Oncological Outcomes of Stage IIIA Endometrioid Type Endometrial Cancer: A Multicenter Study

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ABSTRACT

The objective of this retrospective study was to evaluate Stage IIIA endometrioid type endometrial carcinomas (ECCs) and to analyze clinical and pathological determinants of prognosis in three tertiary hospitals between January 2007 and January 2017. Forty-seven patients with a median age of 61 (range: 31 to 76) years were diagnosed with Stage IIIA disease. Median follow-up was 45 (range: 6 to 116) months. The five-year disease-free survival (DFS) rate was 57.2%, and the overall survival (OS) rate was 59.7%. In the univariate analysis, age and grade of the disease (1-2 versus 3) disease were found to be significant factors for DFS. Univariate analysis also revealed the presence of cervical stromal involvement and grade of the disease were associated with decreased OS. In the multivariate analysis, however, only patients with an advanced histological grade had a reduced risk for OS (hazard ratio [HR] 2.9; 95% confidence interval [CI] 1.020-8.615; p= 0.040). In conclusion, histological grade seems to be an independent prognostic factor for OS in patients with Stage IIIA ECCs.

Keywords: Endometrial cancer, Stage IIIA, Prognostic factor

ÖZET

Evre IIIA Endometrioid Tip Endometrial Kanserin Onkolojik Sonuçları: Retrospektif, Çok Merkezli Çalışma

Bu retrospektif çalışmada, Ocak 2007 – Ocak 2017 tarihleri arasında üç üniversite hastanesinde Evre IIIA endometrioid tip endometrial karsinomlar (EEK) değerlendirildi ve prognozun klinik ve patolojik belirleyicileri incelendi. Çalışmaya medyan yaşı 61 (dağılım: 31-76) yıl olan ve Evre IIIA hastalık ile tanılanan 47 hasta alındı. Medyan takip süresi 45 (dağılım: 6-116) ay idi. Beş yıllık hastalıksız sağkalım (DFS) oranı %57.2, genel sağkalım (OS) oranı %59.7 idi. Tek değişkenli analizde yaş ve hastalığın gradı (1-2 veya 3) DFS'yi etkileyen anlamlı faktörler olarak bulundu. Ayrıca, tek değişkenli analizde, servikal stromal tutulum ve hastalığın gradının azalmış OS süresi ile ilişkili olduğu tespit edildi. Bununla birlikte, çok değişkenli analizde, yalnızca ileri evre histolojik gradı olan hastalarda OS riskinde bir azalma görüldü (risk oranı [HR] 2.9; %95 güven aralığı [CI] 1.020-8.615; p= 0.040). Sonuç olarak, histolojik gradın Evre IIIA EEK'li hastalarda OS'nin bağımsız prognostik bir faktörü olduğu düşünülmektedir.

Anahtar Kelimeler: Endometrial kanser, Evre IIIA, Prognostik faktör

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INTRODUCTION

Endometrial cancer is the most common gynecological cancer.[1] The most commonhistological type is endometrioid type endometrial cancer (EEC).[2] Prognosis is considerably good in early stage endometrial cancer. The rate of five-year survival is 81 to 91% in early stage disease, whereas five-year survival rate ranges between 17 to 60% in advanced-stage disease.[3] Disease staging is based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines.[4] According to the FIGO staging system, Stage III and IV endometrial cancer are classified as advanced-stage diseases.[4] This staging system was revised in 2009.[4] After the latest revision, positive pertioneal cytology was accepted as a factor which requires investigation, but which does not influence disease stage. According to the revised staging criteria, involvement of uterus, serosa and/or adnexa indicates Stage IIIA disease. This staging system offers vital information on the prognosis, guiding adjuvant therapy. This patient subpopulation has a high risk for recurrence and mortality. Disease confined to the uterus has an excellent prognosis, while Stage IIIA disease has a poorer prognosis with a five-year overall survival (OS) rate of 56%.[5] Stage IIIA has been recognized as a heterogeneous population of patients who can be treated with different types of adjuvant therapy or can be monitored following surgery.

