

ORIGINAL RESEARCH ARTICLE

Clinicopathological determinants of lymph node metastasis and lymphovascular space invasion in endometrial carcinoma: Impact on recurrence-free and overall survival outcomes

Akbar Ibrahimov*, Ahlman Amiraslanov, Abuzar Gaziye, and Fidan Novruzova

Department of Oncology, Faculty of General Medicine, Azerbaijan Medical University, Baku, Azerbaijan

Abstract

Introduction: Lymph node metastasis (LNM) and lymphovascular space invasion (LVSI) are established prognostic markers in endometrial carcinoma (EC), yet their clinicopathological determinants and prognostic impact remain incompletely characterized in underrepresented regional populations.

Objective: This study aims to identify predictors of LNM and LVSI and their influence on disease-free survival (DFS) and overall survival (OS) in EC patients.

Methods: A retrospective cohort of 462 histologically confirmed EC patients who underwent primary surgical staging at Azerbaijan Medical University was analyzed. Fisher's exact test, Student's t-test, and the Mann-Whitney U test were used for between-group comparisons. Univariate logistic regression was used to assess associations with LNM and LVSI. Kaplan-Meier methodology and univariate Cox proportional hazards regression were applied to DFS and OS. An exploratory multivariate Cox model was constructed for each endpoint using variables selected a priori based on clinical relevance and univariate significance ($p < 0.05$).

Results: LNM was present in 17.6% of patients undergoing lymphadenectomy; LVSI in 22.7% with known status. Non-endometrioid histology, grade III differentiation, myometrial invasion $> 50\%$, serosal extension, cervical involvement, and adnexal spread were each independently associated with LNM and LVSI. In exploratory multivariate analysis, grade III independently predicted shorter DFS (hazard ratio [HR] = 2.24; 95% CI: 1.03–4.90; $p = 0.043$) and LNM predicted shorter OS (HR = 2.39; 95% CI: 1.06–5.39; $p = 0.035$); both findings should be considered hypothesis-generating.

Conclusion: Adverse clinicopathological features, including high histological grade, non-endometrioid subtype, deep myometrial invasion, and locoregional extension, are significant predictors of LNM and LVSI. These findings support their systematic incorporation into perioperative risk stratification. Prospective studies with molecular profiling and extended follow-up are warranted.

Keywords: Endometrial carcinoma; Lymph node metastasis; Lymphovascular space invasion; Disease-free survival; Overall survival; 2023 FIGO staging system; Clinicopathological predictors

***Corresponding author:**Akbar Ibrahimov
(eibrahimov1@amu.edu.az)

Citation: Ibrahimov A, Amiraslanov A, Gaziye A, Novruzova F. Clinicopathological determinants of lymph node metastasis and lymphovascular space invasion in endometrial carcinoma: Impact on recurrence-free and overall survival outcomes. *Eurasian J Med Oncol.* 2026;10(4):026210226. doi: 10.36922/EJMO026210226

Received: May 19, 2026**Revised:** May 29, 2026**Accepted:** June 8, 2026**Published online:** June 22, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Uterine corpus carcinoma of endometrial origin is the sixth most commonly diagnosed malignancy in women globally and the predominant gynecological cancer in economically developed nations. Global surveillance data from GLOBOCAN 2020 estimated approximately 417,000 incident cases and nearly 97,400 deaths attributable to this disease worldwide, with the highest burden concentrated in high-income regions.¹⁻³ Rising prevalence in both high- and middle-income regions has been attributed to the widening epidemic of obesity, physical inactivity, and metabolic dysregulation—well-established hormonal risk factors for endometrial tumorigenesis. Epidemiological data specific to Azerbaijan and the South Caucasus remain sparse, representing a gap that the present work partly addresses.

Known predisposing factors include advanced age, obesity, type 2 diabetes mellitus, nulliparity, unopposed exogenous estrogen exposure, tamoxifen therapy, and hereditary cancer syndromes such as Lynch syndrome.⁴⁻⁷ Owing to the early and specific warning signs of abnormal uterine bleeding, most patients present with organ-confined disease, conferring a comparatively favorable prognosis. In the standard surgical approach, total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) is combined with lymphadenectomy or sentinel lymph node (SLN) biopsy to achieve complete staging.^{8,9} When high-risk pathological features are identified, including advanced staging, high-grade histology, lymph node involvement, and lymphovascular invasion, adjuvant systemic therapy or radiotherapy is recommended to reduce the probability of recurrence.¹⁰

Numerous tissue-based biomarkers have been proposed as indicators of recurrence risk and patient survival in endometrial carcinoma (EC). Among these, tumor stage, histological grade, invasion depth into the myometrium, lymphovascular space invasion (LVSI), locoregional extension, and nodal involvement have the strongest and most reproducible evidence base.^{11,12} Nodal metastasis in EC ranges 10–15% across published series, with rates dependent on surgical approach, pathological thoroughness, and patient risk profile.¹³⁻¹⁵ Under the 2023 revised International Federation of Gynecology and Obstetrics (FIGO) staging framework, the detection of pelvic nodal involvement upgrades the disease to stage IIIC1, whereas para-aortic nodal metastasis defines stage IIIC2, both carrying substantially worse prognoses than node-negative equivalents.¹⁶ Experimental work has further illuminated the mechanistic role of lymph node colonization, demonstrating that it may facilitate immune tolerance and potentiate distant metastatic spread.¹⁷

Clinicopathological factors repeatedly linked to nodal involvement include histological grade, tumor dimensions, histological subtype, depth of myometrial infiltration, cervical extension, LVSI, and positive peritoneal cytology.¹⁸⁻²⁰ Reported five-year disease-free survival (DFS) for patients with retroperitoneal node-positive disease spans a wide range from 10% to 75%, reflecting the heterogeneity of patient populations and adjuvant treatment strategies.²¹ LVSI, operationally defined as the presence of malignant cells within vascular or lymphatic lumina, has been consistently identified as a prognostically adverse feature independently associated with both nodal metastasis and reduced survival.^{22,23} The clinical weight of LVSI has been further elevated by its formal incorporation into the 2023 FIGO staging system, which now uses LVSI extent to further substage disease within stages I and II.^{16,24} Recent evidence has drawn an important distinction between focal and substantial LVSI. Capasso *et al.*²⁵ demonstrated in a large multicenter cohort of 2,091 stage I endometrioid carcinomas that substantial LVSI, but not focal LVSI, independently predicted inferior DFS and overall survival (OS) at multivariable analysis, with both LVSI-negative and LVSI-focal groups sharing similar outcomes. This clinically actionable finding reinforces the necessity of semiquantitative LVSI reporting in contemporary pathology practice.

Despite a growing body of literature, large-scale studies simultaneously examining the combined clinicopathological determinants of both lymph node metastasis (LNM) and LVSI within the same cohort, alongside their long-term prognostic impact, remain limited, particularly in the South Caucasus and Central Asian regions. The present investigation was therefore designed to bridge this gap by characterizing LNM and LVSI predictors and examining their prognostic significance for DFS and OS in patients surgically treated at a tertiary oncology center in Azerbaijan.

2. Materials and methods

2.1. Study design and patient selection

This single-center, retrospective cohort study was conducted within the Department of Oncology at Azerbaijan Medical University, Baku, Azerbaijan. Ethical clearance was obtained from the local Institutional Review Board of the Oncological Department at Azerbaijan Medical University (Approval No. N138; February 3, 2024). All procedures were carried out in conformity with the ethical principles outlined in the Declaration of Helsinki.

Inclusion criteria comprised: (i) adult female patients; (ii) histologically confirmed primary EC; (iii) primary surgical treatment performed at the study

institution between January 2018 and December 2024; and (iv) availability of minimum clinicopathological documentation, including histological subtype, surgical procedure, and follow-up data.

Exclusion criteria included: (i) prior history of uterine or gynecological malignancy; (ii) synchronous non-uterine malignancy precluding attribution of outcomes to EC; (iii) incomplete medical records rendering key variables unavailable; and (iv) no documented follow-up contact after primary surgery.

After applying these criteria, 462 consecutive patients formed the study population. All retrieved variables, including patient age, tumor size, histopathological subtype, tumor grade, depth of myometrial invasion, LVSI status, cervical involvement (glandular and stromal), adnexal-ovarian extension, omental involvement, peritoneal cytology results, lymph node status, tumor stage, adjuvant treatment received, and recurrence and survival events, were extracted from clinical records and pathology reports. Tumor staging adhered to the anatomical substage framework of the 2023 FIGO staging system.¹⁶ Full molecular subtyping encompassing DNA polymerase epsilon (POLE) mutational analysis, mismatch repair (MMR) deficiency testing, and *TP53* mutation profiling was not routinely available at the study institution during the observation period, representing a recognized resource limitation in this low-to-middle-income healthcare context.

2.2. Surgical and pathological procedures

The primary surgical procedure was TAH-BSO, accompanied by systematic pelvic and para-aortic lymph node dissection together with infracolic omentectomy in 303 patients (65.6%). A total of 127 patients (27.5%) underwent TAH-BSO without systematic lymphadenectomy, primarily those with early-stage disease and low-risk features where lymphadenectomy was not indicated or was not feasible. The remaining 32 patients (6.9%) underwent alternative or abbreviated procedures. All pathological specimens were evaluated by pathologists with expertise in gynecological oncology. LVSI determination was based on standard hematoxylin-eosin-stained sections and was documented as present or absent; semiquantitative classification into focal versus substantial LVSI was not routinely performed during the study period, which is acknowledged as a limitation. Nodal evaluation encompassed pelvic and para-aortic compartments, with individual node counts recorded.

