Predictors of recurrence and survival in lymphovascular space invasion negative early-stage endometrioid endometrial cancer patients

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Abstract

Objective: The purpose of this study was to assess prognostic factors correlated with recurrence and decreased oncologic outcomes, as well as the role of adjuvant treatment on survival in women with stage I and II endometrioid endometrial cancer without lymphovascular space invasion (LVSI).

Material and Methods: Patients with LVSI negative, early-stage endometrioid endometrial cancer patients were retrospectively reviewed. Multivariable logistic regression models were used for identifying predictors of recurrence. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method, and survival curves were compared by log-rank test. Univariable and multivariable analyses were performed to establish factors affecting OS and DFS. Hazard ratios with 95% confidence intervals were calculated.

Results: A total of 289 patients were included, with a mean age of 58 years and the median surveillance time of 45 (6-147) months. The majority of the patients (54%) had grade 1 tumors. Adjuvant therapy was administered to 68 (23.5%). A total of 13 (4.5%) recurred with median time to recurrence of 52 months. Patients receiving adjuvant treatment were more likely to recur ($p=0.015$), and grade was the only independent predictor of recurrence ($p=0.029$). Five-year OS and DFS were 95.8% and 97.9%, respectively. While tumor size ($p=0.018$) and grade 3 histology ($p=0.045$) were related with shorter DFS, age ($p<0.001$) was the only related factor for decreased OS.

Conclusion: Recurrence rate was low among LVSI negative, early-stage endometrioid endometrial cancer patients. Although recurrences were seen more frequently in patients who received adjuvant treatment, it wasn't an independent prognostic factor. Neither recurrence nor adverse uterine risk factors were associated with shorter OS. While age was the only prognostic factor for decreased OS, grade 3 histology and tumor size were associated with decreased DFS. (J Turk Ger Gynecol Assoc 2023; 24: 261-70)

Keywords: Endometrial cancer, recurrence, lymphovascular space invasion, survival

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Introduction

Cancer of the endometrium is usually diagnosed in the early stages when the disease is limited to uterus and the prognosis is generally good (1,2). Although 5-year overall survival (OS) has been reported as more than 90%, the recurrence rate has been reported as being as high as 30% for the early-stage patients (3,4). Grade, histologic subtype, deep myometrial invasion (MI), lymphovascular space invasion (LVSI), tumor size and age were all found as risk factors for recurrence in stage I and II endometrial cancer (5-7). Based on these risk factors, patients are classified as low, intermediate, high-intermediate and high risk, and adjuvant therapy is recommended for certain risk groups to lower the recurrence rates (8,9).

LVSI has been of particular research interest in the last decade and has been established as an independent risk factor for recurrence, even when there are no metastatic lymph nodes (10-12). Thus, LVSI has been incorporated into the guidelines as an important prognostic factor, and adjuvant vaginal brachytherapy (BRT) is recommended to LVSI positive patients (9,13).

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However, Neal et al. (14) reported that LVSI was not a prognostic factor in patients with negative nodes after adjusting other prognostic factors. In another study, it was suggested that irrespective of histologic subtype, patients without LVSI and nodal metastasis should be regarded as very low risk of recurrence (15).

Although survival rate is high, and no adjuvant treatment is recommended, recurrences can still be seen in LVSI negative, early-stage patients. Hence, to investigate the effect of LVSI, we planned this retrospective study to identify factors associated with recurrence and the role of adjuvant treatment on outcomes in stage I and II endometrioid endometrial cancer patients without LVSI.

