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Comparison of Grade 3 endometrioid type endometrial cancer with clear cell and serous type endometrial cancer in terms of clinicopathology and survival, and examination of prognostic factors affecting survival

Grade 3 endometrioid tip endometrium kanseri ile berrak hücreli ve seröz tip endometrium kanserlerinin klinikopatolojik ve sağ kalım açısından karşılaştırılması ve sağ kalımı etkileyen prognostik faktörlerin incelenmesi

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ABSTRACT

Aim: Comparison of the similarities of grade 3 endometrioid type endometrial cancer with clear cell and serous type endometrial cancer in terms of clinicopathology and survival and examination of prognostic factors affecting survival.

Materials and Methods: The medical records of 207 patients who were diagnosed with clear cell, serous and grade 3 endometrioid type endometrial cancer and who underwent surgery at Zekai Tahir Burak Women's Health Training and Research Hospital between June 2007 and September 2019 and at Ankara City Hospital between September 2019 and April 2022 were reviewed and their demographic, surgical and pathological features were analyzed. The patients were divided into two groups as grade 3 endometrioid type endometrial cancer and serous/clear cell endometrial cancer, and the patients were compared in terms of clinical and demographic features with univariate-multivariate analyses.

Results: The mean age of the patients was 63.3±9.3 years. The rate of early stage disease in the grade 3 endometrioid group was significantly higher (66.3%-44.9%, p=0.002). In the grade 3 endometrioid group, adnexal invasion rate (13.5%-31.4%, p=0.003), uterine serosal invasion rate (10.1%-22%, p=0.023), positive cytology rate (10.1%-29.7%, p=0.001), lymph node metastasis rate (20.2%-43.2%, p=0.001) and abdominal metastasis rate (9%-28%, p=0.001) were significantly lower than in the serous/clear cell group. There was no significant difference between the two groups in terms of overall survival times of 12-18-24-36 months (p=0.910). According to the univariate analysis between the groups, there was a significant risk for overall survival in age categories (p=0.039) and stages (p=0.034). In the multivariate analysis, age over 63 and advanced stage disease were evaluated as poor prognostic factors.

Conclusion: There was no significant difference in survival between grade 3 endometrial cancer and serous and clear cell endometrial cancers. Being over 63 years of age and having advanced-stage disease were considered poor prognostic factors.

Keywords: Endometrioid, serous, clear cell

ÖZ

Amaç: Grade 3 endometrioid tip endometrium kanseri ile berrak hücreli ve seröz tip endometrium kanserinin klinikopatolojik ve sağkalım açısından benzerliğinin karşılaştırılması ve sağ kalımı etkileyen prognostik faktörlerin incelenmesi.

Gereç ve Yöntemler: Haziran 2007 ile eylül 2019 yılları arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi ile Eylül 2019 ile Nisan 2022 yılları arasında Ankara Şehir Hastanesi'nde ameliyat olup berrak hücreli, seröz ve grade 3 endometrioid tip endometrium kanseri tanısı almış 207 adet hastanın medikal kayıtları incelenerek demografik, cerrahi ve patolojik özellikleri analiz edildi. Hastalar grade 3 endometriod tip endometrium kanseri ve seröz/berrak hücreli endometrium kanseri olarak iki gruba ayrıldı ve hastalar klinik ve demografik özellikler yönünden univaryan-multivaryan analizlerle karşılaştırıldı.

Bulgular: Hastaların yaş ortalaması 63.3±9.3 idi. Grade 3 endometrioid grubun erken evre olma oranı anlamlı şekilde daha yüksekti (%66.3-%44.9, p=0,002). Grade 3 Endometrioid grubunda, seröz/berrak hücreli gruba göre adneksal invazyon oranı (%13.5-%31.4, p=0,003), uterin serozal invazyon oranı (%10.1-%22, p=0,023), pozitif sitoloji oranı (%10.1-%29.7, p=0,001), lenf nodu metastazı oranı (%20.2-%43.2, p=0,001) ve abdominal metastaz oranı (%9-%28, p=0,001) anlamlı olarak daha düşüktü. Her iki grup arasında 12-18-24-36 aylık genel sağkalım süreleri açısından anlamlı fark yoktu (p=0,910). Gruplar arasında yapılan tek değişkenli analize göre yaş kategorilerinde (p=0,039) ve evreler arasında (p=0,034) genel sağkalım için anlamlı bir risk vardı. Multivariant analizde yaşın 63'ün üzerinde olması ve ileri evre hastalık kötü prognostik faktör olarak değerlendirildi.