Currently, there are no prospective studies or clinical trials which specifically address Stage IIIA disease. In addition, there is a limited number of studies in the literature evaluating patients with Stage IIIA EEC classified according to the FIGO 2009 staging system. Therefore, we aimed to evaluate Stage IIIA EECs and analyze possible clinical and pathologic determinants of prognosis to contribute to the body of knowledge on this particular subgroup of patients.

MATERIALS AND METHODS

After retrospective review of databases in three tertiary healthcare centers, we analyzed a total of 47 consecutive women with who underwent primary surgical treatment for Stage IIIA EEC between January 2007 and December 2016. The study protocol was approved by local ethical committee. All patients provided an informed consent for the use of their medical information for research purposes. The study was conducted in accordance with the principles of the Declaration of Helsinki. Data on age, menopausal status, serum CA-125 levels, tumor size, lymphovascular space invasion (LVSI), depth of myometrial invasion, positive peritoneal cytology, cervical stromal involvement, histological grade, adjuvant treatment (chemo-radiotherapy [CRT] vs chemotherapy [CT]), recurrence, and follow-up data of the patients were retrieved from the database.

After surgical staging, patients with Stage IIIA EEC with uterine serosa and/or adnexal involvement according to the FIGO criteria were included in the study.[5] Patients with non-endometrioid histological types, uterine sarcoma, patients with incomplete surgical staging, and patients with only positive peritoneal cytology were excluded from the study.

Surgical staging included total hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, and peritoneal washings. All operations were performed by gynecological oncologists.

All surgical specimens were evaluated by gynecological pathologists. All histological data were retrieved from the primary pathologist's report and were not reviewed centrally. The architectural grading, was defined using standard the FIGO criteria.[5]

The standard primary chemotherapy regimen included paclitaxel 175 mg/m^2 plus carboplatin dosed at an area under the curve of five or six every 21 days for six cycles. Adjuvant chemotherapy or chemo-radiation was administered to all patients. 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.

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, in addition to computed tomography (CT), mag-

netic resonance imaging (MRI), and/or positron emission tomography-CT (PET-CT) scans, 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.

After the initial diagnosis, recurrence was defined as the documented metastasis with physical examination and imaging techniques after a disease-free survival (DFS) of ³3 months. Time to recurrence was defined as the time frame from surgery to physical or radiological evidence of disease recurrence or the date of last contact for patients without recurrence. Disease-free survival was defined as the time from surgery to the first occurrence of recurrence or progression, 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 defined 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

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 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 univariate Cox-regression model was used to evaluate the prognostic factors for DFS and OS. A p value of less than 0.05 in the univariate analysis was included in the multivariate analysis. A pvalue of less than 0.05 was considered statistically significant.

RESULTS

A total of 47 women who underwent comprehensive surgical staging according to the revised 2009 FIGO staging system and were diagnosed with Stage IIIA EEC at two different institutions were included. The median age of the patients was 61 (range: 31 to 76) years. Histologic grade was determined as grade 1 in 7 women (14.9%) while 24 patients had grade 2 (51.1%) and 16 patients (34%) had grade 3 histology. Cervical stromal invasion was detected in 20 (42.6%) patients.

Table 1. Demographic and clinicopathological characteristics of all patients (n= 47)

Characteristics	Values, n (%)
Age, y, median	61 (31-76)
Menopausal status	
Premenopausal	9 (19.1 %)
Postmenopausal	38 (80.9 %)
Baseline Serum CA-125 (IU/ml)	25 (9-600)
Grade	
1	7 (14.9 %)
2	24 (51.1 %)
3	16 (34 %)
Depth myometrial invasion	
< 50	15 (31.9 %)
≥ 50	32 (68.1 %)
LVSI	
Positive	23 (48.9 %)
Negative	24 (51.1 %)
Primary tumor diameter (cm), median	5 (1-14)
Peritoneal cytology	
Positive	13 (27.7 %)
Negative	34 (72.3%)
Cervical stromal invasion	
Yes	20 (42.6 %)
No	27 (57.4 %)
Serosal and/or adnexial involvement	
Only adnexial	22 (46.8 %)
Only Serozal	10 (21.3%)
Boht	15 (31.9 %)
Number of LNs removed	47 (18-102)
Pelvic	31 (14-69)
Para-aortic	14 (4-49)
Recurrence rates	12 (25.5 %)
Adjuvant treatment	
Chemo-radiation	24 (51.1 %)
Chemotherapy	23 (48.9 %)
Median Follow-up time (month)	45 (6-116)