2.3. Definitions of survival outcomes

Disease-free survival was defined as the interval from the date of primary surgery to the first documented event (tumor recurrence or death from any cause), with patients alive and recurrence-free at the last contact censored at that date. OS was defined as the interval from primary surgery to death from any cause, with surviving patients censored at their last recorded follow-up. These composite-event definitions align with standard oncological outcome reporting guidelines.

2.4. Statistical analysis

All statistical computations were conducted using IBM SPSS Statistics (version 29.0; IBM Corp., United States of America). Distributional normality for continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables are described as mean $\pm$ standard error (SE), with the median and full range also reported; categorical variables are expressed as frequencies and proportions. Between-group differences in categorical variables were evaluated using Fisher's exact test. Comparisons of continuous variables across binary groups used either the independent-samples *t*-test or the Mann-Whitney *U* statistic, depending on distributional properties.

Univariate binary logistic regression was used to assess the association between each clinicopathological variable and LNM/LVSI, expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Kaplan-Meier (KM) curves were generated for DFS and OS, with between-group differences evaluated by the log-rank (Mantel-Cox) test. Univariate Cox proportional hazards regression was applied to estimate hazard ratios (HRs) with 95% CIs for each covariate in relation to DFS and OS.

Given the small number of events (DFS events = 48; OS events = 19), formal multivariate modeling was pursued as an exploratory step only. For DFS, the multivariate model incorporated five variables prespecified on the basis of clinical importance and univariate significance ($p < 0.05$): tumor size, LVSI, grade III, cervical stromal involvement, and serosal invasion. For OS, three variables were entered (age, LVSI, LNM), limited by the available event count. In both models, results are regarded as hypothesis-generating and not definitive, given that event-per-variable ratios were below the widely cited minimum of 10 recommended for reliable Cox regression (cf. the 10 events per variable [EPV] rule). All analyses used complete-case data; variables with

missing observations were excluded from the relevant sub-analyses, and denominators are specified accordingly. Statistical significance was defined as a two-tailed p -value below 0.05.

3. Results

3.1. Patient and tumor characteristics

Table 1 summarizes the demographic and clinicopathological profile of the 462 patients. The cohort had a mean age of 59.90 ± 0.48 years (range: 26–85; median: 60). The majority (65.6%; $n = 303$) underwent the complete staging procedure of TAH+BSO combined with para-aortic lymphadenectomy and infracolic omentectomy; TAH+BSO without lymphadenectomy was performed in 27.5% ($n = 127$).

Endometrioid histology was documented in 355 patients (76.9%). Among the 395 patients with available grade data, 262 (66.3%) had grade I tumors, 61 (15.5%) grade II, and 53 (13.5%) grade III. Ninety-two patients (19.8%) had tumors confined to the endometrium without demonstrable myometrial invasion; 195 (42.0%) showed invasion of less than 50% myometrial thickness, and 157 (34.1%) had invasion exceeding 50%. Serosal extension was present in 22 patients (4.8%).

Among 379 patients with available LVSI data, 86 (22.7%) had LVSI confirmed on pathology (LVSI status was unspecified in 82 cases). Cervical glandular involvement was recorded in 100 patients (21.6%), and cervical stromal involvement in 74 (15.9%). Adnexal-ovarian extension was noted in 45 patients (9.7%), omental spread in 28 (6.0%), and positive peritoneal cytology in 32 (6.9%). Among the 369 patients who underwent formal lymphadenectomy, 65 (17.6%) had confirmed LNM—isolated pelvic nodal involvement in 28, combined pelvic and para-aortic metastases in 27, and isolated para-aortic involvement in 10.

By the anatomical substage criteria of the 2023 FIGO staging system, 251 patients (54.1%) were classified as stage IA and 93 (20.0%) as stage IB. Forty patients (8.6%) experienced disease recurrence during follow-up; the most frequent site was the upper abdomen (11 patients; 2.4%). Nineteen patients (4.1%) died during the observation period. The median follow-up duration was 10.09 months (mean: 17.77 ± 0.85 ; range: 0–133). KM restricted mean DFS was 60.72 months, and restricted mean OS was 69.07 months (both restricted to the maximum observed follow-up of 73.9 months). Median DFS and OS were not reached. Estimated 12-month DFS and OS rates were 90.3% and 96.4%, respectively; corresponding 24-month rates were 84.1% and 93.8%; and 60-month rates were

73.4% and 91.9%.

These estimates were derived from KM projections and should be treated with caution, given the median follow-up of only 10.09 months.

3.2. Clinicopathological correlates of lymph node metastasis

Table 2 summarizes the comparative analysis stratified by nodal status. Patients free of LNM underwent TAH-BSO only (without lymphadenectomy) at a significantly higher rate than their LNM-positive counterparts ($p = 0.001$), consistent with pre-surgical risk assessment guiding the extent of nodal surgery. High-grade (III) tumors, non-endometrioid histological subtypes (serous, carcinosarcoma, clear cell), and deep myometrial invasion or serosal extension were each significantly more prevalent among LNM-positive patients (all $p < 0.001$). The co-occurrence of LVSI with LNM was striking: 59.1% of node-positive patients had LVSI compared with only 13.1% of node-negative patients ($p < 0.001$). Cervical glandular (56.7% vs. 17.4%) and stromal (49.3% vs. 11.1%) involvement, adnexal spread (40.3% vs. 4.9%), omental metastasis (26.9% vs. 2.6%), and positive peritoneal cytology (32.8% vs. 2.6%) were all substantially more frequent in the LNM-positive group. Recurrence (22.7% vs. 5.6%) and mortality (16.7% vs. 1.7%) rates were markedly higher in node-positive patients (both $p < 0.001$). Mean age (64.44 vs. 59.45 years; $p = 0.001$) and mean tumor size (6.02 vs. 3.66 cm; $p < 0.001$) were both significantly greater in LNM-positive patients.

3.3. Clinicopathological correlates of lymphovascular space invasion

Table 3 presents the comparison stratified by LVSI status. Serous, carcinosarcoma, and mixed endometrioid-serous subtypes were all more prevalent in LVSI-positive patients ($p < 0.001$), as was grade III differentiation (38.8% vs. 7.2%; $p < 0.001$). LVSI was strongly associated with deep myometrial invasion (63.3% vs. 23.5%; $p < 0.001$), serosal extension (14.4% vs. 0%; $p < 0.001$), and all forms of locoregional spread. Pelvic LNM was present in 43.0% of LVSI-positive versus 1.7% of LVSI-negative patients ($p < 0.001$). Recurrence rates (18.4% vs. 3.5%) and mortality rates (10.0% vs. 1.4%) were both significantly elevated in LVSI-positive patients.

Regarding survival, KM estimated mean DFS was significantly shorter in LVSI-positive patients (44.99 vs. 68.29 months; log-rank $p < 0.001$). Paradoxically, KM-estimated mean OS appeared numerically longer in LVSI-positive patients (110.53 vs. 71.57 months); the log-rank test was statistically significant ($p < 0.001$).

Table 1. Demographic and clinicopathological characteristics of the 462 patients

Variable	<i>n</i> (%) or Mean $\pm$ SE/Median (Min–Max)
Age (years)	59.90 $\pm$ 0.48/60 (26–85)
Surgical procedure	
TAH + BSO	127 (27.5%)
TAH + BSO + PLND + OE	22 (4.8%)
TAH + BSO + PALND + OE	303 (65.6%)
Other	10 (2.2%)
Histological subtype	
Endometrioid	355 (77.0%)
Serous	39 (8.5%)
Carcinosarcoma	16 (3.5%)
Clear cell	12 (2.6%)
Undifferentiated	7 (1.5%)
Stromal	6 (1.3%)
Mixed (Endometrioid + Serous)	5 (1.1%)
Other/mixed subtypes	20 (4.3%)
Histological grade (<i>n</i> = 393)	
Grade I	259 (65.9%)
Grade II	61 (15.5%)
Grade III	53 (13.5%)
Not specified	20 (5.1%)
Myometrial invasion (<i>n</i> = 461)	
Confined to endometrium	90 (19.5%)
<50%	192 (41.6%)
>50%	157 (34.1%)
Serosal invasion	22 (4.8%)

(Cont'd...)

Table 1. (Continued)

Variable	<i>n</i> (%) or Mean $\pm$ SE/Median (Min–Max)
Lymphovascular space invasion (<i>n</i> = 460)	
Absent	289 (62.8%)
Present	90 (19.6%)
Not specified	81 (17.6%)
Cervical involvement	
Cervical glandular involvement -Yes	103 (22.3%)
Cervical stromal involvement -Yes	77 (16.7%)
Locoregional spread	
Adnexa-ovarian involvement -Yes	47 (10.2%)
Omental involvement -Yes	29 (6.3%)
Positive peritoneal cytology	33 (7.2%)
Synchronous ovarian uterine cancer	13 (2.8%)
LNM (<i>n</i> = 372)	
LNM absent	305 (82.0%)
LNM present	67 (18.0%)
Pelvic LNM only	28 (7.5%)
Pelvic + para-aortic LNM	29 (7.8%)
Isolated para-aortic LNM	10 (2.7%)
2023 FIGO stage (<i>n</i> = 460)	
Stage IA	247 (53.7%)
Stage IB	92 (20.0%)
Stage II	24 (5.2%)
Stage IIIA	16 (3.5%)
Stage IIIC1	23 (5.0%)
Stage IIIC2	26 (5.6%)
Stage IVA	2 (0.4%)
Stage IVB	30 (6.5%)

(Cont'd...)

