Original Investigation

Prognostic significance of lymphovascular space invasion in endometrial cancer and its relationship with other prognostic factors

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Abstract

Objective: To investigate the prognostic significance of lymphovascular space invasion (LVSI) and its relationship with other prognostic factors in patients with endometrial cancer.

Material and Methods: Patients with stage IA-IVB endometrial cancer who underwent hysterectomy and/or staging surgery between January 2016 and December 2020 at a tertiary referral center were retrospectively analyzed. Pathological data including histological type, stage, grade, LVSI (lymphatic invasion, vascular invasion), tumor size, depth of myometrial invasion, cervical involvement, lymph node evaluation (pelvic, paraaortic), and peritoneal wash cytology were analyzed using univariate and multivariate methods.

Results: The study included 304 patients. Non-endometrioid tumors were associated with a 6.35-fold higher risk of LVSI. Each 1 mm increase in tumor size raised the risk by 1.03-fold. LVSI was present in 53.3% of cases with lymph node metastasis and was 7.2-fold more frequent in deceased patients (odds ratio: 7.209; 95% confidence interval: 3.137-16.570; $p<0.001$). Multivariate analysis identified tumor grade and survival as independent predictors of LVSI: grade 3 tumors had a 4.88-fold higher risk ($p=0.014$), and mortality was associated with a 4.16-fold higher risk ($p=0.007$). Survival was significantly linked to LVSI, tumor size ≥35 mm, and recurrence, but not to age, histological type, lymph node status, or peritoneal cytology.

Conclusion: Our results demonstrated that LVSI was significantly associated with histological grade and survival. Furthermore, LVSI, tumor diameter ≥35 mm, and recurrence were found to significantly affect survival, highlighting their prognostic relevance for risk assessment and postoperative management. [J Turk Ger Gynecol Assoc.]

Keywords: Endometrial cancer, lymphovascular space invasion, prognostic factors

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Introduction

Endometrioid carcinoma is the most common type of uterine malignancy, with abnormal uterine bleeding as the main symptom. Unopposed estrogen exposure is a key factor in its development (1). Risk factors include nulliparity, late onset of menopause, obesity, polycystic ovary syndrome, diabetes, estrogen-secreting tumors, estrogen therapy without progesterone supplementation during menopause, tamoxifen use, and Lynch II syndrome (2).

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Prognostic factors in endometrial cancer guiding surgery include histological type, grade, tumor size, myometrial invasion depth, cervical involvement, peritoneal fluid cytology, lymphovascular space invasion (LVSI), and lymph node metastasis (3).

LVSI is typically defined as the presence of tumor cells in endothelial-lined channels outside the primary uterine tumor, though its precise definition is still debated (4). LVSI has been demonstrated in several studies as an independent adverse prognostic factor for recurrence and survival (5-7). Tumor spread to vascular and lymphatic spaces is believed to enhance metastasis to pelvic and paraaortic lymph nodes, indicating a more aggressive disease course (7,8).

The aim of this study was to determine the prognostic significance of LVSI in endometrial cancer and evaluate its relationship with other prognostic factors.

Material and Methods

This study includes endometrial cancer cases (stage 1A-4B) who underwent hysterectomy and/or staging surgery at a tertiary referral center between January 1st, 2016, and December 31st, 2020. Retrospective data were collected from patient files and electronic records. Pathological data, including histological type, stage, grade, LVSI (lymphatic invasion, vascular invasion), tumor size, myometrial invasion depth, cervical involvement, lymph node evaluation, and peritoneal fluid cytology, were analyzed according to the 2009 FIGO criteria. Uterine sarcoma cases, those with synchronous primary tumors, and those without LVSI data were excluded.

LVSI was defined as tumor cells or cell clusters attached to the walls of lymphatic and vascular vessels within sections that included both the tumor and surrounding healthy tissue. Tissue samples obtained from the material were transferred to paraffin blocks for LVSI detection. Sections were then cut from these blocks, mounted on slides, and stained with hematoxylin and eosin (H&E). The presence of LVSI was initially examined on H&E-stained slides (Leica Biosystems) containing sections that included both the tumor and surrounding healthy tissue. Subsequently, for slides suspicious of LVSI, new sections were taken from the blocks and stained immunohistochemically using the Leica Bond Max device. In these immunohistochemical analyses, podoplanin (D2-40, Cell Marque) was used to identify lymphatic structures, and CD34 (QBEnd/10, Leica Biosystems), CD31 (1A10, Leica Biosystems), and Factor 8 (von Willebrand factor, 36B11, Leica Biosystems) were used to identify vascular structures.

For stage 1 endometrioid-type endometrial cancer, primary surgery included total abdominal hysterectomy (TAH) + bilateral salpingo-oophorectomy (BSO) ± peritoneal fluid sampling ± lymphadenectomy. Staging surgery was performed if any of the following criteria were met based on frozen section results:

- Non-endometrioid tumor type;
- Tumor grade ≥2;
- Myometrial invasion depth ≥ ½;
- Tumor size >2 cm;
- Cervical invasion.

Staging surgery included TAH + BSO + bilateral pelvic and paraaortic lymph node dissection + omental sampling + peritoneal fluid sampling. Peritoneal cytology was not evaluated by pathology in some patients with stage 1 low-grade diagnosis (stage 1a/1b, grade 1). All cases were reviewed in a multidisciplinary tumor board (gynecology, medical oncology, pathology, radiology), and adjuvant treatment indications (chemotherapy, radiotherapy, or both) were determined based on postoperative final pathological results and directed to the appropriate departments.

Ethics committee approval

This study was approved by the İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinical Research Ethics Committee (approval number: 2021/0529, date: 27.10.2021).

