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High-grade endometrial stromal sarcoma versus undifferentiated uterine sarcoma: a Turkish uterine sarcoma group study-001

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Abstract

Objective Prognostic factors associated with high-grade endometrial stromal sarcoma (HGESS) and undifferentiated uterine sarcoma (UUS) have not been distinctly determined due to the repetitive changes in the World Health Organization (WHO) classification. We aimed to compare clinicopathologic features and outcomes of patients with HGESS with those of patients with UUS.

Methods A multi-institutional, retrospective, cohort study was conducted including 71 patients, who underwent surgery at 13 centers from 2008 to 2017. An experienced gynecopathologist from each institution re-evaluated the slides of their own cases according to the WHO_{2014} classification. Factors associated with refractory/progressive disease, recurrence or death were examined using logistic regression analyses. Kaplan–Meier method and log-rank test were used for survival comparisons.

Results The median disease-free survival (DFS) for HGESS and UUS was 12 months and 6 months, respectively. While the median overall survival was not reached in HGESS group, it was 22 months in the UUS group. Kaplan–Meier analyses revealed that patients with UUS had a significantly poorer DFS than those with HGESS ($p=0.016$), although OS did not differ between the groups ($p=0.135$). Lymphovascular-space involvement (LVSI) was the sole significant factor associated with progression, recurrence or death for HGESS (Hazard ratio: 9.353, 95% confidence interval: 2.539–34.457, $p=0.001$), whereas no significant independent factor was found for UUS.

Conclusions UUS has a more aggressive behavior than HGESS. While no significant predictor of prognosis was found for UUS, LVSI is the sole independent prognostic factor for HGESS, with patients 9.3 times more likely to experience refractory/progressive disease, recurrence or death.

Keywords High-grade endometrial stromal sarcoma · Undifferentiated uterine sarcoma · Prognostic factors · Survival

Introduction

High-grade endometrial stromal sarcoma (HGESS) and undifferentiated uterine sarcoma (UUS) are the least described types of uterine sarcomas given the rarity of these tumors, as well as the repetitive changes in the World Health Organization (WHO) classification [1, 2]. According to the WHO_{2003} classification, endometrial stromal tumors were classified as endometrial stromal nodule, low-grade endometrial stromal sarcoma (LGESS), and undifferentiated endometrial sarcoma [1]. The WHO_{2003} classification ignored the term of HGESS, and endometrial stromal sarcoma was limited to LGESS, with cytologically bland spindle cells resembling those of proliferative phase endometrial stroma [1].

Based on the discoveries of underlying molecular alterations, a significant change took place in the WHO_{2014} classification [2]. The term "HGESS" was reintroduced in the classification as a distinct entity while the term "*undifferentiated endometrial sarcoma*" was replaced with UUS. Thus, endometrial stromal tumors were re-classified as endometrial stromal nodule, LGESS, HGESS, and UUS [2]. UUS is characterized by infiltrative sheets of pleomorphic epithelioid and/or spindle cells and lacking a specific line of differentiation, whereas HGESS has features that are intermediate between LGESS and UUS [2].

HGESS and UUS have been discovered to have mutations with unifying features, which also have several morphologic

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implications. If classified based on those genetic alterations, several subgroups such as *YWHAE-NUTM2 fusion-positive HGESS*, *ZC3H7B-BCOR fusion-positive HGESS*, *BCOR-internal tandem duplication (ITD)-positive HGESS*, *NUTM2 and ZC3H7B-BCOR fusion-positive HGESS* and *SMARCA4-deficient UUS* appear [3, 4]. However, it seems impossible to integrate a classification based on molecular features into clinical daily practice since molecular testing would not be available at most pathology laboratories worldwide.

Because of the changes in the terminology, it has been difficult to study HGESS and UUS separately. There are only five studies reporting on more than ten patients in the literature [5–9], with the largest series having only 39 patients with HGESS or UUS [9]. Although poor prognosis seems to be a constant feature in all previous studies with an approximately 25% of 5-year overall survival (OS) rate [5–8], prognostic factors associated with HGESS and UUS have not been clearly delineated. In the current study, we conducted a multi-institutional, retrospective, cohort study to compare clinicopathologic features and disease outcomes in patients with HGESS and UUS. To the best of our knowledge, this is one of the largest series that reported the outcomes of HGESS and UUS, with 71 patients in total.