Table 1. (Continued)

Variable	<i>n</i> (%) or Mean $\pm$ SE/Median (Min–Max)
Adjuvant therapy (<i>n</i> = 460)	
None	228 (49.6%)
Radiotherapy	73 (15.9%)
Chemotherapy	56 (12.2%)
Chemoradiotherapy	67 (14.6%)
Other/combined regimens	36 (7.8%)
Recurrence & survival	
Recurrence -Yes	39 (8.5%)
Vaginal cuff	6 (1.3%)
Other pelvic structures	8 (1.8%)
Upper abdomen	11 (2.4%)
Liver	4 (0.9%)
Lung	6 (1.3%)
Death during study	18 (3.9%)
Tumor size (cm)	4.00 $\pm$ 0.13/3.5 (0–24)
Pelvic lymph node count	20.01 $\pm$ 0.77/17 (0–84)
Para-aortic lymph node count	8.01 $\pm$ 0.53/4 (0–58)
Total lymph node count	27.90 $\pm$ 1.20/23 (0–109)
Follow-up period (months)	17.77 $\pm$ 0.85/11 (0–133)
DFS (months)	109.44 $\pm$ 4.46 (95% CI: 100.70–118.18)
OS (months)	125.18 $\pm$ 1.97 (95% CI: 121.30–129.05)

Notes: Grade percentages are of *n* = 393 (69 missing, 14.9%). LNM rates are expressed as a proportion of the 372 patients who underwent lymphadenectomy. Eighty-one patients with unspecified LVSI status were excluded from LVSI-stratified analyses. DFS and OS values are Kaplan–Meier unrestricted estimated means; median actual follow-up was 11 months (mean: 17.77 months).

Abbreviations: CI: Confidence interval; DFS: Disease-free survival; LNM: Lymph node metastasis; LVSI: Lymphovascular space invasion; OE: Omentectomy; OS: Overall survival; PALND: Para-aortic lymph node dissection; PLND: Pelvic lymph node dissection; SE: Standard error; TAH-BSO: Total abdominal hysterectomy and bilateral salpingo-oophorectomy.

This finding almost certainly reflects a statistical artifact attributable to the extremely small number of OS events (*n* = 4 deaths in the LVSI-absent group vs. *n* = 9 in the LVSI-present group) and heavy censoring, which renders KM mean OS estimates unreliable; this result should not be construed as a biological protective effect of LVSI.

3.4. Univariate logistic regression for lymph node metastasis predictors

Table 4 presents univariate logistic regression results for LNM. Age per year (OR = 1.047; 95% CI: 1.020–1.075; *p* = 0.001), tumor size per cm (OR = 1.362; 95% CI: 1.218–1.524; *p* < 0.001), LVSI (OR = 45.0; 95% CI: 16.7–121.2; *p* < 0.001), and positive peritoneal cytology (OR = 17.5; 95% CI: 7.3–41.7; *p* < 0.001) emerged as among the strongest univariate predictors of LNM. Grade III histology was associated with a 4.1-fold increased LNM risk compared with grade I tumors. Carcinosarcoma conferred a 14.4-fold elevation in risk, and serosal invasion a 49.2-fold elevation. Stage III and IV disease (combined) showed OR values exceeding 400–700 relative to stage IA, reflecting the definitional overlap between staging and nodal status.

3.5. Univariate logistic regression for lymphovascular space invasion predictors

Table 5 presents the corresponding analysis for LVSI. The largest OR estimates were associated with LNM (OR = 45.0; 95% CI: 16.7–121.2), stage IIIC2 (OR = 157.6; 95% CI: 32.3–769.8), and stage IIIC1 (OR = 111.3; 95% CI: 22.1–559.6). Deep myometrial invasion (>50%) carried an OR of 29.3, cervical stromal involvement an OR of 14.6, and grade III an OR of 14.0. All associations were statistically significant at *p* < 0.001.

3.6. Univariate Cox regression for disease-free survival

Table 6 and Figure 1 present DFS results. Variables significantly associated with shorter DFS in univariate Cox regression included age (HR = 1.07; *p* < 0.001), tumor size (HR = 1.20; *p* < 0.001), LVSI (HR = 6.50; *p* < 0.001), LNM (HR = 6.03; *p* < 0.001), cervical glandular involvement (HR = 2.81; *p* < 0.001), cervical stromal involvement (HR = 3.85; *p* < 0.001), adnexal-ovarian extension (HR = 6.23; *p* < 0.001), omental spread (HR = 6.89; *p* < 0.001), positive peritoneal cytology (HR = 6.89; *p* < 0.001), grade III (HR = 6.63; *p* < 0.001), serous subtype (HR = 3.26; *p* = 0.001), carcinosarcoma (HR = 4.74; *p* = 0.001), clear cell carcinoma (HR = 5.65; *p* = 0.004), undifferentiated carcinoma (HR = 4.44; *p* = 0.040), myometrial invasion >50% (HR = 1.89; *p* = 0.029), serosal invasion (HR = 7.38; *p* < 0.001), and advanced FIGO stages (Stage IIIA: HR = 2.75; *p* = 0.033;

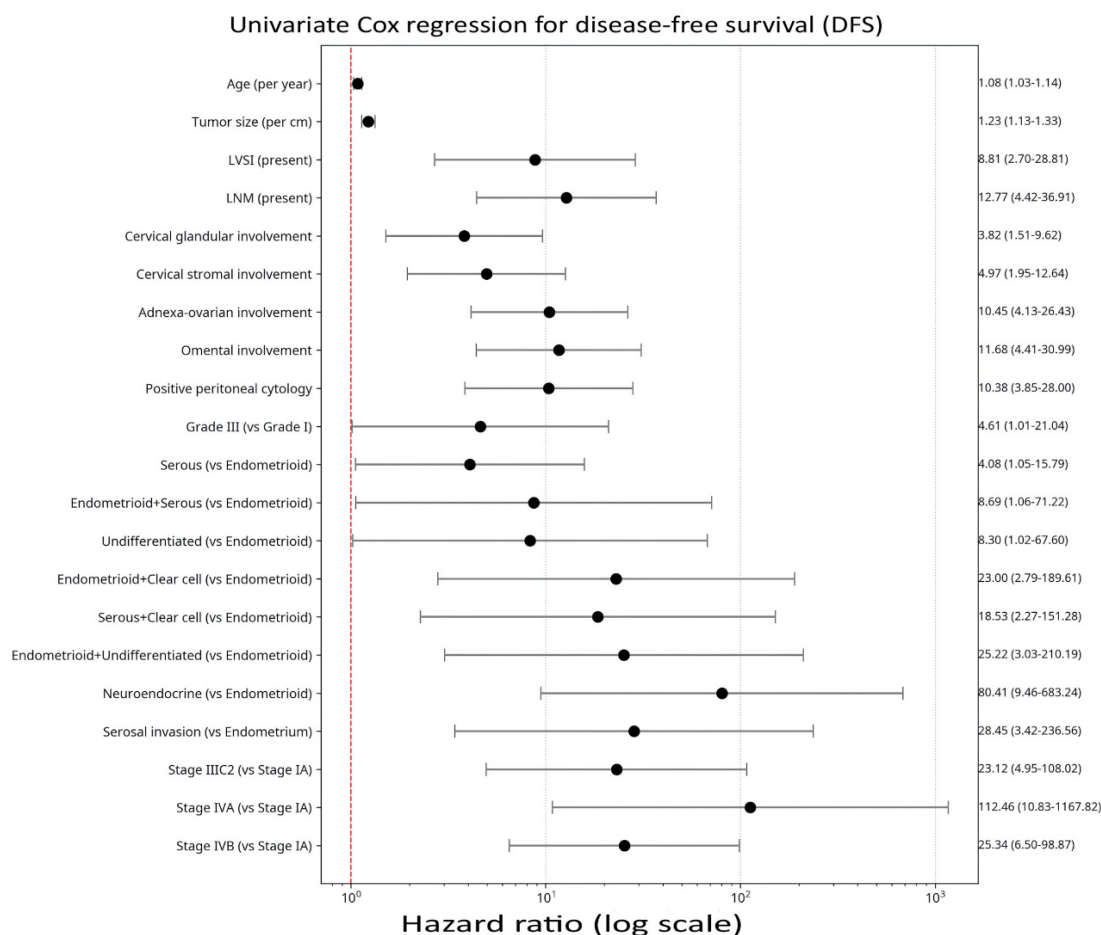


Figure 1. Forest plot displaying hazard ratios (HRs) from univariate Cox proportional hazards regression for disease-free survival ($n = 462$; events = 48). Point estimates are plotted on a logarithmic scale with horizontal bars denoting 95% confidence intervals. A vertical reference line at HR = 1.0 indicates no effect. Variables with near-complete event separation (Stage IVA: $n = 2$ patients; HR = 138.21, 95% CI: 14.93–1,279.72) are truncated at HR = 200 for display clarity.

Abbreviations: CI: Confidence interval; LNM: Lymph node metastasis; LVSI: Lymphovascular space invasion; MI: Myometrial invasion.

Stage IIIC2: HR = 5.52; $p < 0.001$; Stage IVB: HR = 7.81; $p < 0.001$).

In the subsequent exploratory multivariate model (tumor size, LVSI, grade III, cervical stromal involvement, serosal invasion), grade III was the only covariate that retained independent significance (HR = 2.24; 95% CI: 1.03–4.90; $p = 0.043$). This model was constructed on 296 complete cases with 19 DFS events, yielding an event-per-variable ratio of approximately 3.8, substantially below the recommended threshold, and results must therefore be regarded as exploratory only.