Material and Methods

After the approval of the Ankara University Faculty of Medicine Institutional Review Board (approval number: 10-420-14, date: 09.06.2014), records of 660 women diagnosed with endometrial adenocarcinoma who were treated with surgery at a university hospital from January 2006 till October 2021 were retrospectively reviewed. Four hundred seven patients had tumors without LVSI. Of these patients, 20 were excluded due to non-endometrioid histology, 18 due to stage III/IV disease according to final pathology report and 74 due to missing follow-up data or less than six months of clinical follow-up. A further six patients were also excluded from the analysis because they died of intercurrent diseases in the first six months after surgery. Thus, 289 women with stage I and II endometrioid endometrial cancer without LVSI were included to the final analysis. A written informed consent was obtained from all the patients in order to use their medical data for scientific purposes.

All patients underwent a total hysterectomy ± salpingo-oophorectomy, via open, vaginal or minimally invasive (laparoscopically or robotic assisted) approaches. Four patients, aged between 34 and 40 years had bilateral salpingectomy and the rest had salpingo-oophorectomy. Surgical route was chosen based on surgeon's experience as well as patients' age, weight and co-morbidities. Lymphadenectomy was not performed in 39 patients due to low-risk uterine factors according to Mayo criteria (grade 1-2 endometrioid tumors, <2 cm and <1/2 MI) in frozen section analysis and/or medical comorbidities. In the rest of the patients, lymph node evaluation was performed by sentinel lymph node (SLN) removal only (n=18), SLN mapping followed by pelvic ± paraaortic lymphadenectomy (n=71) or pelvic ± paraaortic lymphadenectomy (n=161). The extent of paraaortic lymphadenectomy varied from removal of suspicious nodes only to systematic lymphadenectomy up to the level of left renal vein, since management practices changed over the duration of the study period. Peritoneal washings were obtained from all patients who underwent surgery before 2009, but it was not a routine part of the surgery thereafter. Gynecologic oncologists performed all of the surgeries and all specimens were reviewed by experienced gynecologic pathologists.

Following surgery, based on the adverse uterine risk factors (age, grade, deep MI and cervical stromal invasion), patients were either observed or received radiotherapy (RT). Adjuvant RT comprised of BRT and/or external beam radiotherapy (EBRT).

Patients were followed up every three months in the first two years, every six months in the subsequent three years and then annually. Physical and vaginal examination, as well as transvaginal ultrasonography, were performed in each follow-up visit. Computed tomography, magnetic resonance imaging or positron emission tomography were performed only if a recurrence was suspected. Site of recurrences were classified as locoregional, intraabdominal, retroperitoneal and distant.

The demographic data included age, body mass index [(BMI), kg/m^2] and menopausal status of the patients. Histopathological data included depth of MI, grade, tumor size and cervical stromal invasion. Clinical and surgical data consisted of CA-125 levels, date of surgery, route of surgery, lymphadenectomy status (yes/no), type of lymphadenectomy, adjuvant treatment (yes/no), type of adjuvant treatment, recurrence (yes/no), recurrence site, recurrence time, last follow-up time and survival.

Disease-free survival (DFS) was defined as time from the surgery until the date of recurrence, or to the date of last contact or death in patients without a recurrence. OS was defined as the time from the surgery until the date of the last follow-up or death.

Statistical analysis

After performing Kolmogorov-Smirnov test to assess normality for continuous variables, data were expressed as median (range) or mean ± standard deviation accordingly and compared using Mann-Whitney U test for non-parametric distributions and Student's t-test for normal distributions. Categorical variables were presented as number (percentage) and compared using chi-square or Fisher's exact tests. Statistically significant factors were assessed with multivariate analysis. By using the Kaplan-Meier method, OS and DFS rates were calculated and the log-rank test was used to calculate statistical significance between the groups. Cox multivariate analysis was used to determine prognostic factors for DFS. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. SPSS version 23.0 (IBM Corp, Armonk, NY, USA) was used for statistical calculations and a p-value less than 0.05 was considered significant.

