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Journal of Cancer Research and Pharmacology. 2025; 1(2): 101-106
https://doi.org/10.22034/jcrph.2025.553688.1012

Research Article Open Access

Predictors of lymphatic metastasis and indications for lymphadenectomy in epithelial ovarian carcinoma

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Received: 13 November 2025 **Revised:** 19 November 2025 **Accepted:** 10 December 2025 **e-Published:** 31 December 2025

Abstract

Background and Aims: Systematic lymphadenectomy remains integral to the surgical staging of ovarian cancer, yet the procedure carries considerable risk of morbidity. Refining the criteria for lymph node dissection by identifying robust preoperative predictors of metastasis could spare low-risk patients from these associated complications.

Methods: In this cross-sectional analysis, we reviewed 66 consecutive cases of epithelial ovarian cancer treated at two tertiary care centers in Tehran from 2019 to 2021. Preoperative clinical, imaging, and serological parameters were documented. All patients underwent comprehensive surgical staging, including lymphadenectomy. Associations between clinicopathological variables and lymph node metastasis were evaluated using chi-square tests, with multivariate logistic regression employed to define independent predictors.

Results: Lymph node involvement was present in 26 patients (39.4%). Univariate analysis identified significant correlations between nodal metastasis and younger age (≤50 years), bilateral adnexal involvement, serous histology, grade 3 differentiation, and International Federation of Gynecology and Obstetrics (FIGO) stage 3 disease. On multivariate analysis, each factor retained independent predictive value: age ≤50 years (odds ratio [OR] 3.07, 95% CI 1.02–9.24), bilateral tumors (OR 2.56, 95% CI 0.94–6.95), serous histology (OR 4.38, 95% CI 1.41–13.58), grade 3 (OR 14.25, 95% CI 4.12–49.30), and stage 3 (OR 20.09, 95% CI 5.87–68.79).

Conclusion: Our findings confirm that a distinct profile -characterized by younger age, bilaterality, serous histotype, high-grade differentiation, and advanced stage- significantly elevates the risk of lymphatic spread in ovarian carcinoma. Consequently, lymphadenectomy might be safely deferred in a carefully selected subset of patients with opposing low-risk features: age >50 years, unilateral, mucinous, grade 1 tumors confined to stage I. This selective approach could mitigate surgical morbidity while preserving oncologic safety.

Keywords: Ovarian cancer, Lymph node metastasis, Lymphadenectomy, Predictive factors, Tumor grade.

Introduction

Ovarian cancer, while ranking as the third most common malignancy of the female genital tract following cervical and uterine cancers, represents a disproportionately lethal disease.[1] In the United States, it remains the fifth leading cause of cancer-related mortality.[2] Although tumors originating from the ovaries and fallopian tubes account for only 15–20% of all gynecologic cancers, they are responsible for more deaths than all other primary pelvic malignancies combined.[2] The estimated incidence in Iran approximates 4 cases per 100,000 individuals.[3] Notably, its incidence is substantially lower than that of breast cancer, yet ovarian cancer carries a mortality rate roughly three times higher.[4] Overall five-year survival averages 40–50%, a figure that is critically dependent upon the stage at diagnosis.[5]

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Primary treatment for most patients involves surgical intervention.[6,7] Surgery serves to confirm the diagnosis, establish disease extent, and, where feasible, achieve complete cytoreduction. For patients not initially eligible for optimal tumor resection, surgery may instead be utilized for tumor debulking, often preceding or following systemic therapy.[8] Adjuvant chemotherapy is standard in most cases; indeed, some patients with advanced disease may first receive neoadjuvant chemotherapy to improve resectability.[9]

The selection of surgical procedure is guided principally by disease stage.[10,11] This may range from unilateral salpingo-oophorectomy to total abdominal hysterectomy with bilateral salpingo-oophorectomy.[12] A further complex component is regional lymphadenectomy, which aims to remove sites of potential micrometastasis. Beyond its therapeutic intent, lymph node dissection provides critical prognostic information for accurate staging and subsequent treatment planning.[13] However, evidence suggests that extensive lymphadenectomy in certain contexts does not confer a survival benefit.[13] This procedure also elevates surgical morbidity, prolongs operative time, increases intraoperative blood loss and transfusion requirements, and extends hospital stay.[13, 14]

Objectives

Consequently, there is a clear need to develop refined criteria for performing lymphadenectomy. Identifying patients who will not benefit from this procedure would reduce unnecessary surgical risk and alleviate the associated burden on healthcare systems.

