Original Article

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Prognostic Importance of Lymph-Vascular Space Involvement in Stage I Endometrioid Type Endometrial Cancer

Evre 1 Endometrioid Tip Endometriyal Kanser Olgularında Lenfovasküler Alan İnvazyonunun Prognostik Önemi

Caner KÖSE[1], Mehmet Mutlu MEYDANLI[2]

[1]Ankara Etlik City Hospital, Clinic of Gynecology, Ankara, Turkey
[2]Gaziantep Medical Point Hospital, Clinic of Obstetrics and Gynecology, Division of Gynecological Oncology, Gaziantep, Turkey

ABSTRACT

Objective: The study aimed to investigate the prognostic significance of lymph-vascular space invasion (LVSI) in patients with stage I endometrioid-type endometrial carcinoma (EC) and to determine its impact on overall survival (OS) and disease-free survival (DFS).

Methods: Medical records of 611 patients with stage I endometrioid-type EC who underwent surgery at our Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital Gynecology Clinic were retrospectively analyzed. The patients were divided into two groups based on the presence or absence of LVSI. The primary outcome measures were DFS and OS, and the prognostic significance of LVSI was assessed using univariate and multivariate analyses.

Results: We identified 52 LVSI-positive patients among 611 patients with stage I endometrioid EC during the study period; 489 (80%) were classified as stage IA and 122 (20%) as stage IB. The total number of recurrences was 26 (4.3%). LVSI was observed in only 4 patients with recurrence (15.3%). For the LVSI positive patients, the 5-year DFS was 88.7%, whereas the 5-year OS rate was 91.6%. Age >60 years [hazard ratio (HR) 4.08, 95% confidence interval (CI) 1.57-10.59; p=0.004] and tumor size >2.8 cm (HR 2.48, 95%, CI 1.001-6.148; p=0.05) were found to be independent prognostic factors of decreased OS.

Conclusion: We found that LVSI in stage I endometrioid-type EC was not a significant predictor of DFS and OS. Patient's age and tumor size were independent prognostic factors of crude survival. These results suggest that LVSI may not be a useful prognostic marker in this patient population and that further studies are needed to identify more reliable predictors of survival in EC.

Keywords: Endometrioid-type EC, lympho-vascular space invasion, stage I disease

ÖZ

Amaç: Bu çalışmada endometrioid tip evre 1 endometriyal kanser (EK) olgularında lenfovasküler alan invazyonun (LVAİ) prognostik öneminin araştırılması, genel sağkalım ve hastalıksız sağkalım üzerine etkisinin belirlenmesi amaçlanmıştır.

Yöntemler: Ankara Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim Araştırma Hastanesi Jinekolojik Onkoloji Kliniği'nde opere edilmiş 611 evre 1 endometrioid tip EK olgusunun verileri retrospektif olarak tarandı. Olguların demografik özellikleri, klinik bulguları, patoloji verileri, takip ve nüks bilgileri hasta dosyaları ve hastane sistemi üzerinden toplandı. Elde edilen veriler doğrultusunda LVAİ'nin sağkalım üzerine olan etkisi araştırıldı.

Bulgular: Altı yüz on bir evre 1 endometrioid tip EK olgusunun 52'sinde LVAİ olduğu saptandı. Olguların 489'u (%80) evre 1A iken 122'si (%20) evre 1B idi. Takip süresinde 26 (%4,3) hastada nüks gerçekleşti. Nüks olan 26 hastanın 4'ünde (%15,3) LVAİ tespit edilmişti. Çalışma süresinde LVAİ pozitif hastalarda 5 yıllık hastalıksız sağkalım %88,7 iken, 5 yıllık genel sağkalım oranı %91,6 idi. Yaş >60 yıl (tehlike oranı [TO] 4,08, %95 güven aralığı [GA] 1,57-10,59; p=0,004) ve tumor boyutu >2,8 cm ([TO] 2,48, %95 GA 1.001-6.148; p=0,05) olması genel sağkalıma etki eden bağımsız risk faktörleri olarak bulundu.