Sonuç: Grade 3 endometrium kanseri ile seröz ve berrak hücreli endometrium kanserleri arasında sağkalım açısından anlamlı bir fark yoktu. 63 yaş üzeri olmak ve ileri evre hastalığa sahip olmak kötü prognostik faktör olarak değerlendirildi.

Anahtar Kelimeler: Endometrioid, seröz, berrak hücreli

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INTRODUCTION

Endometrial carcinoma (EC) is the second most common gynecological malignancy worldwide, considering both developed and resource-limited countries (1). The incidence of EC is increasing due to several factors, including increasing life expectancy, prevalence of obesity, and changes in reproductive behavior (eg, increasing prevalence of nulliparity). Available data suggest that the presence of early symptoms, such as metrorrhagia or postmenopausal bleeding, allows approximately 67% of patients diagnosed with EC to be diagnosed at an early stage when the disease is confined to the uterus (2).

The histological type of the tumor is an important prognostic factor in EC. In the classification of uterine corpus tumors published in 2020, the World Health Organization (WHO) defined the histological subgroups of EC's as follows: endometrioid carcinoma, serous carcinoma, clear cell carcinoma, mixed carcinoma, undifferentiated/dedifferentiated carcinoma, carcinosarcoma and rare EC subtypes (3). Endometrioid carcinoma (EEC) is the most common EC histology, accounting for 75 to 80 percent of cases. This is followed by serous carcinoma (SEC) at approximately 10% and clear cell carcinoma (CCEC) at <5%. The International Federation of Gynecology and Obstetrics (FIGO) 2023 staging system also divides EC into two categories: aggressive and non-aggressive tumors (4). Histopathological findings were centralized in the renewed FIGO staging system. In this revised staging, non-aggressive histological types are composed of low-grade EEC (grade 1 and 2), while aggressive histological types are composed of high-grade EEC (grade 3), SEC, CCEC, undifferentiated carcinoma, carcinosarcoma, and mesonephric-like and gastro-intestinal type mucinous carcinomas. Aggressive histological types have a higher incidence of extrauterine disease at presentation(5).

Histological grade is another factor that determines the prognosis, especially in EEC (6). EECs are graded using the FIGO classification system, which primarily based on architectural features. Low-grade EECs are defined into grade 1 and 2 tumors, which exhibit up to 5% and 6%–50% solid non-glandular growth, respectively. On the other hand, high-grade EECs (grade 3) are characterized by 50% or more solid component (7). These two categories differ in incidence and clinical behavior and affect postoperative adjuvant therapy. The aim of this study is to compare grade 3 EEC with SEC and CCEC in terms of clinicopathology and survival.

MATERIALS AND METHODS

We included 207 patients with clear cell, serous and grade 3 endometrioid type endometrial cancer diagnosed at Zekai Tahir Burak Women's Health Training and Research Hospital between June 2007 and September 2019 and Ankara City Hospital between September 2019 and April 2022. Medical and pathology reports of the patients were retrospectively analyzed. Patients who received neoadjuvant treatment, patients with incomplete medical information, patients diagnosed with secondary primary endometrial cancer were not included in the study. Ethics committee approval for our study was received from Ankara City Hospital Ethics Committee No. 2. (Number: E. Committee- E2-22-2080). All patients' consent that their medical information could be used in academic studies was obtained during the application process to the hospital, and the study was conducted in accordance with the Declaration of Helsinki.

