ORIGINAL ARTICLE

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The clinical significance of lymphovascular space invasion in patients with low-risk endometrial cancer

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SUMMARY

OBJECTIVE: The aim of this study was to assess the effect of lymphovascular space invasion on recurrence and disease-free survival in patients with low-risk endometrial cancer.

METHODS: The study included patients with stage 1A, grade 1–2 endometrioid endometrial cancer who underwent a total hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy. Independent prognostic predictors of endometrial cancer recurrence were assessed using the Cox regression model. Binary logistic regression analysis was used to identify the predictors of distant recurrence. Kaplan-Meier analysis was used to describe survival curves, and the log-rank test was used to compare the differences in survival curves.

RESULTS: A total of 189 patients met the inclusion criteria, of whom 24 (12.7%) had lymphovascular space invasion. The median follow-up time was 60 (3–137) months. Distant recurrence was present in 11 of 22 patients who developed recurrence. Kaplan-Meier survival analysis showed that the 5-year disease-free survival rates of patients with lymphovascular space invasion(+) and lymphovascular space invasion(-) were 62.5 and 91.9%, respectively, which were significantly lower (p<0.001). In multivariate Cox regression analysis, the presence of lymphovascular space invasion (p<0.001) and age ≥60 years (p=0.017) remained as prognostic factors for reduced disease-free survival. In binary logistic regression analysis, only lymphovascular space invasion (adjusted OR=13, 95%CI=1.456–116.092, p=0.022) was a prognostic factor for distant recurrence.

CONCLUSION: lymphovascular space invasion is a prognostic risk factor for recurrence and distant metastasis and also a predictor of poorer disease-free survival outcomes in low-risk endometrial cancer.

KEYWORDS: Disease-free survival. Endometrial cancer. Recurrence.

INTRODUCTION

Low-risk endometrial cancer (EC) is defined as tumors confined to the uterine corpus with grade 1 or 2 endometrioid histology or invading less than 50% of the myometrium[1]. The 5-year survival rate for patients with low-risk EC is above 90%; however, 5–10% of these patients develop distant or locoregional recurrences afterward[2].

Lymphovascular space invasion (LVSI) is defined as the presence of adenocarcinoma of any extent within lymphatic vessels and/or small capillaries, outside the invasive tumor[3]. Although LVSI is considered a prognostic factor for EC by the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP), it has not yet been included in the International Federation of Gynecology and Obstetrics (FIGO) staging system[4,5]. Numerous studies have confirmed that the presence of LVSI is an independent predictor of distant or locoregional recurrence and decreased disease-free survival (DFS) in EC patients with FIGO stage I–III[6-15]. The prognostic significance of LVSI in low-risk EC is still unclear.

Therefore, we aimed to evaluate the impact of LVSI on recurrence and DFS in patients with low-risk EC.

METHODS

The study was approved by the Ethics Committee of Tepecik Education and Research Hospital (Ref: 2022/10-20) and conducted in accordance with the principles of the Declaration of Helsinki. The medical reports of patients who underwent

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surgery between January 2010 and December 2021 were used to collect pathological, surgical, and demographic data.

The inclusion criteria were as follows: (1) patients with an endometrioid histological subtype of EC, less than 50% myometrial invasion, and grade 1–2; (2) patients who had undergone pelvic lymph node dissection; (3) patients with no intraoperative evidence of extrauterine spread; and (4) patients with complete medical files containing information about age, comorbidities (hypertension or diabetes), detailed surgical procedures, pathological results (i.e., tumor size, LVSI, histological type, and grade), and postoperative adjuvant treatment.

The exclusion criteria were as follows: (1) patients with a non-endometrioid or mixed histological subtype of EC, or grade 3; (2) patients with FIGO stage higher than IA; (3) patients with concurrent malignancies; (4) patients with a history of radiotherapy or chemotherapy before surgery; and (5) patients with incomplete medical records and follow-ups.

All surgeries were performed by gynecological oncologists. The patients underwent a total hysterectomy and bilateral salpingo-oophorectomy surgeries, with a minimum requirement of pelvic lymphadenectomy. Pelvic lymphadenectomy was defined as the removal of lymphatic tissue from the external, internal, common iliac, and obturator regions. Expert gynecological pathologists evaluated all surgical specimens.