Abbreviations: LN= Lymph node, LVSI= Lymphovascular space invasion, CRT= Chemo-radiation, CT= Chemotherapy

Table 2. Univariate and multivariate analysis for disease-free survival in Stage IIIA endometrioid endometrial cancer patients

	DFS*	Events**	Univariate p	HR	Multivariate CI 95%	p
Age, y						
<60	70.3%	6/24 (25%)				
≥60	42.9%	12/23 (52.1%)	0.040	0.42	0.157- 1.149	0.092
Menopausal Status						
Premenopausal	87.5%	1/9 (11.1%)				
Postmenopausal	49.6%	17/38 (44.7%)	0.085			
MMI						
<50 %	70.6%	4/15 (26.6%)				
≥50 %	50.9%	14/32 (43.7%)	0.399			
Grade						
1-2	73.7	8/31 (25.8%)				
3	31.7	10/16 (62.5%)	0.044	0.45	0.178-1.178	0.105
Peritoneal cytology						
Positive	54.4%	5/13 (38.4%)				
Negative	57.3%	13/34 (38.2%)	0.881			
Tm size (cm)						
<5	69.2%	4/17 (23.5%)				
≥5	51.6%	14/30 (46.6%)	0.252			
Serum CA-125 (IU/ml)						
<35	61.9%	11/31 (22.2%)				
≥35	54.5%	7/16 (40%)	0.174			
Cervical stromal involvement						
Yes	43.6%	10/20 (50%)				
No	68.1%	8/27 (29.6%)	0.174			
LVSI						
Yes	44.1%	11/23 (47.8%)				
No	70.4%	7/24 (29.1%)	0.222			
Serosal-adnexial involvement						
Serosal	70.0%	3/10 (30%)				
Adnexial	55.5%	7/22 (31.8%)				
Both	51.4%	8/15 (53.3%)	0.337			
Adjuvant treatment						
Chemo-radiation	57.2%	8/24 (33.3%)				
Chemotherapy	66.2%	10/23 (43.4%)	0.604			

*: 5-year disease-free survival rate

**: The number of cases with recurrence or death whichever occurred first.

Abbreviations: ECC: Endometrioid type endometrial cancer, MMI: Myometrial invasion, LVSI: Lymphovascular space invasion, DFS: Disease-free -free Survival, HR: Hazard ratio, CI: Confidence interval

Median tumor size was 5 cm (range 1-14). Adnexal involvement was detected in 22 patients (46.8%), serosal involvement in 10 (21.3%) and both adnexal and serosal involvement was detected in 15 (31.9%) patients. Recurrence was observed in 12 (25.5%) patients. As an adjuvant therapy, solely chemotherapy was given to 23 (48.9%) patients whereas chemoradiotherapy was given to 24 (51.1%) patients. The clinical and histological characteristics of the patients are presented in Table 1.

The median follow-up period was 45 (range: 6 to 116) months. The five-year DFS and OS rates were 57.2% and 59.7%, respectively. Univariate

Table 3. Univariate and multivariate analysis for overall survival in Stage IIIA endometrioid endometrial cancer patients