All 207 patients included in the study underwent total hysterectomy + bilateral salpingoophorectomy (TAH + BSO) ± pelvic and/or paraaortic lymphadenectomy (PLND and/or PPLND) with laparoscopy or laparotomy procedure in primary surgical treatment. All materials were evaluated by gyneco-oncologic pathologists in the pathology department of our hospital. FIGO 2009 surgical staging and FIGO 1988 grading system were used for endometrial cancer staging. Cases treated before 2009 were restaged according to the FIGO 2009 staging system. Pelvic lymph node dissection was defined as excision of external iliac, internal iliac, common iliac and obturator lymph nodes, while paraaortic lymph node dissection was defined as excision of lymph nodes above the inferior vena cava and aorta up to the level of the renal vein. Blood samples for the analysis of cancer antigen-125 (CA-125) levels were obtained from the patients during the preparation for surgery.

Demographic, clinical, surgical and pathological characteristics were determined and analyzed from the patients medical records. Grade, tumor size, depth of myometrial invasion (MI), lymph node (LN) metastasis (pelvic, paraaortic), cervical involvement, adnexal metastasis, uterine serosal involvement, cytology and lymphovascular space invasion (LVSI) were evaluated. SEC/CCEC and grade 3 EEC were divided into two groups and compared by univariate-multivariate analyses in terms of clinical and demographic characteristics such as age, CA-125, stage, surgery performed, tumor size, depth of MI, cervical involvement, adnexal metastasis, uterine serosal involvement, cytology and LVSI.

Statistical analysis

The analyses were evaluated in SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 package program. Descriptive data were presented as n and % values for categorical data, mean±standard deviation (Mean±SD) and median (minimum-maximum) values for continuous data. Chi-square analysis (Pearson chi-square) was used to compare categorical variables between

groups. The compatibility of continuous variables with normal distribution was evaluated by Kolmogorov-Smirnov test. Student's t-test was used for normally distributed variables and Mann Whitney U-test was used for non-normally distributed variables. Overall and progression-free survival were evaluated by Kaplan-Meier for univariate analysis. Log rank (Mantel-Cox) analysis was used to compare survival time between categorical variables. For multivariate analysis of local control, Cox regression including all factors in the univariate analysis was performed. Statistical significance level was accepted as $p<0.05$ in the analyses.

RESULTS

A total of 207 patients were included in the study, 89 (43%) of whom were grade 3 EEC and 118 (57%) were SEC/CCEC. The mean age of grade 3 EEC patients was 63.6±9.6 years and the mean age of SEC/CCEC patients was 63.2±9.2 years and there was no statistically significant difference between them (p=0.786). The median CA-125 value of the patients was calculated as 16.0 IU/ml (range, 2.0-5536). While 146 (74.5%) of the patients had a CA-125 value of 35 IU/ml and below, 50 (25.5%) had a CA-125 value of 35 IU/ml and above. There was no significant difference between the groups in terms of CA-125 (p=0.059).

Total abdominal hysterectomy and bilateral salpingoopherectomy + cytology was performed in 4 (1.9%) patients, TAH + BSO + cytology + PLND in 5 (2.4%) patients, and TAH + BSO + cytology + PPLND in 198 (95.6%) patients. The median tumor size was 4.0 cm (range, 0.1-20.0). Cervical involvement was seen in 62 (30%), adnexal involvement in 49 (23.7%), uterine serosal involvement in 35 (16.9%), and LVSI in 125 (60.4%) patients. The depth of MI was <50% in 87 (42%) patients and 50% or more in 120 (58%) patients. Lymph node metastases were seen in 69 (33.3%) patients, 22 (10.6%) had isolated pelvic LN, 12 (5.8%) had isolated paraaortic LN and 41 (19.8%) had abdominal metastases. According to the 2009 FIGO staging system, in the grade 3 EEC, stage IA was seen in 28.1%, stage IB in 28.1%, stage II in 10.1%, stage IIIA in 6.7%, stage IIIB in 1.1%, stage IIIC in 18% and stage IV in 7.9%. On the other hand, 22% of the patients in the SEC/CCEC group had stage IA, 16.1% had stage IB, 6.8% had stage II, 0.8% had stage IIIB, 28.8% had stage IIIC and 25.4% had stage IV and there was a significant difference between the groups in terms of stage (p<0.001). The early stage rate of the grade 3 EEC group (66.3%) was significantly higher than the early stage rate of the SEC/CCEC group (44.9%) (p=0.002). The tumor size of the grade 3 EEC group was significantly higher than the tumor size of the SEC/CCEC group (p=0.001).

