

ORIGINAL ARTICLE

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Clinicopathological risk factors for pelvic lymph node metastasis in endometrioid endometrial adenocarcinoma

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Abstract

Lymph node metastasis (LNM) represents a key determinant of prognosis in endometrial cancer, with a direct impact on disease staging and decisions regarding adjuvant therapy. Although endometrioid-type endometrial carcinoma (EEC) generally has a favorable prognosis, lymphatic spread may occur even in the early stages. The present study aimed to identify clinicopathologic variables independently associated with pelvic lymph node involvement among patients with EEC who underwent comprehensive lymphadenectomy. The retrospective analysis included 478 women with histologically verified EEC who underwent primary surgical staging with systematic pelvic lymphadenectomy. Univariate and multivariate logistic regression analyses were performed to identify the risk factors associated with pelvic LNM. Among the study population, 49 patients (10.2%) had pelvic LNM, while 429 (89.8%) were node-negative. Serum CA125 levels (34.1 vs. 19.5 U/mL), tumor diameters (4.6 vs. 3.5 cm), grade 3 rate (32.7% vs. 17.7%), deep myometrial invasion rate (61.2% vs. 38%), lymphovascular space invasion (LVSI) rate (59.2% vs. 22.4%), and cervical stromal invasion rate (34.7% vs. 9.1%) were significantly higher in those with nodal metastases. Multivariate analysis identified LVSI (HR=4.04), cervical stromal invasion (HR=3.53), tumor size (HR=1.06), and grade 3 histology (HR=1.39) as independent predictors of pelvic nodal metastasis ($p<0.05$). Age, Body Mass Index (BMI), and myometrial invasion did not reach statistical significance in the multivariate analysis. LVSI, cervical stromal involvement, tumor dimension, and higher tumor grade independently predicted pelvic lymph node metastasis in EEC. Integrating these parameters into preoperative and intraoperative evaluation could improve patient selection for lymphadenectomy and optimize individualized surgical management.

Keywords: Endometrial carcinoma, nodal metastasis, lymphovascular space invasion, grade, cervical stromal involvement

Introduction

Approximately 80–90% of all endometrial cancer cases are classified as endometrioid-type endometrial carcinoma (EEC), which represents the most common histological subtype of this malignancy. Compared to non-endometrioid forms such as serous or clear cell carcinoma, EEC typically has a better prognosis [1,2]. A subset of patients with EEC, despite the generally indolent nature of the disease, may still encounter lymphatic spread and recurrence, even at early clinical stages. By evaluating the lymph nodes, the stage of the patients is known precisely and provides important information for prognosis and adjuvant treatment guidance [3,4].

Lymph node assessment with hysterectomy remains the standard approach recommended by guidelines such as the National

Comprehensive Cancer Network (NCCN) and the European Society of Gynaecological Oncology (ESGO) [3,5]. The sentinel lymph node (SLN) mapping technique is the current standard surgical approach for lymph node assessment in endometrial cancer. Nevertheless, systematic lymphadenectomy—encompassing both pelvic and para-aortic node dissection—is also recommended as an alternative surgical approach for endometrial cancer [5-7]. Lymph node metastasis is a recognized prognostic determinant, closely linked to both disease recurrence and reduced survival outcomes. Nevertheless, the clinical benefit of performing systematic lymphadenectomy continues to be debated. Although certain retrospective investigations, such as the SEPAL study, have suggested a potential survival advantage in carefully selected high-risk patients, large randomized controlled trials—including ASTEC and Benedetti Panici—did

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not confirm any significant improvement in either overall or disease-free survival [8-10].

Given these conflicting data, selective lymphadenectomy aims to balance accurate staging with reduced surgical morbidity [11]. Identifying reliable preoperative or intraoperative predictors of nodal involvement is therefore crucial to optimize patient selection for lymph node dissection. Multiple clinicopathological parameters, such as higher grade, the occurrence of lymphovascular space invasion (LVSI), deep myometrial invasion, and elevated serum CA125 levels, have been suggested as potential indicators of lymphatic spread [12-14]. However, most previous analyses included heterogeneous histologic subtypes, potentially confounding risk assessment specific to endometrioid tumors.

We aimed to identify the independent clinicopathological parameters of pelvic nodal metastasis in women with endometrioid-endometrial cancer.

