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Prognostic factors in high-grade endometrial cancer: does subtype matter?

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Summary

Objective: To assess the clinicopathologic features, prognostic factors, and survival of all histotypes of high-grade endometrial cancer. *Materials and Methods:* The authors performed a multicenter retrospective cohort study in 378 women with high-grade histotypes of endometrial cancer: 141 grade 3 endometrioid carcinomas (G3E), 65 clear-cell carcinomas (CCC), 95 uterine serous cancer (USC), and 77 carcinosarcomas (CS) diagnosed between 2001 and 2014. All patients underwent a hysterectomy and bilateral salpingo-oophorectomy as first-line treatment, and 254 subsequently had a lymphadenectomy. Demographic, histological, and survival data were abstracted from medical records. Disease-free survival (DFS) and overall survival (OS) were analyzed using Kaplan-Meier curves and Cox multivariate regression analysis. *Results:* The mean age was 68.7 ± 10.5 years and was similar in the four histotypes. USC and CS were diagnosed in an advanced stage more frequently than G3E and CCC ($p < 0.01$). After a median follow-up of 34.6 (interquartile range 16.6-73.6) months, DFS was lower in USC [adjusted hazard ratio (HR): USC 2.20, 95% confidence interval (CI) 1.38-3.52] and CS (2.6, 1.63-4.30) compared with G3E and CCC (1.35, 0.78-2.32). Similar results were observed in terms of OS. Independent predictor factors of DFS and OS were: age, USC, and CS histotypes, deep myometrial invasion (MI), advanced FIGO Stage, and p53 overexpression. Adjuvant chemo-radiation was an independent factor of good prognosis. *Conclusions:* High-grade EC histotypes have high rates of recurrence and mortality. There are differences among histotypes, as USC and CS are more aggressive than G3E and CCC.

Key words: Endometrial carcinoma; Survival; High-grade; Clinicopathologic prognostic factors; Outcomes.

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries. In the United States, there were roughly 52,500 newly diagnosed cases per year and 8,500 deaths in 2014 associated with this disease [1]. In Europe, the incidence rate of EC in 2012 was 13.9 per 100,000 women, with a mortality rate of 2.6 per 100,00 women [2]. More than 75% of patients with EC are diagnosed in early stage, with a five-year overall survival (OS) of about 70% for all EC [3].

Poorly differentiated endometrioid tumors (G3E), clear-cell carcinoma (CCC), uterine serous cancer (USC), and carcinosarcoma (CS) are a subset of aggressive high-risk EC histological types with high rates of molecular abnormalities and extrauterine spread at diagnosis. These subtypes are associated with a higher risk of recurrence, and despite its low prevalence, they account for the majority of deaths related to uterine cancer [4-6].

The 1988 International Federation of Gynecology and Obstetrics (FIGO) initially classified CS as uterine sarcomas. However, the most recent revision of FIGO stating criteria concluded that CS tumors should be considered epithelial EC. This change of criteria was based on the histogenetic similitude of CS with epithelial EC and its tendency to metastasize through the lymphatic system, in contrast with uterine sarcomas [7, 8]. Nowadays, CS is considered a metaplastic carcinoma included in EC subtype II [9].

Only a few studies have examined survival differences among all types of high-grade EC (USC, CCC, G3E, and CS) [10, 11]. The similarities and differences among these high-risk histological types have not been clearly defined yet. Therefore, it is important that studies on the four histotypes of EC are conducted to clarify these questions and determine the optimal management of patients diagnosed with these aggressive tumors.

The aim of this study was to evaluate the clinical behavior and prognostic factors of high-grade EC and assess the impact of histotype on survival.

Materials and Methods

The authors conducted a multicenter retrospective study between 2001 and 2014 at three tertiary medical centers in Spain ("Hospital Clinico San Carlos" in Madrid, "Hospital Virgen del

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Rocio" in Seville and "Hospital Universitario Miguel Servet" in Zaragoza). These Centers manage EC following the same clinical guidelines and protocols. A total of 1,509 women were diagnosed with EC in these institutions during the study period. In total, 388 women diagnosed with poorly-differentiated EC histotypes with complete medical records were identified. Sarcomas and well- or moderately-differentiated endometrioid EC were excluded. The study was approved by the institutional review board of each participant Center.