Comparison of clinical features of patients according to groups is shown in Table 1. The rate of adnexal invasion (13.5%-31.4%, p=0.003), uterine serosal invasion (10.1%-22%, p=0.023), positive cytology (10.1%-29.7%, p=0.001), LN metastasis (20.2%-43.2%, p=0.001), and abdominal metastases (9%-28%, p=0.001) were significantly different between the groups.

Table 1. Comparison of clinical characteristics of patients according to groups

n=207		Grade 3 Endometrioid		Serous/ clear cell		p*
		Number	%	Number	%	
Cervical involvement	Yes	22	24,7	40	33,9	0,153
	No	67	75,3	78	66,1	
Adnexal involvement	Yes	12	13,5	37	31,4	**0,003**
	No	77	86,5	81	68,6	
Uterine serosal involvement	Yes	9	10,1	26	22,0	**0,023**
	No	80	89,9	92	78,0	
Lymphovascular space invasion	Yes	52	58,4	73	61,9	0,617
	No	37	41,6	45	38,1	
Cytology	Positive	9	10,1	35	29,7	**0,001**
	Negative	80	89,9	83	70,3	
Depth of myometrial invasion	<50	37	41,6	50	42,4	0,908
	≥50	52	58,4	68	57,6	
LN metastasis	Yes	18	20,2	51	43,2	**0,001**
	No	71	79,8	67	56,8	
Isolated pelvic LN metastasis	Yes	7	7,9	15	12,7	0,263
	No	82	92,1	103	87,3	
Isolated paraaortic LN metastasis	Yes	3	3,4	9	7,6	0,195
	No	86	96,6	109	92,4	
Abdominal metastasis	Yes	8	9,0	33	28,0	**0,001**
	No	81	91,0	85	72,0	

* Chi-square analysis was performed.

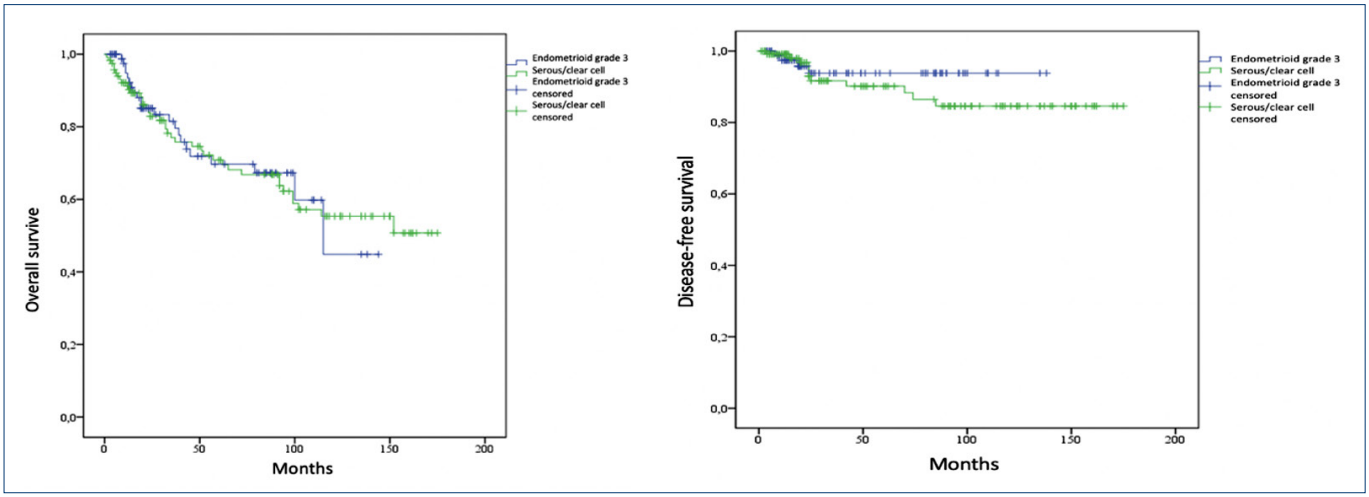

Figure 1. Overall survival and disease- free survival graphs according to groups

Table 2. Univariate and multivariate analyses for overall survival in all patients