Materials and methods

Study population and data

The study population included patients with postoperative histopathological diagnoses of HGESS or UUS, who underwent surgery with a curative intent at 13 gynecologic oncology centers from January 2008 to December 2017. Clinicopathologic and survival data involving preoperative imaging, surgical procedures, tumor histotype, tumor size, number of mitoses per 10 high-power fields (HPFs), lymphovascular space involvement (LVSI), adnexal involvement, omental metastasis, lymph node metastasis, peritoneal cytology, stage of the disease, adjuvant therapies, disease status on or after primary therapy, disease recurrence, length of follow-up and survival status were extracted from each institution's database following Institutional Review Board's approval. Each patient included in the study provided an informed consent regarding use of her medical records.

An experienced gynecopathologist from each institution re-evaluated the slides of their own cases according to the WHO_{2014} classification before including them in the study. Immunohistochemical studies including cyclin-D1, c-kit, CD10, h-caldesmon, SMA, desmin, DOG1, ER, PR, Ki67, keratin, and EMA were performed to classify tumors more precisely. However, molecular testing for *YWHAE-NUTM2*, *ZC3H7B-BCOR* or *BCOR-ITD* was not performed routinely to confirm the diagnosis. In the current study, UUS represented a diagnosis of exclusion which failed to fulfill the morphological and immunohistochemical criteria for smooth muscle or endometrial stromal differentiation [2]. The criteria for diagnosis of HGESS were stated as marked mitotic activity, loss of ER and PR, diffuse and strong expression of cyclin-D1 and c-kit while being negative for smooth muscle markers, DOG1, EMA and cytokeratin [2, 3]. The FIGO2009 (International Federation of Gynecology and Obstetrics) staging system was employed for staging purposes [10].

Patients whose histopathological diagnoses were revised to other pathologies, patients who received neoadjuvant chemotherapy, and patients with incomplete medical records were excluded as well as those with synchronous malignancies.

Data analysis

Continuous variables were expressed as medians and ranges; binary variables were reported as counts and percentages. Refractory or progressive disease was defined as stabile disease or progression on or after primary therapy without ever sustaining a complete clinical and radiological response. Recurrence was defined as documentation of relapse of the tumor after a disease-free interval of ≥ 3 months. Univariate analyses were performed to determine factors associated with refractory/progressive disease, recurrence or death. Variables with a p value < 0.25 in univariate analyses were included in the backward stepwise Cox proportional hazard models for multivariate analyses. Kaplan–Meier method was used to generate survival curves, and the log-rank test was performed for detecting differences between curves. Disease-free survival (DFS) was defined as the duration in months between the date of surgery and the date of first recurrence or death from any cause, whichever occurred first, or the date of last visit for patients alive without disease. Patients alive with no evidence of disease were censored at the date they were last known to be alive in DFS analyses. The duration in months between the date of surgery and the date of death from any cause or the date of last contact was defined as OS. Patients alive at the last known follow-up were censored in OS analyses.

Results

During the study period, a total of 659 uterine sarcomas were treated at participating centers. Of those, 84 had a diagnosis of HGESS or UUS. Thirteen patients were excluded from the analysis: four had different diagnosis after review of the slides, four had neoadjuvant chemotherapy, one had synchronous malignancy, and four had incomplete medical records. Thus, final analyses were performed in a total of 71

patients, involving 26 patients with HGESS and 45 patients with UUS.

Table 1 presents immunohistochemistry characteristics of patients. Staining with ER and PR were identified in 42.3% and 38.5% of patients with HGESS, respectively, whereas there was no staining with ER or PR in the UUS group. CD10 was positive in 30.8% and 71.1% of patients with HGESS and UUS, respectively. While all patients with HGESS showed positivity for staining with cyclin D1, this rate was only 8.9% for patients with UUS. In the UUS group, there were no staining with desmin, caldesmon, and SMA, whereas 34.6%, 38.5%, and 26.9% of patients with HGESS were positive with desmin, caldesmon, and SMA, respectively.

