EOC

EOC: *Epithelial ovarian cancer, FIGO: International Federation of Gynecology and Obstetrics*