The multidisciplinary tumor board made decisions regarding adjuvant treatments based on ESGO, ESTRO, and the National Comprehensive Cancer Network (NCCN) guidelines. Patients were followed up every 3 months for the first 2 years, biannually for up to 5 years, and annually thereafter. At each follow-up visit, pelvic examination and ultrasonography of the pelvis and abdomen were performed. If there was suspicion of recurrence, a biopsy was performed if possible. If not, a computed tomography, magnetic resonance imaging, bone scintigraphy, or positron emission tomography scan was performed. Radiologists or gynecological pathologists with experience confirmed the recurrence on the multidisciplinary tumor board. Recurrences at the vaginal cuff, vagina, bladder, rectum, and pelvic lymph nodes were classified as locoregional, while all other recurrences (lymph nodes outside the pelvis, peritoneal carcinomatosis, liver, bone, lung, and abdomen) were classified as distant. If there were multiple recurrence sites, the recurrence was classified as distant. DFS was defined as the time from the date of surgical staging to the date of recurrence.

The study data were analyzed using version 20.0 of SPSS (statistical software package) by IBM Corp. in Armonk, NY, USA. The data were presented using number, percentage, mean, standard deviation, median, minimum, and maximum values. The t-test was used as a parametric test, while the Mann-Whitney U test was used as a non-parametric test based on the results of the normal distribution conformity test. The analysis of categorical data was conducted using the χ^2 test. The assessment for predictors of distant recurrence was performed using binary logistic regression analysis. Variables with $p<0.05$ in univariate regression were included in a multivariable model. The multivariate Cox regression model included independent prognostic predictors of EC recurrence with a p-value<0.05 in the univariate Cox regression model. To describe the survival curves, Kaplan-Meier analysis was used, and the differences between survival curves were compared using the log-rank test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 189 eligible patients were identified, and the characteristics of low-risk EC patients by LVSI status are shown in Table 1.

Tumor recurrence was reported in various locations, including the vaginal cuff (isolated) in nine patients, the pelvic and inguinal lymph nodes in one patient, the vaginal cuff and pelvic lymph nodes in two patients, the vaginal cuff and rectosigmoid colon in one patient, the lung and bone in one patient, the inguinal lymph nodes (isolated) in one patient, the small intestines in one patient, the liver and brain in one patient, and the peritoneum (peritonitis carcinomatosa) in five patients (not shown in table).

The patients were followed up for a median of 60 months (range, 3–137 months). Analysis using the Kaplan-Meier method showed that the 5-year DFS rates were significantly lower in patients with LVSI(+) (62.5%) compared to those with LVSI(-) (91.9%) ($p<0.001$) (Figure 1).

Furthermore, the results of univariate Cox regression analysis demonstrated that the presence of LVSI ($p=0.001$) and age ≥60 years ($p=0.04$) were associated with a reduced DFS. After conducting multivariate Cox regression analysis, the presence of LVSI ($p<0.001$) and age ≥60 years ($p=0.017$) were still found to be independent prognostic factors for a reduced DFS (Table 2).

Out of 22 patients who developed recurrence, 11 had a distant recurrence. Among those with distant recurrence, five had no LVSI while six had LVSI, and seven received adjuvant brachytherapy while four did not. Additionally, five out of six patients with LVSI and distant metastases received adjuvant brachytherapy. Binary logistic regression analysis was performed with age (<60 vs. ≥60 years), tumor size (<2 cm vs. ≥2 cm), grade (1 vs. 2), LVSI (no vs. yes), and adjuvant brachytherapy (no vs. yes) to evaluate the predictors of distant recurrence.

Table 1. Characteristics of low-risk endometrial cancer patients according to lymphovascular space invasion status.

Characteristics	Total n=189	LVSI (+)	LVSI (–)	p-value
		n=24 (12.7%)	n=165 (87.3%)	
Age (years, mean±SD)	57.3 (±9.09)	56.63 (±8.32)	57.39 (±9.21)	0.7
Age (years)				
<60	113 (59.8%)	16 (66.7%)	97 (58.8%)	0.462
≥60	76 (40.2%)	8 (33.3%)	68 (41.2%)	
Tumor size (cm)				
<2 cm	33 (17.5%)	2 (8.3%)	31 (18.8%)	0.262*
≥2 cm	156 (82.5%)	22 (91.7%)	134 (81.2%)	
Grade				
1	59 (31.2%)	2 (8.3%)	57 (34.5%)	0.01
2	130 (68.8%)	22 (91.7%)	108 (65.5%)	
Adjuvant brachytherapy				
No	125 (66.1%)	0 (0%)	125 (75.8%)	<0.001
Yes	64 (33.9%)	24 (100%)	40 (24.2%)	
Recurrence				
No	167 (88.4%)	16 (66.7%)	151 (91.5%)	0.002*
Yes	22 (11.6%)	8 (33.3%)	14 (8.5%)	

LVSI: lymphovascular space invasion; SD: standard deviation. *Fisher's exact test.