3.7. Univariate Cox regression for overall survival

Table 7 and Figure 2 present OS results. Given that only 19 deaths occurred among 462 patients (4.1%), all OS

analyses are inherently underpowered and should be interpreted with substantial caution. Significant univariate predictors included: age (HR = 1.09; $p < 0.001$), LVSI (HR = 8.31; $p < 0.001$), LNM (HR = 11.85; $p < 0.001$), cervical glandular involvement (HR = 3.44; $p = 0.009$), cervical stromal involvement (HR = 4.51; $p = 0.002$), grade III (HR = 5.96; $p = 0.021$), and stage IIIC2 (HR = 5.84; $p = 0.002$). Complete separation (zero deaths in Grade II patients) precluded estimation of a Grade II HR. Stages II and IIIC1 were similarly non-estimable. Variables with near-complete separation (adnexal involvement, omental metastasis, positive cytology, serosal invasion) showed numerically high but statistically unstable HR estimates in this context, and their DFS associations (Table 6) are more reliable.

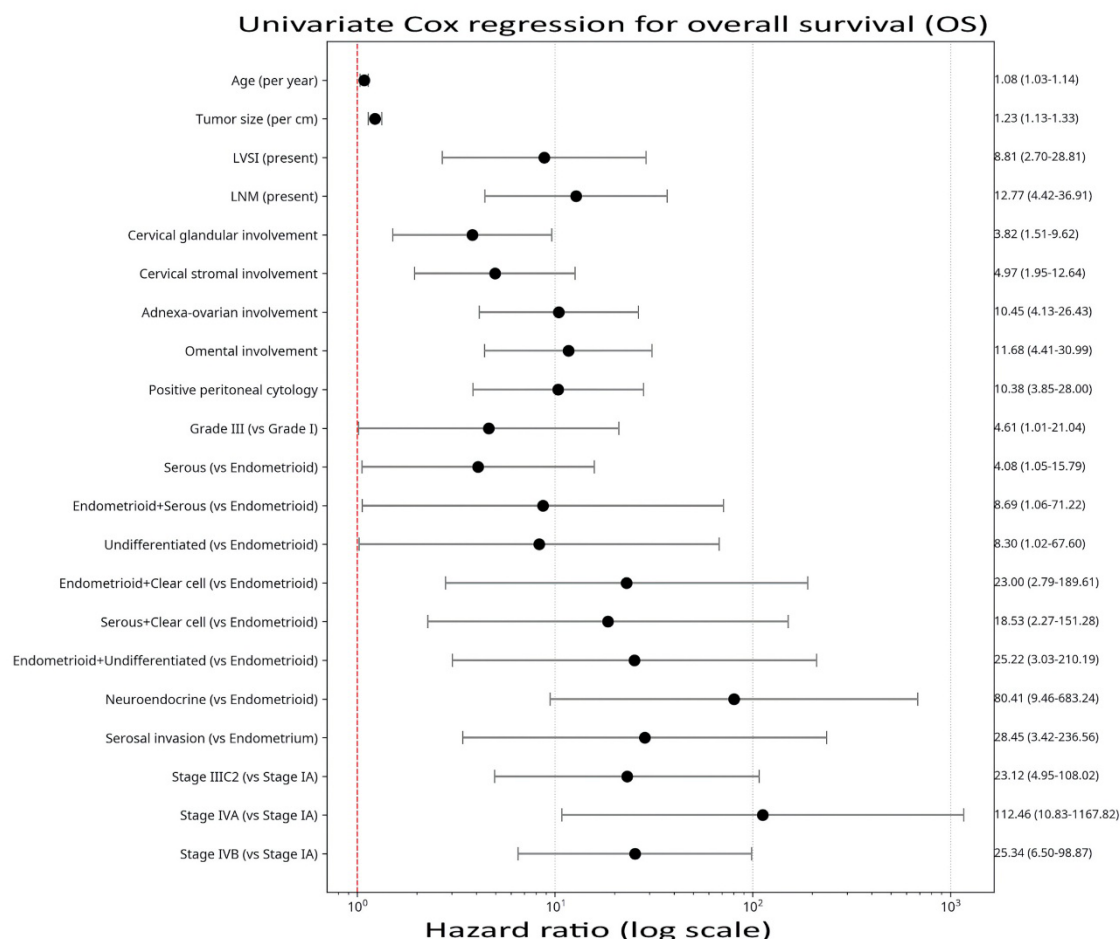


Figure 2. Forest plot displaying hazard ratios (HRs) from univariate Cox proportional hazards regression for overall survival ($n = 462$; events = 19). All estimates are univariate. Given the very low event count (4.1%), all results should be interpreted with caution. Grade II is not depicted (complete separation: zero deaths in this subgroup). Variables excluded due to near-complete separation are adnexal involvement, omental metastasis, positive peritoneal cytology, and serosal invasion. The Stage IVA bar is truncated at HR = 200 for display; the actual estimate is HR = 112.46 (95% CI: 10.83–1,167.82).

Abbreviations: CI: Confidence interval; LNM: Lymph node metastasis; LVSI: Lymphovascular space invasion.

In the exploratory multivariate OS model (age, LVSI, LNM), LNM retained nominal significance (HR = 2.39; 95% CI: 1.06–5.39; $p = 0.035$). This model had only 19 events overall and should be regarded as strictly preliminary.

4. Discussion

This retrospective investigation examined clinicopathological predictors of LNM and LVSI and their prognostic implications in 462 surgically staged EC patients from Azerbaijan, contributing regional data from a geographic and healthcare context underrepresented in the international literature. Non-endometrioid histological subtype, high tumor grade, deep myometrial invasion, serosal extension, and locoregional spread,

particularly cervical invasion, adnexal extension, omental involvement, and peritoneal cytology positivity, were each significantly associated with both LNM and LVSI in univariate analyses. In exploratory multivariate modeling, grade III independently predicted shorter DFS, and LNM independently predicted shorter OS; however, the statistical reliability of these findings is constrained by low event counts and should be interpreted accordingly.

4.1. Lymph node metastasis: Predictors and clinical significance

Lymph node involvement is a pivotal staging criterion in EC and constitutes one of the most powerful determinants of long-term prognosis.^{16,26} Rates of 10–18% across

Table 2. Comparison of clinicopathological parameters by lymph node metastasis (LNM) status

Variable	LNM absent (n = 305)	LNM present (n = 67)	Test/p-value
Surgical procedure			
TAH+BSO	42 (13.8%)	0 (0%)	$\chi^2 = 15.42; p = 0.001$
TAH+BSO+PALND	241 (79.0%)	61 (91.0%)	
Histological subtype			
Endometrioid	248 (81.3%)	31 (46.3%)	$\chi^2 = 50.38; p < 0.001$
Serous	23 (7.5%)	13 (19.4%)	
Carcinosarcoma	5 (1.6%)	9 (13.4%)	
Clear cell	6 (2.0%)	6 (9.0%)	
Histological grade			
Grade I	179 (66.5%)	17 (38.6%)	$\chi^2 = 16.01; p = 0.001$
Grade II	45 (16.7%)	9 (20.5%)	
Grade III	33 (10.8%)	13 (29.5%)	
Myometrial invasion			
Confined to endometrium	57 (18.7%)	0 (0%)	$\chi^2 = 79.03; p < 0.001$
<50%	143 (46.9%)	13 (19.4%)	
>50%	100 (32.8%)	38 (56.7%)	
Serosal invasion	5 (1.6%)	16 (23.9%)	
LVSI			
Absent	231 (75.7%)	5 (7.6%)	$\chi^2 = 111.18; p < 0.001$
Present	40 (13.1%)	39 (59.1%)	
Cervical involvement			
Cervical glandular -Yes	53 (17.4%)	38 (56.7%)	$\chi^2 = 46.01; p < 0.001$
Cervical stromal -Yes	34 (11.1%)	33 (49.3%)	$\chi^2 = 54.02; p < 0.001$
Locoregional spread			
Adnexa-ovarian -Yes	15 (4.9%)	27 (40.3%)	$\chi^2 = 65.66; p < 0.001$
Omental -Yes	8 (2.6%)	18 (26.9%)	$\chi^2 = 49.48; p < 0.001$
Positive cytology	8 (2.6%)	22 (32.8%)	$\chi^2 = 68.38; p < 0.001$
FIGO stage			
Stage IA	177 (58.2%)	0 (0%)	$\chi^2 = 315.28; p < 0.001$
Stage IB	82 (26.9%)	1 (1.5%)	
Stage IIIC1	0 (0%)	23 (34.3%)	
Stage IIIC2	1 (0.3%)	25 (37.3%)	
Stage IVB	10 (3.3%)	17 (25.4%)	

(Cont'd...)

Table 2. (Continued)

Variable	LNM absent (n = 305)	LNM present (n = 67)	Test/p-value
Recurrence & survival			
Recurrence -Yes	17 (5.6%)	15 (22.7%)	$\chi^2 = 19.94; p < 0.001$
Death	5 (1.7%)	11 (16.7%)	$\chi^2 = 29.46; p < 0.001$
Age (years; mean $\pm$ SE)	59.45 $\pm$ 0.60	64.44 $\pm$ 1.26	$t = -3.50; p = 0.001$
Tumor size (cm; mean $\pm$ SE)	3.66 $\pm$ 0.12	6.02 $\pm$ 0.46	$Z = -5.91; p < 0.001$
DFS (months; mean, 95% CI)	65.85 $\pm$ 1.70 (62.50–69.19)	40.40 $\pm$ 4.32 (31.92–48.88)	LR = 30.00; $p < 0.001$
OS, (months; mean, 95% CI)	129.18 $\pm$ 1.73 (125.78–132.57)	48.69 $\pm$ 3.91 (41.02–56.36)	LR = 35.09; $p < 0.001$

Notes: χ^2 indicates Fisher's exact test; Z indicates the Mann–Whitney U test; t indicates the independent samples t-test. DFS and OS are Kaplan–Meier estimated mean values, not directly observed durations.