Sonuç: Bu çalışmada, evre 1 endometrioid tip EK olgularında LVAİ'nin genel sağkalım ve hastalıksız sağkalım üzerinde anlamlı bir etkisi bulunmamıştır. Bu bilginin geniş kapsamlı çalışmalarla desteklenmesi gerekmektedir.

Anahtar Sözcükler: Endometrioid tip EK, lenfovasküler invazyonu, evre 1 hastalığı

Address for Correspondence: Caner KÖSE, Ankara Etlik City Hospital, Clinic of Gynecology, Ankara, Turkey
E-mail: dr.canerkose@gmail.com **ORCID ID:** orcid.org/0000-0002-3044-4804

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Introduction

Endometrial carcinoma (EC) is a prevalent gynecologic malignancy and the fourth most common cancer in developed countries (1). It primarily affects women over 50 years of age, and it often manifests at an early stage (2). The well-established risk factors for EC include nulliparity, late menopause, obesity, polycystic ovary syndrome, estrogen-secreting tumors, estrogen therapy without progesterone during menopause, tamoxifen use, diabetes, and Lynch syndrome II (3).

Hysterectomy and concurrent salpingo-oophorectomy is the primary treatment for EC, while lymphadenectomy, omentectomy, and debulking surgery may also be performed if necessary (4). Histopathologically, EC is classified into two main groups: Type I and Type II (5). The endometrioid-type is the most common histological subtype of EC, with a 5-year survival rate exceeding 90% in early-stage and low-grade patients (6,7).

However, factors such as lymph node metastasis (LN), surgical stage, grade, myometrial invasion, and lymph-vascular space invasion (LVSI) can affect the prognosis of EC. LVSI has a significant impact on the risk of recurrence in early-stage disease and is associated with LN metastasis, particularly in distant and para-aortic regions (8,9). Despite its importance, LVSI is not included in the international federation of gynecology and obstetrics (FIGO) staging system for EC (10).

This study aims to investigate the prognostic importance of LVSI in patients with stage I endometrioid-type EC, including its impact on overall survival (OS) and disease-free survival (DFS), and to identify other prognostic factors that may affect the outcome of these patients.

Methods

This retrospective study analyzed the data of 611 patients with FIGO stage I endometrioid-type EC who underwent hysterectomy (TAH) and/or bilateral salpingo-oophorectomy (BSO) alone or with pelvic and para-aortic LN dissection (PPLND) at Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital between 2014 and 2019. Pathology specimens were reviewed and re-evaluated by a gynecologic pathologist to confirm the diagnosis of endometrioid-type EC and to identify LVSI. LVSI positivity was defined as the presence of tumor cells or clusters on the vessel wall detected by hematoxylin-eosin staining. Study was approved by the ethics committee (07/17/2018/E.44).

Patients with EC other than endometrioid-type, patients with a prior history of cancer, patients with metastatic disease, patients with comorbid conditions such as severe heart or lung disease, patients who received neoadjuvant therapy prior to surgery, patients who were pregnant or breastfeeding, patients with a history of blood clots or bleeding disorders, and patients with incomplete medical records were excluded from the study.

DFS was calculated as the time from the start of treatment to recurrence in patients who developed recurrence, the date of last follow-up in patients without recurrence, or the date of death from any cause. OS was calculated as the time from diagnosis to death or last admission. The site of recurrence was categorized as vagina, pelvis, abdomen, lymph node, or liver. Frozen sectioning was routinely performed in patients with EC. Surgical staging, which involves removal of lymph nodes and other tissues to determine the extent of cancer spread, is typically recommended for patients with high-risk features such as deep myometrial invasion, high-grade tumors, or lymphovascular invasion (11). Minimum, pelvic and para-aortic LN dissection, along with TAH and BSO, omentectomy, and cytological sampling are performed in patients with intermediate or high-risk EC.

The surgeries were performed by the department of gynecologic oncology, and adjuvant treatment was decided by the Gynecologic Oncology Council. Patients were followed up every 3 months for the first 2 years and then every 6 months for 3 years, with whole blood tests, blood biochemistry, pelvic examination, and abdominal ultrasonography. Annual chest radiographs were also performed. Computed tomography of the chest and abdomen was conducted when necessary, and Ca-125 and Papanicolaou smears were not routinely performed.

