Taiwanese Journal of Obstetrics & Gynecology 58 (2019) 82–89

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Recurrence patterns and prognostic factors in lymphovascular space invasion-positive endometrioid endometrial cancer surgically confined to the uterus

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ARTICLE INFO

Article history:
Accepted 16 July 2018

Keywords:
Endometrioid adenocarcinoma
Endometrial cancer
Recurrence
Lymphovascular space invasion
Negative lymph nodes

ABSTRACT

Objective: The purpose of this study was to determine the patterns of failure and prognostic factors for lymphovascular space invasion (LVSI)-positive endometrioid endometrial cancer (EC) patients in the setting of negative lymph nodes (LNs).
Materials and methods: A multicenter, retrospective department database review was performed to identify LVSI-positive patients with disease surgically confined to the uterus at two gynecologic oncology centers in Turkey. Demographic, clinicopathological and survival data were collected.
Results: We identified 185 LVSI-positivewomen with negative LNs during the study period. Fifty-five (29.7%) were classified as Stage IA, 94 (50.8%) as Stage IB, and 36 (19.5%) as Stage II. The median age at diagnosis was 59 years and the median duration of follow-up was 44 months. The total number of the recurrences was 12 (6.5%). We observed 5 (2.9%) loco-regional recurrences, 3 (1.5%) retroperitoneal failures, and 4 (2.0%) distant relapses. The 5-year progression-free survival (PFS) was 86.1% while the 5-year overall survival (OS) rate was 87.7%. Grade 3 histology (Hazard Ratio [HR] 2.9, 95% Confidence Interval [CI] 1.02–8.50; $p = 0.04$), cervical stromal invasion (HR 4.5, 95% CI 1.61–12.79; $p = 0.004$) and age $\geq$ 60 years (HR 5.8, 95% CI 1.62–21.32; $p = 0.007$) were found to be independent prognostic factors for decreased OS. Adjuvant treatment did not appear as a prognostic factor for OS even in univariate analysis.
Conclusion: The recurrence rate among LVSI-positive endometrioid EC patients is low in the setting of negative LNs. However, one out of three patients with a recurrence experiences distant relapses which usually portend worse outcomes.
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Introduction

Lymphovascular space invasion (LVSI), which is currently considered to be one of the first steps in the metastatic spread of endometrial cancer (EC) [1] has been recognized as an important adverse prognostic factor for a long time [2]. Even in women with surgically staged EC confined to the uterus with negative lymph

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https://doi.org/10.1016/j.tjog.2018.11.016
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nodes (LNs), the positive association between LVSI and recurrence risk has been reported [3–6].

However, it is not clear which LVSI-positive patients have increased risk of recurrence when the LNs are negative. Additionally, there is a paucity of data with regards to recurrence patterns in this unique group of patients. Mahdi et al. [7]reported the total recurrence rate as 11.8% among 110 women with positive LVSI and negative nodal status. The rate of distant recurrence was 7.9% whereas the rate of para-aortic failure was 1.8% in that study [7].

The role of LVSI in relation to recurrence patterns has not been well defined [8]. It is not certain if the presence of LVSI alone is sufficient for decision-making in favor of adjuvant therapy in women who have undergone systematic LN dissection and found to have negative nodal status. However, LVSI is the cornerstone of risk stratification according to the European Society for Medical Oncology (ESMO)-modified criteria [9]. Regardless of myometrial invasion (MMI), the ESMO-modified criteria recommend adjuvant treatment for all International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2 endometrioid type tumors if LVSI is positive. Nevertheless, characterizing and understanding the behavior of surgically-staged, LVSI-positive endometrioid tumors with negative nodal status may have profound implications about treatment options and prognosis.

Therefore, we conducted this retrospective, dual-institutional study in order to shed some more light on these issues. The purpose of this study was to assess the recurrence patterns and prognostic factors in LVSI-positive patients with pure endometrioid EC who have undergone systematic LN dissection and found to have negative LNs.

Materials and methods

Medical records of consecutive women who underwent primary surgical treatment for EC between January 2007 and December 2016 at two gynecologic oncology centers Ankara, Turkey were retrospectively reviewed. The study protocol was approved by the Local Institutional Review Board. All patients provided an informed consent for the use of their medical information for research purposes. The study population included women with endometrioid type EC confined to the uterus who underwent comprehensive surgical staging. Patients were eligible if the final pathology report revealed negative nodal status with LVSI positivity. Women with non-endometrioid type EC, those with mixed histologies, patients with negative LVSI status, patients with more extensive disease than stage II on the final pathology report, and those with incomplete medical records were excluded from the study. We also excluded patients with less than 15 LNs in the final pathology report as well as those with synchronous malignancies. Some of the patients in this study were in the context of our previous studies [10,11].