Material and Methods

Patient Selection

Our study was planned retrospectively and included patients diagnosed with endometrioid-endometrial carcinoma who underwent comprehensive surgical staging together with systematic lymph node dissection in our clinic between January 2000 and May 2025.

Patients were excluded if they had non-endometrioid histologic subtypes, concurrent malignancies, distant metastases at diagnosis, or incomplete surgical or pathological information. All eligible cases underwent surgical staging (total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection). Para-aortic lymphadenectomy was performed selectively according to predefined clinical and surgical criteria, including tumor grade, depth of myometrial invasion, presence of lymphovascular space invasion, intraoperative findings, patient-related comorbidities, and the surgeon's assessment of operative risk. Para-aortic lymphadenectomy was not routinely performed in patients considered to have low-risk disease or in those with an increased surgical risk.

Sentinel lymph node mapping has become the standard approach in patients with low-risk endometrial cancer, and we also recognize the clinical importance of SLN assessment. However, this surgical technique was introduced at our institution relatively recently and has only been applied in a limited number of cases. Therefore, due to the small sample size and the lack of sufficient follow-up, patients who underwent SLN mapping were not included in the present study.

Clinicopathologic Data Collection

Demographic, surgical, and histopathologic parameters were retrieved from institutional medical and pathology reports. The following variables were recorded: age, Body Mass Index (BMI), CA125, grade, tumor diameter, depth of myometrial invasion, LVSI, cervical stromal invasion, peritoneal cytology results,

International Federation of Gynecology and Obstetrics (FIGO) 2009 stage, and the number of pelvic lymph nodes harvested.

All pathological assessments were conducted by specialized gynecologic pathologists. Tumor size was determined as the greatest dimension observed on gross examination. The presence of lymphovascular space invasion was confirmed only when malignant cells were detected within endothelial-lined vascular or lymphatic channels beyond the primary tumor. Pelvic lymph node metastasis (LNM) was defined as histological evidence of tumor deposits in a lymph node, irrespective of its size or count. Based on nodal status, patients were categorized into two cohorts: those with and without pelvic LNM. Comparative analyses of clinicopathologic features between these groups were performed to identify parameters linked to nodal metastasis.

Despite the long study period (2000–2025), the fundamental principles of surgical and pathological evaluation remained consistent throughout the study, thanks to our institution's advantage as a tertiary care center. Surgical staging was performed according to the standards applicable at the time, and all patients were systematically evaluated by experienced gynecologic oncologists. Similarly, pathological evaluation was performed by specialist gynecologic pathologists following institutional protocols, and key parameters such as depth of myometrial invasion, tumor grade, and lymph node status were assessed using standardized criteria.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median values with range and compared between groups using the Mann–Whitney U test, as the data did not follow a normal distribution. Categorical variables were presented as frequencies and percentages, and comparisons were made using the chi-square test or Fisher's exact test, as appropriate based on expected cell counts.

Initially, univariate logistic regression analysis was performed to evaluate the association between clinicopathologic factors and the occurrence of LNM. Variables with a p-value less than 0.10 in the univariate analysis were subsequently included in a multivariate logistic regression model using a backward stepwise selection method to identify independent predictors of pelvic LNM. The results were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), and a p-value of <0.05 was considered statistically significant.

Ethical Approval

This study received ethical approval from the Health Research Ethics Committee of Bursa Uludağ University (No: 2025/842/15-33; Date: 10 September 2025). As this study was conducted retrospectively, obtaining written informed consent from participants was not deemed necessary. The study was carried out in compliance with the principles of the Declaration of Helsinki, which outlines globally recognized ethical guidelines for research involving human subjects.

Results

Negative pelvic lymph nodes were found in 429 patients (89.8%) and positive in 49 patients (10.2%). The study cohort had a median age of 62 years (range: 27–90) and a median BMI of 35.0 kg/m² (range: 18.4–64.0). The median serum CA-125 concentration was 21 U/mL (range: 3.3–44.1), and the median tumor dimension was 4.0 cm (range: 0.4–14.0). A median of 21 pelvic lymph nodes (range: 2–82) were dissected and submitted for pathologic assessment. Histopathologically, 47.5% of patients had stage 1 disease, 33.3% had stage 2 disease, and 19.2% had stage 3 disease. According to FIGO staging, 74.8% of patients were in stage I, 7.9% in stage II, and 17.3% in stage III. The proportion of patients with less than half myometrial invasion was 59.6%, and more than half was 40.4%. LVSI was positive in 26.2% of patients, cervical stromal invasion in 11.7%, and positive peritoneal cytology in 1.0% (Table 1).