Data analysis

The data were analyzed using IBM SPSS Statistics version18 (IBM Inc, Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Categorical variables are expressed as frequencies (n) and percentages (%). Continuous variables meeting the assumptions for parametric tests are presented as mean ± standard deviation (SD), while those not meeting the assumptions are presented as median (minimum and maximum) values. For the analysis of categorical variables, Pearson's chi-square test, Fisher's exact test, or the Fisher-Freeman-Halton exact test were applied, and Yates' continuity correction and post-hoc Bonferroni adjustment were performed as necessary. For comparing the medians between two groups, the Mann-Whitney U test was used, as parametric assumptions were not met. Univariate and multivariate logistic regression analyses were employed to identify independent risk factors associated with dependent variables, and variables with $p<0.02$ in univariate analyses were included in the multivariate model. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Survival probabilities were estimated using the Kaplan-Meier method, and the log-rank test was conducted to assess differences in survival probabilities across variable levels. Cox regression analysis was performed to identify factors influencing survival. A significance level of 0.05 was considered statistically significant for all analyses.

Results

The mean ± SD age of the 304 patients included in the study was 61.52±10.27 years. The youngest patient was 28 years old, and the oldest was 90 years old. The age distribution of the patients is shown in Figure 1.

The analysis of histological features is presented in Table 1.

Upon analysis of the cases, the most common histological type was endometrioid carcinoma, accounting for 84.5% (n=257), while non-endometrioid histological types accounted for 15.5% (n=47).

The distribution of cases based on invasion areas is presented in Table 2.

Lymphatic invasion was observed in 36 patients (11.8%), vascular invasion in 30 patients (9.9%), and LVSI (involving lymphatic, vascular, or both) in 50 patients (16.4%), as seen in Table 2.

The relationship between lymphatic invasion in patients and independent variables was analyzed, and the results are shown in Table 3.

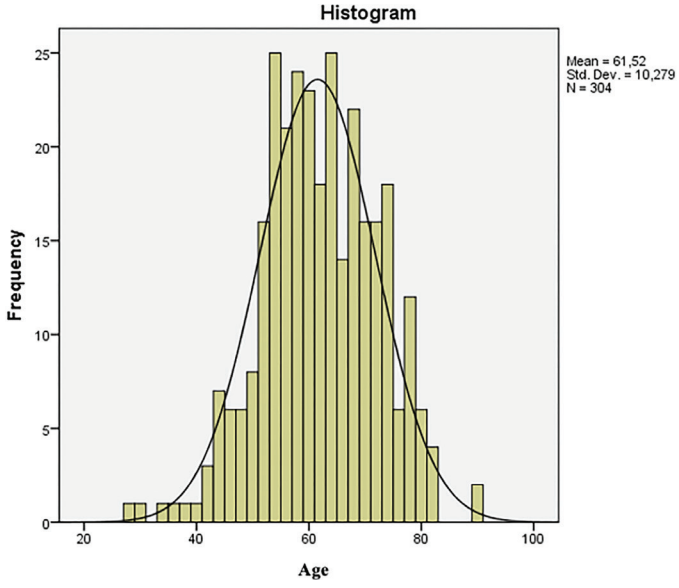

Figure 1. Age distribution histogram of the patients

Table 1. Histological features

Histological features (n=304)	n	%
Endometrioid	257	84.5
Serous	17	5.6
Dedifferentiated endometrioid	12	3.9
Clear cell	8	2.6
Mixed	4	1.3
Undifferentiated endometrioid	3	1.0
Mucinous	2	0.7
Serous papillary	1	0.3

Lymphatic invasion was present in 8.2% of endometrioid tumors but was significantly more common in non-endometrioid tumors at 31.9% (p<0.001). The rates of lymphatic invasion were 5.5% in stage 1, 13.0% in stage 2, 51.6% in stage 3, and 30.8% in stage 4, with significant differences observed across stages (p<0.001). Further analysis revealed that lymphatic invasion was significantly lower in stage 1 compared to stages 3 and 4, while stage 3 had a significantly higher rate than stages 1 and 2. A significant difference was also observed based on grade, with lymphatic invasion in grade 3 being notably higher at 30.3%. In our series, lymph node metastasis occurred in 53.3% of patients with lymphatic invasion. The invasion rate was 47.1% in those with pelvic-only metastasis and 87.5% in those with both pelvic and paraaortic metastasis, significantly higher than in patients without metastatic lymph nodes or those not undergoing lymphadenectomy (p<0.001). Cervical stromal invasion was found in 50 patients, with 43 having stromal invasion. Lymphatic invasion was seen in 27.9% of these patients, compared to 9.1% in those without cervical involvement (p=0.002). Tumor size was larger in patients with lymphatic invasion (median 45 mm) compared to those without it (median 32 mm), a statistically significant difference (p<0.001).

Survival analysis showed that 9.4% of surviving patients had lymphatic invasion, while 37.0% of deceased patients had lymphatic invasion (p<0.001). No significant associations were found between lymphatic invasion and age (p=0.813), positive peritoneal wash fluid (p=0.130), or recurrence (p=0.194).

The relationship between vascular invasion and independent variables was analyzed, and the results are shown in Table 4.

Vascular invasion was found in 6.2% of endometrioid tumors and 29.8% of non-endometrioid tumors (p<0.001). The rates of vascular invasion were 3.0% in stage 1, 21.7% in stage 2, 38.7% in stage 3, and 46.2% in stage 4, with significant differences across stages (p<0.001). Further analysis showed that vascular invasion was significantly lower in stage 1 compared to stages 3 and 4. Vascular invasion was also higher in grade 3 (31.8%) than in grade 1 (1.8%) and grade 2 (5.5%) (p<0.001).