	OS*	Events**	Univariate p	HR	Multivariate CI 95%	p
Age, y						
<60	65.4 %	6/24 (25 %)				
≥60	53.5 %	8/23 (34.7 %)	0.405			
Menopausal Status						
Premenopausal	87.5 %	1/9 (11.1 %)				
Postmenopausal	52.7 %	13/38 (34.2 %)	0.224			
MMI						
<50 %	75 %	3/15 (20 %)				
≥50 %	53.6 %	11/32 (34.3 %)	0.362			
Grade						
1-2	73.2%	6/31 (19.3 %)				
3	34.6%	8/16 (50 %)	0.034	2.9	1.020-8.615	0.040
Peritoneal cytology						
Positive	71.1 %	5/13 (38.4%)				
Negative	80 %	9/34 (26.4 %)	0.385			
Tm size (cm)						
<5	68.9 %	4/17 (23.5 %)				
≥5	57.4 %	10/30 (33.3 %)	0.853			
Serum CA-125 (IU/ml)						
<35	65.1%	8/31 (25.8 %)				
≥35	55.8%	6/16 (37.5 %)	0.052			
Cervical stromal involvement						
Yes	38.2 %	9/20 (45 %)				
No	78.3 %	5/27 (18.5 %)	0.044	2.8	0.967-8.678	0.058
LVSI						
Yes	44.1%	10/23 (43.4 %)				
No	79.3 %	4/24 (16.6 %)	0.112			
Serosal-adnexial involvement						
Serosal	78.8 %	2/10 (20 %)				
Adnexial	57.6%	6/22 (27.2 %)				
Both	48.9 %	6/15 (40 %)	0.541			
Adjuvant treatment						
Chemo-radiation	56.5 %	7/24 (29.1 %)				
Chemotherapy	65 %	7/23 (30.4 %)	0.934			

*: 5-year overall survival rate

**: The number of cases with recurrence or death whichever occurred first.

Abbreviations: VSI: Lymphovascular space invasion, MMI: Myometrial invasion, OS: Overall Survival, HR: Hazard ratio, CI: Confidence interval

analysis revealed that age (< 60 vs ≥ 60 years) and advanced histological grade (1-2 vs3) were associated with lower DFS (p= 0.040, p= 0.044, respectively). Menopausal status, tumor size, LVSI, depth of myometrial invasion, positive peritoneal cytology, cervical stromal involvement, serum CA-125 level, and the type of adjuvant treatment (CRT vs CT) had no significant effect on DFS. Multivariate analysis revealed no independent prognostic factor for DFS (Table 2).

Univariate analyses showed a statistically significant difference in OS in terms of disease grade (1-2 vs3, p= 0.034) (Figure 1) and cervical stromal involvement (p= 0.044). Menopausal status, tumor

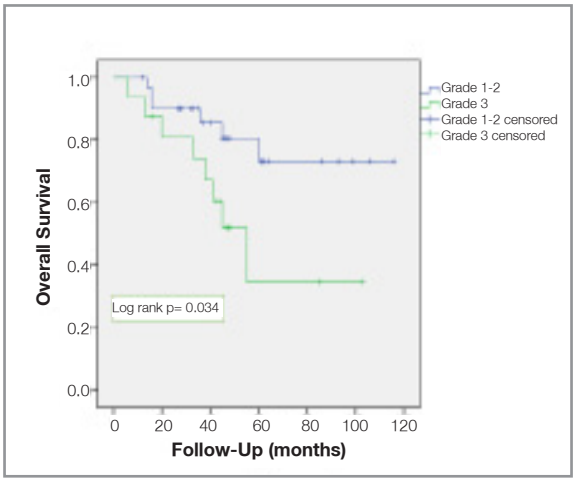

Figure 1, Overall survival of patients with Stage IIIA according to the histological grade in the Kaplan-Meier analysis (n= 47).

size, LVSI, depth of myometrial invasion, positive peritoneal cytology, cervical stromal involvement, serum CA-125 level, and the type of adjuvant treatment had no significant effect on OS (Table 3). In multivariate analysis for OS, only grade 3 disease was found to be predictive for OS (HR, 2.9; 95% CI, 1.020-8.615; p= 0.040). Recurrence was observed in twelve patients (25.5%). Treatment characteristics and recurrence patterns of Stage IIIA patients are shown in Table 4.