Abbreviations: CI: Confidence interval; DFS: Disease-free survival; FIGO: International Federation of Gynecology and Obstetrics; LR: log-rank (Mantel–Cox) χ^2 ; LVSI: Lymphovascular space invasion; OS: Overall survival; PALND: Para-aortic lymph node dissection; SE: Standard error; TAH-BSO: Total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Table 3. Comparison of clinicopathological parameters by lymphovascular space invasion (LVSI) status

Variable	LVSI absent (n = 289)	LVSI present (n = 90)	Test/p-value
Surgical procedure			
TAH+BSO	90 (31.1%)	14 (15.6%)	$\chi^2 = 9.44; p = 0.024$
TAH+BSO+PALND	179 (61.9%)	68 (75.6%)	
Histological subtype			
Endometrioid	257 (88.9%)	50 (55.6%)	$\chi^2 = 64.44; p < 0.001$
Serous	12 (4.2%)	17 (18.9%)	
Carcinosarcoma	5 (1.7%)	5 (5.6%)	
Histological grade			
Grade I	205 (77.4%)	20 (29.9%)	$\chi^2 = 72.33; p < 0.001$
Grade II	36 (13.6%)	13 (19.4%)	
Grade III	19 (7.2%)	26 (38.8%)	
Myometrial invasion			
Confined to endometrium	70 (24.2%)	2 (2.2%)	$\chi^2 = 108.20; p < 0.001$
<50%	151 (52.2%)	18 (20.0%)	
>50%	68 (23.5%)	57 (63.3%)	
Serosal invasion	0 (0.0%)	13 (14.4%)	
Cervical involvement			
Cervical glandular -Yes	33 (11.4%)	48 (53.3%)	$\chi^2 = 71.75; p < 0.001$
Cervical stromal -Yes	17 (5.9%)	43 (47.8%)	$\chi^2 = 90.05; p < 0.001$
Lymph nodes			
Pelvic LNM -Yes	4 (1.7%)	34 (43.0%)	$\chi^2 = 95.37; p < 0.001$
Para-aortic LNM -Yes	2 (0.9%)	26 (32.9%)	$\chi^2 = 74.20; p < 0.001$

(Cont'd...)

Table 3. (Continued)

Variable	LVSI absent (<i>n</i> = 289)	LVSI present (<i>n</i> = 90)	Test/ <i>p</i> -value
Locoregional spread			
Adnexa-ovarian -Yes	6 (2.1%)	28 (31.1%)	$\chi^2 = 70.85; p < 0.001$
Omental -Yes	3 (1.2%)	13 (15.9%)	$\chi^2 = 30.08; p < 0.001$
Positive cytology	5 (1.7%)	15 (16.7%)	$\chi^2 = 31.33; p < 0.001$
FIGO stage			
Stage IA	204 (71.1%)	11 (12.2%)	$\chi^2 = 161.95; p < 0.001$
Stage IB	61 (21.3%)	19 (21.1%)	
Stage IIIC1	2 (0.7%)	12 (13.3%)	
Stage IIIC2	2 (0.7%)	17 (18.9%)	
Stage IVB	4 (1.4%)	12 (13.3%)	
Recurrence & survival			
Recurrence -Yes	10 (3.5%)	16 (18.4%)	$\chi^2 = 22.93; p < 0.001$
Death	4 (1.4%)	9 (10.0%)	$\chi^2 = 15.38; p < 0.001$
Age (years; mean $\pm$ SE)	58.61 $\pm$ 0.61	54.50 $\pm$ 0.75 ^a	$t = -4.33; p < 0.001$
Tumor size (cm; mean $\pm$ SE)	3.27 $\pm$ 0.11	5.96 $\pm$ 0.36	$Z = -8.39; p < 0.001$
Pelvic lymph node count (mean $\pm$ SE)	18.10 $\pm$ 0.96	24.39 $\pm$ 1.93	$Z = -2.95; p = 0.003$
Para-aortic lymph node count (mean $\pm$ SE)	6.66 $\pm$ 0.59	11.59 $\pm$ 1.40	$Z = -3.48; p < 0.001$
Total lymph node count (mean $\pm$ SE)	24.55 $\pm$ 1.42	36.10 $\pm$ 3.03	$Z = -3.42; p = 0.001$
DFS (months; mean, 95% CI)	68.29 $\pm$ 1.52 (65.30–71.29)	44.99 $\pm$ 4.87 (35.43–54.54)	LR = 30.09; $p < 0.001$
OS (months; mean, 95% CI)	71.57 $\pm$ 0.73 (70.13–73.00)	110.53 $\pm$ 7.86 (95.11–125.95)	LR = 17.37; $p < 0.001$

Notes: ^aAge SE for the LVSI-present group was corrected from an erroneous entry of 7.50 to 0.75 (confirmed from SPSS output). χ^2 indicates Fisher's exact test; Z indicates the Mann–Whitney U test; t indicates the independent samples t -test. DFS and OS are Kaplan–Meier estimated mean values, not directly observed durations. OS estimates should be interpreted with caution: only 13 deaths occurred (LVSI-absent: $n = 4$; LVSI-present: $n = 9$); the numerically longer Kaplan–Meier mean OS in the LVSI-present group is a censoring artifact, not a biological protective effect.

Abbreviations: CI: Confidence interval; DFS: Disease-free survival; FIGO: International Federation of Gynecology and Obstetrics; LNM: lymph node metastasis; LR: log-rank (Mantel–Cox) χ^2 ; OS: Overall survival; PALND: Para-aortic lymph node dissection; SE: Standard error; TAH-BSO: Total abdominal hysterectomy and bilateral salpingo-oophorectomy.

different study populations are broadly consistent with findings in the published literature.^{13,14,21} The constellation of risk factors predictive of LNM in our cohort, specifically non-endometrioid histology, grade III, deep myometrial invasion, serosal extension, LVSI, cervical infiltration, and adnexal involvement, mirrors findings from multiple earlier investigations.^{18–20,27–29} Taskiran *et al.*³⁰, in an analysis of 278 surgically staged patients, similarly identified grade, histological type, and depth of myometrial invasion as independent logistic predictors of retroperitoneal node metastases.

The magnitude of the univariate OR associated with LVSI (OR = 45) and serosal invasion (OR = 49) in predicting LNM underscores the importance of these

pathological features in triaging patients for systemic lymphadenectomy or SLN biopsy. Current European and North American guidelines^{8,9,31} recognize non-endometrioid histology, MI $\geq$ 50%, and high-grade endometrioid carcinoma as primary indications for formal nodal staging, findings fully corroborated in our cohort. Of note, a contemporary SLN mapping study by Praiss *et al.*³² at Memorial Sloan Kettering Cancer Center (756 patients) found that LVSI (OR = 8.0) and deep myoinvasion (OR = 3.3) were the strongest multivariate predictors of SLN macro-metastases, supporting our univariate observations even across different methodological frameworks.

The prognostic impact of LNM on survival is well-established. Historical data from Creasman *et al.*³³ reported

Table 4. Univariate logistic regression analysis of variables associated with lymph node metastasis (LNМ)

Variable	Odds ratio (OR)	95% CI	p-value
Age (per year)	1.047	1.020–1.075	0.001
Tumor size (per cm)	1.362	1.218–1.524	<0.001
LVSI (present vs. absent)	45.045	16.743–121.187	<0.001
Cervical glandular involvement	6.230	3.535–10.982	<0.001
Cervical stromal involvement	7.736	4.258–14.056	<0.001
Adnexa-ovarian involvement	13.050	6.400–26.610	<0.001
Omental involvement	13.592	5.604–32.965	<0.001
Positive peritoneal cytology	17.500	7.336–41.745	<0.001
Histological grade			
Grade I	Reference	-	-
Grade II	2.106	0.881–5.034	0.094
Grade III	4.148	1.842–9.343	0.001
Histological subtype			
Endometrioid	Reference	-	-
Serous	4.522	2.081–9.823	<0.001
Carcinosarcoma	14.400	4.536–45.716	<0.001
Clear cell	8.000	2.430–26.339	0.001
Undifferentiated	8.000	1.547–41.377	0.013
Myometrial invasion			
Confined to endometrium	Reference	-	-
>50%	5.846	2.980–11.470	<0.001
Serosal invasion	49.231	15.584–155.520	<0.001

Notes: All analyses are univariate binary logistic regression. The <50% myometrial invasion category was not statistically significant vs. the reference (confined to endometrium) and is not displayed.

Abbreviations: CI: Confidence interval; LVSI: Lymphovascular space invasion.

Table 5. Univariate logistic regression analysis of variables associated with lymphovascular space invasion (LVSI)

Variable	Odds ratio (OR)	95% CI	<i>p</i> -value
Age (per year)	1.053	1.027–1.079	<0.001
Tumor size (per cm)	1.622	1.414–1.861	<0.001
LNM (present vs. absent)	45.045	16.743–121.187	<0.001
Cervical glandular involvement	8.866	5.113–15.372	<0.001
Cervical stromal involvement	14.584	7.681–27.694	<0.001
Adnexa-ovarian involvement	21.301	8.459–53.641	<0.001
Omental involvement	16.077	4.456–58.011	<0.001
Positive peritoneal cytology	10.809	3.793–30.800	<0.001
Number of lymph nodes	1.020	1.009–1.030	<0.001
Histological grade			
Grade I	Reference	—	—
Grade II	3.701	1.692–8.098	0.001
Grade III	14.026	6.633–29.659	<0.001
Histological subtype			
Endometrioid	Reference	-	-
Serous	7.282	3.276–16.184	<0.001
Carcinosarcoma	5.140	1.435–18.414	0.012
Endometrioid+Serous	15.420	1.572–151.263	0.019
Myometrial invasion			
Confined to endometrium	Reference	-	-
>50%	29.338	6.889–124.943	<0.001
Tumor stage (2023 FIGO)			
Stage IA	Reference	-	-
Stage IB	5.776	2.607–12.801	<0.001
Stage II	20.606	6.957–61.033	<0.001
Stage IIIA	25.964	7.089–95.090	<0.001
Stage IIIC1	111.273	22.126–559.585	<0.001
Stage IIIC2	157.636	32.281–769.767	<0.001
Stage IVB	55.636	15.408–200.897	<0.001

Notes: All analyses are univariate binary logistic regression. Stage IIIC1 and IIIC2 OR estimates (111 and 158, respectively) have wide 95% CIs owing to small subgroup sizes; hence, they should be interpreted cautiously. The Endometrioid+Serous histological subtype is based on *n* = 5 patients; its CI width reflects sparse data.