Table 1. Baseline clinicopathologic characteristics of the study cohort	
Variable	Total cohort n (%) or Median (Range)
Age (years)	62 (27–90)
BMI (kg/m ²)	35.0 (18.4–64.0)
CA125 (U/mL)	21 (3.3–443.1)
Tumor size (cm)	4.0 (0.4–14.0)
Pelvic LN harvested (n)	21 (2–82)
Grade	
1	227 (47.5%)
2	159 (33.3%)
3	92 (19.2%)
FIGO stage	
I	358 (74.8%)
II	38 (7.9%),
III	82 (17.3%)
Myometrial invasion	
<50%	285 (59.6%)
>50%	193 (40.4%)
LVSI	
Absent	350 (73.2%)
Present	125 (26.2%)
Unknown	3 (0.6%)
Cervical stromal invasion	
Absent	422 (88.3%)
Present	56 (11.7%)
Peritoneal cytology	
Absent	466 (97.5%)
Present	5 (1.0%)
Unknown	7 (1.5%)
Pelvic lymphatic metastasis	
Absent	429 (89.8%)
Present	49 (10.2%)

When patients were stratified according to pelvic lymph node status, those with pelvic LNM had significantly higher median CA125 levels (34.1 vs. 19.5 U/mL, p<0.001) and larger tumor size (4.6 vs. 3.5 cm, p<0.001). When examined according to grade, grade 3 tumors were more common in patients with pelvic nodal metastases (32.7% vs. 17.7%, p=0.008). Metastasis was significantly more frequent in patients with deep myometrial invasion (>50%) (61.2% vs. 38.0%, p=0.004). Similarly, LVSI (59.2% vs. 22.4%, p<0.001) and cervical stromal invasion (34.7% vs. 9.1%, p<0.001) were strongly associated with pelvic lymphatic dissemination. No significant differences were seen in age, body mass index, or peritoneal cytology status (Table 2).

Table 2. Comparison of clinicopathologic characteristics between patients with and without pelvic lymph node metastasis			
Variable	Pelvic LNM (- 429 (89.8%)	Pelvic LNM (+) 49 (10.2%)	p-value
Age (years)	62.0 (27.0-90.0)	62.0 (44.0-77.0)	0.913
BMI (kg/m ²)	35.0 (18.4-64.0)	34.9 (23.0-51.0)	0.784
CA125 (U/mL)	19.5 (3.3-400.0)	34.1 (4.2-443.1)	<0.001
Tumor size (cm)	3.5 (0.4-14.0)	4.6 (1.5-11.5)	<0.001
Pelvic LN harvested (n)	21.0 (2.0-82.0)	23.0 (12.0-55.0)	0.062
Grade			
1	213 (49.7%)	14 (28.6%)	0.008
2	140 (32.6%)	19 (38.8%)	
3	76 (17.7%)	16 (32.7%)	
FIGO Stage			
I	357 (83.2%)	0 (0.0%)	<0.001
II	38 (8.9%)	0 (0.0%)	
III	34 (7.9%)	49 (100%)	
Myometrial invasion			
<50%	266 (62.0%)	19 (38.8%)	0.004
>50%	163 (38.0%)	30 (61.2%)	
LVSI			
Absent	330 (76.9%)	20 (40.8%)	<0.001
Present	96 (22.4%)	29 (59.2%)	
Unknown	3 (0.7%)	0 (0.0%)	
Cervical stromal invasion			
Absent	390 (90.9%)	32 (65.3%)	<0.001
Present	39 (9.1%)	17 (34.7%)	
Peritoneal cytology			
Absent	419 (97.7%)	47 (95.9%)	0.721
Present	4 (0.9%)	1 (2.0%)	
Unknown	6 (1.4%)	1 (2.0%)	