Tumor characteristics were abstracted from original pathology reports, and the following data were recorded: primary tumor diameter (PTD) (as a continuous variable or dichotomous [<4 cm or ≥4 cm]), depth of myometrial invasion (MMI) (<50% or ≥50%), and the status of peritoneal cytology examination (negative or positive) and the stage of disease. The date of diagnosis, adjuvant treatment modality (radiotherapy, chemoradiotherapy, or chemotherapy), recurrence (if applicable), time to recurrence (as a continuous variable in months, if applicable) [11], site of recurrence (loco-regional, retroperitoneal, distant), length of follow-up and survival were noted.

Surgical staging consisted of total hysterectomy ± bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and peritoneal washings. Adequate pelvic lymphadenectomy was defined as the removal of at least 15 pelvic lymph nodes, and adequate para-aortic lymphadenectomy was defined as the removal of at least five para-aortic LNs [12,13]. All operations were performed by gynecological oncologists.

LVSI was defined as the presence of adenocarcinoma of any extent; in endothelium lined channels of uterine specimens extracted at the time of surgery [5]. LVSI was assessed on hematoxylin-eosin stained sections by the primary pathologist. All tumors were staged according to the 2009 FIGO staging system [14]. In patients treated before 2009, stage was determined retrospectively on the basis of surgical and pathologic assessment.

The adjuvant treatment policies were decided by the attending physician or by the multidisciplinary tumor board at each participating institution. Postoperative management was established on the basis of histological findings on surgical specimens, age and the general condition of the patient. Brachytherapy only was administered to women with MMI < 50% and grade 3 disease as well as patients with MMI ≥ 50% and grade 1 or 2 disease. Vaginal vault brachytherapy (median 27.5 Gy in 5 fractions) was delivered using a vaginal cylinder via high-dose rate after-loading iridium-192 source. The first 4 cm of the cylinder was activated and the dose was prescribed to 0.5 cm depth. Patients with MMI ≥50% and grade 3 disease, or cervical involvement usually received external beam pelvic irradiation, with addition of brachytherapy in selected cases who had isthmic or stromal cervical involvement. Standard external beam radiation therapy (EBRT) was applied as postoperative radiation therapy (RT). The EBRT dose varied, being most commonly between 45 and 50.4 Gy. Chemoradiotherapy was delivered as radiotherapy with concurrent cisplatin 40 mg/m^2 weekly.

All patients were scheduled for follow-up every three months for the first two years, every six months for the next three years, and annually, thereafter. Clinical examinations performed at each visit included pelvic examination, ultrasonographic examination, and CA-125 determination. Computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography-CT (PET-CT) scans were performed when indicated. The cut-off date of survival data was December 31, 2016. The survival status of the patients was determined as alive or dead at the time of the final follow-up. For all non-survivors, death status was confirmed through a social security death index search.

Peritoneal, hematogenous, and LN recurrences outside the retroperitoneal area (i.e. inguinal, axillary, mediastinal, and supraclavicular) were considered as distant failures [15]. Recurrences located in pelvic and/or para-aortic LNs were considered as retroperitoneal failures whereas relapses at vaginal vault, vagina, and/or central pelvis were considered as loco-regional relapses. In case of several concomitant recurrence localizations, the patient was involved in the group with the most advanced disease [11].

After initial diagnosis, recurrence was defined as documentation of metastasis with physical examination and imaging techniques after a recurrence-free survival (RFS) ≥ 3 months. Progressive disease was defined according to the RECIST 1.1 criteria [16]. Time to recurrence (TTR) was defined as the time frame from surgery to physical or radiologic evidence of disease recurrence or the date of last contact for patients without recurrence. RFS was defined as the time from surgery to the first identification of recurrence, or death from any cause, whichever occurred first, or the date of last contact for patients remaining alive without recurrent disease. Overall survival (OS) was calculated as the time period between initial surgery to the date of death or the last contact. Surviving patients were censored at their last known follow-up.

Statistical analysis was performed using the SPSS version 22.0 statistical software (IBM Corp., Armonk, NY, USA). The data were expressed in median and range for continuous variables. The continuous variables such as age and tumor size were divided into

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Table 1
Demographic and clinicopathological characteristics of all patients (n = 185).