Ten patients were excluded because they were treated with chemotherapy or hormonotherapy alone. Finally, the authors selected 373 patients who had undergone a hysterectomy and bilateral salpingo-oophorectomy as first-line treatment. Pelvic lymph node dissection associated or not with para-aortic lymphadenectomy (LDN) was performed in 252 patients. The reasons for not performing a LDN included an advanced age, morbid obesity, presence of comorbidities, and tumor classification as no high-grade EC based on presurgical imaging data. All procedures were performed in each Center by the same team. Staging biopsies, omentectomy, and cytoreductive procedures were carried out in all patients. All patients were managed following the guidelines approved by the Spanish Society of Gynecology and Obstetrics and signed a specific consent form.

Histotype was reviewed by at least two local gynecological pathologists using current World Health Organization (WHO) criteria. Mixed tumors (two patterns of differentiation with at least > 5% of the tumor) were reclassified according to the presence of serous carcinoma or CCC within the endometriod tumor. Serous/clear-cell mixed carcinomas were considered USC. The reason is that USC seems to have worse prognosis, and the clinical behavior and outcomes of USC coexisting with other types of EC are more consistent with those of serous carcinoma, compared to endometrioid EC [12]. Patients were staged according to 2009 FIGO staging classification criteria [13].

External beam radiotherapy (EBRT), brachytherapy (BT), and chemotherapy were selectively administered postoperatively based on Local Tumor Committee's decision. Local Tumor Committees were integrated by radiation oncologists, clinical oncologists, pathologists, and gynecological oncologists. Follow-up was performed according to local practice and guidelines. The follow-up data collected included EC recurrence, therapy, and patient health status.

Continuous variables were expressed as means and standard deviations (SD) and interquartile ranges (IQR). Comparative analysis was performed using either ANOVA test for normally distributed data or Kruskal Wallis test for non-parametrical data. Discrete variables were compared using χ^2 test or Fisher's exact test for small cell comparisons. Magnitude of association was assessed using odds ratio (OR) with a 95% confidence interval (CI). Factors independently associated with survival were assessed by Cox´s method. Multivariate modeling was performed using Cox's proportional hazard models including only the variables that were statistically significant according to univariate analysis. Multivariate modeling yielded a subset of independent predictors of disease-free survival (DFS) and overall survival (OS). Hazard ratio (HR) with 95% CI was calculated. Kaplan-Meier's method was used to estimate the distribution of survival across study groups. The Wilcoxon test (Breslow) was used to calculate statistically significant differences between groups in terms of recurrence and survival. All statistical tests were two-sided. Statistical significance was defined as a p value less than 0.05. Statistical analyses were performed using SPSS Statistic version 20.

Results

A total of 373 patients with high-grade histotypes were included in the study: 135 G3E, 64 CCC, 96 USC, and 78 CS. Demographic data and risk factors are shown in Table 1. CS was associated with a family history of cancer (breast and colon) ($p = 0.009$) and tamoxifen use ($p < 0.001$), and with less association with hypertension ($p = 0.033$).

Histopathological data at diagnosis are shown in Table 2. Estrogen and progesterone receptors were more frequently overexpressed in G3E ($p < 0.01$), and G3E was diagnosed in earlier stages; p53 overexpression and positive peritoneal washings were more common in USC ($p < 0.01$). Deep myometrial invasion (MI) was less frequent in CCC ($p = 0.022$), and CS was the group with the highest tumor size ($p = 0.024$). After surgical staging, 213 (57.1%) patients were diagnosed in early stages (I and II), and 160 (42.9%) in advanced stages (III and IV), without significant differences among histotypes. Disease spread at diagnosis (Stage IV) was significantly more common in USC (16.7%) and CS (16.6%) than in G3E (4.4%) and CCC (4.7%) ($p = 0.004$) (Table 2).