The univariate logistic regression analysis revealed that multiple factors were significantly correlated with the presence of pelvic nodal metastasis. These included higher tumor grade (grade 3 vs. grades 1–2; HR=2.89, 95% CI: 1.91–3.95, p=0.019), greater tumor diameter (HR=1.24, 95% CI: 1.09–1.41, p<0.001), deep

myometrial infiltration (HR=1.56, 95% CI: 1.11–1.99, p=0.011), presence of lymphovascular space invasion (LVSI; HR=5.46, 95% CI: 2.89–10.31, p<0.001), cervical stromal involvement (HR=5.65, 95% CI: 2.83–11.28, p<0.001), and elevated serum CA125 levels (HR=1.03, 95% CI: 1.01–1.09, p=0.036). In the multivariate logistic regression model, lymphovascular space invasion (LVSI) (HR=4.04, 95% CI: 1.92–8.49, p<0.001), cervical stromal involvement (HR=3.53, 95% CI: 1.58–7.85, p=0.002), larger tumor size (HR=1.06, 95% CI: 1.02–1.24, p<0.001), and high-grade (grade 3) histology (HR=1.39, 95% CI: 1.09–2.19, p=0.024) were identified as independent predictors of pelvic lymph node metastasis. Conversely, patient age, BMI, and depth of myometrial invasion were not statistically significant in the multivariate analysis (Table 3).

Table 3. Univariate and multivariate logistic regression analysis for predictors of pelvic lymph node metastasis

Variable	Univariate HR (95% CI)	p- value	Multivariate HR (95% CI)	p- value
Age	1.0 (0.97–1.03)	0.985	–	–
BMI	0.99 (0.96–1.04)	0.718	–	–
CA125	1.03 (1.01–1.09)	0.036	1.01 (0.92–1.05)	0.314
Grade				
1-2 (ref.)	1.00			
3	2.89 (1.91–3.95)	0.019	1.39 (1.09–2.19)	0.024
Tumor size	1.24 (1.09–1.41)	<0.001	1.06 (1.02–1.24)	<0.001
Myometrial invasion				
<50% (ref.)	1.00			
>50%	1.56 (1.11–1.99)	0.011	1.51 (0.77–2.96)	0.231
LVSI				
Absent (ref.)	1.00			
Present	5.46 (2.89–10.31)	<0.001	4.04 (1.92–8.49)	<0.001
Cervical stromal invasion				
Absent (ref.)	1.00			
Present	5.65 (2.83–11.28)	<0.001	3.53 (1.58–7.85)	0.002
Peritoneal cytology				
Absent (ref.)	1.00			
Present	2.72 (0.28–26.69)	0.391	–	–

Discussion

In this large single-institution cohort of surgically staged women with endometrioid type endometrial carcinoma, pelvic nodal metastasis was identified in 10.2% of the cases. The incidence observed in our series is consistent with previously reported rates ranging from 3% to 12% in similar homogeneous endometrioid cohorts [13,15,16]. Our analysis demonstrated that tumor size, LVSI, cervical stromal invasion, and high tumor grade were distinct risk factors of pelvic nodal metastasis. These findings support the notion that patients with endometrioid endometrial cancer have biologically aggressive disease despite a favorable histologic subtype.

In our study, consistent with previous reports, LVSI emerged as the most powerful distinct risk factor of pelvic nodal involvement. Yalcin et al. and numerous studies, including those by [17,18], have highlighted LVSI as a critical determinant of lymphatic spread and recurrence. The presence of LVSI reflects the invasion

of tumor cells into vascular and lymphatic channels, facilitating regional and distant spread. In our multivariate analysis, LVSI increased the likelihood of pelvic nodal metastasis approximately fourfold, highlighting its clinical importance in surgical planning and adjuvant therapy decision-making.

Cervical stromal invasion was another strong independent predictor of pelvic nodal involvement in our study. This result aligns with data from Li et al. and Sun et al., who similarly reported significantly higher lymphatic spread in patients with cervical invasion [16,19]. Cervical involvement provides the tumor with direct access to the rich lymphatic plexus of the cervix, thus increasing the likelihood of nodal metastasis. Hence, this factor should be thoroughly assessed through preoperative imaging and intraoperative evaluation to guide the appropriate extent of lymphadenectomy.

Tumor size was likewise identified as an independent determinant of pelvic nodal involvement in our study. Multiple

investigations have demonstrated a positive relationship between tumor size and lymphatic metastasis, which may be attributed to the increased likelihood of deeper myometrial invasion and lymphovascular spread in larger lesions [20,21]. Our findings support the inclusion of tumor size in preoperative risk models and demonstrate that each unit increase in tumor size is associated with an approximately 6% increase in the risk of pelvic lymph node metastasis (HR=1.06, 95% CI: 1.02–1.24, $p<0.001$).