Statistical Analysis

Statistical analysis was performed using statistical package for the social sciences (SPSS) v.23 software (SPSS, Inc. Chicago, IL) on a sample of 611 patients. Descriptive statistics were presented as mean ± standard deviation and median (range) for continuous variables. The Shapiro-Wilk test was used to determine the normality of the data.

For normally distributed data, The Independent-Samples t-test was used, while The Mann-Whitney U test was used for variables that were not normally distributed. Pearson correlation was used to assess the relationship between continuous variables. For categorical variables, the chi-square test or Fischer's exact test was used.

Univariate analyses were used to determine the relationship between OS and variables. Variables that showed a significant association with OS in the univariate analysis were then included in the multivariate analysis. The hazard ratio (HR) was calculated to determine the effect of each variable on survival. The Kaplan-Meier method was used for the analysis of "time-to-event" data. Data were analyzed with a 95% confidence interval, and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 611 patients were included in the study. The median age of the patients was 57 years (range 28-85), with 376 (61.5%) patients under 60 years of age and 235 (38.5%) patients aged 60 years or older. Of these patients, 130 underwent TAH/BSO alone, 13 underwent TAH/BSO with pelvic lymphadenectomy and cytology, and 468 underwent TAH/BSO with PPLND and cytology. The median number of pelvic lymph nodes removed was 34 (range 10-110), and the median number of para-aortic lymph nodes removed was 14 (range 1-58) (Table 1).

Table 1. Clinicopathologic features of 611 women with stage I endometrioid-type endometrial cancer undergoing surgery

Characteristics	Values n (%)
Age (year), (median, range)	57 (28-85)
<60 age	376 (61.5)
≥60 age	235 (38.5)
LVSI	
Positive	52 (8.5)
Negative	559 (91.5)
CA125 (IU/mL) (median, range)	13 (3-991)
Missed	54 (8.8)
≥35	49 (8)
<35	508 (83.1)
Type of surgery	
TAH/BSO	130 (21.3)
TAH/BSO + cytology + pelvic LN	13 (2.1)
TAH/BSO + cytology + pelvic para-aortic LN	468 (76.6)
Grade	
1	424 (69.4)
2	162 (26.5)
3	25 (4.1)
Stage	
1A	489 (80)
1B	122 (20)
Peritoneal cytology	
Missed	7 (1.1)
Negative	599 (98)
Positive	5 (0.9)
Tumor size (media, range cm)	2.8 (1-10)
Missed	1 (0.2)
<2.8	312 (51.1)
≥2.8	298 (48.9)
Adjuvant treatment	
Missed	219 (35)
Yes	77 (12.6)
No	315 (51.4)
Adjuvant treatment	
RT	72 (11.7)
CT	4 (0.007)
CRT	1 (0.001)
Site of recurrence	
Vagina	13 (50)
Pelvic	5 (19.3)
Abdominal	2 (7.7)
Lymph node	3 (11.5)
Multiple	2 (7.6)
Liver	1 (3.9)
Total	26 (100)

LVSI: Lymph-vascular space invasion, TAH/BSO: Total abdominal hysterectomy and bilateral salpingo-oophorectomy, LN: Lymph node metastasis, RT: Radiation therapy, CT: Computed tomography, CRT: Chemoradiotherapy

Lymph- vascular space invasion was detected in 52 patients (8.5%), while 559 patients (91.4%) were LVSI-negative. Adjuvant treatment was given to 77 (12.6%) patients, while 315 (51.4%) patients did not receive adjuvant treatment. A total of 26 (4.3%) patients experienced recurrence, and the remaining 585 (95.7%) patients did not experience recurrence. Of the 26 patients with recurrence, 4 had LVSI involvement, while 22 did not have LVSI. Within the recurrence group, 3 patients had grade 3 and 9 patients had myometrial invasion ≥50% (Table 1).