Abbreviations: CI: Confidence interval; FIGO: International Federation of Gynecology and Obstetrics; LNM: Lymph node metastasis.

Table 6. Univariate Cox proportional hazards regression: Factors associated with disease-free survival (DFS)

Variable	Hazard ratio (HR)	95% CI	p-value
Age (per year)	1.036	1.004–1.070	0.028
Tumor size (per cm)	1.181	1.096–1.272	<0.001
LVSI (present)	7.699	3.374–17.565	<0.001
LNM (present)	6.178	3.044–12.538	<0.001
Cervical glandular involvement	3.294	1.748–6.207	<0.001
Cervical stromal involvement	5.426	2.819–10.447	<0.001
Adnexa-ovarian involvement	5.815	2.967–11.397	<0.001
Omental involvement	6.172	2.892–13.174	<0.001
Positive peritoneal cytology	5.877	2.616–13.201	<0.001
Histological grade			
Grade I	Reference	-	-
Grade II	4.269	1.414–12.885	0.010
Grade III	8.180	2.717–24.629	<0.001
Histological subtype			
Endometrioid	Reference	-	-
Serous	5.594	2.371–13.200	<0.001
Carcinosarcoma	13.150	5.049–34.246	<0.001
Clear cell	6.197	1.414–27.165	0.016
Undifferentiated	8.273	1.889–36.236	0.005
Stromal	8.243	1.882–36.094	0.005
Endometrioid + Clear cell	11.374	1.487–87.024	0.019
Serous + Clear cell	11.249	1.474–85.829	0.020
Endometrioid + Undifferentiated	12.487	1.623–96.080	0.015
Myometrial invasion			
Confined to endometrium	Reference	-	-
>50%	12.600	1.696–93.599	0.013
Serosal invasion	36.135	4.436–294.325	0.001
Tumor stage (2023 FIGO)			
Stage IA	Reference	-	-
Stage IB	2.500	0.757–8.255	0.133
Stage II	5.915	1.142–30.647	0.034
Stage IIIA	10.518	2.801–39.502	<0.001
Stage IIIC1	7.471	1.993–28.003	0.003
Stage IIIC2	33.853	10.332–110.919	<0.001
Stage IVA	138.208	14.926–1279.720	<0.001
Stage IVB	25.292	8.563–74.704	<0.001

Notes: All analyses are univariate Cox proportional hazards regression. The <50% myometrial invasion category was not statistically significant vs. the confined-to-endometrium reference and is not displayed (included in the SPSS model). Stage IVA ($n = 2$), serosal invasion, and all mixed or rare histological subtypes are based on small subgroups, with wide 95% CIs, indicating substantial imprecision; interpret with caution.

Abbreviations: CI: Confidence interval; FIGO: International Federation of Gynecology and Obstetrics; LNM: Lymph node metastasis; LVSI: lymphovascular space invasion.

Table 7. Univariate Cox proportional hazards regression: Factors associated with overall survival (OS)

Variable	Hazard Ratio (HR)	95% CI	p-value
Age (per year)	1.084	1.034–1.137	0.001
Tumor size (per cm)	1.227	1.134–1.328	<0.001
LVSI (present)	8.813	2.696–28.806	<0.001
LNM (present)	12.765	4.415–36.906	<0.001
Cervical glandular involvement	3.818	1.515–9.625	0.005
Cervical stromal involvement	4.967	1.952–12.641	0.001
Adnexa-ovarian involvement	10.451	4.132–26.433	<0.001
Omental involvement	11.684	4.405–30.989	<0.001
Positive peritoneal cytology	10.377	3.847–27.995	<0.001
Histological grade			
Grade I	Reference	-	-
Grade II	Not estimable	-	0.983
Grade III	4.614	1.012–21.043	0.048
Histological subtype			
Endometrioid	Reference	-	-
Serous	4.081	1.055–15.789	0.042
Endometrioid + Serous	8.686	1.059–71.224	0.044
Undifferentiated	8.304	1.020–67.603	0.048
Endometrioid + Clear cell	22.997	2.789–189.608	0.004
Serous + Clear cell	18.529	2.270–151.283	0.006
Endometrioid + Undifferentiated	25.220	3.026–210.192	0.003
Neuroendocrine	80.410	9.463–683.239	<0.001
Myometrial invasion			
Confined to endometrium	Reference	-	-
<50%	2.214	0.259–18.952	0.468
>50%	3.459	0.416–28.730	0.251
Serosal invasion	28.447	3.421–236.563	0.002
Tumor stage (2023 FIGO)			
Stage IA	Reference	-	-
Stage IB	0.756	0.079–7.282	0.809
Stage IIIA	4.219	0.438–40.681	0.213
Stage IIIC2	23.124	4.950–108.016	<0.001
Stage IVA	112.461	10.830–1,167.815	<0.001
Stage IVB	25.344	6.497–98.872	<0.001

Notes: All analyses are univariate Cox proportional hazards regression. Only 19 deaths occurred (3.9% event rate); all HR estimates are imprecise and should be interpreted with caution. Grade II: complete separation (zero deaths); HR not estimable. Stages II and IIIC1 are absent due to zero events; their absence does not imply zero risk. Stage IVA is based on $n = 2$ patients; 95% CI reflects extreme imprecision. All mixed and rare histological subtypes have small subgroup sizes and wide CIs.

Abbreviations: CI: Confidence interval; FIGO: International Federation of Gynecology and Obstetrics; LNM: Lymph node metastasis; LVSI: lymphovascular space invasion.

recurrence in 57% of LNM-positive versus 11% of LNM-negative patients; our corresponding figures of 22.7% versus 5.6% are somewhat lower, potentially reflecting the shorter observation window and differences in adjuvant treatment eras. Five-year DFS rates ranging from 90% for node-negative stage I–II patients to 38% for para-aortic node-positive patients have been reported³⁴, highlighting the dose-response relationship between nodal burden and outcome. A post-hoc analysis of the JGOG2043 trial³⁵ further demonstrated that patients with two or more para-aortic metastases had independently worse DFS (HR = 1.72; $p = 0.019$), underscoring the importance of nodal extent quantification rather than simple presence/absence.

It should be acknowledged that LNM, as an OS predictor in EC, is expected, given that nodal involvement defines stage IIIC disease and has been robustly associated with inferior survival across multiple large datasets.^{15,16,33} The specific value of confirming this relationship in our cohort lies in (i) establishing its applicability within the Azerbaijani and South Caucasus healthcare context, where local outcome data have been essentially absent; (ii) quantifying the magnitude of association under real-world conditions, including limited molecular profiling; and (iii) providing a foundation for evidence-based advocacy for systematic nodal staging protocols in resource-limited settings where practices may not yet fully align with international standards.

4.2. Lymphovascular space invasion: Predictors and prognostic role

Lymphovascular space invasion reflects the capacity of tumor cells to penetrate lymphatic and vascular channels and represents a critical intermediate step in the metastatic cascade.^{36,37} Among the prognostic variables evaluated in our study, LVSI was among the strongest univariate predictors of both LNM (OR = 45.0) and DFS (HR = 6.50), consistent with multiple prior reports.^{11,23,37,38} A meta-analysis covering 79 published studies and 68,870 patients confirmed that LVSI is independently associated with LNM, recurrence, and OS in EC.¹²

Under the revised 2023 FIGO staging system, LVSI has been formally incorporated as a staging determinant, with focal LVSI now qualifying stage IA disease as stage IB in certain configurations, and with extensive LVSI elevating staging within stage II.^{16,24} This change elevates LVSI from a purely prognostic biomarker to a staging-relevant criterion with direct implications for adjuvant therapy selection. Our study predated routine semiquantitative LVSI scoring, and therefore, all LVSI determinations in our dataset represent a binary present/absent classification.

This is acknowledged as a significant limitation: the critical distinction between focal and substantial LVSI, which has now been standardized in pathology guidelines following the landmark analysis by Capasso *et al.*²⁵, was not applied. Capasso *et al.* demonstrated that focal LVSI conferred no significantly worse DFS or OS compared with LVSI-negative disease, whereas substantial LVSI carried independent adverse prognostic implications. This finding is now reflected in the World Health Organization (WHO) Classification of Female Genital Tumors guidelines and should be incorporated into future prospective analyses in this institution.

The association of DFS with LVSI in our cohort (HR = 6.50; $p < 0.001$) aligns with a recent Turkish multicenter study by Yalcin *et al.*³⁹, who reported in 469 node-negative stage I patients that LVSI independently predicted both recurrence (HR = 4.80; 95% CI: 1.62–14.21) and overall mortality (HR = 3.33; 95% CI: 1.43–7.77). Furthermore, from a sentinel node perspective, Praiss *et al.*³² found LVSI to be the single strongest multivariate predictor of occult SLN macro-metastases (OR = 8.0; 95% CI: 4–16), reinforcing its critical role in guiding the extent of surgical staging.