Characteristics	Values, n (%)
Age, y, median	59 (27–88)
Menopausal status	
Premenopausal	22/185 (11.9%)
Postmenopausal	163/185 (88.1%)
Baseline Serum CA-125 (IU/ml)	18 (4–452)
Grade	
1	46/185 (24.9%)
2	87/185 (47%)
3	52/185 (28.1%)
Depth myometrial invasion, n, %	
<50	67/185 (36.2%)
≥50	118/185 (63.8%)
Primary tumor diameter (cm), median	4 (0.9–13)
<4 cm	76 (41.1%)
≥4 cm	109 (58.9%)
Peritoneal cytology, n, %	
Positive	5/185 (2.7%)
Negative	180/185 (97.3%)
Cervical stromal invasion	
Yes	36/185 (19.5%)
No	149/185 (80.5%)
Number of LNs removed	44 (20–164)
Pelvic	30 (15–68)
Paraaortic	14 (5–99)
Stage	
IA	55/185 (29.7%)
IB	94/185 (50.8%)
II	36/185 (19.5%)
Recurrence rate	12/185 (6.5%)
Median follow-up time (months, range)	44 (4–116)

Abbreviations: n: Number, LN: Lymphnode.

categories according to the median values. Binary variables were reported as number and percentage. Survival curves were generated using the Kaplan–Meier method, and the differences between survival curves were calculated using the log-rank test. A multivariate Cox-regression model was used to evaluate the prognostic factors for RFS and OS. A *p* value of less than 0.05 in the univariate analysis was included in the multivariate analysis. A *p* value of less than 0.05 was considered statistically significant.

Results

During the study period, we have identified 1131 women with endometrioid EC surgically confined to the uterus. Among those 185 patients (16.3%) had LVSI-positive status: 55 (29.7%) were classified as Stage IA, 94 (50.8%) as Stage IB, and 36 (19.5%) as Stage II. The median age at diagnosis was 59 years (range, 27–88 years) and the median duration of follow-up was 44 months (range, 4–116 months). Histologic grade was determined as grade 1 in 46 women (24.9%) whereas 87 patients had grade 2 (47.0%), and 52 (28.1%) had grade 3 disease. The median PTD was 4.0 cm (range, 0.9–13 cm). MMI was <50% in 67 women (36.2%) while 118 (63.8%) had MMI ≥ 50%. Table 1 demonstrates the clinical and pathological characteristics of LVSI-positive women who had negative nodal status with disease surgically confined to the uterus.

All women in the current study underwent pelvic and para-aortic lymphadenectomy. Adequate lymphadenectomy was achieved in all patients. The median number of total LNs harvested was 44 (range, 20–164). The median number of pelvic and para-aortic LNs removed was 30 (range, 15–68), and 14 (range, 5–99), respectively.

Seventy six (41.1%) women had no additional treatment following surgery. Adjuvant treatment modalities included brachytherapy only in 66 (35.7%) women whereas 25 (13.5%) patients received EBRT plus brachytherapy in the postoperative period. Thirteen (7.0%) women received EBRT only as adjuvant treatment while 5 (2.7%) women were treated with chemo-radiation. The total number of the recurrences was 12 (6.5%). We observed 5 (2.9%) loco-regional recurrences, 3 (1.5%) retroperitoneal failures, and 4 (2.0%) distant relapses. The clinical and pathological characteristics of patients with recurrent disease are summarized in Table 2. Median TTR was 42 months (range, 4–116 months). Site of recurrences, and type of salvage therapies are shown in Table 3.

Overall, for the entire study cohort, the 5-year PFS rate was 86.1% while the 5-year OS rate was 87.7%. Fig. 1 shows the Kaplan–Meier plots for RFS and OS of LVSI-positive women with negative nodal status. Univariate analysis revealed that RFS was significantly decreased in patients with age ≥60 years (p = 0.017), grade 3 histology (p = 0.002), and cervical stromal involvement (p = 0.003) (Table 4). At the end of multivariate analysis, grade 3 disease (Hazard Ratio [HR]2.6, 95% Confidence Interval [CI] 1.03–6.87; p = 0.042), and age≥60 years (HR 4.0, 95% CI 1.40–11.64; p = 0.009), and cervical stromal involvement (HR 4.4, 95% CI 1.70–11.45; p = 0.002) remained as independent prognostic factors for decreased RFS (Table 4). We were not able to define the absence of adjuvant treatment as a prognostic factor for decreased RFS even in univariate analysis. Recurrence-free survival curves of LVSI-positive endometrioid EC patients surgically confined to the uterus with regard to age at diagnosis, postoperative histologic grade, and cervical stromal invasion are shown in Figs. 1a, 2a and 3a, respectively.