LDN was performed in 252 (67.6%) patients, and node involvement was present in 79 (31.1%) patients. The mean number of para-aortic nodes removed was 14.04 (SD 7.34; IQR 9) and 7.34 (SD 7.31; IQR 8), respectively. Node involvement was more frequent in patients with CCC, although differences were not statistically significant. Compared with G3E, the OR of having nodes involved was 2.07, 95%CI 1.01-4.26 for CCC, 1.73, 95%CI 0.89-3.33 for USC, and 1.36, 95%CI 0.66-2.80 for CS. Pelvic LDN was performed in 248 patients (141 pelvic LDN alone and 107 associated with para-aortic LDN). The rates of pelvic node involvement (28.2%) were similar in all histotypes, with an upward trend in CCC. Para-aortic LDN was performed in 111 patients (four para-aortic alone and 107 associated with pelvic LDN). Node involvement in the para-aortic area (23.4%) was similar in all histotypes (Table 2). A total of 6.5% of patients had para-aortic metastases with negative pelvic nodes.

Adjuvant pelvic irradiation and/or chemotherapy were administered to 298 (79.9%) patients. Eighty-six patients did not receive any treatment due to complications of surgery, advanced age, comorbidities, or refusal. The administration of adjuvant treatment was significantly less frequent in G3E with respect to other histotypes. Adjuvant radiotherapy was administered to 255 (68.4%) patients, chemotherapy to 138 (37%), and 95 (25.5%) patients received the two treatments. Irradiation (EBRT and/or BT) was significantly more common in G3E, and chemotherapy was more frequent in USC and CS histotypes. Chemo-radiotherapy was also statistically more frequent in patients with USC and CS, compared to the other histotypes (Table 2).

The median follow-up of patients was 31.5 months (IQR

Table 1. — *Demographic and risk factors details of 373 patients with high-grade endometrial cancer. Data are shown as mean (standard deviation) or cases (%).*

	EG3 (n=135)	USC (n=96)	CCC (n=64)	CS (n=78)	*p* value
Age (years)	69 (11.5)	69.6 (9.4)	71.9 (10)	68.9 (9.7)	0.683
History of cancer in family	43 (31.8)	29 (30.2)	15 (23.4)	21 (26.9)	0.610
Personal history of cancer	17 (12.7)	17 (17.9)	8 (12.7)	23 (30.3)	0.009
Menopause					0.69
Postmenopausal	126 (93.3)	94(97.9)	61 (95.3)	74 (94.8)	
Premenopausal	9 (6.7)	4 (2.1)	3 (4.7)	4 (6.2)	
Hypertension	73 (54.1)	56 (58.9)	35 (54.7)	29 (37.3)	0.033
Diabetes	29 (21.2)	24 (25)	20 (31.2)	13 (16.6)	0.232
Obesity (BMI >30)	70 (52.6)	56 (58.3)	26 (40.6)	31 (39.7)	0.062
Nulliparity	33 (24.4)	15 (15.6)	9 (14.1)	21 (26.9)	0.127
Hormonal treatment	4 (3)	2 (2.1)	1 (1.6)	2 (2.6)	0.939
Tamoxifene treatment	13 (9.6)	9 (9.3)	4 (6.2)	15 (19.2)	<0 .001

BMI: body mass index.

Table 2. — *Histological, surgical, and adjuvant features in 373 patients with high-grade endometrial cancer. Data are shown as mean (standard deviation) or cases (%).*