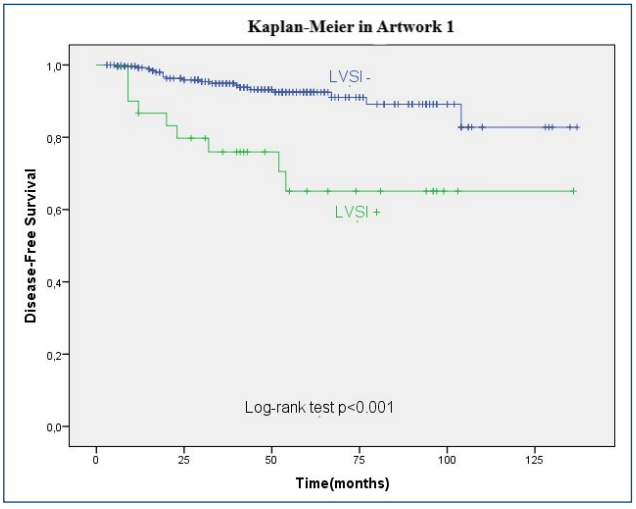

Figure 1. Kaplan-Meier curve.

Univariate analysis showed that LVSI (unadjusted OR=10.667, 95%CI=2.957–38.477, p£0.001) and adjuvant brachytherapy (unadjusted OR=3.715, 95%CI=1.045–13.204, p=0.043) were associated with distant recurrence. In multivariate analysis, only LVSI (adjusted OR=13, 95%CI=1.456–116.092, p=0.022) remained a prognostic factor for distant recurrence (data not shown in table).

DISCUSSION

This study demonstrated that LVSI is a significant predictor of decreased DFS and an independent risk factor for the development of distant recurrence in patients with low-risk EC. This result is consistent with previous studies by Tortorella et al.[16] and Ørtoft et al.[10] which also reported LVSI as a prognostic risk factor for recurrence, distant metastasis, and reduced DFS[10,16]. Although the Tortorella's study utilized a three-tiered scoring system for LVSI, distinguishing between absent, focal, and substantial involvement, it is worth noting that 45.7% (16/35) of patients with focal LVSI and 27.3% (6/22) of patients with substantial LVSI did not undergo lymph node evaluation[16]. According to the study by Ørtoft et al.[10] it was found that only a small proportion (9.4%) of patients in the low-risk group (defined as grades 1 and 2 with <50% myometrial invasion) underwent lymph node resection. However, there were no available data on the percentage of patients who tested positive for LVSI and underwent lymph node resection in this group[10]. Jorge et al.[17] demonstrated that the presence of LVSI elevated the risk of lymph node metastasis from 0.7 to 11.4% in stage 1A grade 1 tumors and from 1.3 to 13.2% in stage 1A grade 2 tumors[17]. According to the Tortorella's study, the lack of lymph node evaluation in a considerable proportion of LVSI-positive patients (38.8% or 22/57) and, according to the Ørtoft's study,

Table 2. The univariate and multivariate Cox regression analysis for disease-free survival in women with low-risk endometrial cancer.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	p-value	Hazard ratio (95%CI)	p-value
Age (years)				
<60	1			
≥60	2.435 (1.044–5.682)	0.040	2.849 (1.210–6.711)	0.017
Tumor size (cm)				
<2 cm	1			
≥2 cm	3.090 (0.687–13.905)	0.142	–	–
Grade				
1	1			
2	1.004 (0.417–2.421)	0.992	–	
LVSI				
No	1			
Yes	4.219 (1.767–10.073)	0.001	4.887 (2.024–11.798)	<0.001
Adjuvant brachytherapy				
No	1			
Yes	1.074(0.456–2.529)	0.869		-

LVSI: lymphovascular space invasion; CI: confidence interval.

the absence of information on the proportion of LVSI-positive patients who underwent lymph node resection may have led to confusion in assessing the prognostic significance of LVSI, as patients with occult lymph node metastasis may have been included. In contrast, our study performed lymph node dissection in all patients, eliminating the possibility of occult lymph node metastasis and ensuring greater clarity in the assessment of the prognostic value of LVSI.