Univariate analysis revealed age ≥60 years (p = 0.006), grade 3 disease (p = 0.001), and, cervical stromal invasion (p = 0.003) as

Table 2
Clinical and pathological characteristics and outcome of patients with recurrent disease.

Patient	Age (y)	Stage	Tm Size (cm)	MI	Grade	Recurrence location	Adjuvant Treatment	Recurrence Treatment	Outcome
1	66	IB	3,5	>50%	2	Lung	BRT	CRT	DOD
2	68	II	6	>50%	2	Lung	EBRT	Surgery + CT	DOD
3	63	II	5.5	>50%	2	Vaginal cuff + pelvic Side wall	EBRT + BRT	CT	DOD
4	56	II	6	<50%	2	Vaginal cuff + sigmoid colon + para-aortic LN	EBRT	Surgery + CT	DOD
5	75	II	13	>50%	3	Pelvic side wall + small bowel + pelvic + para-aortic LN	EBRT + BRT	CT	DOD
6	54	II	6.5	>50%	3	Para-aortic LN	EBRT + BRT	Surgery + CT	DOD
7	69	II	6.5	>50%	3	Pelvic and para-aortic LN	EBRT	Surgery + CRT	DOD
8	55	IB	7	>50%	2	Para-aortic LN	BRT	Surgery + CT	ANED
9	83	IB	3	>50%	3	Vaginal cuff + pelvic Side wall	BRT	CT	DOD
10	63	IB	3.5	>50%	3	Vaginal Cuff	BRT	Surgery + CRT	ANED
11	58	II	8	<50%	2	Vaginal Cuff	EBRT + BRT	Surgery + CRT	ANED
12	56	II	1.4	>50%	3	Pelvic side wall	EBRT	CRT	DOD

Abbreviations: ANED: Alive with no Evidence of Disease; CRT: Chemo-radiotherapy; CT: Chemotherapy; DOD: Dead of Disease; DOID: Dead of Intercurrent Disease; EBRT: External Beam Radiotherapy; BRT: Brachytherapy; LN: Lymph node.

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Table 3
Recurrence patterns and treatment characteristics of women having positive LVSI with endometrioid type endometrial cancer (*n*: 185) surgically confined to the uterus.

Characteristics	Values, n (%)
No additional treatment,	76/185 (41.1%)
Adjuvant treatment	
Brachytherapy only	66 (35.7%)
EBRT	13 (7.0%)
EBRT + Brachytherapy	25 (13.5%)
Chemo-radiation	5 (2.7%)
Distant recurrence	4 (2.2%)
Peritoneal	2/185 (1.1%)
Hematogenous	2/185 (1.1%)
Loco-regional relapse	5 (2.7%)
Vaginal cuff	2/185 (1.1%)
Central Pelvic	1/185 (0.5%)
Vaginal cuff + Central pelvic	2/185 (1.1%)
Retroperitoneal failures	3 (1.6%)
Para-aortic LN	2/185 (1.1%)
Pelvic + para-aortic	1/185 (0.5%)
Salvage Therapies	
Chemotherapy alone	3/185 (1.6%)
Surgery + Chemotherapy	4/185 (2.2%)
Surgery + Chemo-radiation	3/185 (1.6%)
Chemo-radiation	2/185 (1.1%)
Median time to recurrence (months, Range)	42 (4–116)

Abbreviations: n: Number; LN: Lymph node; LVSI: Lymphovascular space invasion; EBRT: External Beam Radiotherapy.

significant factors for decreased OS (Table 5). At the end of multivariate analysis, grade 3 histology (HR 2.9, 95% CI 1.02–8.50; p = 0.04), cervical stromal invasion (HR 4.5, 95% CI 1.61–12.79; p = 0.004) and age ≥ 60 years (HR 5.8, 95% CI 1.62–21.32; p = 0.007) remained as independent prognostic factors for decreased OS (Table 5). Adjuvant treatment did not appear as a prognostic factor for OS even in univariate analysis. Table 6 summarizes the clinicopathologic characteristics of LVSI-positive patients with disease surgically confined to the uterus with regard to adjuvant treatment. Overall survival curves of LVSI-positive endometrioidEC patients surgically confined to the uterus with regard to age at diagnosis, postoperative histologic grade, and cervical stromal invasion are shown in Figs. 1b, 2b and 3b, respectively.

There were no patients with progressive disease. However, we have detected 12 recurrences during the study period. At the time of reporting, of 185 LVSI-positive women with node-negative disease, 16 (8.6%) were dead whereas 169 (91.4%) were alive.