	EG3 (n=135)	USC (n=96)	CCC (n=64)	CS (n=78)	*p* value
Tumor size (mm)	26.1(24)	20.2(24.1)	12.8(18.8)	36.4(33.4)	0.024
Myometrial invasion					0.022
• No invasion	7 (5.2)	18 (18.8)	10 (15.6)	10 (12.8)	
• < 50%	26 (19.2)	12 (12.5)	16 (25)	13 (16.7)	
• > 50%	102 (75.6)	66 (68.7)	38 (59.4)	55 (70.5)	
Lymphovascular space involvement (n=312)	46 (43.3)	51 (54.3)	18 (39.1)	31 (47)	0.298
Hormone receptor overexpression					
• Estrogen (n=130)	42 (82.4)	19 (52.8)	4 (26.7)	12 (42.9)	0.000
• Progesterone (n=130)	41 (80.4)	20 (55.6)	5 (33.3)	12 (42.9)	0.001
P53 overexpression (n=123)	19 (45.2)	26 (83.9)	13 (61.9)	16 (55.2)	0.009
Ki67 expression (n=100)	69.3% (15.2)	68.6% (21.2)	61.8% (21.4)	58.6% (25.4)	0.362
Positive peritoneal washings (n=351)	15 (11.5)	19 (20.2)	18 (12.7)	8 (12.5)	0.000
Istmo affectation (n=257)	20 (25.6)	35 (38.9)	13 (37.1)	18 (33.3)	0.315
Cervical estroma affectation	32 (23.7)	30 (31.3)	16 (25)	17 (21.8)	0.458
Anexal involvement	14 (10.4)	22 (22.9)	9 (14.1)	12 (15.4)	0.084
Parametrium invasion	15 (11.1)	11 (11.5)	4 (6.3)	5 (6.4)	0.459
Vagina invasion	3 (2.2)	3 (3.2)	2 (3.1)	1 (1.3)	0.850
Node involvement (n=251)	21/94 (22.3)	24/69 (34.7)	18/43 (41.8)	16/46 (34.7)	1.130
Localization of positive nodes					
• Pelvic (n=248)	19/93 (20.4)	21/68 (30.8)	16/41 (39)	14/46 (30.4)	0.216
• Para-aortic (n=111)	5/36 (14.7)	10/38 (26.3)	6/21 (28.5)	5/18 (27.7)	0.461
Adjuvant treatment					
• None	17 (12.5)	22 (22.9)	19 (29.7)	17 (21.8)	0.029
• Irradiation	86 (63.7)	24 (25)	30 (46.9)	20 (25.6)	0.005
• Chemotherapy	11 (8.1)	12 (12.5)	4 (6.3)	16 (20.5)	< 0.001
• Irradiation and chemotherapy	21 (15.6)	38 (39.6)	11 (17.2)	25 (32.1)	< 0.001
FIGO Stage					0.004
• IA	42 (31.1)	28 (29.2)	25 (39.1)	26 (33.3)	
• IB	36 (26.7)	13 (13.5)	9 (14.1)	9 (11.5)	
• II	7 (5.2)	8 (8.3)	4 (6.3)	6 (7.7)	
• IIIA	12 (8.9)	7 (7.3)	4 (6.3)	9 (11.5)	
• IIIB	12 (8.9)	5 (5.2)	1 (1.6)	1 (1.3)	
• IIIC	20 (14.8)	19 (19.8)	18 (28.1)	14 (17.9)	
• IVA	1 (0.7)	2 (2.1)	0 (0)	3 (3.8)	
• IVB	5 (3.7)	14 (14.6)	3 (4.7)	10 (12.8)	
FIGO Stage initial/advanced					0.248
• I/II	85 (63)	49 (51)	38 (59.4)	41 (52.5)	
• III/IV	50 (37)	47 (49)	26 (40.6)	37 (47.5)	

Table 3. — *Recurrence and mortality in 378 patients with high-grade endometrial cancer. Data are shown as cases (%).*

	Total (n=373)	EG3 (n=135)	USC (n=96)	CCC (n=64)	CS (n=78)	*p* value
Recurrence overall	150 (40.2)	43 (31.9)	45 (46.9)	23 (35.9)	39 (50)	0.026
Site of recurrence						0.095
• Local	20 (13.3)	6 (14)	6 (13.3)	2 (8.7)	6 (15.4)	
• Pelvis	41 (27.3)	10 (23.2)	18 (40)	5 (21.7)	8 (20.5)	
• Nodes*	26(17.3)	10 (23.2)	4 (8.9)	5 (21.7)	7 (17.4)	
• Spread**	60 (40)	16 (37.2)	15 (33.3)	11 (47.8)	18 (46.1)	
• No data	3(2)	1 (2.3)	2 (4.4)	0 (0)	0 (0)	
Mortality overall	129 (34.6)	35 (25.9)	40 (41.7)	20 (31.2)	34 (43.6)	0.001
Survival						< 0.001
• Alive and well	244 (65.4)	100 (74.1)	56 (58.3)	44 (68.7)	44 (56.4)	
• Dead for tumor	104 (27.8)	23 (17)	38 (39.6)	14 (21.9)	29 (37.1)	
• Dead for other causes	22 (5.9)	10 (7.4)	1 (1)	6 (9.4)	5 (6.4)	
• Dead for cause unknown	3 (0.8)	2 (1.5)	1 (1)	0 (0)	0 (0)	