Methods

This cross-sectional study was conducted at Amir Alam and Imam Khomeini hospitals in Tehran between March 2019 and February 2021. The sample size was determined using parameters from the study by Erdem et al.,[15] Assuming an 82% prevalence of non-involved lymph nodes, with a type I error of 5% and study power of 80%, a minimum of 66 participants was required.

Eligible patients included those diagnosed with ovarian cancer or presenting with symptoms suggestive of a pelvic mass -such as palpable abdominal or pelvic findings, ascites, bloating, pain, early satiety, or urinary urgency or frequency- in whom no alternative primary malignancy was identified. Diagnosis was confirmed through standard radiological and pathological examinations.

Prior to surgery, comprehensive clinical data were collected, including family history, obstetric history, and menstrual status. Preoperative assessment included physical examination of the abdomen and pelvis, abdominopelvic computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), serum cancer antigen-125 (CA-125) measurement, complete blood count (CBC), basic biochemical panels, and liver function tests (LFTs). All enrolled patients underwent surgical lymphadenectomy as part of their management.

Exclusion criteria comprised metachronous tumors, borderline ovarian tumors, advanced metastatic disease deemed inoperable, as well as significant comorbidities including advanced cirrhosis or poorly controlled diabetes.

Statistical analysis

Statistical analysis employed descriptive statistics (mean±SD; frequencies/percentages). Categorical variable associations with nodal status used the Chi-square test. Univariable and multivariable logistic regression models identified predictors of lymph node metastasis, reporting odds ratios (OR) with 95% confidence intervals (CI). Analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). A p-value<0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. The study protocol received approval from the ethics committee of Tehran University of Medical Sciences. All procedures conformed to relevant ethical guidelines and regulations, and written informed consent was obtained from every participant.

Results

A total of 66 patients were analyzed to identify predictors of nodal non-involvement, thereby potentially obviating the need for lymphadenectomy in ovarian cancer. Lymph node metastasis was present in 26 patients (39.4%) and absent in 40 (60.6%). The mean patient age was 51.35 ±

14.213 years (range: 13–82 years). Stratification by age revealed a significant association with nodal status (p=0.029). Among patients aged ≤50 years (n=25), 56% (n=14) had nodal involvement, compared to 29.3% (n=12) of those >50 years (n=41). Younger age (≤50 years) was associated with a higher likelihood of lymph node metastasis [Table 1].

Table 1. Association between patient age and lymph node involvement (n=66).

Age	Total	Lymph+	Lymph-	P value
>50	25 (37.9%)	14 (56%)	11 (44%)	0.029
<50	41 (62.1%)	12 (29.3%)	29 (70.7%)	

Tumor laterality also demonstrated a significant relationship with nodal involvement (p=0.05). For patients with unilateral tumors (n=32), 28.1% (n=9) had positive nodes. In contrast, nodal involvement was observed in 50% (n=17) of patients with bilateral disease (n=34) [Table 2].

Table 2. Association between tumor laterality and lymph node involvement (n=66).

Involvement	Total	Lymph+	Lymph-	P value
Unilateral	32 (48.5%)	9 (28.1%)	23 (71.9%)	0.05
Bilateral	34 (51.5%)	17 (50%)	17 (50%)	

Histopathological subtype was significantly correlated with nodal status (p=0.016). Among mucinous tumors (n=15), 33.3% (n=5) were node-positive. The rate of nodal involvement was substantially higher (68.6%, n=35) in patients with serous carcinomas (n=51) [Table 3].