Discussion

The key findings of the current study indicate that 6.5% of LVSI-positive endometrioid EC patients had recurrences in the setting of negative LNs. Of those women with recurrences, 41.7% experienced loco-regional recurrences whereas 25.0% had retroperitoneal failures, and 33.3% had distant relapses. Grade 3 disease, cervical stromal invasion and age≥60 years were found to be independent prognostic factors for decreased RFS and OS in LVSI-positive women with endometrioid EC in the absence of nodal involvement.

A Dutch study in 2005 revealed that presence of LVSI was associated with an increased risk of EC recurrences even in low-risk group without LN metastasis [4]. Jorge et al. [17] reported that when stratified on the presence or absence of nodal metastases, LVSI remained associated with survival in node-negative patients (HR = 2.06, 95% CI, 1.65–2.58). However, little data exists regarding the patterns of recurrence and prognostic factors in LVSI-positive endometrioid EC patients in the setting of negative LNS. Weinberg at al [18]. have identified LVSI as the most consistent poor prognostic factor in a cohort of 388 women with at least one high-risk feature (LVSI, grade 2 or 3, MMI ≥ 50%) in surgically treated stage I-II endometrioid EC with selective lymphadenectomy. The authors reported the total recurrence rate as 28.3% among 99 LVSI positive patients within this cohort. Sixteen (16.1%) had vaginal recurrence, 19 (19.1%) had local recurrence and 20 (21.2%) had distant recurrence [18].

Narayan et al. [19] reported the relapse rate as 23.9% (17/71) for LVSI-positive, node-negative patients with intermediate and high-risk EC. The authors proposed that irrespective of histologic type, patients without LVSI or LN metastasis should be regarded as having a very low risk of recurrence whereas patients with LVSI without LN metastasis should be regarded as an intermediate to high-risk of recurrence. The total recurrence rate was 6.5% among node-negative, LVSI-positive endometrioid EC patients in our study. Our results are not in accordance with those of Narayan et al. [19]who suggested that LVSI-positive and node-negative patients as having intermediate-high risk of failure. However, it should be reminded that non-endometrioid histologies were included in the Narayan study [19] whereas 49 women (26.5%) in our cohort had

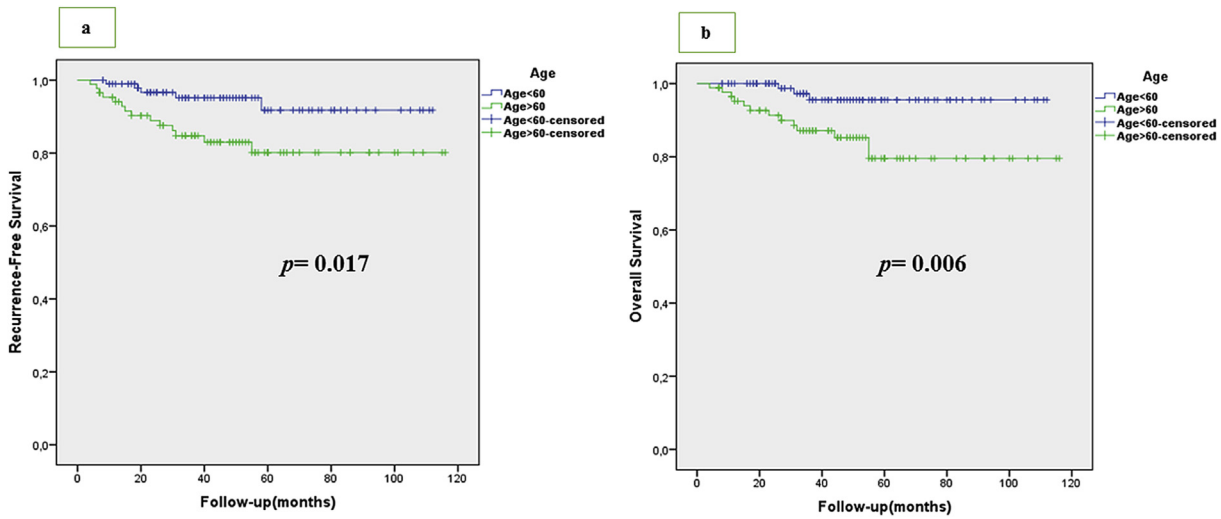

Fig. 1. Recurrence-free survival (1a) and overall survival (1b) curves of lymphovascular space invasion-positive endometrioid endometrial cancer patients surgically confined to the uterus with regard to age at diagnosis.

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Table 4
Univariate and multivariate analysis for recurrence-free survival in lymphovascular space invasion-positive women with negative nodal status.