Results

The mean age of the 289 patients meeting the inclusion criteria was 58±10.4 years, and ranged from 32 to 86 years. Mean BMI was 33.6±7.4 kg/m^2. Demographic, clinicopathologic and treatment characteristics of the patients are presented in Table 1. The majority of cases had grade 1 tumors (n=156, 54%) and had ≤1/2 MI (n=231, 80.9%). While 227 (78.5%) had stage IA disease, 54 (18.7%) had stage IB and 8 (2.8%) had stage II disease. One hundred and eighty-five patients (64%) were operated via laparotomy, 101 (34.9%) via a minimally invasive approach and 3 (1%) vaginally. Lymphadenectomy was omitted in 39 (13.5%) patients. Of those undergoing lymph node evaluation, median number of pelvic, paraaortic and SLNs removed were 18 (1-74), 9 (1-41) and 4 (1-20), respectively. A total of 68 (23.5%) patients received adjuvant therapy, including BRT (n=42), EBRT (n=22) and EBRT + BRT (n=4).

The median follow-up time was 45 (6-147) months. A total of 13 (4.5%) patients recurred. Median time to recurrence was 52 (5-138) months. As shown in Table 2, 5 (38.5%) patients had distant, 4 (30.8%) had vaginal vault, 2 (15.4%) had intraperitoneal, in 1 patient there were both distant and nodal, and in a further 1 patient there was both distant and vaginal vault recurrence. Recurrences were managed by surgery (n=1), RT (n=3), chemotherapy (CT) (n=3) or surgery + CT (n=5), and 1 patient refused treatment. While two of these patients died of disease, seven are alive without disease and four are alive with disease. Both patients who died of disease had distant metastases.

Univariate analysis revealed that tumor size (p=0.034), grade (p=0.004), depth of MI (p=0.006), cervical stromal invasion (p=0.045), stage (p=0.002) and adjuvant treatment (p=0.015) were significantly different between the patients with and without recurrence. These significant factors, except for stage (since it did not match the goodness of fit model and is directly associated with depth of MI and cervical stromal invasion) were entered into the multivariate analysis. In multivariate analysis, only grade remained as a significant predictor of recurrence (p=0.029) (Table 3).

Five-year DFS was 97.9%. Cox univariate and multivariate analysis of DFS are presented in Table 4. Age (p=0.005), grade 3 histology (p=0.002), tumor size (p=0.002), deep MI (p=0.002), cervical stromal invasion (p=0.005), stage (p=0.020 for IB and p=0.001 for II) and receiving adjuvant treatment (p=0.008) were related with shorter DFS in univariate analysis. Stage was not entered to the multivariate analysis due to the reasons given above. Only tumor size (HR: 1.07, 95% CI: 1.01-1.13, p=0.018) and grade 3 histology (HR: 12.94, 95% CI: 1.06-157.84, p=0.045) were associated with shorter DFS in the multivariate model (Figure 1a, 2a).

Table 1. Clinicopathological, demographic and treatment characteristics of the patients

Age, years, mean (SD)	58 (±10.4)
BMI, kg/m^2, mean (SD)	33.6 (±7.4)
CA-125, median (range)	12.8 (1.2-460.3)
Menopausal status, n (%)	
Postmenopausal	215 (74.4)
Premenopausal	74 (25.6)
Surgical route, n (%)	
Laparotomy	185 (64)
Laparoscopy	94 (32.5)
Robotic	7 (2.4)
Vaginal	3 (1)
Tumor size, n (%)	
≤2 cm	116 (40.1)
>2 cm	173 (59.9)
Tumor size, mm, median (range)	25 (2-100)
Grade, n (%)	
1	156 (54)
2	114 (34.9)
3	19 (6.6)
MI, n (%)	
None	50 (17.3)
≤1/2	181 (62.6)
>1/2	58 (20.1)
Cervical stromal invasion, n (%)	
Absent	281 (97.2)
Present	8 (2.8)
Stage, n (%)	
IA	227 (78.5)
IB	54 (18.7)
II	8 (2.8)
Lymphadenectomy, n (%)	
Omitted	39 (13.5)
Only SLND	18 (6.2)
BPLND	112 (38.8)
BPPALND	120 (41.5)
Cytology	
Negative	136 (99.3)
Positive	1 (0.7)
Adjuvant therapy	
No	221 (76.5)
BRT	42 (14.5)
EBRT	22 (7.6)
EBRT + BRT	4 (1.3)
Recurrence, n (%)	13 (4.5)

