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Clinicopathologic characteristics and prognosis comparison of the uterine high grade endometrial carcinomas

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ABSTRACT

Objectives: Grade 3 endometrioid adenocarcinomas (G3 EAC), type two endometrial carcinomas (Type 2 EC), and also uterine carcinosarcomas (UCS) are considered as high-grade endometrial adenocarcinomas. The aim of this study was to compare the clinicopathologic features and survival of patients with UCS, G3 EAC, Type2 EC.

Material and methods: We included two hundred and thirty-five patients in this study. Patients were divided into three groups according to the type of tumor as uterine G3 EAC (group 1, n = 62), Type 2 EC (serous, clear and mixed types; group 2, n = 93), and UCS (group 3, n = 80). We compared the groups according to age, initial symptom, surgical approach, stage, myometrial invasion (MI), lymph node invasion (LNI), lymphovascular space invasion (LVSI), adjuvant therapy, and survival. When comparing the survival outcomes the Kaplan-Meier analysis was performed.

Results: The groups were similar according to age, menopausal status, nulliparity, initial symptoms, stage, LVSI, and LNI. Positive cytology was determined significantly more in group 3. There was a significant difference between the groups in terms of myometrial invasion degree. Optimal cytoreduction was similar among the groups. The primary adjuvant treatment was chemotherapy for UCS and Type2 EAC whereas radiotherapy was the main adjuvant treatment for G3 EAC. There were no significant differences among the groups according to overall survival (OS) (p = 0.290).

Conclusions: Although the survival difference among the groups can not be revealed, these patients have different clinical and pathological features and they should be considered as different groups.

Key words: endometrial cancer; high-grade endometrioid adenocarcinoma; overall survival; uterine carcinosarcoma; type 2 endometrial cancer

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INTRODUCTION

Endometrial cancer is the most common gynecological cancer according in developed countries [1]. Today, the diagnosis and classification of endometrial cancer is mainly based on morphological features and, when necessary, evaluation by immunohistochemical methods. The management of patients is decided based on the risk groups evaluated according to their clinical and pathological features [2]. Although surgical treatment is the basis of the treatment, adjuvant therapy (radiotherapy, chemotherapy and sometimes together) is recommended for patients at high risk [3]. There may be some problems, particularly in the management of patients with high-grade endometrial cancer (HGEAC). Grade 3 endometrioid adenocarcinomas (G3 EAC), type 2 adenocarcinomas (Type 2 EC), and also uterine carcinosarcomas (UCS) are considered as high-grade endometrial adenocarcinomas. Soslow et al. [4] recommends moving toward a binary scheme to grade endometrial endometrioid carcinomas by considering International Federation of Gynecology and Obstetrics defined grades 1 and 2 tumors as "low grade" and grade 3 tumors as "high grade." One thing is for sure that patients with high-grade carcinomas are at risk for recurrence and death [5]. Endometrial cancer is divided into two groups , type 1 and 2, according to their etiopathogenesis, clinical and pathological features by Bockman [6]. While endometrioid tumors constitute the type 1 group, non-endometrioid tumors (serous, clear cell and mixed) are accepted in type 2. Although advances in

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the classification and management of endometrial cancer according to its molecular characteristics are very current [7–9], Bockman's classification is still widely used due to its practical meaning [2, 3]. Approximately 15% of all cases are described in the high-risk group and mainly consisted of G3 EAC and type 2 non-endometrioid tumors [10]. Above 50% solid growth of endometrial neoplasm was defined as G3 EAC. UCS (malignant mixed mullerian tumors) are biphasic tumors (both carcinoma and sarcomatous) tumors with poor prognosis should be considered as an HGEAC [11].

Endometrial cancer is a heterogeneous group of cancer, not only in histopathological types but also in subgroups [12]. While there are many studies comparing type 1 and 2 endometrial cancer at molecular and histopathological levels [13–17], there are few studies comparing HGEAC in itself according to clinical features and prognosis [18–22]. The studies in the literature generally involve comparing the two groups, such as UCS vs G3 EAC. Therefore, we aimed to compare the clinicopathologic features and survival of patients with G3 EAC, Type2 EAC, and UCS.