	RFS[a]	Events[b]	Univariate p	Multivariate		
				HR	95% CI	p
Age, y						
<60	91.7%	5/99 (5.1%)	**0.017**	**4.0**	**1.407–11.640**	**0.009**
≥60	80.1%	14/86 (16.3%)				
Menopausal Status						
Premenopausal	100%	0/22 (0%)	0.096			
Postmenopausal	82.8%	19/163 (11.6%)				
Myometrial invasion						
<50%	85.9%	6/67 (8.9%)	0.715			
≥50%	85.7%	13/118 (11%)				
Grade						
1 or 2	90.3	8/133 (6%)	**0.002**	**2.6**	**1.034–6.871**	**0.042**
3	76	11/52 (21.2%)				
Peritoneal cytology						
Positive	75%	1/5 (20%)	0.476			
Negative	86.5%	18/180 (10%)				
Tm size (cm)						
<4	85%	8/76 (10.5%)	0.808			
≥4	86.9%	11/109 (10.1%)				
Serum CA-125 (IU/ml)						
<35	84.2%	17/150 (11.3%)	0.870			
≥35	88.5%	5/52 (9.6%)				
Cervical stromal involvement						
Yes	69.5%	8/36 (22.2%)	**0.003**	**4.4**	**1.706–11.454**	**0.002**
No	92.8%	8/149 (5.3%)				
Adjuvant treatment						
Yes	82.7%	14/109 (12.8%)	0.186			
No	91.4%	5/76 (6.6%)				

Abbreviations: LN: Lymph node; RFS: Recurrence-free survival; HR: Hazard ratio; CI: Confidence interval.
Significant results were expressed in bold.
[a] 5-year recurrence-free survival rate.
[b] The number of cases with recurrence or death whichever occurred first.

low-risk features (endometrioid type, grade 1 or 2 disease with MMI<50%) (Data not shown).

LVSI-positive endometrioid EC patients with negative nodal status (n = 110) have been reported to have a recurrence rate of 11.8% (13/110) [7]. The rate of distant recurrence was 7.9% whereas the rate of paraaortic nodal failure was 1.8% in that study [7]. The corresponding figures were 6.5%, 2.2% and 1.6% respectively in the current study. The lower recurrence rates in the present study may be explained by the 100% systematic lymphadenectomy rate as well as the high rate (26.5%) of low-risk patients. Mahdi et al. [7] have reported the 5-year PFS and OS for node-negative, LVSI-positive patients as 76% and 82%, respectively. The corresponding figures were found to be 86.1%, and 87.7% respectively in the current study; higher than those of Mahdi et al. [7].

Neal et al. [20] have suggested that if LNs are negative after complete surgical staging, LVSI is not an important prognostic factor after adjusting for other known prognostic variables;

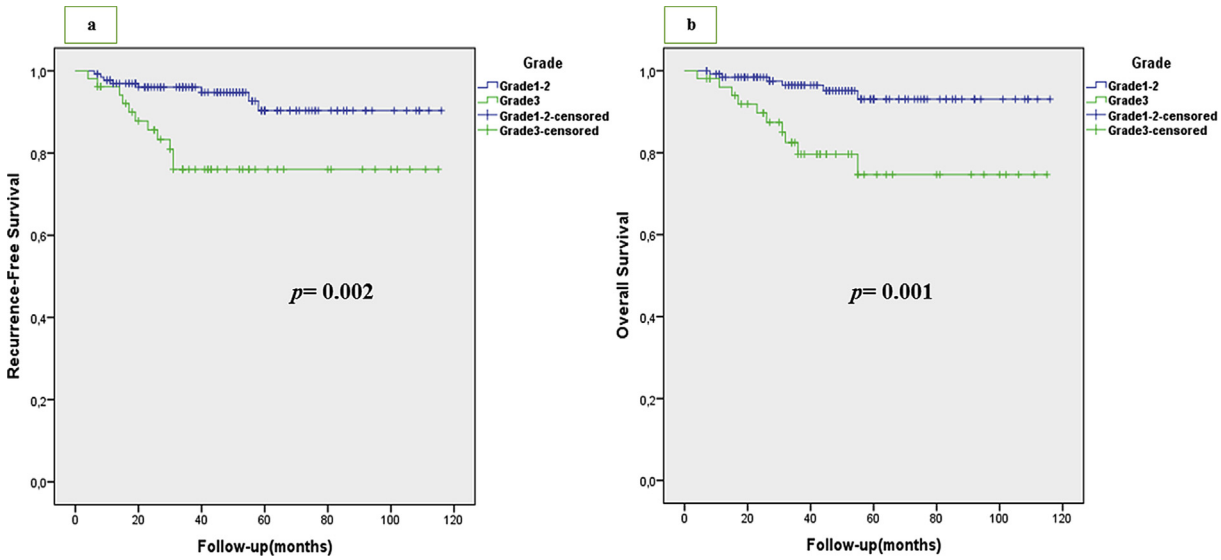

Fig. 2. Recurrence-free survival (2a) and overall survival (2b) curves of lymphovascular space invasion-positive endometrioid endometrial cancer patients surgically confined to the uterus with regard to postoperative histologic grade.