SD: Standard deviation, BMI: Body mass index, CA-125: Cancer antigen-125, MI: Myometrial invasion, SLND: Sentinel lymph node dissection, BPLND: Bilateral pelvic lymph node dissection, BPPALND: bilateral pelvic and paraaortic lymph node dissection, BRT: Brachytherapy, EBRT: External beam radiotherapy

Table 2. Characteristics of the patients with recurrence

Patient	Stage	Type	Grade	Depth of MI	Tm size, mm	Adjuvant therapy	Time to recurrence, months	Site of recurrence	Vital status
#1	IA	Endometrioid	1	≤1/2	20	No	138	Vaginal vault + distant	Alive with disease
#2	IA	Endometrioid	2	≤1/2	30	No	76	Distant + nodal	Alive with disease
#3	II	Endometrioid	3	>1/2	50	EBRT	24	Distant	Died of disease
#4	II	Endometrioid	2	>1/2	55	EBRT	5	Distant	Alive with disease
#5	IA	Endometrioid	3	≤1/2	45	BRT	20	Distant	Alive with disease
#6	IA	Endometrioid	2	≤1/2	20	No	81	Distant	Died of disease
#7	IB	Endometrioid	1	>1/2	50	No	76	Distant	Alive with NED
#8	IA	Endometrioid	2	≤1/2	30	No	47	Intraperitoneal	Alive with NED
#9	IA	Endometrioid	2	≤1/2	35	No	52	Intraperitoneal	Alive with NED
#10	IB	Endometrioid	2	>1/2	40	EBRT	15	Vaginal vault	Alive with NED
#11	IB	Endometrioid	2	>1/2	18	BRT	85	Vaginal vault	Alive with NED
#12	IB	Endometrioid	2	>1/2	20	BRT	82	Vaginal vault	Alive with NED
#13	IB	Endometrioid	3	>1/2	25	BRT	10	Vaginal vault	Alive with NED

EBRT: External beam radiotherapy, BRT: Brachytherapy, NED: No evidence of disease

Table 3. Predictors of recurrence

Patients, n (%)	No recurrence, (n=276) (95.5)	Recurrence, (n=13) (4.5)	Univariate	Multivariate		
			p-value	OR	95% CI	p-value
Age, years, median (range)	57 (32-86)	58 (50-80)	0.144			
BMI, kg/m², median (range)	33.2 (18.6-58.7)	28.5 (20.5-43)	0.337			
CA-125, median (range)	12.6 (1.2-460.3)	16.8 (11.1-54.2)	0.929			
Menopausal status, n (%)			1.000			
Premenopausal	71 (25.7)	3 (23.1)				
Postmenopausal	205 (74.3)	10 (76.9)				
Tumor size, n (%)			0.516			
≤2 cm	112 (40.6)	4 (33.3)				
>2 cm	164 (59.4)	9 (66.7)				
Tumor size, mm, median (range)	25 (2-100)	30 (18-55)	**0.034**	1.01	0.97-1.06	0.520
Grade, n (%)			**0.004**			
1	154 (55.8)	2 (15.4)				
2	106 (38.4)	8 (61.5)		4.13	0.81-21.07	0.088
3	16 (5.8)	3 (23.1)		10.12	1.28-81.37	**0.029**
MI, n (%)			**0.006**			
≤1/2	225 (81.5)	6 (46.2)				
>1/2	51 (18.5)	7 (53.8)		2.96	0.62-14.13	0.174
Cervical stromal invasion, n (%)			**0.045**			
Absent	270 (97.8)	11 (84.6)				
Present	6 (2.2)	2 (15.4)		5.38	0.67-43.50	0.114
Stage, n (%)			**0.002**			
IA	221 (80.1)	6 (46.2)				
IB	49 (17.8)	5 (38.5)				