MATERIAL AND METHODS

This study was performed by examining the data of 235 patients who were operated on in our clinic and had their follow-up between January 1996 and December 2016. Patients whose pathological examination was not performed in our faculty and who were not followed-up on in our clinic were excluded. There were 62 patients were in the G3 EAC group, 93 patients were in the type 2 EC and 80 patients were in the UCS group. Type 2 EC group consisted of 24 patients with serous EC, 16 patients with clear cell EC, and 53 patients with mixed type. The patients were evaluated in terms of age, main symptom (presenting symptom) menopause status, medical history (the previous cancer history and co-morbidity), surgical history (laporoscopy or laparotomy, in terms of omentectomy, bowel resection, and lymph node dissection), whether they achieved optimal cytoreduction and whether they performed secondary cytoreductive surgery due to recurrences. Stage, the degree of MI (It was separated as less than 50% and more), LNI, LVSI, the presence of positive cytology, the type of adjuvant treatment (radiotherapy, chemotherapy or both), and survival outcomes [disease free-survival (DFS) and overall survival (OS)] were evaluated and compared among the groups. The staging was performed according to the FIGO 2009. The primary surgical procedures were laparotomic or laparoscopic total hysterectomy and bilateral salpingo-oophorectomy (TH + BSO) and pelvic/para-aortic lymphadenectomy with or without omentectomy. A maximum residual tumor of < 1cm was the optimal cytoreduction. For high-risk patients, chemotherapy and radiotherapy was administered for systemic and locoregional control, respectively. Follow-up was performed in three months intervals within the first year, and then six months intervals up to five years. The time (months) between the surgery/ /diagnosis and death or last follow-up was defined as OS. The time (months) from surgery to disease progression or last follow-up was defined as DFS.

Data were analyzed using the SPSS software version 20.0 (IBM, Armonk, NY, USA). Comparisons the three groups were performed using the one-way ANOVA test. Bonferroni correction was used. A Chi-Square test was used for categorical data analysis. Results were demonstrated as mean ± SD and median (min-max), and n (%). All recorded p-values are two-tailed. With the Kaplan–Meier method, the effects of clinical variables and histopathologic subtypes on survival data were analysed. The differences of the survival curves were evaluated using the log-rank test.

RESULTS

Two hundred thirty-five patients were eligible for the study, 62 of them were in the G3 EAC (group 1) , 93 were in the type 2 EC (group 2), and 80 were in the UCS (group 3). There were no significant differences between the groups in terms of age. In groups, abnormal uterine bleeding was the main symptom, while abdominal distension was high in the group 2. We did not find a statistically significant difference between the groups regarding the menopausal status and medical history. But there were seven patients with history of another cancer, four of them had breast cancer and two of them had colon cancer and one of them had skin cancer in the group 3. Laparoscopic surgery was performed more in groups 1 and 2 than in group 3 (p = 0.002). Omentectomy rates were also significantly different between the groups (p = 0.001). Lymph node dissection rates were similar (p = 0.080). Rates of bowel resection, reaching optimal surgery, and secondary cytoreductive surgery were similar among the groups. In total, 26 patients underwent bowel resection. Secondary cytoreductive surgery was performed in 30 patients due to recurrence. The comparison of the groups in terms of demographic features and surgical approach is summarized in Table 1.

The groups were similar in terms of stage, LVSI and nodal involvement (p = 0.340, 0.071, 0.139; respectively). In the group 2, endometrium-limited polypoid tumors without myometrial invasion are more than the others (p = 0.001). Positive cytology is higher in the group 2 and 3 than the group 1 (p = 0.024). Adjuvant treatment options were significantly different between groups. While chemotherapy was the first adjuvant option in groups 2 and 3, patients in group 1 received radiotherapy as the first adjuvant option.

Mean OS was 50 months for group 1, 45 months in group 2, and 35 months in group 3. The difference between the groups in terms of OS did not reach a signifi-

Table 1. The comparison of the groups in terms of demographic features and surgical approach

	Studied groups (Mean ± SD, n%)			
	Group 1 HGEAC (n = 62)	**Group 2 Type 2 EAC (n = 93)**	**Group 3 UCS (n = 80)**	**p***
Age [years]	59.3 ± 10.2	61.7 ± 9.0	62.2 ± 10.4	0.194
Presenting symptom Bleeding Abdominal distention Pain Others	 45 (73%) 5 (8%) 5 (8%) 7 (11%)	 57 (61%) 17 (18%) 2 (2%) 17 (18%)	 66 (82%) 4 (5%) 5 (6%) 5 (6%)	0.010
Postmenopausal status (+)	52 (83%)	49 (53%)	68 (85%)	0.583
Medical history Previous cancer diagnosis Co-morbidity	 2 (3%) 30 (48%)	 0 43 (46%)	 7 (9%) 30 (38%)	0.071
Nodal dissection None PLN PPALND	 16 (26%) 7 (11%) 39 (63%)	 20 (22%) 15 (16%) 55 (59%)	 7 (9%) 5 (6%) 68 (85%)	0.080
Omentectomy (infracolic or total))	26 (42%)	63 (68%)	42 (53%)	0.001
Colon resection	4 (6%)	8 (9%)	14 (18%)	0.169
Optimal cytoreduction	46 (74%)	73 (78%)	74 (93%)	0.214
Secondary cytoreduction surgery	8 (13%)	15 (16%)	7 (9%)	0.115

HGEAC — high grade endometrioid adenocarcinoma; Type 2 EC — type 2 endometrial cancer; UCS — utrerine carcinosarcoma; PLN — pelvic lymph node dissection; PPALND — pelvic-paraaotic node dissection; p* — the p values obtained by comparing all 3 groups using the one-way Anova test

cant level (p = 0.290). DS was significantly different among the groups (p = 0.019). The mean DFS was found to be 45 months in group 1, 29 months in group 2 and 19 months in group 3. Figure 1 shows the prognosis of the groups in terms of OS. Figure 2 shows the prognosis of the groups for DFS.