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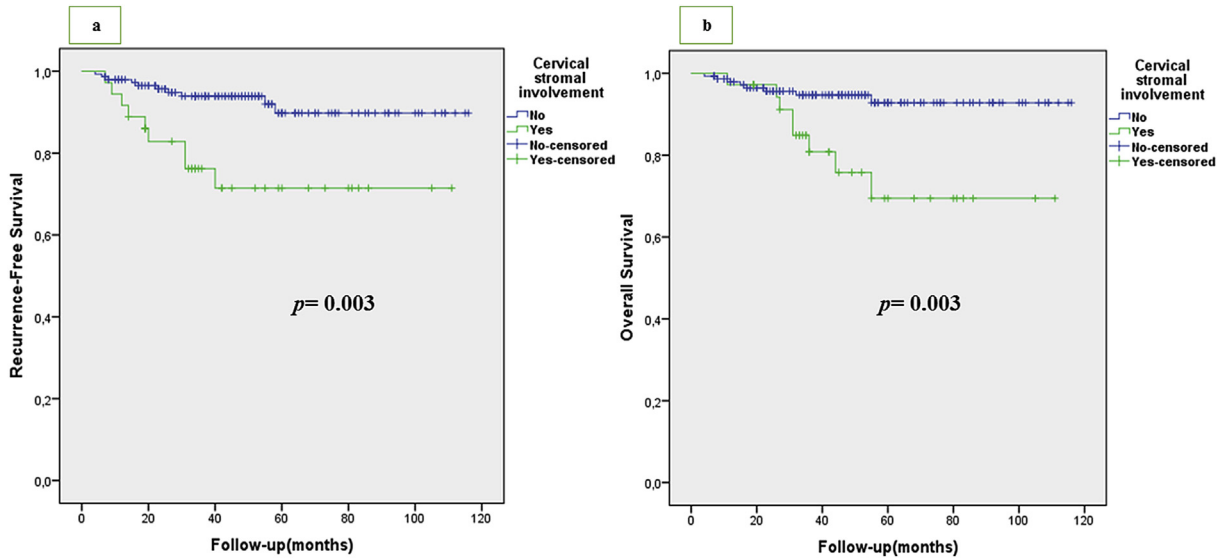

Fig. 3. Recurrence-free survival (3a) and overall survival (3b) curves of lymphovascular space invasion-positive endometrioid endometrial cancer patients surgically confined to the uterus with regard to cervical stromal invasion.

therefore, adjuvant therapy is not indicated based upon LVSI alone. Our results are in agreement with those of Neal et al. [20]. The recurrence rate in the adjuvant treatment group was significantly higher than that of the no additional treatment group in our study (Table 6). This finding is definitely associated with significantly higher rates of uterine adverse factors in the adjuvant treatment group (Table 6).

An absolute proportion of patients with LVSI will go on to develop recurrence and it is therefore important to identify those patients who are at greatest risk and who may benefit from adjuvant treatment [21]. We have found out cervical stromal invasion, grade 3 histology and age ≥60 years as independent prognostic factors for decreased RFS and OS among LVSI-positive endometrioid EC patients with negative nodal status.

The major limitations of the current study are inherent drawbacks from its retrospective nature and the associated biases, as well as the low number of events. Another potential weakness of our study is that there was no central pathology review to evaluate

Table 5
Univariate and multivariate analysis for overall survival in lymphovascular space invasion-positive women with negative nodal status.