Table 2. Invasion features

Variables (n=304)	n	%
Lymphatic invasion		
No	268	88.2
Yes	36	11.8
Vascular invasion		
No	274	90.1
Yes	30	9.9
Lymphovascular invasion		
No	254	83.6
Yes	50	16.4

Table 3. Relationship between lymphatic invasion and independent variables

Variable (n=304)	Lymphatic invasion		p-value
	No (n=268)	Yes (n=36)	
Age (years)	61.57±10.40	61.14±9.42	0.813
Histological type			
Endometrioid	236 (91.8)	21 (8.2)	**<0.001**
Non -endometrioid	32 (68.1)	15 (31.9)	
Stage			
1[a]	224 (94.5)	13 (5.5)	**<0.001**
2[a,b]	20 (87.0)	3 (13.0)	
3[c]	15 (48.4)	16 (51.6)	
4[b,c]	9 (69.2)	4 (30.8)	
Grade			
1[a]	107 (97.3)	3 (2.7)	**<0.001**
2[a]	115 (89.8)	13 (10.2)	
3[b]	46 (69.7)	20 (30.3)	
Lymph node metastasis			
No lymphadenectomy[a]	116 (95.9)	5 (4.1)	**<0.001**
No[a]	138 (90.2)	15 (9.8)	
Yes[b]	14 (46.7)	16 (53.3)	
metastatic lymph node location			
No lymphadenectomy[a]	116 (95.9)	5 (4.1)	**<0.001**
No[a]	138 (90.2)	15 (9.8)	
Pelvic region only[b]	9 (52.9)	8 (47.1)	
Paraaortic region only[a,b]	4 (80.0)	1 (20.0)	
Both regions[b]	1 (12.5)	7 (87.5)	
Cervical involvement			
No[a]	231 (90.9)	23 (9.1)	**0.002**
Superficial invasion[a,b]	6 (85.7)	1 (14.3)	
Stromal invasion[b]	31 (72.1)	12 (27.9)	
Cytology			
Not evaluated**	145 (90.6)	15 (9.4)	0.130
Benign	119 (86.2)	19 (13.8)	
Malignant	4 (66.7)	2 (33.3)	
Tumor size (mm)	32 (1-125)	45 (12-130)	**<0.001**
Number of pelvic lymph nodes removed	8 (0-60)	21 (0-54)	**<0.001**
Number of paraaortic lymph nodes	0 (0-42)	5 (0-74)	**<0.001**
Follow-up time (months)	35 (1-69)	35 (2-60)	0.579
Recurrence			
No	251 (89.0)	31 (11.0)	0.194
Yes	17 (77.3)	5 (22.7)	
Survival			
Alive	251 (90.6)	26 (9.4)	**<0.001**
Deceased	17 (63.0)	10 (37.0)	

Results are presented as mean ± standard deviation, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters

**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)

Table 4. Relationship between vascular invasion and independent variables

Variable (n=304)	Vascular invasion		p-value
	No (n=274)	Yes (n=30)	
Age (years)	61.30±10.45	63.57±8.s40	0,251
Histological type			
Endometrioid	241 (93.8)	16 (6.2)	**<0.001**
Non-endometrioid	33 (70.2)	14 (29.8)	
Stage			
1[a]	230 (97.0)	7 (3.0)	**<0.001**
2[a,b]	18 (78.3)	5 (21.7)	
3[c]	19 (61.3)	12 (38.7)	
4[b,c]	7 (53.8)	6 (46.2)	
Grade			
1[a]	108 (98.2)	2 (1.8)	**<0.001**
2[a]	121 (94.5)	7 (5.5)	
3[b]	45 (68.2)	21 (31.8)	
Lymph node metastasis			
No Lymphadenectomy[a]	115 (95.0)	6 (5.0)	**<0.001**
No[a]	140 (91.5)	13 (8.5)	
Yes[b]	19 (63.3)	11 (36.7)	
Metastatic lymph node location			
No lymphadenectomy[a]	115 (95.0)	6 (5.0)	**<0.001**
No[a]	140 (91.5)	13 (8.5)	
Pelvic region only[b]	14 (82.4)	3 (17.6)	
Paraaortic region only[a,b]	3 (60.0)	2 (40.0)	
Both regions[b]	2 (25.0)	6 (75.0)	
Cervical involvement			
No[a]	241 (94.9)	13 (5.1)	**<0.001**
Superficial invasion[a,b]	5 (71.4)	2 (28.6)	
Stromal invasion[b]	28 (65.1)	15 (34.9)	
Cytology			
Not evaluated**	146 (91.2)	14 (8.8)	0.489
Benign	123 (89.1)	15 (10.9)	
Malignant	5 (83.3)	1 (16.7)	
Tumor size (mm)	32 (1-125)	57.5 (25-130)	**<0.001**
Number of pelvic lymph nodes removed	9 (0-60)	16 (0-54)	0.104
Number of paraaortic lymph nodes	0 (0-42)	3 (0-74)	**0.001**
Follow-up time (months)	35.5 (1-69)	25 (1-60)	**0.017**
Recurrence			
No	257 (91.1)	25 (8.9)	0.084
Yes	17 (77.3)	5 (22.7)	
Survival			
- Alive	258 (93.1)	19 (6.9)	**<0.001**
- Deceased	16 (59.3)	11 (40.7)	

Results are presented as mean ± standard devaition, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters

**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)

In patients with lymph node metastasis (36.7%), vascular invasion was notably higher than in those without metastasis (8.5%) or who did not undergo lymphadenectomy (5.0%) (p<0.001). In cases with metastasis in the paraaortic region or both pelvic and paraaortic regions, the rate of vascular invasion was significantly higher than in patients who did not undergo lymphadenectomy (p<0.001). In patients with cervical stromal (34.9%) or superficial involvement (28.6%), the rate of vascular invasion was significantly higher compared to those without cervical involvement (5.1%) (p<0.001). The median tumor size in patients with vascular invasion was 57.5 mm, compared to 32 mm in those without (p<0.001). The median number of paraaortic lymph nodes removed was 3 in patients with vascular invasion, compared to 0 in those without (p=0.001). The median follow-up duration was 25 months for patients with vascular invasion and 35.5 months for those without (p=0.017). Survival analysis showed 6.9% of survivors had vascular invasion, while 40.7% of deceased patients did (p<0.001).