**Recurrence in nodes as first localization; **Recurrence in two or more sites, or distant metastases.*

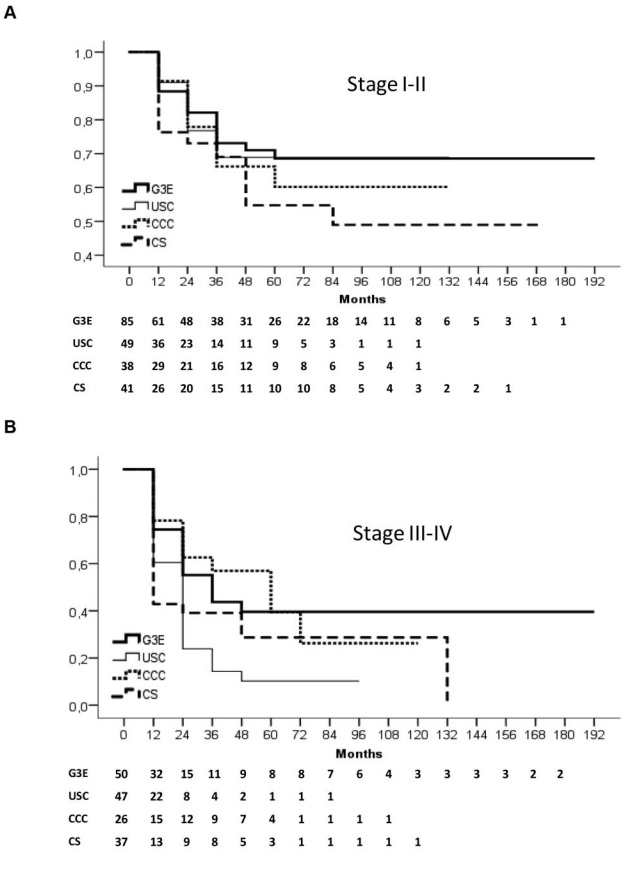

Figure 1. — Disease-free survival in patients with high-risk histology endometrial cancer divided by FIGO Stage. A) Disease-free survival in Stage I/II patients (Breslow test: pooled p = 0.433). B) Disease-free survival in Stage III/IV patients (Breslow test: pooled p = 0.010).

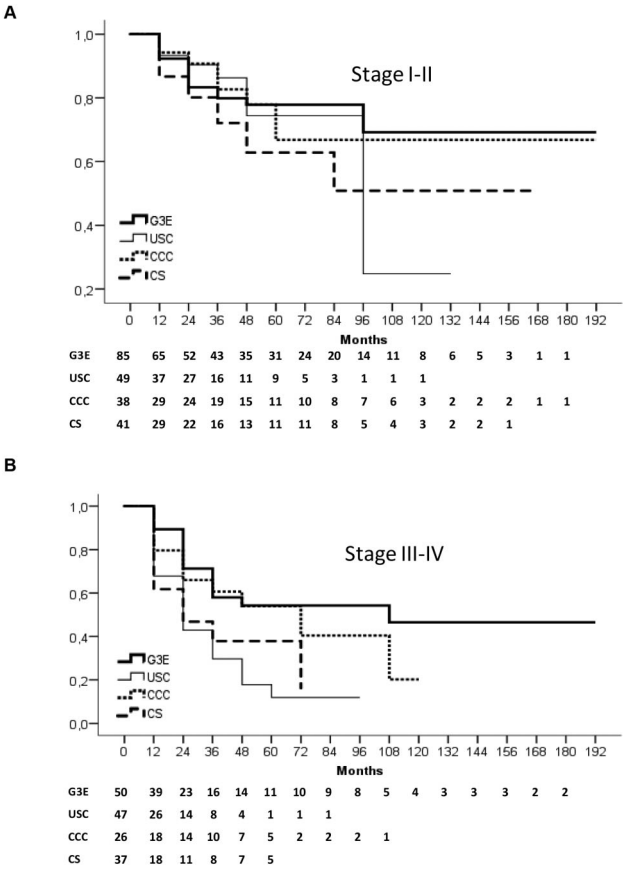

Figure 2. — Overall survival in patients with high-risk histology endometrial cancer divided by FIGO Stage. A) Overall survival in Stage I/II patients (Breslow test: pooled p = 0.486). B) Overall survival in Stage III/IV patients (Breslow test: pooled p = 0.005).