DISCUSSION

In our study, we showed that all three groups were similar according to OS, whereas there was a difference between the groups in terms of DFS. The G3 EAC group had the best DFS, while the worst group was the UCS group. The number of studies comparing these groups is also limited. Because the frequency of this group of tumors is low, and the results of the current studies' results are limited and contradictory due to few cases numbers, difficulties in pathological evaluation and identification, inclusion criteria, and variety of adjuvant treatments.

When we look at studies comparing G3 EAC and type 2EAC, there are different results in terms of prognosis. Ayeni et al. compared 119 G3 EAC cases with 211 serous and 40 clear cell EAC [23]. They didn't show any differences with the prognosis in the groups. Myometrial invasion degree was found higher in the G3 EACs group like our results, but stage 4 disease was found higher in serous EC. Hamilton et al. [24] perform the widest comparison (serous n = 1453, clear cell n = 391, and G3 EAC n = 2316) using Surveillance, Epidemiology, and End Results Program (SEER data). This study showed that serous and clear cell type predict for lower survival rate. In another study comparing 52 patients with G3 EAC with 87 patients with serous EC, the prognosis in serous EC was reported to be worse than G3 EAC [25]. Similarly Crisano et al. showed that even in the early stage, type 2 ECs (serous n = 53, clear cell n = 18) have a higher recurrence rate and worse prognosis than other ECs (n = 509), including G3 EACs (n = 90) in accordance with the result of our study [26]. McGunigal et al. [27] also demostrated that G3 EAC had better prognsosis. Unlike the results of this study, there is also a study showing that serous and clear cell EC have better prognostic features similar to G3EAC for only stage 1 [27]. Soslow et al. [28] performed a comparison analysis among the G3 EAC (n = 89), serous EC (n = 61), and clear cell EC (n = 37) cases and they reported that there was no significant difference in the prognosis between these groups.

If we look at the studies comparing UCS with other HGEAC, our study showed a poorer prognosis in UCS. The groups were similar in terms of OS, however, in accordance with the literature, DFS was significantly shorter in UCS than the others groups. Previous studies compared the prognosis of UCS with G3 EAC [19–21, 29] and high-risk

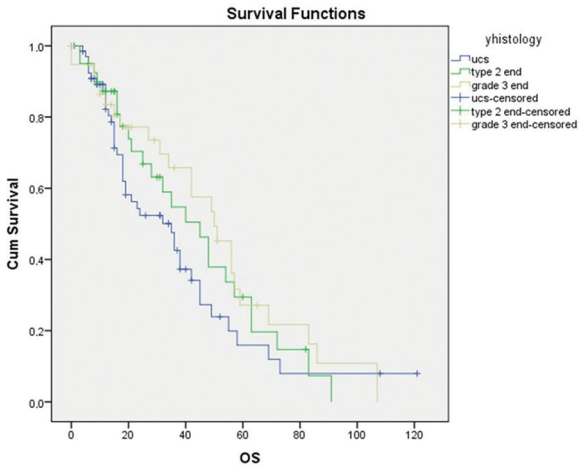


Figure 1. The comparison analysis of overall survival (OS) of the studied groups (ucs: uterine carcinosarcoma; Type 2 and: Type 2 endometrial cancer; Grade 3 and: Grade 3 endometrioid adenocarcinomas)

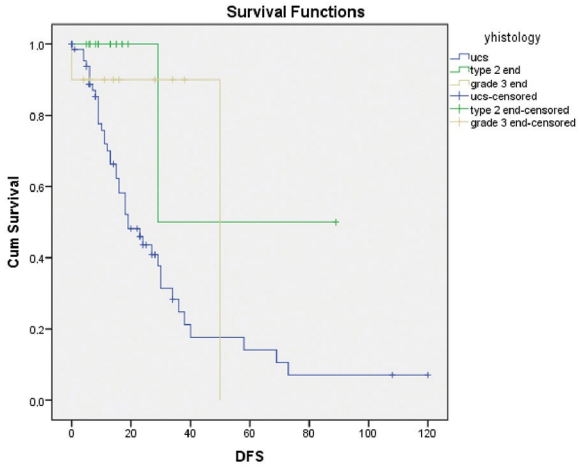


Figure 2. The comparison analysis of disease-free survival (DFS) of the studied groups (ucs: uterine carcinosarcoma; Type 2 and: Type 2 endometrial cancer; Grade 3 and: Grade 3 endometrioid adenocarcinomas)

endometrial cancer type including serous, clear, HGEAC [22, 30–32]. In a large scale study, a poorer five-year survival rate was found for all stages of UCS [19]. However, in another study similar results were reported for UCS with others [22].