Table 3. Association between tumor histologic type and lymph node involvement (n=66).

Tumor type	Total	Lymph+	Lymph-	P value
Mucinous	15 (22.7%)	5 (33.3%)	10 (66.7%)	0.016
Serous	51 (77.3%)	35 (68.6%)	16 (31.4%)	

Tumor grade significantly influenced the probability of nodal metastasis (p=0.011). Nodal involvement was present in 7.7% (n=1) of grade 1 tumors (n=13), 33.3% (n=6) of grade 2 tumors (n=18), and 54.3% (n=19) of grade 3 tumors (n=35) [Table 4].

Table 4. Association between tumor grade and lymph node involvement (n=66).

Tumor Grading	Total	Lymph+	Lymph-	P value
Grade 1	13 (19.7%)	1 (7.7%)	12 (92.3%)	
Grade 2	18 (27.3%)	6 (33.3%)	12 (66.7%)	0.011
Grade 3	35 (53%)	19 (54.3%)	16 (45.7%)	

A significant association was also found with surgical stage (p=0.003). Patients were grouped as follows: Group A (Stages IA–IC, n=14), Group B (Stages IIA–IIB, n=24), and Group C (Stages IIIA–IIIC, n=28). Nodal involvement rates were 7.1% (n=1) in Group A, 33.3% (n=8) in Group B, and 60.7% (n=17) in Group C [Table 5].

Table 5. Association between tumor stage and lymph node involvement (n=66).

Tumor Staging	Total	Lymph+	Lymph-	P value
Stage A	14 (21.2%)	1 (7.1%)	13 (92.9%)	
Stage B	24 (36.4%)	8 (33.3%)	16 (66.7%)	0.003
Stage C	28 (42.4%)	17 (60.7%)	11 (39.3%)	

In univariable logistic regression analysis, age ≤50 years (OR: 3.485), serous histology (OR: 5.893), grade 2 (OR: 15.192), and grade 3 (OR: 35.442) were significant predictors of lymph node involvement [Table 6].

Table 6. Multivariate logistic regression analysis for factors associated with lymph node involvement (reduced model).

Variabilities	β regression	Odds ratio	95% C.I.	p-value
Age	1.248	3.485	0.933 - 13.02	0.05
Tumor type	1.774	5.893	1.050 - 33.087	0.044
Grade2/1	2.721	15.192	1.176 - 196.291	0.037
Grade3/1	3.568	35.442	3.025 - 415.31	0.001

A subsequent multivariable logistic regression model, incorporating all variables simultaneously, identified five independent predictors. Age ≤50 years, bilateral disease, serous histology, grade 3 tumor, and Stage III disease each retained a significant association with nodal metastasis (all

p<0.05). The adjusted odds ratios were as follows: age ≤50 years (OR: 3.067), bilateral tumor (OR: 2.556), serous type (OR: 4.375), grade 3 (OR: 14.250), and Stage III (OR: 20.090) [Table 7].

Table 7. Crude (univariate) logistic regression analysis for factors associated with lymph node involvement.

Variables	β regression	Odds ratio	95% C.I.	p-value
Age	1.124	3.067	1.090 - 8.679	0.034
Menopause	0.577	1.780	0.645 - 4.917	0.266
Pregnancy Hx	0.659	1.933	0.682 - 5.484	0.215
Family Hx	0.036	1.037	0.355 - 3.032	0.947
Ascites	1.030	2.800	0.876 - 8.954	0.083
Lymphadenopathy	0.499	1.648	0.576 - 4.716	0.352
Chemotherapy Hx	0.357	1.429	0.459 - 4.447	0.538
CA125	0.001	0.999	0.998 - 1.001	0.296
Side involvement	0.938	2.556	1.010 - 7.106	0.05
Tumor type	1.476	4.375	1.284 - 14.903	0.018
Grade 2/1	1.792	6.000	0.624 - 57.681	0.121
Grade 3/1	2.650	14.250	1.660 - 121.80	0.015
Stage 2/1	1.872	6.500	0.717 - 58.893	0.096
Stage 3/1	3.000	20.090	2.292 - 176.094	0.007