Table 2 compares clinical and pathological features of patients. Study groups were comparable for median age (57 vs. 58 years, $p=0.531$), tumor size (7 vs. 9 cm, $p=0.171$), surgical procedures, number of mitoses (19 vs. 17, $p=0.718$), and adjuvant therapies ($p=0.792$). Although not statistically significant, prominent tumor necrosis (77.8% vs. 95.2%), LVSI (50% vs. 60%), adnexal involvement (12.5% vs. 34.9%), LN metastasis (11.8% vs. 32.4%), omental metastasis (17.6% vs. 29.4%), positive peritoneal cytology (7.7% vs. 22.2%), and extrauterine disease (42.3% vs. 60.0%) were identified more in patients with UUS than in patients with HGESS.

The median follow-up time was 19 months (range, 1–89 months) for both groups. Among 71 patients, there were 10 patients with refractory/progressive disease [1 (3.8%) in the HGESS group vs. 9 (20.0%) in the UUS group, $p=0.059$)], 42 patients with disease recurrence [14 (53.8%) in the HGESS group vs. 28 (62.2%) in the UUS group, $p=0.071$)], and 42 deaths [12 (46.2%) in the HGESS group vs. 30 (66.7%) in the UUS group, $p=0.090$)]. The median DFS for HGESS and UUS was 12 months [95% confidence interval (CI) 3.19–20.80] and 6 months (95% CI 4.81–7.18), respectively. While the median OS was not reached in HGESS group, it was 22 months (95% CI 7.08–36.91) in the UUS group (Table 2). Kaplan–Meier analyses revealed that patients with UUS had a significantly poorer DFS than those with HGESS ($p=0.016$), (Fig. 1a) although OS did not differ between HGESS and UUS ($p=0.135$), (Fig. 1b).

Analyses of factors associated with refractory/progressive disease, recurrence or death for HGESS and UUS were presented in Table 3 and Table 4, respectively. In univariate analyses, positive LVSI and stage of the disease were found to be as significant factors both for HGESS and UUS. In multivariate analyses, however, LVSI [Hazard Ratio (HR): 9.353, 95% CI 2.539–34.457, $p=0.001$)] remained to be sole significant factor associated with progression, recurrence or death for HGESS (Table 3), whereas no statistically significant independent factor was found for UUS (Table 4).

Table 1 Immunohistochemistry characteristics of patients

	HGESS ($N=26$)	UUS ($N=45$)
ER (+)	11 (42.3)	0 (0)
PR (+)	10 (38.5)	0 (0)
CD10 (+)	8 (30.8)	32 (71.1)
Cyclin D1 (+)	26 (100)	4 (8.9)
Desmin (+)	9 (34.6)	0 (0)
Caldesmon (+)	10 (38.5)	0 (0)
SMA (+)	7 (26.9)	0 (0)
Ki 67 ≥ 10%	3 (11.5)	45 (100)

HGESS high-grade endometrial stromal sarcoma, *UUS* undifferentiated uterine sarcoma, *ER* estrogen receptor *PR* progesterone receptor, *SMA* smooth muscle actin

Values are given as *N* (%)

Discussion

Since the classification of uterine sarcomas differs before and after 2014, the data coming from the studies published before 2014 cannot be applied to the studies performed after 2014 thoroughly. The terminology used in the studies published between 2003 and 2014 particularly deserves attention that "*high-grade undifferentiated sarcoma*" term was used persistently in some reports [5, 11, 12], whereas others preferred to use the official term of "*undifferentiated endometrial sarcoma*" suggested by the WHO_{2003} classification [7, 13]. Another issue that needs to be addressed is whether the WHO_{2003} classification that eliminated the HGESS category has simply substituted "*undifferentiated endometrial sarcoma*" in its place. It is not surprising to observe that some recent studies are still using the former classifications because of the ambiguous criteria for histological diagnoses as well as the time interval during which the patients were included [14]. The terminologically chaotic environment has forced the researchers to handle HGESS and UUS together instead of studying them separately [9]. In the current study, however, we preferred to study HGESS and UUS separately, as they have distinct pathologic and molecular features, and there is a clear need for determining the clinical behavior of these tumors.