Table 3. Continued

Patients, n (%)	No recurrence, (n=276) (95.5)	Recurrence, (n=13) (4.5)	Univariate	Multivariate		
			p-value	OR	95% CI	p-value
II	6 (2.2)	2 (15.4)				
Cytology			0.942			
Negative	128 (99.2)	8 (100)				
Positive	1 (0.8)	0 (0)				
Adjuvant treatment			0.015			
No	215 (77.9)	6 (46.2)				
Yes	61 (22.1)	7 (53.8)		0.77	0.15-3.98	0.756
LND			0.455			
Omitted	38 (13.8)	1 (7.7)				
Performed	238 (86.2)	12 (92.3)				

BMI: Body mass index, CA-125: Cancer antigen-125, OR: Odds ratio, CI: Confidence interval, MI: Myometrial invasion, LND: Lymph node dissection

Table 4. Cox univariate and multivariate analysis of DFS in LVSI negative early-stage endometrioid endometrial cancer patients

	Univariate			Multivariate		
Covariate	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.09	1.03-1.16	0.005	1.06	0.98-1.15	0.121
CA-125	1.01	0.99-1.03	0.503			
Tumor size						
≤2 cm	Ref					
>2 cm	2.53	0.68-9.40	0.167			
Tumor size, mm	1.07	1.02-1.11	**0.002**	1.07	1.01-1.13	**0.018**
Grade						
1	Ref			Ref		
2	7.12	0.89-57.07	0.065	6.19	0.75-51.16	0.091
3	38.76	3.78-397.58	**0.002**	12.94	1.06-157.84	**0.045**
Depth of MI						
≤1/2	Ref			Ref		
>1/2	6.03	1.90-19.16	**0.002**	2.26	0.48-10.63	0.303
Cervical stromal invasion						
No	Ref			Ref		
Yes	9.68	2.00-46.78	**0.005**	6.36	0.96-42.07	0.055
Stage						
IA	Ref					
IB	4.40	1.26-15.30	**0.020**			
II	16.45	2.98-90.71	**0.001**			
Adjuvant treatment						
No	Ref			Ref		
Yes	4.79	1.50-15.32	**0.08**	1.51	0.30-7.70	0.620
LND						
Omitted	Ref					
Performed	2.59	0.33-20.40	0.365			

DFS: Disease-free survival, LVSI: Lymphovascular space invasion, HR: Hazard ratio, CI: Confidence interval, CA-125: Cancer antigen-125, MI: Myometrial invasion, LND: Lymph node dissection

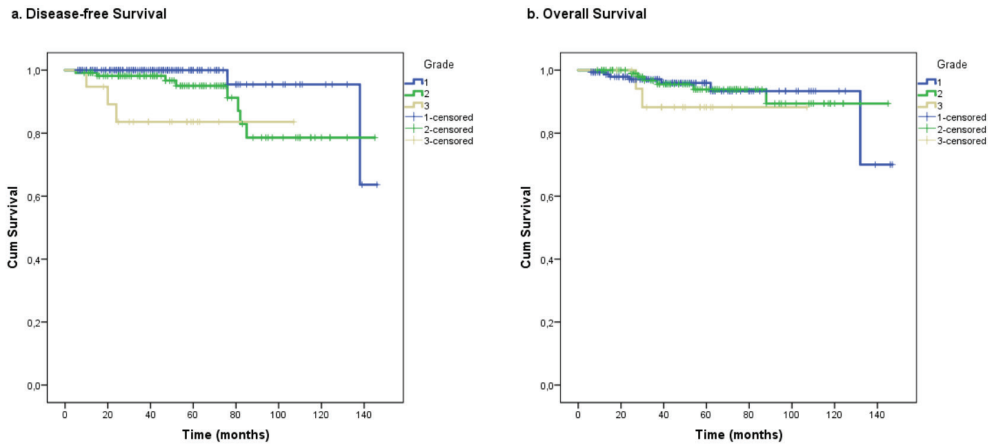

Figure 1. Kaplan-Meier estimate of disease-free survival: (a) and overall survival (b) according to grade