The apparent paradox of a longer KM-estimated mean OS in LVSI-positive patients in our series (110.53 vs. 71.57 months) warrants further consideration. As discussed in Section 3, this finding reflects a methodological artifact rather than biology. With only 19 total deaths, just 4 in the LVSI-absent group and 9 in the LVSI-present group, the KM mean survival estimator is highly susceptible to distortion from censoring patterns and the timing of late events. When event counts are this low, KM-estimated means are known to be unreliable; median survival, which was not reached in either group, would be a more appropriate summary statistic. Several additional factors may contribute to the apparent discrepancy: LVSI-positive patients received adjuvant chemotherapy or chemoradiotherapy at higher rates, which may confer a therapeutic benefit that partially offsets the intrinsic prognostic disadvantage of LVSI within this short observation window. Lead-time effects and differential dropout rates may also play a role. This finding should not be interpreted as a protective or neutral effect of LVSI; rather, it illustrates the fundamental limitation of drawing OS conclusions from survival analyses with very few events and short follow-up.

4.3. Myometrial invasion and histological subtype

Depth of myometrial invasion is one of the foundational risk stratifiers in EC, distinguishing early-stage organ-confined disease (stage IA) from more advanced local

invasion (stages IB and beyond) under both the 2009 and 2023 FIGO frameworks. In our cohort, myometrial invasion exceeding 50% conferred significantly elevated risks of LNM, LVSI, and recurrence, with an OR of 29.3 for LVSI and an HR of 1.89 for DFS in univariate analysis. These findings are consistent with a large-scale meta-analysis by Wang *et al.*¹², which included 68,870 patients and confirmed deep myometrial invasion as an independent predictor of LNM, LVSI, recurrence, and OS across all included studies.

Non-endometrioid histological subtypes, particularly serous carcinoma, carcinosarcoma, and clear cell carcinoma, carried markedly elevated risks of LNM and LVSI, and were associated with substantially worse DFS in our series. Carcinosarcoma was associated with a 14.4-fold elevated LNM risk and a 4.74-fold higher DFS hazard compared with endometrioid carcinoma. These observations are biologically consistent with the aggressive phenotype of uterine carcinosarcoma, which is now classified as a metaplastic carcinoma under current WHO taxonomy and carries a stage-for-stage worse prognosis than endometrioid carcinoma.¹⁶

4.4. The 2023 FIGO staging revision: Context and implications

The 2023 FIGO staging revision represents the most substantial reclassification of EC since 2009, introducing molecular subtype-informed staging, LVSI extent as a substage determinant, and more granular anatomical substances within stages I and II.^{16,26} Validation studies from Spain and Thailand have demonstrated that the 2023 system provides superior prognostic discrimination for both DFS and OS compared with the 2009 classification, with 20–27% of patients experiencing stage migration.^{40–42}

Our study applied only the anatomical substage components of the 2023 FIGO system, as routine molecular profiling was not available. This is an acknowledged limitation arising from the resource-constrained setting of the study. POLE hotspot mutation analysis, MMR immunohistochemistry, and *TP53* sequencing were not systematically performed, precluding molecular classification that is now central to FIGO 2023's integrated staging approach. The importance of molecular data is underscored by evidence that MMR-deficient tumors, despite often carrying adverse histopathological features such as deep invasion and LVSI, may have better outcomes than *TP53*-aberrant carcinomas of similar stage.³² Future research at this institution should prioritize implementation of at least MMR immunohistochemistry as a cost-effective

step toward molecular integration.

4.5. Multivariate analysis: Limitations and interpretation

The present study identified grade III as an exploratory independent predictor of DFS and LNM as an exploratory independent predictor of OS in multivariate Cox models. However, as detailed in the methods and results sections (Sections 2 and 3), these models were constructed on very small event sets: 19 DFS events across 296 complete cases for the DFS model and 19 OS events (from the full data set) for the OS model. With five predictors in the DFS model and three in the OS model, both analyses fall short of the 10 events per variable criterion for reliable estimation. All *p*-values, while nominally below 0.05, should therefore be treated with caution, and the HR estimates carry wide confidence intervals that reflect statistical imprecision. These findings are best regarded as hypothesis-generating signals that warrant confirmation in larger, prospectively designed studies with longer accrual and follow-up.

Nodal involvement is a definitional component of adverse staging, and its univariate and multivariate association with OS in smaller retrospective series has been repeatedly described.^{15,33} The confirmatory value of this association within an understudied Azerbaijani cohort lies primarily in regional contextualization and in generating benchmarks against which future prospective Azerbaijani EC registries can be compared, rather than in novel mechanistic discovery.

4.6. Limitations

Several limitations constrain the interpretation of these findings. First, the retrospective design introduces inherent risks of ascertainment bias and incomplete variable capture; LVSI status, histological grade, and lymph node staging were unavailable in subsets of patients. Second, single-center data from Azerbaijan limit generalizability to other populations or healthcare settings. Third, the short median follow-up (10.09 months) substantially reduces the reliability of all survival estimates, particularly OS; the median OS was not reached, and KM projections beyond the follow-up horizon carry significant uncertainty. Fourth, molecular classification, now central to the 2023 FIGO staging paradigm, was not available, precluding integrated molecular-anatomical staging. Fifth, LVSI was assessed as a binary variable (present/absent) without semiquantitative focal/substantial categorization, limiting comparability with contemporary staging and prognostic literature. Sixth, the multivariate models are severely constrained by event counts and should be considered strictly exploratory.

Future work should incorporate prospective data collection, standardized molecular profiling, semiquantitative LVSI assessment, and adequate follow-up to allow reliable survival analysis.

5. Conclusion

In this retrospective cohort of 462 EC patients from a single center in Azerbaijan, non-endometrioid histology, grade III differentiation, depth of myometrial invasion, serosal extension, cervical involvement, adnexal spread, and omental metastasis emerged as significant univariate predictors of both LNM and LVSI. These variables, together with LVSI, LNM, and positive peritoneal cytology, were each associated with shorter DFS in univariate Cox regression. Exploratory multivariate analysis identified grade III as a potential independent predictor of DFS and LNM as a potential independent predictor of OS; however, both findings should be regarded as hypothesis-generating given the limited number of events. The short median follow-up and low overall mortality rate (4.1%) substantially limit conclusions regarding OS, and all survival projections require confirmation in studies with longer observation periods. Integrating these adverse pathological features into preoperative risk-stratification algorithms remains clinically meaningful for decisions regarding surgical extent and adjuvant therapy. Future prospective studies with molecular profiling, standardized semiquantitative LVSI scoring, and long-term follow-up are necessary to further characterize these associations within the Azerbaijani and broader South Caucasus patient population.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Akbar Ibrahimov

Formal analysis: Akbar Ibrahimov, Fidan Novruzova

Investigation: Akbar Ibrahimov, Fidan Novruzova

Methodology: Ahliman Amiraslanov, Abuzar Gaziyeu,
Fidan Novruzova

Supervision: Akbar Ibrahimov

Writing—original draft: Akbar Ibrahimov

Writing—review & editing: Akbar Ibrahimov

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Oncological Department at Azerbaijan Medical University (Approval No. N138, dated February 3, 2024). Given the retrospective and observational nature of the study, the Ethics Committee of Azerbaijan Medical University waived the requirement for written informed consent.

Consent for publication

Not applicable.

Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-249.
doi: 10.3322/caac.21660
2. Cakir I, Gulseren V, Ozdemir IA, *et al.* Characteristics of patients with late recurrence endometrial cancer. *J Cancer Res Ther.* 2024;20(1):232-237.
doi: 10.4103/jcrt.jcrt_888_22
3. Gavriluk O, Braaten T, Weiderpass E, Licaj I, Lund E. Lifetime number of years of menstruation as a risk index for postmenopausal endometrial cancer in the Norwegian Women and Cancer Study. *Acta Obstet Gynecol Scand.* 2018;97(10):1168-1177.
doi: 10.1111/aogs.13381
4. Hutt S, Mihaies D, Karteris E, Michael A, Payne AM, Chatterjee J. Statistical Meta-Analysis of Risk Factors for Endometrial Cancer and Development of a Risk Prediction Model Using an Artificial Neural Network Algorithm. *Cancers.* 2021;13(15):3689.
doi: 10.3390/cancers13153689
5. Koutoukidis DA, Beeken RJ, Manchanda R, *et al.* Diet and exercise in uterine cancer survivors (DEUS pilot): study protocol for a randomized controlled trial. *Trials.* 2016;17(1):130.
doi: 10.1186/s13063-016-1260-1
6. Njoku K, Agnew HJ, Crosbie EJ. Impact of Type 2 Diabetes Mellitus on Endometrial Cancer Survival: A Prospective