The relationship between the presence of LVSI and independent variables was analyzed, with results presented in Table 5.

LVSI was significantly less common in endometrioid tumors compared to dedifferentiated, undifferentiated endometrioid, and serous tumors (p<0.001). LVSI rates were 7.6% in stage 1, 30.4% in stage 2, 58.1% in stage 3, and 53.8% in stage 4, with significant differences across stages (p<0.001). Further analysis showed that LVSI was significantly less common in stage 1 compared to other stages. In grade 3, LVSI (43.9%) was significantly more common than in grade 1 (4.5%) and grade 2 (12.5%) (p<0.001).

In patients with lymph node metastasis (60.0%), LVSI was significantly more frequent than in those without lymph node metastasis (15.0%) or those who did not undergo lymphadenectomy (7.4%) (p<0.001). LVSI rates were also higher in patients with pelvic-only or combined pelvic and paraaortic metastasis compared to those without metastasis. LVSI rate was 46.5% in patients with cervical stromal involvement, compared to 11.0% in those without cervical involvement (p<0.001). In addition, LVSI rates were significantly higher in patients with myometrial invasion of ½ or more, compared to those with no or less than ½ myometrial invasion (p<0.001).

Table 5. Relationship between LVSI presence and independent variables

Variables (n=304)	LVSI		p-value
	No (n=254)	Yes (n=50)	
Age (years)	61.38±10.41	62.24±9.60	0.589
Histological features			
Endometrioid[a]	228 (88.7)	29 (11.3)	**<0.001**
Dedifferentiated endometrioid[b]	5 (41.7)	7 (58.3)	
Undifferentiated endometrioid[b]	0 (0.0)	3 (100.0)	
Serous[b]	10 (58.8)	7 (41.2)	
Clear cell[a,b]	6 (75.0)	2 (25.0)	
Mucinous[a,b]	2 (100.0)	0 (0.0)	
Papillary serous[a,b]	0 (0.0)	1 (100.0)	
Mixed[a,b]	3 (75.0)	1 (25.0)	
Stage			
1[a]	219 (92.4)	18 (7.6)	**<0.001**
2[b]	16 (69.6)	7 (30.4)	
3[b]	13 (41.9)	18 (58.1)	
4[b]	6 (46.2)	7 (53.8)	
Grade			
1[a]	105 (95.5)	5 (4.5)	**<0.001**
2[a]	112 (87.5)	16 (12.5)	
3[b]	37 (56.1)	29 (43.9)	
Lymph node metastasis			
No lymphadenectomy[a]	112 (92.6)	9 (7.4)	**<0.001**
No[a]	130 (85.0)	23 (15.0)	
Yes[b]	12 (40.0)	18 (60.0)	

Table 5. Continued

Variables (n=304)	LVSI		p-value
	No (n=254)	Yes (n=50)	
Metastatic lymph node location			
No lymphadenectomy[a]	112 (92.6)	9 (7.4)	**<0.001**
No[a]	130 (85.0)	23 (15.0)	
Pelvic region only[b]	8 (47.1)	9 (52.9)	
Paraaortic region only[a,b]	3 (60.0)	2 (40.0)	
Both regions[b]	1 (12.5)	7 (87.5)	
Cervical involvement			
No[a]	226 (89.0)	28 (11.0)	**<0.001**
Superficial invasion[a,b]	5 (71.4)	2 (28.6)	
Stromal invasion[b]	23 (53.5)	20 (46.5)	
Myometrial invasion			
No invasion[a]	27 (100.0)	0 (0.0)	**<0.001**
<1/2[a]	148 (95.5)	7 (4.5)	
≥1/2[b]	79 (64.8)	43 (35.2)	
Cytology			
Not evaluated**	138 (86.2)	22 (13.8)	0.188
Benign	112 (81.2)	26 (18.8)	
Malignant	4 (66.7)	2 (33.3)	
Tumor size (mm)	30 (1-125)	46 (12-130)	**<0.001**
Number of pelvic lymph nodes removed	8 (0-60)	19.5 (0-54)	**0.002**
Number of paraaortic lymph nodes	0 (0-42)	3.5 (0-74)	**<0.001**
Follow-up time (months)	35.5 (1-69)	30.5 (1-60)	**0.029**
Recurrence			
No	239 (84.8)	43 (15.2)	0.085
Yes	15 (68.2)	7 (31.8)	
Survival			
- Alive	241 (87.0)	36 (13.0)	**<0.001**
- Deceased	13 (48.1)	14 (51.9)	

Results are presented as mean ± standard deviation, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters
**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)

The median tumor size was 46 mm (12-130) in patients with LVSI and 30 mm (1-125) in those without LVSI ($p<0.001$). The median number of pelvic lymph nodes removed was 19.5 (0-54) in patients with LVSI and 8 (0-60) in those without ($p=0.002$). The median number of paraaortic lymph nodes removed was 3.5 (0-74) in patients with LVSI and 0 (0-42) in those without ($p<0.001$). Follow-up duration was shorter for patients with LVSI ($p=0.029$). Survival analysis showed that 13.0% of survivors had LVSI, while 51.9% of those who died had LVSI ($p<0.001$). No significant differences were found between LVSI occurrence and age ($p=0.589$), abdominal wash fluid positivity ($p=0.188$), or recurrence ($p=0.085$) (Table 5).