DISCUSSION

Stage IIIA ECC is rare. Although many studies on this subject have used FIGO 1988 staging criteria[6] positive peritoneal cytology has been completely dropped from the revised 2009 FIGO staging criteria for endometrial cancer.[4] There is a limited number of studies which excluded positive peritoneal cytology from the staging criteria. When the factors indicating Stage III disease was analyzed, 87% of patients with Stage III disease manifest positive cytology, 71% had adnexal and 41% had uterine serosal involvement.[7,8] This necessitates conduction of further studies on rare subgroup of patients with Stage III disease. Another issue with studies on Stage IIIA disease is that endometrioid type has been addressed together with aggressive histopathological subtypes of non-endometrioid group such as serous, clear-cell, and mixed type. It is well-established that histological subtypes such as serous and clear-cell carcinoma lead to

Table 4. Clinical and pathological characteristics and outcome of patients with Stage IIIA recurrent disease

Patient	Age(y)	CSI	LVSI	MI	Grade	Recurrence location	Adjuvant Treatment	Recurrence Treatment	Outcome
1	73	+	+	>50%	2	Pelvic+para-aortic LN	CT	Surgery+ CRT	DOD
2	72	+	+	>50%	3	Para-aortic LN	CT+EBRT	Surgery+ CRT	DOD
3	58	+	+	>50%	3	Sigmoid colon+ small bowel	CT	Surgery+CT	DOD
4	62	-	-	<50%	1	Vaginal cuff	CT	Surgery +BRT	ANED
5	62	+	-	>50%	3	Vaginal cuff	CT+EBRT	Syrgery+BRT	ANED
6	72	-	-	>50%	3	Vaginal cuff	CT	Surgery+BRT	ANED
7	53	-	+	>50%	2	Para-aortic LN	CT+EBRT	Surgery+CRT	DOD
8	61	+	+	<50%	2	Transvers colon+ omentum	CT+EBRT+ BRT	Surgery+CT	DOD
9	62	-	+	>50%	2	Vaginal cuff	CT+EBRT+BRT	Surgery+BRT	ANED
10	76	-	+	>50%	3	Small bowel	CT+EBRT+BRT	Surgery+CT	DOD
11	62	+	+	>50%	2	Lung+Brain	CT	CRT	DOD
12	58	+	-	>50%	2	Peritoneal carcinomatosis	CT+EBRT+BRT	CT	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, CSI: Cervical stromal invasion, LVSI: Lymphovascular space invasion

advanced-stage disease, and extrauterine disease is commonly observed even in patients with disease macroscopically confined to the uterus.[9]

In our study, no independent prognostic factor affecting progression-free survival (DFS) was found. However, presence of Grade 3 disease ([HR] 2.9; 95% confidence interval [CI] 1.020-8.615; p= 0.040) seemed to be an independent prognostic factor for decreased OS in women with Stage IIIA EEC.

In the endometrial cancer literature, the prognostic value of peritoneal cytology has been debated. Several studies have shown it as an independent prognostic feature[10,11], whereas some others have demonstrated it to be more likely correlated with other adverse prognostic features[12,13] or were undecided about its significance.[14] In the 2009 FIGO staging system of endometrial cancer, positive peritoneal cytology has been excluded as a criterion for Stage IIIA disease and it is recommended that positive peritoneal cytology should be reported as another pathological feature, such as LVSI and cervical involvement.[4] Our study found no significant difference in the OS and PFS of patients with positive peritoneal cytology. This is consistent with an analysis of the 2009 FIGO staging system by Cooke et al.[15] who found no difference in cause-specific survival between patients with positive peritoneal cytology and 2009 Stage IIIA disease using a multivariate model.

In another study of 55 patients diagnosed with Stage IIIA disease according to the 2009 FIGO staging system, Lum et al.[16] reported a five-year overall survival rate of 55%. Non-endometrioid type, LVSI, and adjuvant therapy were found to be significant prognostic factors affecting OS. In the aforementioned study, five-year OS rate of 23 patients diagnosed with Grade 3 disease was found to be 40%, whereas the five-year OS rate was reported to be 68% for patients with Grade 1-2 disease. However, no significant effect of grade on OS was demonstrated.

Similarly, in the present study, five year OS was 59.7%. However, in the study by Lum et al. (Lum et al. 2015), the five-year OS rate was reported as 14% for non-endometrioid tumors and 56% for endometrioid tumors. Different from their study, the present study found no prognostic effect of LVSI and adjuvant therapy on OS. Only Grade 3 disease was identified as an independent prognostic factor for OS.