Among the 604 patients with cytologic records available, 5 (0.8%) patients were cytologically positive and 599 (99.2%) were cytologically negative. The median tumor size was 2.8 cm (range 1-10), and the median follow-up time was 61 months (range 8-146 months) (Table 1).

In survival analysis, the 5-year DFS for LVSI-negative patients was 94.2%, compared to 88.7% for LVSI-positive patients. However, the difference between survival rates was not statistically significant (p=0.31) (Figure 1). The 5-year OS for LVSI-negative patients was 96.9%, compared to 91.6% for LVSI-positive patients. Again, the difference in survival rates was not statistically significant (p=0.39) (Figure 2).

Multivariate analysis revealed that disease stage had no effect on crude survival, but patient's age and tumor size were the independent prognostic factors of crude survival. Patients over 60 years of age had a HR of 4 times higher than patients under 60 years of age (95% CI: 1.57-10.5, p=0.004). Similarly, patients with a tumor size of 2.8 cm or more had a HR of 2.5 times higher than patients with a tumor size less than 2.8 cm (95% CI: 1,001-6,148, p=0.05) (Table 2).

Discussion

The role of LVSI in the prognosis of EC has been extensively studied, but previous studies have reported conflicting findings regarding its prognostic significance. Our study evaluated the prognostic significance of LVSI in patients with FIGO stage I

Table 2. Univariate and multivariate analyses of prognostic factors for overall survival

	Variable n/total (%)	Univariate analysis	Multivariate analysis		
		p	HR	95% CI	p
Age, y					
≥60	12/235 (5.1)	0.001	4.080	1.572-10.590	0.004
<60	6/376 (1.5)				
Cytology					
Negative	16/599 (2.6)	0.06			
Positive	1/5 (20)				
Grade					
1	12/424 (2.8)	0.309			
2	4/162 (2.4)				
3	2/25 (8)				
Tumor size					
<2.8 cm	4/312 (1.2)	0.02	2.48	1.001-6.148	0.05
≥2.8 cm	14/298 (4.6)				
Stage					
IA	12/489 (2.4)	0.02	1.52	0.63-3.64	0.34
IB	6/122 (5)				
LVSI					
Negative	15/559 (2.6)	0.39			
Positive	3/52 (5.7)				
Surgical staging					
No	3/133 (2.2)	0.82			
Yes	15/468 (3.1)				
Adjuvant treatment					
Yes	2/77 (2.5)	0.62			
No	6/315 (1.9)				

HR: Hazard ratio, CI: Confidence interval, LVSI: Lymph-vascular space invasion

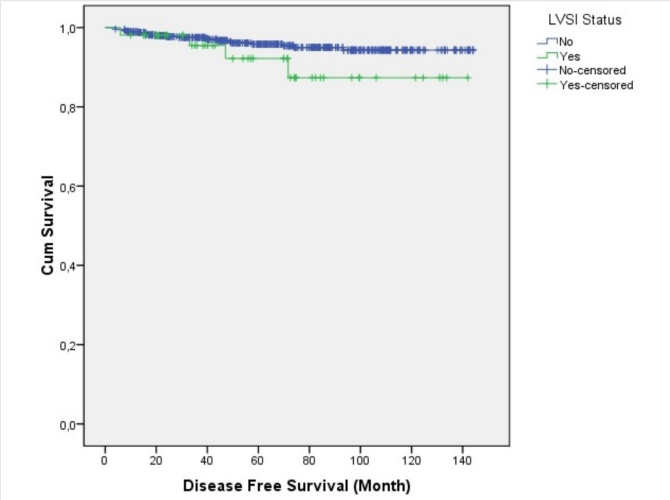

Figure 1. The effect of LVSI on disease-free survival
LVSI: Lymph-vascular space invasion