The correlation between histologic grade and the occurrence of lymphatic metastasis has been thoroughly established in previous studies [22]. High-grade (grade 3) tumors exhibit increased cellular atypia and proliferative activity, predisposing them to early lymphatic spread. In our analysis, grade 3 histology independently predicted pelvic nodal metastasis, consistent with previous multicenter studies and meta-analyses. This finding highlights the importance of accurately evaluating and grading the preoperative endometrial biopsy.

In contrast, myometrial invasion depth lost statistical significance in the multivariate model, likely due to its close correlation with LVSI and tumor size. While deep invasion is traditionally considered a major risk factor for nodal involvement [13,19], our results suggest that its prognostic effect may be mediated through coexisting LVSI and high-grade disease. Similarly, serum CA125 levels were significant in the univariable model but lost significance following adjustment for confounding factors, suggesting a limited independent prognostic value.

In the overall cohort, the rate of pelvic nodal metastasis was 10.2%, and a substantial proportion of patients who underwent lymphadenectomy had no evidence of lymph node metastasis. However, this finding should not be interpreted as indicating that lymphadenectomy was unnecessary at the time it was performed. Rather, it demonstrates that these patients showed no evidence of nodal spread and that, with appropriate patient selection, the risks associated with lymph node removal could potentially be avoided. Sentinel node detection has gained recognition as an effective substitute for extensive nodal dissection, providing accurate staging information while reducing surgical morbidity [3,5,7]. However, predictive models derived from complete dissection cohorts like ours remain important for identifying patients who may still benefit from extended nodular evaluation, particularly in centers where SLN mapping is unavailable or unvalidated.

The updated FIGO 2023 staging system aims to refine prognostic assessment in endometrial cancer beyond the traditional anatomy-based staging approach. In parallel, the role of molecular classification in risk stratification and treatment planning has gained increasing importance in recent years [23]. The molecular subgroups defined by The Cancer Genome Atlas (TCGA)—namely POLE-mutated, mismatch repair (MMR)-deficient, p53-abnormal, and no specific molecular profile (NSMP) tumors—have been incorporated

into the current FIGO and ESGO/ESTRO/ESP guidelines [5]. Molecular classification has been shown to provide prognostic information beyond conventional clinicopathologic factors, particularly in early-stage endometrioid endometrial cancer, thereby influencing adjuvant treatment decision-making. However, our findings remain clinically relevant in real-world practice, particularly in resource-limited settings where advanced molecular testing is not routinely available. In such centers, clinical decision-making continues to rely largely on traditional clinicopathologic parameters. Within this context, our study provides a practical and applicable approach for predicting the risk of pelvic lymph node metastasis in the absence of molecular classification.

The strengths of this study lie in its large, histologically uniform patient cohort and the use of standardized surgical and pathological procedures within a single tertiary institution, which reduced variability in sample assessment. Nevertheless, several limitations of the present study should be acknowledged. Its retrospective design inherently carries potential methodological constraints, including the possibility of selection bias. Temporal changes in surgical techniques and pathological practices constitute an inherent limitation of long-term retrospective studies, including the present study. The lack of molecular profiling data (e.g., POLE, p53, MMR status) is particularly limiting for risk classification in endometrial cancer. The lack of SLN use should be considered a limitation of this study. Although SLN mapping has become a standard approach in the surgical management of low-risk endometrial cancer, it was not routinely implemented during much of the study period. As a result, SLN data were unavailable for inclusion in the analysis, which may limit the applicability of our findings to contemporary practice settings where SLN mapping is widely adopted.

Conclusion

In conclusion, our findings indicate that women with endometrioid type endometrial carcinoma are at an increased risk of pelvic nodal metastasis when exhibiting larger tumor size, higher histological grade, lymphovascular space involvement, and cervical stromal invasion. Incorporating these factors into clinical decision-making algorithms may help refine the extent of lymph node evaluation and support individualized surgical planning.

Ethical Approval

Approved by the Health Research Ethics Committee of Bursa Uludağ University (No: 2025/842/15-33; Date: 10 September 2025).

Patient Consent

Informed consent was waived due to the retrospective design.

Conflict of Interest

The authors declare no conflict of interest.

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