n=207		Univariate analysis		Multivariate analysis		
		N of events (%)	p	HR	95% CI	p
Group	Grade 3 Endometrioid	22/89 (%75,3)	0,910			
	Serous/ clear cell	39/118 (%66,9)				
Age	≤63	23/97 (%76,3)	**0,039**	1,843	1,104-3,077	**0,019**
	>63	38/110 (%65,5)				
CA-125	≤35	39/146 (%73,3)	0,082			
	>35	19/50 (%62,0)				
Phase	Early stage	25/112 (%77,7)	**0,034**	1,849	1,098-3,111	**0,021**
	Late stage	36/95 (%62,1)				
Cervical involvement	There is	16/62 (%74,2)	0,226			
	No	45/145 (%69,0)				
Adnexal involvement	There is	16/49 (%67,3)	0,616			
	No	45/158 (%71,5)				
Uterine serosal involvement	There is	15/35 (%57,1)	0,146			
	No	46/172 (%73,3)				
Lymphovascular space invasion	There is	42/125 (%66,4)	0,182			
	No	19/82 (%76,8)				
Cytology	Positive	20/44 (%54,5)	0,232			
	Negative	41/163 (%74,8)				
Depth of myometrial invasion	<50	20/87 (%77,0)	0,090			
	≥50	41/120 (%65,8)				
LN metastasis	There is	23/69 (%66,7)	0,610			
	No	38/138 (%72,5)				
Isolated pelvic LN metastasis	There is	9/22 (%59,1)	0,378			
	No	52/185 (%71,9)				
Isolated paraaortic LN metastasis	There is	1/12 (%91,7)	0,141			
	No	60/195 (%69,2)				
Abdominal metastasis	There is	15/41 (%63,4)	0,449			
	No	46/166 (%72,3)				
Adjuvant treatment	Received	56/185 (%69,7)	0,658			
	Did not receive	5/22 (%77,3)				
Relapse	There is	9/15 (%40,0)	0,100			
	No	52/192 (%72,9)				

One hundred and eighty five (89.4%) patients received adjuvant treatment, of which 38 (20.5%) received radiotherapy (RT), 79 (42.7%) received chemotherapy (CT) and 68 (36.8%) received CT + RT. Recurrence was seen in 15 (7.2%) patients, 3 of them (20%) had local metastases and 12 of them (80%) had distant metastases and 61 (%29.4) of the patients died during the follow-up. While 43.8% of the grade 3 EEC group received RT, 10% received CT and 46.3% received RT + CT, 2.9% of the SEC/CCEC group received RT, 67.6% received CT and 29.5% received RT + CT and there was a significant difference in the type of adjuvant treatment between the groups ($p<0.001$). There was no significant difference between the groups in terms of adjuvant treatment status ($p=0.834$), recurrence status ($p=0.185$), localization of recurrence ($p=0.154$) and mortality ($p=0.193$).

In our study, the mean follow-up period was 40 months (range, 1-171 months), and during this follow-up period, 61 (%29.4) of 207 patients died from direct disease-related causes, and our overall survival rate during our follow-up period was 70.5%. The 12-month survival rate was 92.2%, 18-month survival rate was 88.8%, 24-month survival rate was 83.8% and 36-month survival rate was 78.8%. There was no significant difference in overall survival ($p=0.910$) or disease-free survival ($p=0.299$) between the groups (Figure 1).

Recurrence was observed in 15 (7.2%) of the 207 patients included in the study and the disease-free survival rate was 92.8%. When all patients were evaluated together, the mean survival time was 158.4. The 12-month survival rate was 98.4%, 18-month survival rate 97.7%, 24-month survival rate 96.3% and 36-month survival rate 92.5%.