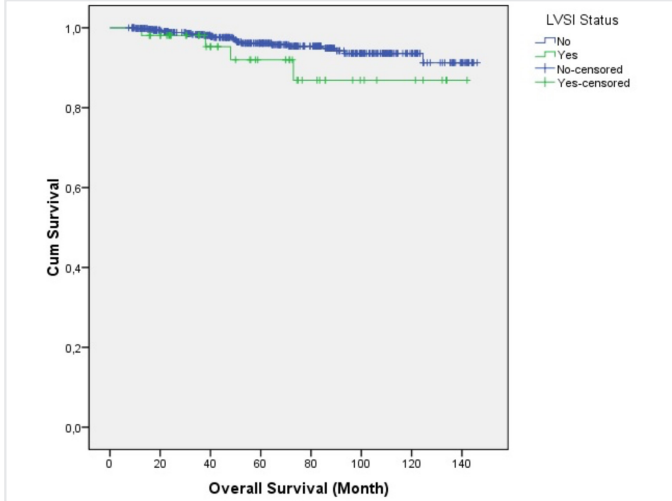

Figure 2. The effect of LVSI on overall survival
LVSI: Lymph-vascular space invasion

endometrioid-type EC. LVSI positivity was detected in 8.5% of the patients, which was consistent with previous studies reporting rates of LVSI positivity ranging from 3.9% to 23% in patients with early-stage EC (12-14).

In our study, LVSI positivity was not found to be a significant predictor of DFS or OS. While the 5-year DFS rate was slightly lower in LVSI-positive patients compared to LVSI-negative patients, the difference was not statistically significant. Similarly, there was no statistically significant difference in OS between the two groups. These findings were consistent with some previous studies that reported no significant association between LVSI and survival outcomes (13,15-18). However, other studies reported that LVSI positivity was a strong predictor of poor prognosis, with higher rates of recurrence and decreased survival (15,18-20). It was important to note that the number of recurrences in our study was relatively low (4.3%), which might contribute to the lack of statistical significance. In addition, our study had a median follow-up time of 61 months, which might not be sufficient to fully capture the long-term impact of LVSI on survival outcomes.

In multivariate analysis, patient LN metastasiss age and tumor size were found to be the independent prognostic factors of crude survival. Patients over 60 years of age had a 4-fold higher HR for crude survival compared to younger patients, which was consistent with previous studies showing that age was an important predictor of survival outcomes in patients with EC (21,22). Similarly, tumor size was found to be an independent predictor of survival. Patients with tumor size of 2.8 cm or more had a 2.5-fold higher HR compared to patients with smaller tumors. This is consistent with previous studies that have shown that tumor size is an important prognostic factor for patients with EC (20,21).

LVSI involvement has been associated with a higher recurrence rate and increased tumor-related mortality rate. However, in some studies, LVSI was not found to be related to mortality. The discrepancies in findings between studies may be due to differences in patient populations, sample sizes, and methodology used to assess LVSI status (22-25).

Histological grade is another prognostic factor for EC, and high-grade tumors are associated with worse prognosis. In the present study, no association was found between DFS and tumor grade, which could be due to the small number of patients with high grade. Age is also accepted as an independent prognostic factor in recent studies in multivariate analyzes that include variables such as adjuvant radiotherapy and histopathologic type. In the present study, age was found to be a significant prognostic factor in the early-stage EC.

Study Limitations

Our study has several strengths, including the large sample size, the use of standardized surgical and pathological protocols, and the long-term follow-up. However, there are also some limitations that should be considered. First, our study was retrospective in nature, which might lead to selection bias and incomplete data collection. Second, our study was conducted at a single institution, which might limit the generalizability of our findings.

Conclusion

In conclusion, our study provides further evidence on the prognostic significance of LVSI in patients with early-stage EC While LVSI positivity was not found to be a significant predictor of survival outcomes in our study, age and tumor size were identified as important prognostic factors. Further studies are needed to better understand the role of LVSI in the prognosis of EC and to identify other potential prognostic factors that may help guide treatment decisions for patients with early-stage EC.

Ethics

Ethics Committee Approval: The study was approved by the institutional review board of Clinical Research Ethics Committee on July 17, 2018 (17/07/2018# 44/2018).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.M.M., Concept: C.K., M.M.M., Design: C.K., M.M.M., Data Collection or Processing: C.K., Analysis or Interpretation: C.K., Literature Search: C.K., Writing: C.K., M.M.M.

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