	OS[a]	Events[b]	Univariate p	Multivariate		
				HR	95% CI	p
Age, y						
<60	95.5%	3/99 (3%)	**0.006**	**5.8**	**1.621–21.327**	**0.007**
≥60	79.5%	13/86 (15.1%)				
Menopausal Status						
Premenopausal	100%	0/22 (0%)	0.128			
Postmenopausal	86.1%	16/163 (9.8%)				
Myometrial invasion						
<50%	93%	4/67 (5.9%)	0.365			
≥50%	84.8%	12/118 (10.1%)				
Grade						
1 or 2	93.1	6/133 (4.5%)	**0.001**	**2.9**	**1.025–8.508**	**0.045**
3	74.7	10/52 (19.2%)				
Peritoneal cytology						
Positive	75%	1/5 (20%)	0.372			
Negative	88.2%	15/180 (8.3%)				
Tumor size (cm)						
<4	86.4%	7/76 (9.2%)	0.675			
≥4	88.6%	9/109 (8.2%)				
Serum CA-125 (IU/ml)						
<35	87.5%	12/138 (8.7%)	0.950			
≥35	89.1%	4/47 (8.5%)				
Cervical stromal involvement						
Yes	69.5%	8/36 (22.2%)	**0.003**	**4.5**	**1.614–12.791**	**0.004**
No	92.8%	8/149 (5.3%)				
Adjuvant treatment						
Yes	84.4%	11/109 (10.1%)	0.431			
No	91.3%	5/76 (6.6%)				

Abbreviations: LN: Lymph node; OS: Overall Survival; HR:Hazard ratio; CI: Confidence interval.
Significant results were expressed in bold.
[a] 5-year overall survival rate.
[b] The number of cases with death.

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Table 6
Comparison of lymphovascular space-positive women with negative nodal status with respect to adjuvant treatment.

Characteristics	No additional treatment (n = 76)	Adjuvant treatment (n = 109)	P value
Age, years (median)	58 (27–88)	60 (35–87)	0.183
Menopausal status, n			
Postmenopausal	67 (88.2%)	96 (88.1%)	0.986
Premenopausal	9 (11.8%)	13 (11.9%)	
Stage, n			**<0.001**
IA	43 (56.5%)	12 (11%)	
B	28 (36.9%)	66 (60.6%)	
II	5 (6.6%)	31 (28.4%)	
Myometrial invasion			**<0.001**
<50%	44 (57.9%)	23 (21.1%)	
≥50%	32 (42.1%)	86 (78.9%)	
Grade			**<0.001**
1	28 (36.8%)	18 (16.5%)	
2	42 (55.3%)	45 (41.3%)	
3	6 (7.9%)	46 (42.2%)	
Tumor Size, cm (median)	3.6 (1–10.5)	4.5 (0.9–13)	**0.001**
Serum CA 125 (median, IU/ml)	17.3 (4–452)	19 (5–400)	0.161
Peritoneal cytology, n			0.383
Positive	3 (3.9%)	2 (1.8%)	
Negative	73 (96.1%)	107 (98.2%)	
Number of LNs removed (median)	43 (21–106)	49 (20–164)	0.456
Number of pelvic LNs removed	30 (16–60)	30 (15–68)	0.686
Number of para-aortic LNs removed	13 (5–50)	15 (5–99)	0.139
Cervical stromal invasion			**<0.001**
Positive	5 (6.6%)	31 (28.4%)	
Negative	71 (93.4%)	78 (71.6%)	
Recurrence, n			**0.017**
Yes	1 (1.3%)	11 (10.1%)	
No	75 (98.7%)	98 (89.9%)	
Status			0.403
Alive	71 (93.4%)	98 (89.9%)	
Dead	5 (6.6%)	11 (10.1%)	
Median following time (month)	46 (4–116)	42 (7–115)	0.836

Abbreviations: LN: Lymph node.
Significant results were expressed in bold.

for the presence or absence of LVSI. However, LVSI is often criticized for its subjectivity and poor reproducibility [22]. For these reasons, we conducted a dual-institutional study involving more than 8 pathologists and the subjectivity was diminished by the variety of pathologists studying LVSI. Therefore, we believe that the pathology associated with LVSI in the current study reflects the "real world" diagnosis.

These limitations are somewhat balanced by a uniform policy among all surgeons whose patients contributed to the current study of rigorous lymphadenectomy limiting the bias in the area of LN dissection. The current study was designed to create a dataset as uniform as possible excluding, for instance, non-endometrioid histologies and patients with inadequate LN dissection, thereby minimizing the confounding factors. However, our study is one of the few studies detailing the prognostic factors and recurrence patterns in this unique patient population.

In conclusion, the recurrence rate among LVSI-positive endometrioid EC patients is low in the setting of negative LNs. However, one out of three patients with a recurrence seems to experience distant relapses which usually portend worse outcomes. Age ≥60 years and uterine factors such as grade 3 disease, and cervical stromal invasion seem to be independently associated with decreased RFS and OS in LVSI-positive women with negative nodal status. Further studies are needed in order to identify the most appropriate adjuvant treatment strategy for those patients.

Conflict of interest

Authors declare that there is neither financial nor academic support of relationships that may pose potential conflict of interest.

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