According to univariate analysis, there was a significant risk for overall survival in age categories ($p=0.039$). According to the univariate analysis, there was a significant risk for overall survival between stages ($p=0.034$). A multivariate model was created for those who were significant in the univariate analysis and accordingly, age over 63 years and advanced stage were considered as poor prognostic factors (Table 2).

DISCUSSION

In the 2023 FIGO EC staging system, histopathological findings were redefined as prognostic risk factors. Histological type and tumor grade were categorized as aggressive/non-aggressive histology and low-grade/high-grade. In our study, we compared the clinicopathological features and prognostic factors of patients with uterine SEC/CCEC and grade 3 EEC, which constitute the aggressive group according to FIGO 2023 staging. We retrospectively analyzed the data of 207 patients with a follow-up period of up to 172 months (median follow-up period 40 months).

In one of the largest series in the literature comparing prognostic factors and outcomes of SEC and CCEC patients with grade 3 EEC; Hamilton et al. (8) studied 1478 patients with SEC, 391 with CCEC, and 2316 with grade 3 EEC, and found that a greater proportion of those with SEC or CCEC were diagnosed at an advanced stage (stage III-IV) than those with grade 3 EEC. The 5-year disease-specific survivals for women with SEC, CCEC, and grade 3 EEC were 55, 68, and 77%, respectively. On multivariate analysis, advanced disease ($p<0.001$), aggressive histology ($p<0.001$), and older age at diagnosis ($p<0.001$) were found to be independent prognostic factors for poor outcome. In our study, no significant difference was found in overall survival and disease-free survival rates between the grade 3 EEC and SEC/CCEC groups. In multivariate analysis, age > 63 and advanced stage disease were determined as poor prognostic factors.

In a meta-analysis examining a total of 6 studies including 11029 patients (4995 uterine carcinosarcoma, 4634 SEC, 1346 CCEC and 54 SEC or CCEC), it was seen that SEC and CCEC had a similar prognosis compared to other histological groups (9). Boruta et al. (10) retrospectively studied 52 grade 3 EEC and 87 SEC patients and found no significant difference between the two groups in terms of age, depth of MI, and LVSI (all P values < 0.05). Although these findings support our study, the rate of cervical involvement in SEC was lower in our study. When both groups were compared in terms of survival, no difference was found between advanced stage grade 3 EEC and SEC in terms of overall survival and disease-free survival, and SEC was found to have a worse prognosis in early stage patients. In the study by Ayeni et al. (11), in which they compared 119 grade 3 EEC, 211 SEC and 40 CCEC patients, they found no significant difference in overall survival between these 3 subgroups. Creasman et al. (12) retrospectively analyzed 148 SEC, 59 CCEC, and 325 grade 3 EEC patients and reported 5-year survival of 72% and 81% for early-stage SEC and CCEC, respectively; these results are similar to the 76% found for grade 3 EEC.

There are also studies in the literature that identify complete surgical staging and extent of LN dissection as other prognostic factors that may affect survival (13,14). In our study, except for 4 patients (patients who could not tolerate long surgery times due to their comorbidities), all 203 patients underwent surgical staging according to FIGO criteria. The literature has shown a survival advantage associated with comprehensive lymphadenectomy, and in light of this information we aimed to determine whether the extent of LN dissection and the presence of LN metastases contribute

to prognosis. According to our findings, the number of removed LN was not statistically different between the endometrioid and nonendometrioid groups. Additionally, we could not reveal the effect of the number of removed LN and the presence of LN metastasis on survival.

CONCLUSION

According to our findings, no significant difference was found in overall survival and disease-free survival rates between the grade 3 EEC and SEC/CCEC groups. In multivariate analysis, age > 63 years and advanced stage disease were determined as poor prognostic factors in both groups. There is no consensus in the literature regarding the prognosis of these three high-risk endometrial cancers that we examined, therefore, studies with larger patient populations are needed to clearly determine the prognostic factors affecting survival.

Conflict of interest
The authors have no conflicts of interest to report.

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