12-65 months). A total of 150 (40.2%) patients experienced a relapse and 129 (34.6%) died (104 deaths were disease-related). At the end of the study, 47 patients were alive with disease. Distant metastases were significantly more common than pelvic or nodal recurrence. Patients with USC and CS were at a higher risk for metastasis. Mortality rates were significantly higher in USC and CS (Table 3). Recurrence was treated with surgical resection in 17 patients, ra-

Table 4. — *Univariate and multivariate analysis of disease-free survival and overall survival using Cox's model*

	Disease-free survival	Overall Survival		
	HR (95)CI)	Adjusted HR* (95)CI)	HR (95)CI)	Adjusted HR* (95)CI)
Age (lineal increment per year)	1.03 (1.01-1.05)	1.022 (1.01-1.04)	1.06 (1.04-1.08)	1.05 (1.03-1.07)
Adjuvant Treatment				
• None	1	1	1	1
• Irradiation	0.51 (0.33-0.78)	0.64 (0.64-0.40)	0.42 (0.28-0.65)	0.46 (0.29-0.73)
• Chemotherapy	1.51 (0.91-2.50)	1.08 (0.63-1.84)	0.80 (0.44-1.44)	0.52 (0.28-0.97)
• Irradiation and Chemotherapy	0.60 (0.37-0.97)	0.39 (0.23-0.66)	0.55 (0.33-0.90)	0.33 (0.19-0.57)
Histological Subtype				
• Endometrioid G3	1	1	1	1
• Clear Cell	1.04 (0.62-1.73)	1.04 (0.62-1.73)	1.24 (0.72-2.15)	1.16 (0.66-2.05)
• Serous	1.82 (1.18-2.73)	1.72 (1.11-2.66)	2.25 (1.42-3.57)	1.98 (1.23-3.19)
• Carcinosarcoma	1.91 (1.24-2.94)	1.73 (1.09-2.75)	2.12 (1.37-3.52)	2.28 (1.34-3.68)
Myometrial invasion				
• < 50)	1	1	1	1
• ≥ 50)	1.97 (1.32-2.94)	1.58 (1.03-2.44)	2.45 (1.54-3.93)	2.14 (1.29-3.56)
FIGO Stage				
• I-II	1	1	1	1
• III-IV	3.01 (2.12-4.30)	2.94 (2.02-4.23)	3.15 (2.20-4.52)	3.18 (2.12-4.77)

*HR= Hazard Ratio. CI = confidence interval. * Adjusted HR in multivariate analysis including all variables.*

diotherapy in six patients, chemotherapy alone in 81 patients, and radiotherapy in seven patients. Forty-five patients only received palliative care. Treatments were similar for all histological types.

Survival analysis showed a three-year DFS of 62.1% for the G3E histotype, 62.8% for CCC, 38.4% for USC, and 54.7% for CS, with statistically significant differences among groups ($p = 0.039$). FIGO Stage was considered for DFS analysis: in initial stages (I and II) DFS was worse for CS and USC, although differences were not significant ($p = 0.433$). However, differences in DFS became significant in advanced stages (III and IV) ($p = 0.01$) (Figure 1).

Cox univariate analysis identified age, histotypes USC and CS, deep MI, lymphovascular space involvement (LVSI), p53, lower uterine segment (LUS) involvement, LDN, and advanced FIGO Stage as predictor factors of recurrence, and adjuvant chemo-radiation as a protective factor of recurrence. Size tumor ($p = 0.186$), hormone receptor expression ($p = 0.389$), and Ki67 proliferation index (0.264) were not predictors of recurrence in high-grade EC. In multivariate analysis, age, histotypes USC and CS, deep MI, and advanced FIGO Stage were found to be independent predictors of recurrence. Adjuvant chemotherapy was a protective factor of recurrence (Table 4).