There are four studies in the literature comparing the G3 EAC, type 2 EC, and UCS [22, 30, 34, 35]. Felix et al. compared the 81 UCS, 254 G3 EAC, 73 clear cell EC, and 147 serous EC cases. They showed similar results for the OS and recurrence free survival among the groups by the stratified stages [22]. The other study was performed by Amant et al. [30]. They evaluated 50 cases with G3 EAC, 54 cases with serous or clear cell EC, and 33 cases with UCS. The worst prognosis in this study was found in the UCS group, consistent with the results of other studies [34, 35]. However, in our study, this difference did not reach a statistically significant level. Amant et al. reported that the LNI was found higher in the UCS group than the others. There is also a significant difference among the groups in terms of LNI in the Felix et al. study [26]. LNI was not found different among the groups in our study. We found the positive cytology rate higher in the type 2 EC (20%) and UCS (18%) group compared to the G3 EAC (2%) group ($p = 0.024$). This rates were reported as 30% for UCS, 18.6% for type 2 EC, and 11.6% for G3 EAC group in the Amant et al.'s study ($p = 0.14$) [30]. While there was no difference in our study in terms of stage, the other two studies found a significant difference for the stages among the groups [22, 30]. In our study, there was a significant difference between groups in terms of adjuvant treatment options. While chemotherapy was the main adjuvant option in the type 2 EC group and the UCS group, radiotherapy was the main adjuvant treatment option in the G3 EAC group. Similar results were reported in the Felix et al study. But Amant et al. did not evaluated the adjuvant therapy option [30].

Although we had a relatively good number of cases (for only one center), more cases are needed to reveal differences in prognosis. Our evaluation was meant to reveal clinicopathological differences not only in terms of prognosis. It would not be appropriate to discuss the results of adjuvant therapy in these patient numbers. It is not easy to reach a conclusion for the studies on relatively rare group tumors. As a matter of fact, heterogeneity is high at the molecular level even in a single group [13, 14–17]. Increasing molecular studies show that these groups are very different tumors and therefore exhibit different clinical and prognosis.

CONCLUSIONS

As a conclusion, We did not show a significant difference among the groups in terms of prognosis, but there were differences among the groups in terms of prognostic clinical-pathological features. A better understanding of these tumors at the molecular level will allow them to be better managed.

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Table 2. The comparison of the clinic/pathologic characterizations and survival [no reference in the text]

	Group 1 HGEAC (n = 62)	Group 2 Type 2 EAC (n = 93)	Group 3 UCS (n = 80)	p*
Stage				
1	32 (52%)	39 (42%)	44 (55%)	0.340
2	5 (8%)	14 (15%)	5 (6%)	
3	22 (35%)	35 (27%)	29 (36%)	
4	3 (5%)	5 (6%)	2 (3%)	
Myometrial invasion				
0				
< 50%	2 (3%)	18 (19%)	5 (6%)	0.001
≥ 50%	18 (%29)	34 (37%)	30 (40%)	
	42 (68%)	41 (44%)	45 (56%)	
LVSI				
-	14 (23%)	30 (32%)	29 (36%)	0.071
+	48 (77%)	63 (68%)	51 (64%)	
Nodal involvement	(n = 46)	(n = 70)	(n = 73)	
0	28 (60%)	49 (70%)	38 (52%)	
Pelvic	9 (20%)	8 (11%)	16 (22%)	0.139
Pelvic + PA	9 (20%)	13 (19%)	22 (30%)	
Cytology	n = 48	n = 65	n = 76	
negative	47%	54%	62%	0.024
positive	1 (2%)	11(17%)	14 (18%)	
Adjuvant therapy				
Chemotherapy	27 (44%)	65 (70%)	55 (69%)	0.002
Radiotherapy	48 (77%)	41 (44%)	37 (33%)	0.001
OS [month] median ± SD	50.0 ± 6.2	45.0 ± 7.3	35.0 ± 7.5	0.290
DS [month]	45.0 ± 6.7	29.0 ± 5.6	19 ± 3.7	0.019

HGEAC — high grade endometrioid adenocarcinoma; Type 2 EC — type 2 endometrial cancer; UCS — utrerine carcinosarcoma; LVSI — lymphovascular space invasion; OS — overall survival; DFS — disease free survival; p*— The p values obtained by comparing all 3 groups using the one-way Anova test

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