The factors affecting the presence of LVSI were analyzed using logistic regression, and the results are shown in Table 6.

The risk of LVSI was 6.35 times higher in non-endometrioid tumors. When tumor stages were considered, the risk of LVSI was 5.32 times higher in stage 2 tumors, 16.84 times higher in stage 3 tumors, and 14.19 times higher in stage 4 tumors compared to stage 1 tumors ($p<0.05$)

The risk of LVSI was 3.00 times higher in grade 2 tumors and 16.45 times higher in grade 3 tumors compared to grade 1 tumors ($p<0.05$). There was no significant change in LVSI risk in patients with superficial cervical invasion ($p=0.173$), but it was 7.01 times higher in patients with cervical stromal

Table 6. Factors affecting the presence of lymphovascular space invasion–findings of univariate and multivariate logistic regression analysis

	Univariate		Multivariate	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Histological type				
Endometrioid	Reference	-	Reference	-
Non-endometrioid	6.350 (3.176-12.696)	**<0.001**	1.637 (0.538-4.982)	0.386
Stage				
1	Reference	-	Reference	-
2	5.323 (1.939-14.613)	**0.001**	0.625 (0.095-4.122)	0.625
3	16.846 (7.128-39.816)	**<0.001**	3.260 (0.915-11.612)	0.068
4	14.194 (4.311-46.734)	**<0.001**	1.700 (0.316-9.158)	0.537
Grade				
1	Reference	-	Reference	-
2	3.000 (1.062-8.478)	0.038	1.854 (0.603-5.700)	0.281
3	16.459 (5.933-45.662)	**<0.001**	4.886 (1.385-17.233)	**0.014**
Cervical involvement				
No	Reference	-	Reference	-
Superficial invasion	3.229 (0.598-17.431)	0.173	0.625 (0.042-9.236)	0.732
Stromal invasion	7.019 (3.429-14.368)	**<0.001**	3.027 (0.744-12.319)	0.122
Tumor size (mm)	1.038 (1.024-1.053)	**<0.001**	1.016 (0.996-1.035)	0.116
Survival				
- Alive	Reference	-	Reference	-
- Deceased	7.209 (3.137-16.570)	**<0.001**	4.160 (1.470-11.774)	**0.007**
CI: Confidence interval, OR: Odds ratio				

invasion (OR: 7.019; 95% CI: 3.429-14.368; p<0.001). A one-unit increase in tumor size was found to increase the likelihood of LVSI by 1.03 times (OR: 1.038; 95% CI: (1.024-1.053); p<0.001). In survival analysis, LVSI was 7.20 times more common in deceased patients compared to those who survived (OR: 7.209; 95% CI: (3.137-16.570); p<0.001). The multivariate analysis revealed that grade and survival were significantly associated with LVSI. LVSI was found to be 4.88 times more common in grade 3 patients compared to grade 1 patients [OR: 4.886; 95% CI: (1.385-17.233); p=0.014] and 4.16 times more common in deceased patients compared to survivors [OR: 4.160; 95% CI: (1.470-11.774]; p=0.007).

The relationship between the patients' survival status and independent variables was analyzed, and the findings are shown in Table 7.

Stage 1 patients had a significantly lower mortality rate (5.1%) compared to Stage 2 (21.7%) and Stage 4 (38.5%) (p<0.001). Similarly, Grade 3 tumors showed higher mortality (22.7%) than Grade 1 (3.6%) and Grade 2 (6.2%) (p<0.001). Patients with both pelvic and para-aortic lymph node metastases had higher mortality than those without lymphadenectomy (p=0.036). Although cervical stromal invasion was initially associated with survival, this was not confirmed in multivariate analysis. Median tumor size was significantly larger in deceased patients (46 mm) than in survivors (33 mm) (p<0.001). Mortality was also higher among patients with recurrence (40.9%) compared to those without (6.4%) (p<0.001). No significant associations were found between overall survival and histological type (p=0.064), lymph node metastasis (p=0.137), or positive peritoneal cytology (p=0.795) (Table 7).

Survival analyses based on the general clinical characteristics of the patients are presented in Table 8.

The overall survival time of patients was 63.16 months. Patients aged 60 years and below had significantly longer survival times than those over 60 years (64.94 vs. 60.50 months; p=0.016).