The three-year OS rate was 70.6% for the G3E histotype, 74% for CCC, 52.2% for USC, and 56.2% for CS. OS was significantly poorer for USC and CS ($p = 0.005$). OS in initial stages (I and II) was worse for CS and USC, although differences were not significant ($p = 0.486$). Conversely, differences in OS in advanced stages (III and IV) were significant ($p = 0.01$), as shown by Kaplan-Meier curves (Figure 2).

Cox univariate analysis identified age, histotypes USC and CS, deep MI, LVSI, p53, LUS involvement, LDN, and advanced FIGO Stage as predictor factors of death, and adjuvant chemo-radiation as a protective factor. Size of tumor ($p = 0.103$), hormone receptor expression ($p = 0.861$), and Ki67 proliferation index ($p = 0.627$) were not predictors of OS in high-grade EC. In multivariate analysis, age, histotypes USC and CS, deep MI, and advanced FIGO Stage were found to be independent predictors of poor OS, and adjuvant chemo-radiation was a factor of good prognosis (Table 4).

Discussion

The present study revealed significant differences in the behavior of high-grade EC, with a worse prognosis for USC and CS, compared to CCC and G3E. Two groups of high-grade EC were identified based on their clinical behavior: a low-risk group (ECG3 and CCC) and an aggressive group with a worse prognosis (USP and CS).

There is no consensus in the literature regarding the differences in prognosis among high-grade EC histotypes. Some studies report no significant differences [14-18], whereas other studies suggest that USC or CCC are associated with an unfavorable prognosis, as compared to G3E [19-23]. Although CS has been recently identified as a type II EC in FIGO classification, there is controversy whether CS should be included in the same group as USC, CCC, and G3E in clinical trials. A limited number of studies have compared CS subtype against other high-grade EC [10, 11, 24-28]. In most cases, these studies showed that CS is the subtype with the worst prognosis. Thus, authors have concluded that CS should be considered a particular subtype of high-risk epithelial EC [28].

Multivariate analysis identified age, histotypes USC and CS, deep MI, and advanced FIGO Stage as independent predictor factors of recurrence and overall survival.

Disease spread (Stage IV) at diagnosis was more frequent in USC and CS, compared to G3E and CCC, which might explain their worse prognosis. This finding is consistent with the results of previous studies, although variability in the incidence of Stage IV disease (22-40% USC, 19.8-36% CS) is high among studies [4, 10]. In contrast, the longest study of high-grade EC revealed statistically significant differences in survival for Stages III and IV among histotypes [27].

Myometrial invasion has been widely studied as a factor of poor prognosis in EC. Deep MI has been recognized as a predictor of extra-uterine metastasis and an independent prognostic factor in low- and high-grade EC. Mariani *et al.* reported that the presence of deep MI was the best predictor of hematogenous dissemination in corpus cancer [29]. In the present study, deep MI was an independent prognostic factor in all stages. Other studies, such as that by Ayeni *et al.*, identify deep MI as an independent factor of OS only in Stage I/II [4].

LDN is usually recommended for all types of high grade EC, as all entail a high-risk for nodal involvement. This is confirmed by the high rates of nodal involvement found in the present study, with no statistically significant differences among groups. In this study, nodal spread was not found to be an independent prognostic factor. There is no conclusive evidence demonstrating that LDN has a positive impact on survival. In a critical review of literature, the rationale for the performance of a LDN was that, apart from facilitating disease staging, this procedure seems to offer a measurable survival benefit [30]. However, some studies have found no evidence that LDN provides any survival benefit in high-risk EC [31,32].

Tumor size has been extensively studied as a prognostic factor in low-grade EC. In contrast, data on patients with poorly differentiated tumors are limited. In the present study, the authors found that tumor size was significantly larger in the CS group, as compared to the other histotypes, although differences were not statistically significant. In a study that included 75 EG3, 35 USC, 12 CCC, and 26 CS, no significant differences were observed in tumor size among subtypes. No association was observed either between tumor size and DFS in multivariate analysis, which is consistent with the results of the present study. According to the authors, tumor size in EC seems to correlate with other adverse prognostic factors as a surrogate measure of risk of nodal involvement, but it does not independently increase the risk of recurrence [33].