In a study of 62 patients diagnosed with Stage III EC, Ayhan et al.[17] reported the five-year DFS and OS rates as 60% and 68% for Stage IIIA disease, respectively, with a median follow-up period of 62 months. The most interesting finding in their study was the presence of a no significant difference between Stage IIIA and IIIC disease in terms of DFS and OS. Positive peritoneal cytology and high disease grade were identified as independent prognostic factors for DFS and OS. In the current study, the median follow-up period was 45 months, and the five-year DFS and OS rates were 57.2% and 59.7%, respectively. Grade 3 disease was found to be the sole independent prognostic factor for OS.

In another study, on 94 patients which included all histopathological subtypes (IIIA: 56, IIIB: 10, IIIC: 28), age (> 70 years), LVSI, Grade (3 vs1-2), and adjuvant therapy (CRT vs CT or RT) were found to be independent prognostic factors for DFS and OS in multivariate analysis.[18] The only similarity with the present study is that they found high disease Grade (1-2 vs3) as an independent prognostic factor. Unlike their study, the present study was not able to show the prognostic significance of age (> 60 years), LVSI, and adjuvant therapy (CRT vs CT) on both DFS and OS.

In a study involving the data of 93 patients diagnosed with Stage IIIA EEC at 18 different centers according to the 2009 FIGO staging system, and evaluating the effectiveness of adjuvant therapy, age (< 60 vs > 60), Grade (1 vs2-3) and lymphovascular space invasion (LVSI) were found to be significant factors for DFS in univariate analysis.[19] These findings are consistent with the findings of the present study. In our study, age (< 60 vs > 60 years) and Grade (1 vs 2-3) had a significant effect on DFS (Table 2). Similar to our study, this study also excluded non-endometrioid histological subtypes. In the aforementioned study, only age was a significant factor for OS, whereas Grade (1 vs 2-3), LVSI, tumor size (< 5 cm versus > 5 cm), and adjuvant therapy had no significant effect on OS. In multivariate analysis, age (< 60 versus > 60 years),

LVSI, grade (1 vs 2-3), and adjuvant therapy (RT alone vs CRT) showed no significant effect on both DFS and OS. Only grade disease appeared as an independent prognostic factor for OS (Table 3).

Stage IIIA has been recognized as a heterogeneous population of patients who are able to be treated with different types of adjuvant therapy. Currently, there are no prospective or clinical studies which specifically address the outcomes of Stage IIIA patients. The ESMO-ESGO-ESTRO guidelines[20] state that, for FIGO Stage IIIA endometrial cancer, a combination of CT and EBRT should be used for all histological grades. Still, there is a lack of consensus among practitioners for the optimal management of these patients, and studies still remain unclear whether there is a survival advantage for particular types of adjuvant therapy.[21-24] The most prominent idea is that RT provides local control of recurrence to a great extent, although it had no effect on OS. Chemotherapy is a more appropriate treatment option in these patients and it can be used alone or in combination with RT. Recently, the final results of the PORTEC-3 trial showed that the combination of adjuvant chemotherapy and radiotherapy for high-risk endometrial cancer did not significantly improve overall survival.[25] However, chemoradiotherapy did improve 5-year disease -free survival compared with radiotherapy alone.[25] In the present study, 23 patients received chemotherapy alone and 24 patients received chemoradiotherapy. Adjuvant therapy had no significant effect on DFS and OS.

Nonetheless, there are some limitations to this study. Relatively small sample size with Stage IIIA EEC, relatively short median follow-up period, its retrospective design, and the lack of central pathology review can be regarded as the main limitations. In addition, although experienced gynecological pathologists reported all of the tumor pathology, it is likely that variations in the assessment of tumor pathology may have occurred due to lack of a central pathology review. Despite these limitations, however, we believe that our study provides additional information to the body knowledge on this subject.

In conclusion, histological grade seems to be an independent prognostic factor for OS in patients with Stage IIIA ECCs, although further large-scale studies are needed to confirm -our findings.

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