Table 7. Relationship between overall survival and independent variables

Variable (n=304)	Survival		p-value
	Alive (n=277)	Decesead (n=27)	
Age (years)	61.11±10.32	65.70±8.94	**0.026**
Histological type			
Endometrioid	238 (92.6)	19 (7.4)	0.064
Non-endometrioid	39 (83.0)	8 (17.0)	
Stage			
1[a]	225 (94.9)	12 (5.1)	**<0.001**
2[b]	18 (78.3)	5 (21.7)	
3[a,b]	26 (83.9)	5 (16.1)	
4[b]	8 (61.5)	5 (38.5)	
Grade			
1[a]	106 (96.4)	4 (3.6)	**<0.001**
2[a]	120 (93.8)	8 (6.2)	
3[b]	51 (77.3)	15 (22.7)	
Lymph node metastasis			
No lymphadenectomy	115 (95.0)	6 (5.0)	0.137
None	136 (88.9)	17 (11.1)	
Present	26 (86.7)	4 (13.3)	
Site of metastatic lymph node			
No lymphadenectomy[a]	115 (95.0)	6 (5.0)	**0.036**
None[a,b]	136 (88.9)	17 (11.1)	
Pelvic only[a,b]	16 (94.1)	1 (5.9)	
Para-aortic only[a,b]	5 (100.0)	0 (0.0)	
Both regions[b]	5 (62.5)	3 (37.5)	
Cervical involvement			
None[a]	236 (92.9)	18 (7.1)	**0.027**
Superficial invasion[a]	5 (71.4)	2 (28.6)	
Stromal invasion[a]	36 (83.7)	7 (16.3)	
Cytology			
Not evaluated**	146 (91.2)	14 (8.8)	0.795
Benign	126 (91.3)	12 (8.7)	
Malignant	5 (83.3)	1 (16.7)	
Tumor size (mm)	33 (1-130)	46 (10-120)	**<0.001**
Number of pelvic lymph nodes removed	9 (0-60)	25 (0-57)	**0.004**
Number of paraaortic lymph nodes	0 (0-74)	5 (0-35)	**0.001**
Follow-up time (months)	36 (10-69)	20 (1-60)	**<0.001**
Recurrence			
No	264 (93.6)	18 (6.4)	**<0.001**
Yes	13 (59.1)	9 (40.9)	

Results are presented as mean ± standard deviation, median (minimum-maximum), or n (% of total row). Statistical tests used: Student's t-test, Mann-Whitney U test, Pearson's chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test. Differences between groups are indicated with lowercase letters

**Peritoneal cytology was not evaluated by pathology in some stage 1 low-grade patients (stage 1a/1b, grade 1)

Survival was longer for endometrioid tumors (64.38 months) compared to non-endometrioid tumors (52.28 months; $p=0.020$). Survival times by stage were 65.87 months for stage 1, 53.42 months for stage 2, 49.86 months for stage 3, and 42.99 months for stage 4 ($p<0.001$). For grade, survival was 65.79 months for grade 1, 65.23 months for grade 2, and 48.50 months for grade 3 ($p<0.001$). Patients with lymphatic, vascular, or lymphovascular invasion had significantly shorter survival times compared to those without ($p<0.001$ for all). Tumor size ≤35mm was associated with longer survival (65.78 months) compared to tumors >35mm (58.73 months; $p<0.001$). Recurrence significantly reduced survival, with 64.68 months for patients without recurrence and 32.80 months for those with recurrence ($p<0.001$) (Figure 2, Table 8).

A univariate and multivariate Cox regression analysis was performed to identify factors affecting survival in patients (Table 9).

The analysis revealed that patients over 60 years had a 2.76 times higher mortality risk compared to those aged 60 years and below (OR: 2.767; 95% CI: 1.169-6.550; p=0.021). Non-

Table 8. Survival analysis based on general clinical features of patients

	Mean survival (months)	STD ERR	95% CL lower limit	95% CL upper limit	p-value
Overall survival	63.16	1.08	61.03	65.29	-
Age (years)					
≤60 years	64.94	1.12	62.74	67.14	**0.016**
>60 years	60.50	1.82	56.93	64.08	
Histological type					
Endometrioid	64.38	1.01	62.39	66.37	**0.020**
Non-endometrioid	52.28	2.86	46.68	57.89	
Stage					
1	65.87	0.87	64.15	67.59	**<0.001**
2	53.42	4.91	43.78	63.05	
3	49.86	2.88	44.21	55.51	
4	42.99	7.73	27.83	58.14	
Grade					
1	65.79	1.07	63.69	67.90	**<0.001**
2	65.23	1.28	62.70	67.75	
3	48.50	2.77	43.05	53.94	
Lymphatic invasion					
No	65.01	0.93	63.18	66.84	**<0.001**
Yes	48.16	3.58	41.13	55.18	
Vascular invasion					
No	65.39	0.87	63.68	67.10	**<0.001**
Yes	42.45	4.64	33.34	51.56	
Lymphovascular invasion					
No	65.80	0.86	64.12	67.49	**<0.001**
Yes	46.74	3.24	40.39	53.10	
Tumor size (mm)					
≤35 mm	65.78	0.88	64.04	67.52	**<0.001**
>35 mm	58.73	2.09	54.64	62.83	
Recurrence					
No	64.68	0.99	62.73	66.64	**<0.001**
Yes	32.80	3.76	25.41	40.19	

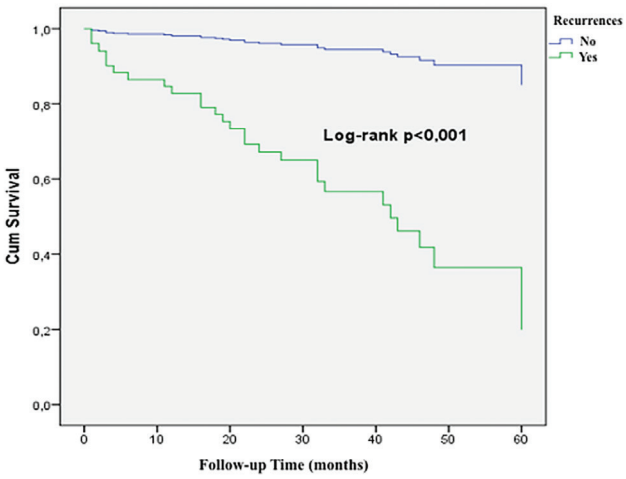

Figure 2. Survival according to recurrence status-Kaplan-Meier, Log-rank test

endometrioid tumors had a 2.58 times higher mortality risk than endometrioid tumors (OR: 2.583; 95% CI: 1.130-5.906; p=0.025). Mortality rates for stage 2, 3, and 4 tumors were 5.25, 3.50, and 9.51 times higher, respectively, than for stage 1 tumors (p<0.05). Grade 3 tumors had an 8.75 times higher mortality rate than grade 1 tumors (p<0.001). Lymphatic invasion (OR: 4.574), vascular invasion (OR: 8.114), LVSI (OR: 6.525), tumor size >35 mm (OR: 4.560), and recurrence (OR: 9.965) were all significantly associated with higher mortality (p<0.001 for all). In multivariate analysis, recurrence remained a significant predictor of higher mortality (OR: 8.100; p<0.001). Other factors showed no significant relationship with survival (p>0.05) (Table 9).