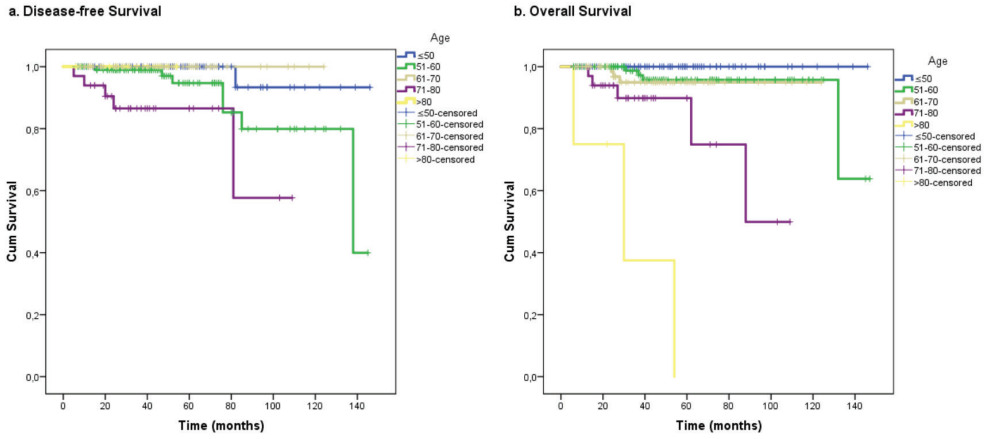

Figure 2. Kaplan-Meier estimate of disease-free survival: (a) and overall survival (b) according to age

Fifteen patients died in our study population and two of these were due to cancer recurrence. Five-year OS was 95.8%. None of the histopathological variables, nor recurrence were associated with reduced OS. Age (HR: 1.16, 95% CI: 1.09-1.22, p<0.001) was found to be the only associated factor for decreased OS (Table 5) (Figure 1b, 2b).

Survival outcomes of stage I patients

Tumor size and adjuvant treatment lost their prognostic significance for recurrence after excluding stage II patients, but grade (p=0.030) and depth of MI (p=0.040) remained significant. In multivariate analysis none of the factors were independently associated with recurrence.

Five-year DFS and OS among the stage I patients were 98.2% and 96.1%, respectively. Although tumor size, grade 3 histology and depth of MI were associated with decreased DFS, none were independent factors for decreased DFS (Table 6). Only age was associated with reduced OS (p<0.001).

Table 5. Cox univariate analysis of OS in LVSI negative stage I and II endometrioid endometrial cancer patients

Covariate	HR	95% CI	p-value
Age	1.16	1.09-1.22	<0.001
CA-125	1.01	0.99-1.02	0.511
Tumor size			
≤2 cm	Ref		
>2 cm	0.83	0.29-2.32	0.725
Tumor size, mm	1.01	0.97-1.05	0.737
Grade			
1	Ref		
2	0.98	0.33-2.94	0.973
3	2.23	0.46-10.89	0.322
Depth of MI			
≤1/2	Ref		
>1/2	1.40	0.44-4.47	0.572

Table 5. Continued

Covariate	HR	95% CI	p-value
Cervical stromal invasion			
No	Ref		
Yes	2.44	0.32-18.68	0.391
Stage			
IA	Ref		
IB	1.08	0.30-3.93	0.907
II	2.48	0.32-19.42	0.387
Adjuvant treatment			
No	Ref		
Yes	0.74	0.21-2.65	0.643
LND			
Omitted	Ref		
Performed	1.12	0.25-5.08	0.879
Recurrence			
No	Ref		
Yes	2.13	0.47-9.64	0.328