- Database Analysis. *Front Oncol.* 2022;12:899262.
doi: 10.3389/fonc.2022.899262
7. Tempfer CB, Hilal Z, Kern P, Juhasz-Boess I, Reznicek GA. Menopausal Hormone Therapy and Risk of Endometrial Cancer: A Systematic Review. *Cancers.* 2020;12(8):2195.
doi: 10.3390/cancers12082195
8. Abu-Rustum N, Yashar C, Arend R, *et al.* Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2023;21(2):181-209.
doi: 10.6004/jnccn.2023.0006
9. Colombo N, Creutzberg C, Amant F, *et al.* ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, Treatment and Follow-up. *Int J Gynecol Cancer.* 2016;26(1):2-30.
doi: 10.1097/IGC.0000000000000609
10. Yarandi F, Shirali E, Akhavan S, Nili F, Ramhormozian S. The impact of lymphovascular space invasion on survival in early stage low-grade endometrioid endometrial cancer. *Eur J Med Res.* 2023;28(1):118.
doi: 10.1186/s40001-023-01084-9
11. Tortorella L, Restaino S, Zannoni GF, *et al.* Substantial lymph-vascular space invasion (LVSI) as predictor of distant relapse and poor prognosis in low-risk early-stage endometrial cancer. *J Gynecol Oncol.* 2021;32(2):e11.
doi: 10.3802/jgo.2021.32.e11
12. Wang J, Xu P, Yang X, *et al.* Association of Myometrial Invasion With Lymphovascular Space Invasion, Lymph Node Metastasis, Recurrence, and Overall Survival in Endometrial Cancer: A Meta-Analysis of 79 Studies With 68,870 Patients. *Front Oncol.* 2021;11:762329.
doi: 10.3389/fonc.2021.762329
13. Lei H, Xu S, Mao X, *et al.* Systemic Immune-Inflammatory Index as a Predictor of Lymph Node Metastasis in Endometrial Cancer. *J Inflamm Res.* 2021;14:7131-7142.
doi: 10.2147/JIR.S345790
14. Mariani A, Dowdy SC, Podratz KC. New surgical staging of endometrial cancer: 20 years later. *Int J Gynaecol Obstet.* 2009;105(2):110-111.
doi: 10.1016/j.jgo.2009.02.008
15. Pelikan HM, Trum JW, Bakers FC, Beets-Tan RG, Smits LJ, Kruitwagen RF. Diagnostic accuracy of preoperative tests for lymph node status in endometrial cancer: a systematic review. *Cancer Imaging.* 2013;13(3):314-322.
doi: 10.1102/1470-7330.2013.0032
16. Berek JS, Matias-Guiu X, Creutzberg C, *et al.* FIGO staging of endometrial cancer: 2023. *Int J Gynaecol Obstet.* 2023;162(Suppl 3):383-394.
doi: 10.1002/ijgo.14923
17. Reticker-Flynn NE, Zhang W, Belk JA, *et al.* Lymph node colonization induces tumor-immune tolerance to promote distant metastasis. *Cell.* 2022;185(11):1924-1942.e23.
doi: 10.1016/j.cell.2022.04.019
18. Altindag SD, Yigit S, Sen S. Is microcystic, elongated, and fragmented pattern of myometrial invasion in endometrioid endometrial carcinoma associated with survival? *Turk J Med Sci.* 2022;52(5):1569-1579.
doi: 10.55730/1300-0144.5497
19. Fu R, Zhang D, Yu X, Zhang H. The association of tumor diameter with lymph node metastasis and recurrence in patients with endometrial cancer: a systematic review and meta-analysis. *Transl Cancer Res.* 2022;11(11):4159-4177.
doi: 10.21037/tcr-22-2595
20. Lampe B, Kurzl R, Hantschmann P. Prognostic factors that predict pelvic lymph node metastasis from endometrial carcinoma. *Cancer.* 1994;74(9):2502-2508.
doi: 10.1002/1097-0142(19941101)74:9<2502::aid-cncr2820740918>3.0.co;2-2
21. Fleming ND, Soliman PT, Westin SN, *et al.* Impact of Lymph Node Ratio and Adjuvant Therapy in Node-Positive Endometrioid Endometrial Cancer. *Int J Gynecol Cancer.* 2015;25(8):1437-1444.
doi: 10.1097/IGC.0000000000000510
22. Lavaud P, Fedida B, Canlorbe G, *et al.* Preoperative MR imaging for ESMO-ESGO-ESTRO classification of endometrial cancer. *Diagn Interv Imaging.* 2018;99(6):387-396.
doi: 10.1016/j.diii.2018.01.010
23. Cusano E, Myers V, Samant R, *et al.* Prognostic Significance of Lymphovascular Space Invasion in the Absence of Lymph Node Metastases in Early-Stage Endometrial Cancer. *Int J Gynecol Cancer.* 2018;28(5):890-894.
doi: 10.1097/IGC.0000000000001229
24. Zheng W. Molecular Classification of Endometrial Cancer and the 2023 FIGO Staging: Exploring the Challenges and Opportunities for Pathologists. *Cancers.* 2023;15(16):4101.
doi: 10.3390/cancers15164101
25. Capasso I, Perrone E, Loverro M, *et al.* Focal lymphovascular space invasion: Friend or foe? A large retrospective analysis on stage I endometrioid endometrial carcinomas. *Eur J Cancer.* 2025;228:115736.
doi: 10.1016/j.ejca.2025.115736
26. Concin N, Creutzberg CL, Vergote I, *et al.* ESGO/ESTRO/ESP Guidelines for the Management of Patients with Endometrial Carcinoma. *Int J Gynecol Cancer.* 2021;31(1):12-39.
doi: 10.1136/ijgc-2020-002230

27. Pollom EL, Conklin CM, von Eyben R, Folkins AK, Kidd EA. Nomogram to Predict Risk of Lymph Node Metastases in Patients With Endometrioid Endometrial Cancer. *Int J Gynecol Pathol*. 2016;35(5):395-401.
doi: 10.1097/PGP.0000000000000246
28. Mandic A, Kokanov D, Maricic S, Ivkovic Kapicl T, Solajic N. Histopathologic Parameters of Positive Lymph Node Predictability in Endometrial Cancer. *Acta Clin Croat*. 2022;61(2):206-213.
doi: 10.20471/acc.2022.61.02.06
29. Rathod PS, Shakuntala PN, Pallavi VR, *et al*. The risk and pattern of pelvic and para aortic lymph nodal metastasis in patients with intermediate and high risk endometrial cancer. *Indian J Surg Oncol*. 2014;5(2):109-114.
doi: 10.1007/s13193-014-0303-x
30. Taskiran C, Yuce K, Geyik PO, Kucukali T, Ayhan A. Predictability of retroperitoneal lymph node metastasis by using clinicopathologic variables in surgically staged endometrial cancer. *Int J Gynecol Cancer*. 2006;16(3):1342-1347.
doi: 10.1111/j.1525-1438.2006.00534.x
31. Jamieson A, Thompson EF, Huvila J, *et al*. Endometrial carcinoma molecular subtype correlates with the presence of lymph node metastases. *Gynecol Oncol*. 2022;165(2):376-384.
doi: 10.1016/j.ygyno.2022.01.025
32. Praiss AM, Dagher C, Zhou Q, *et al*. Lymph node metastases in endometrial carcinoma: A modern assessment in the era of sentinel lymph node mapping and molecular subtyping. *Gynecol Oncol*. 2024;191:37-44.
doi: 10.1016/j.ygyno.2024.09.012
33. Creasman WT, Odicino F, Maisonneuve P, *et al*. Carcinoma of the corpus uteri. *Int J Gynaecol Obstet*. 2003;83(S1):79-118.
doi: 10.1016/s0020-7292(03)90116-0
34. Bendifallah S, Canlorbe G, Laas E, *et al*. A Predictive Model Using Histopathologic Characteristics of Early-Stage Type 1 Endometrial Cancer to Identify Patients at High Risk for Lymph Node Metastasis. *Ann Surg Oncol*. 2015;22(13):4224-4232.
doi: 10.1245/s10434-015-4548-6
35. Konno Y, Mayama M, Takehara K, *et al*. Prognostic significance of para-aortic node metastasis in endometrial cancer: Japanese Gynecologic Oncology Group Study JGOG2043 post hoc analysis. *J Gynecol Oncol*. 2025;36(4):e57.
doi: 10.3802/jgo.2025.36.e57
36. Li Y, Cong P, Wang P, Peng C, Liu M, Sun G. Risk factors for pelvic lymph node metastasis in endometrial cancer. *Arch Gynecol Obstet*. 2019;300(4):1007-1013.
doi: 10.1007/s00404-019-05276-9
37. Stalberg K, Bjurberg M, Borgfeldt C, *et al*. Lymphovascular space invasion as a predictive factor for lymph node metastases and survival in endometrioid endometrial cancer. *Acta Oncol*. 2019;58(11):1628-1633.
doi: 10.1080/0284186X.2019.1643036
38. Bosse T, Peters EE, Creutzberg CL, *et al*. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer. *Eur J Cancer*. 2015;51(13):1742-1750.
doi: 10.1016/j.ejca.2015.05.015
39. Yalcin Y, Kosan B, Yalcin S, Abay M, Ozerkan K. The Impact of Lymphovascular Space Invasion on Recurrence and Survival in FIGO Stage I Node-Negative Endometrioid Endometrial Cancer. *J Clin Med*. 2025;14(18):6535.
doi: 10.3390/jcm14186535
40. Techasontichai M, Santibenchakul S, Phoolcharoen N, *et al*. A prognostic performance of 2023 FIGO for early-stage endometrial cancer staging. *Taiwan J Obstet Gynecol*. 2026;65(3):508-519.
doi: 10.1016/j.tjog.2026.01.021
41. Veiga N, Padilla-Iserte P, Oliver R, *et al*. Improved prognostic stratification with the FIGO 2023 endometrial cancer staging system. A multicenter Spanish cohort study. *Int J Gynaecol Obstet*. 2026;173:956-962.
doi: 10.1002/ijgo.70951
42. Lim JW, Dzyubak O, Moshkovich M, *et al*. Impact of FIGO 2023 staging criteria on stage migration and survival outcomes in early-stage endometrial cancer: A retrospective cohort study. *Gynecol Oncol*. 2025;202:93-101.
doi: 10.1016/j.ygyno.2025.09.015