Table 9. Factors affecting survival-univariate and multivariate Cox regression analysis results

	Univariate		**Multivariate**	
Variables	**OR (95% CL)**	**p**	**OR (95% CL)**	**p**
Age (years)				
≤60 years	1	-	1	-
>60 years	2.767 (1.169-6.550)	**0.021**	2.512 (0.937-6.734)	0.067
Histological type				
Endometrioid	1	-	1	-
Non-endometrioid	2.583 (1.130-5.906)	**0.025**	0.336 (0.103-1.101)	0.072
Stage				
1	1	-	1	-
2	5.256 (1.847-14.958)	**0.002**	1.918 (0.527-6.982)	0.323
3	3.508 (1.230-9.999)	**0.019**	1.549 (0.412-5.826)	0.518
4	9.515 (3.345-27.067)	**<0.001**	3.463 (0.824-14.562)	0.090
Grade				
1	1	-	1	-
2	1.817 (0.546-6.042)	0.330	1.360 (0.385-4.803)	0.633
3	8.751 (2.885-26.541)	**<0.001**	2.735 (0.681-10.987)	0.156
Lymphatic invasion				
No	1	-	1	-
Yes	4.574 (2.093-9.996)	**<0.001**	0.772 (0.169-3.519)	0.738
Vascular invasion				
No	1	-	1	-
Yes	8.114 (3.758-17.517)	**<0.001**	1.850 (0.388-8.813)	0.440
Lymphovascular invasion				
No	1	-	1	-
Yes	6.525 (3.061-13.909)	<0.001	3.829 (0.509-28.808)	0.192
Tumor size (mm)				
≤ 35 mm	1	-	1	-
> 35 mm	4.560 (1.837-11.319)	**0.001**	1.441 (0.459-4.525)	0.531
Recurrence				
No	1	-	1	-
Yes	9.965 (4.368-22.736)	**<0.001**	8.100 (2.967-22.116)	**<0.001**
OR: Odds ratio				

Discussion

Prognostic factors in endometrial cancer have been extensively debated, and it has been demonstrated that these factors can influence success of treatment strategies. Recent studies have identified key prognostic indicators, including poor histological differentiation, older age, deep myometrial invasion, non-endometrioid histology, lymph node involvement, LVSI, lower uterine segment involvement, and molecular markers, as the main factors assessed in predicting the development of recurrence.

Age is commonly recognized as an independent prognostic factor. In a study by Veade et al. (9) the average age of patients without LVSI was 63.2 years, while those with LVSI had an average age of 64.8 years. In our study, the mean age of patients without LVSI was 61.38±10.41 years, and 62.24±9.60 years for those with LVSI, with no significant association found between LVSI and age (p=0.589). Furthermore, patients over 60 years had a 2.76 times higher mortality risk, consistent with existing literature.

In our study, while LVSI was observed in 11.3% of endometrioid tumors, the rate of LVSI in endometrioid carcinoma was found to be significantly lower than that in non-endometrioid histological type carcinomas. In non-endometrioid tumors, LVSI was 6.35 times more common. In a study conducted by Hanh et al, similar to our findings, LVSI was more frequently detected in non-endometrioid tumors, and LVSI was present in 37.2% of patients with endometrioid adenocarcinoma (10).

Myometrial invasion is one of the prognostic factors that alters staging and significantly impacts survival. In our study, 27 patients (8.9%) had no myometrial invasion, while 122 patients (40.1%) had invasion of ½ or more. The rate of LVSI was significantly higher in patients with deeper myometrial invasion. Dane and Bakir (11) found that myometrial invasion depth was the most significant prognostic factor and correlated with pelvic lymph node metastasis, cervical involvement, and LVSI in 122 endometrial cancer cases. A meta-analysis by Wang et al. (12) analyzing 28,904 patients, also found a connection between myometrial invasion depth and LVSI, with a higher risk in patients with invasion of ½ or more.

In our study, the LVSI rate was 46.5% in patients with cervical stromal invasion, compared to 11% in those without cervical involvement, with cervical stromal invasion increasing the likelihood of LVSI by 7.01 times. A study of 671 stage 1 and stage 3 endometrial cancer patients also found a higher incidence of LVSI in those with cervical stromal invasion (13). Similarly, Koskas et al. (14) reported a correlation between LVSI and cervical stromal invasion in 485 stage 1 and 2 endometrial cancer patients.

In terms of tumor stage, 59.5% of cases were stage 1a, 18.4% were stage 1b, and 77.9% were stage 1. LVSI rates were lower in stage 1 patients. Stage 2 had 5.32-fold higher rates of LVSI, stage 3 had 16.84-fold increase times more, and stage 4 had 14.19-fold greater rate of LVSI than stage 1. Similarly, Stålberg et al. (15) reported more advanced stages in LVSI-positive patients. Peters et al. (16) found that increased LVSI in both stage 1-2 and stage 3-4 patients was associated with decreased survival. In the present study and consistent with the literature, the survival time of patients with LVSI was shorter than those without LVSI. Moreover, the mortality rate was 7.20 times higher in the presence of LVSI.