OS: Overall survival, LVSI: Lymphovascular space invasion, HR: Hazard ratio, CI: Confidence interval, MI: Myometrial invasion, LND: Lymph node dissection

Discussion

LVSI is established as an independent risk factor for recurrence in endometrial cancer, even in early-stages (10,16,17). To the best of our knowledge, this is the first study examining risk factors for recurrence in a cohort of LVSI negative stage I-II endometrioid endometrial cancer patients. Recurrence rate was 4.5%. Tumor size, grade, depth of MI, stage and adjuvant therapy were correlated with recurrence. However, only grade 3 disease was an independent factor associated with recurrence (OR: 10.1). Grade 3 disease, along with tumor size, was also associated with decreased DFS.

Deep MI was not an independent prognostic factor for survival in LVSI negative patients in our study. In contrast, some studies found deep MI was a risk factor for distant metastasis but not for locoregional recurrence (18,19). Besides, it was found that RT improved pelvic control and DFS but not OS in stage I-II endometrial cancer patients (18,20). Thus, it may be an option to avoid adjuvant RT in early-stage low-grade LVSI negative endometrioid tumors only because of deep MI. The current NCCN Guideline indicates that BRT is preferred for stage IB grade 1-2 endometrioid tumors as adjuvant treatment, but it also states that observation can be considered when the patients are younger than 60 years and there is no LVSI (9).

Table 6. Cox univariate and multivariate analysis of DFS in LVSI negative stage I endometrioid endometrial cancer patients

	Univariate			Multivariate		
Covariate	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age	1.05	0.99-1.12	0.096			
CA-125	0.99	0.96-1.04	0.904			
Tumor size						
≤2 cm	Ref					
>2 cm	1.89	0.54-6.63	0.320			
Tumor size, mm	1.05	1.00-1.09	**0.043**	1.03	0.98-1.08	0.216
Grade						
1	Ref			Ref		
2	4.05	0.82-19.99	0.086	3.06	0.59-15.84	0.184
3	13.13	1.72-100.37	**0.013**	7.62	0.91-63.74	0.061
Depth of MI						
≤1/2	Ref			Ref		
>1/2	4.19	1.21-14.51	**0.024**	2.11	0.54-8.28	0.284
Adjuvant treatment						
No	Ref					
Yes	3.17	0.92-10.95	0.068			
LND						
Omitted	Ref					
Performed	32.65	0.05-2043.73	0.289			

DFS: Disease-free survival, LVSI: Lymphovascular space invasion, CA-125: Cancer antigen-125, HR: Hazard ratio, CI: Confidence interval, MI: Myometrial invasion, LND: Lymph node dissection

Some authors have investigated the effect of adjuvant CT in early-stage endometrial cancer. In a current study comparing the effect of adjuvant CT versus RT in high-risk, early-stage endometrioid endometrial cancer, CT showed a trend towards lowering the distant relapse rate but the difference was not significant (21). Five-year OS and DFS rates were also similar between the groups in the same study. Similarly, in another study, it was found that adjuvant CT was associated with improved, but not significant, oncologic outcomes in stage I and II high-risk endometrioid endometrial cancer (22). Therefore, adjuvant CT appears to be an overtreatment, even for early-stage high-risk patients at given the current evidence, as it is not related with better survival rates. However, the possibility of distant metastasis along with locoregional failure should always be kept in mind for these patients.

Approximately 20% of patients with early-stage disease recur, irrespective of LVSI status (23). Although tumor size, deep MI and time from biopsy to surgery were found to be independent predictors of recurrence in stage I and II endometrial cancers, grade was the only predictor of recurrence in our study (24). We did not investigate the effect of time from biopsy to surgery, since all the patients were operated within three weeks following diagnosis.