The study conducted by Iida et al.[18] involved 98 patients with stage 1A, grade 1–2 EC, where all patients underwent lymph node dissection. Their results indicated that LVSI is neither a prognostic factor for recurrence nor a predictor of poor DFS[18]. According to the study by Iida et al.[18] the small number of patients who experienced recurrence (only three individuals) and had LVSI (only nine patients) may have limited the statistical power to detect a significant effect of LVSI on DFS rates and could have influenced its ability to act as a prognostic factor for recurrence.

According to the Nwachukwu et al.'s[19] study, only patients with stage 1A, grade 1 EC were evaluated, and LVSI was not found to be a predictive factor for recurrence in EC[19]. However, the exclusion of patients with grade 2 EC, despite being in the low-risk group, may have limited the evaluation of the effect of LVSI on recurrence in that study. In our study, we specifically aimed to assess the impact of LVSI on recurrence in patients with low-risk EC.

Similar to our study, Cusano et al.[7] showed lower DFS rates in patients with LVSI, but they were unable to demonstrate a significant association between LVSI and recurrence[7]. However, the inclusion of patients with stage 1B and grade 3 tumors in the multivariate analysis may have caused LVSI to lose its significance as a prognostic factor.

One of the most comprehensive studies on LVSI in EC was conducted by Ayhan et al.[9] Their study found that patients with LVSI had worse DFS, but the presence of LVSI was not an independent prognostic factor for recurrence[9]. It is worth noting that in this study, 86.3% of all patients and 88.7% of patients with LVSI underwent lymph node dissection, which reduces the likelihood of missing patients with occult lymph node metastases, although not completely. However, according to the Ayhan et al.'s[9] study, the evaluation of LVSI status with hematoxylin-and-eosin stained slides may have caused an underestimation of the true overall rate of tumors with LVSI, which could have led to the loss of its significance as an independent risk factor for recurrence.

In our study, we used D2-40 staining in addition to hematoxylin-and-eosin staining when there was a technical problem in the evaluation of lymphatic vessels. This superior technique

may have contributed to the higher LVSI positivity rates in our study compared to other studies evaluating low-risk EC. It is important to note that our study aimed to assess the effect of the presence of LVSI on recurrence in patients with low-risk EC, similar to the study by Nwachukwu et al.[19] However, unlike their study, which only evaluated stage 1A, grade 1 EC patients, we included all low-risk EC patients regardless of grade and stage[8,9,11,16].

Our study has some limitations. First, this is a retrospective, single-center study. The second limitation is the absence of a three-tiered scoring system used for the evaluation of LVSI status, which is considered an important factor for recurrence. Additionally, the small number of patients with recurrence in low-risk EC, which generally has a good prognosis, was the third limitation of our study investigating the factors affecting recurrence.

Despite these limitations, our study stands out as one of the most important studies in the literature on the low-risk EC group, as all patients underwent lymph node dissection, and the operations were performed by qualified gynecological oncologists with standardized surgical procedures. Furthermore, the surgical specimens were evaluated by expert gynecological pathologists, which enhances the reliability and accuracy of our results.

CONCLUSIONS

The presence of LVSI in low-risk EC is a significant prognostic risk factor for recurrence and distant metastasis, as well as a predictor of decreased DFS. Therefore, when LVSI is detected, adjuvant treatment options should be re-evaluated, considering the risk of distant metastasis. This is particularly important until the data on the definition of molecular classification become clear.

ABBREVIATIONS

EC: endometrial cancer; LVSI: lymphovascular space invasion; ESGO: European society of gynaecological oncology; ESTRO: European society for radiotherapy and oncology; ESP: European society of pathology; DFS: disease-free survival; FIGO: international federation of gynecology and obstetrics; NCCN: national comprehensive cancer network.

ETHICS APPROVAL

This study was approved by the Tepecik Education and Research Hospital ethics committee (Ref:2022/10-20) and conducted in accordance with the Declaration of Helsinki.

AUTHORS' CONTRIBUTIONS

İÇ: Conceptualization, Data curation, Writing – original draft. **CA:** Conceptualization, Data curation, Formal Analysis. **EB:** Data curation, Investigation, Methodology. **VG:** Formal Analysis, Writing – review & editing. **MS:** Formal Analysis, Methodology, Validation. **MÖ:** Software, Supervision, Validation. **SE:** Supervision, Validation, Writing – original draft, Writing – review & editing. **KG:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ZEÇ:** Visualization, Writing – original draft. **MG:** Writing – original draft, Writing – review & editing.

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