There is a strong relationship between histological grade and prognosis in endometrial cancer. In the present study, as the grade increased, the incidence of LVSI also increased. Furthermore, the mortality rate was 8.75-times higher in grade 3 tumors compared to grade 1 tumors. However, when examining survival times and contrary to the literature, survival was similar in grade 1 and grade 2 tumors, while survival was significantly reduced in grade 3 tumors. Similarly, in the study by Berchuck et al. (17) it was reported that survival decreased with the presence of high-grade histology.

Canlorbe et al. (18) showed that low-risk endometrial cancer cases with tumors ≥35 mm have lower rates of recurrence-free survival. Similarly, patients with tumors ≤35 mm in our cohort had longer survival. A study by Çakır et al. (19) reported a 5-year survival rate of 94% in patients with tumors ≤35 mm, compared to 89% in those with tumors >35 mm, and found tumor size was not a recurrence risk factor. Guo et al. (20) demonstrated that, as tumor size increases, the risk of lymph node metastasis and recurrence also rises, with a prognostic cut-off for metastasis and recurrence at 42.5 mm. In our study, the median tumor size was 45 mm in patients with LVSI and 32 mm in those without LVSI. Tumors with vascular invasion had a median size of 57.5 mm, compared to 32 mm in those without vascular invasion. A 1-unit increase in tumor size increased the likelihood of LVSI by 1.03 times. Laufer et al. (21) also reported a significant relationship between LVSI and tumors >20 mm.

Fotopoulou et al. (22) identified LVSI and grade as key prognostic factors for lymph node metastasis, while Briët et al. (23) similarly reported that LVSI increased the likelihood of pelvic lymph node metastasis in stage 1 patients. In our study, lymph node metastasis occurred in 53.3% of LVSI-positive patients, with rates of 47.1% in pelvic-only and 87.5% in combined pelvic and para-aortic metastasis. Consistent with Visser et al. (24) and Wakayama et al. (25), vascular invasion was associated with higher recurrence, while LVSI correlated with lymph node metastasis. Neal et al. (26) further noted LVSI as a significant prognostic factor, even in node-negative

patients, and Jorge et al. (27) reported a 3- to 10-fold increased risk of nodal metastasis with LVSI. Although LVSI was significant in univariate analysis, its loss of significance in the multivariable Cox regression model may be explained by collinearity with established prognostic factors and the limited events-per-variable ratio.

We found no relationship between LVSI and positive peritoneal lavage fluid. In the study by Takenaka et al. (28) which included 1,616 endometrial cancer cases, positive peritoneal cytology was reported as a poor prognostic factor across all stages and tumor types. A 2016 meta-analysis by Lee et al. (29) also concluded that positive peritoneal cytology reduced 5-year overall survival, but like our study, found no correlation between LVSI and positive peritoneal cytology. Furthermore, we found no relationship between positive peritoneal lavage fluid and overall survival, in contrast to several earlier studies.

Based on current TCGA and ProMisE classifications, the prognostic significance of LVSI varies across molecular subtypes in endometrial cancer. While LVSI has been consistently reported as an important risk factor in the "no specific molecular profile" (NSMP) and mismatch repair deficiency (MMRd) tumors, its prognostic relevance appears attenuated in POLE-mutant cases. In the present study, LVSI was significantly associated with advanced stage, higher tumor grade, lymph node metastasis, and adverse survival outcomes, findings that are broadly consistent with previously reported prognostic patterns, particularly within the NSMP/MMRd subgroups. These results suggest that LVSI reflects underlying biological heterogeneity and may provide complementary prognostic information, even in the absence of molecular classification (30,31).

In our cohort, lymphatic invasion, vascular invasion, tumor size >35 mm, and recurrence were significantly associated with survival, in line with the existing literature. In contrast, no significant association was observed between survival and tumor histological type, lymph node metastasis, or positive peritoneal lavage cytology. Histological grade emerged as a strong determinant of both LVSI and survival outcomes. Importantly, this study contributes population-specific data by evaluating the prevalence and prognostic impact of LVSI in a Turkish endometrial cancer cohort, which remains underrepresented in molecular prognostic studies.

Study limitations

The limitations of this study include its uni-centric, retrospective design, reliance on archival data, and incomplete access to certain patient records. Nevertheless, its single-center nature and relatively large sample size provide a homogeneous dataset, strengthening the internal validity of the findings.

Clinical implications

Given the association between LVSI and adverse outcomes, patients with LVSI-positive tumors may benefit from closer postoperative follow-up. In selected cases, LVSI status could also be considered when individualizing adjuvant treatment decisions.

Conclusion

LVSI was strongly associated with tumor grade and survival in patients with endometrial cancer. Tumor size ≥35 mm and recurrence emerged as independent prognostic factors, underscoring their relevance for postoperative management. In addition, LVSI was significantly associated with lymph node metastasis and mortality, reinforcing its role as a marker of aggressive disease biology. Collectively, these findings support the integration of LVSI and tumor burden into postoperative risk stratification and treatment planning. The findings are largely consistent with prior studies and add meaningful value to both regional and international literature by presenting a large, population-based cohort from Türkiye. Further prospective studies incorporating molecular stratification are warranted to validate and extend these results.

Ethic

Ethics Committee Approval: *This study was approved by the İstanbul Medeniyet University, Göztepe Training and Research Hospital, Clinical Research Ethics Committee (approval number: 2021/0529, date: 27.10.2021).*

Informed Consent: *Retrospective study.*

Footnotes

Author Contributions: *Surgical and Medical Practices: A.K., M.K., Concept: A.K., Design: V.N.G., Data Collection or Processing: V.N.G., Analysis or Interpretation: A.K., M.K., Literature Search: V.N.G., Writing: V.N.G.*

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