We managed vaginal vault recurrences either by RT or surgery and intraperitoneal/distant recurrences by CT or surgery followed by CT. Complete remission after isolated vaginal recurrence is reported to be as high as 89% but distant recurrences are mostly fatal (25-27). Our results are in accordance with the literature as all patients with vaginal vault recurrences are disease free and both patients who died of disease had distant recurrences.

In our study, while 10.3% of the patients who received adjuvant treatment recurred, recurrences were seen in 2.7% of the patients who were observed. None of our patients received CT as adjuvant treatment and EBRT or BRT were applied either alone or together. Although the difference appeared significant in univariate analysis, receiving adjuvant treatment was not an independent factor for recurrence on multivariate analysis. This evidence can be explained by the fact that patients with adverse uterine factors were more likely to receive adjuvant treatment. In our study, 5 of the 13 patients with recurrence were in the low-risk group and none of these patients received adjuvant treatment. Interestingly, three of them had distant metastases (either alone or with another site) and two had intraperitoneal recurrences. All five recurrences were seen after 47 months (47-138 months) emphasizing the importance of life-time surveillance.

Since all stage II patients received adjuvant treatment, for more accurate results we performed a subgroup analysis among the stage I patients only. We found that grade and depth of MI were both associated with recurrences. Receiving adjuvant treatment lost its prognostic significance both for recurrence and decreased DFS. With these findings, we believe that observation, rather than adjuvant RT, may be more suitable for grade 3, stage IA patients.

Although it was shown that the impact of age disappears when they are matched with younger patients with the same tumor characteristics, and prognosis of endometrial cancer is more closely associated to stage, grade, and histology rather than age, only age was found to be associated with decreased OS in our study (28,29). This finding is not surprising as our study population consisted mostly of patients with low-risk factors and recurrences were not common. Most (84%) of the relapses responded well to treatment and recurrence was not found to be an associated factor for shorter OS. There was only one recurrence in patients ≤50 years and none of the patients ≤50 years died in our study. Only two of the deaths were due to recurrences and the majority of the deaths were due to intercurrent diseases, which were mostly related to senility.

Since the recurrence rate is very low in this low-risk population, administration of adjuvant treatment is neither cost-effective nor beneficial, and also not recommended (30,31). Molecular characterization may elucidate why recurrences are seen in certain patients. Some genomic alterations, such as TP53 mutation or L1-CAM overexpression are demonstrated to be associated with greater risk of recurrence and molecular-based classification had been recently proposed in endometrial cancer (8,32,33). Therefore, by applying molecular studies, these patients may be reclassified in higher risk groups. However, future studies are needed to illuminate this issue.

Study Limitations

One of the main limitations of our study was its retrospective nature. Another limitation was the small number of events that required us to perform subgroup analysis. Also, since not all patients underwent lymphadenectomy, the small number of nodal metastases might have been missed and these patients might have been understaged. Lastly, due to the long surveillance time, adjuvant therapy indications and practices changed over time. On the other hand, the number of patients was one of the largest that had been reported with long follow-up time. All patients were operated by the same gynecologic oncologists and specimens were reviewed by gynecologic pathologists.

Conclusion

Recurrence rate was low among women with LVSI negative, early-stage endometrioid endometrial cancer and age was the only prognostic factor for shorter OS. In contrast, grade 3 histology and tumor size were independent factors associated

with decreased DFS. Although distant metastases were more common in this group of patients and may be fatal, most of the recurrences were cured. Therefore, even in the presence of risk factors, observation without adjuvant treatment may be the optimal management.

Ethics Committee Approval: *The study protocol was reviewed and approved by Ankara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 10-420-14, date: 09.06.2014).*

Informed Consent: *A written informed consent was obtained from all the patients in order to use their medical data for scientific purposes.*

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