LVSI is considered one of the first steps of metastatic spread in EC, and it is an important prognosis factor of recurrence and survival. Prior authors, in agreement with the results of the present study, suggest that their coexistence do not confer an additional risk of recurrence [34]. Conversely, other studies identify LVSI as an independent prognostic factor in all stages of high-grade EC suggesting that LVSI can be used to identify a treatment refractory subgroup [4, 16]. In the last European consensus conference on endometrial cancer, LVSI was agreed to be an important risk factor that can be employed to define new risk groups and guide adjuvant therapy use. However, this is only applicable to well or moderately differentiated tumors, not to high-grade EC [35].

Hormone receptor overexpression is a characteristic of type I EC, which is associated with excess estrogenic stimulation of the endometrium. The present data, which are supported by other studies [17], suggest that hormone receptor expression in high-grade EC is low, which is a characteristic of the endometrioid histotype, and is not a predictor of survival. Conversely, a recent large study (254 EG3, 287 USC) supported by the Canadian High Risk Endometrial Cancer Consortium (CHREC) revealed that progesterone receptor expression was significantly associated with favorable OS in high-grade EC [36]. The disparity in results may be due to the lack of standardization in the interpretation of immunohistochemical analysis. In the present study, gynecological pathologists set a 5% cut-off to determine a positive result. However, in the CHREC study the cut-off was 1%, which is less restrictive. P53 mutation is common in non-endometrioid EC. However, there is controversy whether p53 is an independent prognostic factor in EC. Whereas some studies suggested in the past that p53 is associated with recurrence [6], more recent studies including high-grade EC have revealed that p53 overexpression is not an independent prognostic factor, which is consistent with the results of the present study [37].

The optimal role of chemotherapy and RT in EC has not yet been clearly elucidated. International guidelines contemplate radiotherapy and chemotherapy for high-grade EC as part of primary treatment based on the hypothesis that combined therapy would confer a survival benefit by improving both local and distant control [35]. Two clinical trials have been performed to determine the optimal adjuvant therapy for patients with high-grade EC FIGO Stage I-III and no residual tumor after surgery. Patients were randomly allocated to adjuvant radiotherapy with or without sequential chemotherapy [38, 39]. A combined analysis of the results of these trials showed that PFS improves with the addition of adjuvant chemotherapy to radiation [40]. In a recent National Cancer Database Analysis that included more than 45,000 women with high-grade EC, receiving RT was found to be protective and was associated with an improved OS [41]. PORTEC 3 is a large randomized collaborative group of ongoing trials currently investigating the benefit of adjuvant chemoradiotherapy compared with radiotherapy alone for women with high-risk EC. Unfortunately, patients with CS are not included in this study. Other studies including patients with CS have demonstrated significant improvements in both, OS and DFS associated

with adjuvant therapy, even in early FIGO Stages [42-45]. Most of the present patients (77.2%) received adjuvant therapy (radiotherapy or chemotherapy alone or in combination). Multivariate analysis indicated significant improvements in both OS and DFS associated with adjuvant chemo-radiotherapy, being an independent factor of good prognosis in all high-grade EC subtypes. Based on these results, the present authors strongly recommend that chemotherapy and radiotherapy are always considered for the management of high-grade EC.

The potential limitations of this study are its retrospective design, the incomplete staging of some patients (LDN was performed in 67.6%), and the median follow-up, which was less than three years. The strengths of the study are the inclusion of CS as a high-grade type and its multicentre design.

In conclusion, this study provides evidence that differences exist among high-risk EC histotypes, especially with respect to the most aggressive histotypes, USC and CS, in terms of recurrence and death. Patients with high-grade EC can benefit from adjuvant chemoradiation, which is associated with improved OS and DFS. Therefore, adjuvant chemoradiation should be included in the standard of care for high-grade EC. Given the lack of prospective randomized trials on this issue, the data provided by this study may guide the management of patients with high-grade EC in the future.

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