Discussion

Our analysis identified several clinicopathological factors significantly associated with lymph node metastasis in ovarian cancer. In the final multivariable model, five independent predictors emerged: patient age ≤50 years, bilateral disease, serous histology, grade 3 tumor differentiation, and Stage III disease. The univariable analysis yielded similar results, though it additionally highlighted tumor grade 2 as a significant factor, an association that was attenuated in the adjusted model, likely due to sample size limitations.

These findings resonate with the established literature. Erdem et al., similarly reported higher nodal involvement rates in cases with bilateral ovarian disease, positive peritoneal cytology, serous histology, and advanced stage.[15] The pattern of metastasis also warrants consideration. As demonstrated by Fournier et al., the para-aortic region is the predominant site of nodal disease, with isolated pelvic involvement being less common.[16] This supports the necessity of a systematic approach to lymphadenectomy that encompasses both regions when nodal dissection is indicated.

The impact of tumor grade is particularly notable. Our data show a pronounced, stepwise increase in nodal metastasis risk with higher grade, a trend corroborated by Kleppe et al.[17] In their series, the incidence of nodal metastasis rose from 4% in grade 1 tumors to 20% in grade 3 tumors. The consensus from multiple studies, including work by Powless et al., and Zhou et al., reinforces that serous histology and higher-grade disease are robust risk factors for lymphatic spread.[18, 20] While our study did not find a statistically significant link between serum CA-125 levels and nodal involvement (p=0.083), the elevated odds ratio suggests a potential association that may have been underpowered to detect; this aligns with other reports that identify elevated CA-125 as a risk factor.[19, 20]

Synthesizing this evidence, a practical clinical algorithm begins to take shape. For a well-defined subset of patients -those over 50 years of age with unilateral, grade 1, mucinous, Stage I tumors- the risk of lymph node metastasis appears sufficiently low to question the routine necessity of lymphadenectomy. This selective approach is consistent with the conclusion of Kleppe et al., who noted that omitting complete lymphadenectomy might be acceptable only in grade 1 mucinous tumors.[17]

Conclusions

This study substantiates several key determinants of lymphatic spread in epithelial ovarian cancer: younger age, bilateral and serous tumors, high-grade histology, and advanced stage. These factors should inform preoperative risk stratification. Importantly, our data contribute to the

growing evidence that a tailored surgical approach is feasible. For patients with opposing, low-risk characteristics -specifically, older age with unilateral, low-grade, mucinous, early-stage disease- lymph node dissection may be safely omitted. Refining surgical indications in this manner can help avoid the morbidity of unnecessary lymphadenectomy without compromising oncologic staging, thereby personalizing surgical management for women with ovarian cancer.

Acknowledgment

We sincerely thank the staff of Imam Khomeini Hospital and Amir Alam Hospital, the study participants, and the ethics committee for their support. Special appreciation is extended to our colleagues, mentors, and loved ones for their invaluable guidance, encouragement, and contributions to this research.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

Computed Tomography: CT; Magnetic Resonance Imaging: MRI; Cancer Antigen-125: CA-125; Complete Blood Count: CBC; Liver Function Tests: LFTs; Standard Deviation: SD; Odds Ratio: OR; Confidence Interval: CI.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

None.

Role of the funding source

None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Tehran University of Medical Sciences (Ethical Approval ID: IRCT20200417050934N1). All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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Cite this article as:
Mohammadi L, Gandomkar H, Mahmoodzadeh H, Moghimi Z, Omranipour R, Sobhanian E. Predictors of lymphatic metastasis and indications for lymphadenectomy in epithelial ovarian carcinoma. J Cancer Res Pharmacol. 2025; 1(2): 101-106. doi: 10.22034/jcrph.2025.553688.1012