"*High-grade/undifferentiated sarcoma*" has been reported to be the rarest type of endometrial stromal tumors [15]. In a more recent study, Abeler et al. reported that "*high-grade undifferentiated sarcoma*" accounted for only 6% of all uterine sarcomas [16]. In different series, the prevalence of "*high-grade/undifferentiated sarcoma*" has been reported to be as low as 3% and as high as 19% [7, 17]. In the current study, we found the prevalence of HGESS and UUS as 4.0% (26/646) and 6.9% (45/646), respectively.

Table 2 Clinical and pathological findings of patients

	HGESS ($N=26$)	UUS ($N=45$)	p
Age, median (range), years	57 (21–84)	58 (19–81)	0.531
Surgery, *N* (%)			
Total hysterectomy	26 (100)	45 (100)	–
Bilateral salpingo-oophorectomy	24 (92.3)	43 (95.6)	0.567
Lymphadenectomy	17 (65.4)	37 (82.2)	0.109
Pelvic	5 (19.2)	11 (24.4)	
Pelvic-paraaortic	12 (46.2)	26 (57.8)	
Number of LNs removed, median (range)	29 (6–76)	35 (9–87)	0.320
Omentectomy	17 (65.4)	34 (75.6)	0.359
Tumor size, cm, median	7 (2–17)	9 (1.5–30)	0.171
Number of mitoses (/10HPF), median (range)	19 (4–40)	17 (9–130)	0.718
Prominent tumor necrosis, *N* (%)	14/18 (77.8)	20/21 (95.2)	0.104
Lymphovascular space invasion, *N* (%)	13 (50.0)	27 (60.0)	0.413
Adnexal involvement, *N* (%)	3/24 (12.5)	15/43 (34.9)	0.070
LN metastasis, *N* (%)	2/17 (11.8)	12/37 (32.4)	0.107
Omental metastasis, *N* (%)	3/17 (17.6)	10/34 (29.4)	0.363
Positive peritoneal cytology, *N* (%)	2 (7.7)	10 (22.2)	0.116
Extrauterine disease, *N* (%)	11 (42.3)	27 (60)	0.150
FIGO2009 stage, *N* (%)			0.065
Stage I	15 (57.7)	18 (40.0)	0.150
IA	6 (23.1)	2 (4.4)	
IB	9 (34.6)	16 (35.6)	
Stage II	4 (15.4)	4 (8.9)	0.404
IIA	1 (3.8)	3 (6.7)	
IIB	3 (11.5)	1 (2.2)	
Stage III	7 (26.9)	22 (48.9)	0.070
IIIA	2 (7.7)	1 (2.2)	
IIIB	3 (11.5)	9 (20.0)	
IIIC	2 (7.7)	12 (26.7)	
Stage IVA	–	1 (2.2)	
Adjuvant therapy, *N* (%)	20 (76.9)	34 (75.6)	0.792
Radiotherapy	11 (42.3)	11 (24.4)	0.104
Chemotherapy	16 (61.5)	32 (71.1)	0.449
Follow-up, months, median (range)	19 (7–70)	19 (1–89)	0.981
Disease status on/after primary treatment, *N* (%)			
Refractory/progressive disease	1 (3.8)	9 (20.0)	0.059
Recurrence	14 (53.8)	28 (62.2)	0.071
Time to recurrence, months, median (range)	7 (3–17)	6 (3–27)	0.443
Disease-free survival, months, median, 95% CI	12 (3.192–20.808)	6 (4.819–7.181)	**0.016**
18 months, %	42.0	25.8	
Death, *N* (%)	12 (46.2)	30 (66.7)	0.090
Overall survival, months, median, 95% CI	Not reached	22 (7.089–36.911)	0.135
18 months, %	65.0	54.1	

HGESS high-grade endometrial stromal sarcoma, *UUS* undifferentiated uterine sarcoma, *LN* lymph node, *HPF* high-power fields, *FIGO* International Federation of Gynecology and Obstetrics, *CI* confidence interval

Bold values denote statistical significance at the $p<0.05$ level

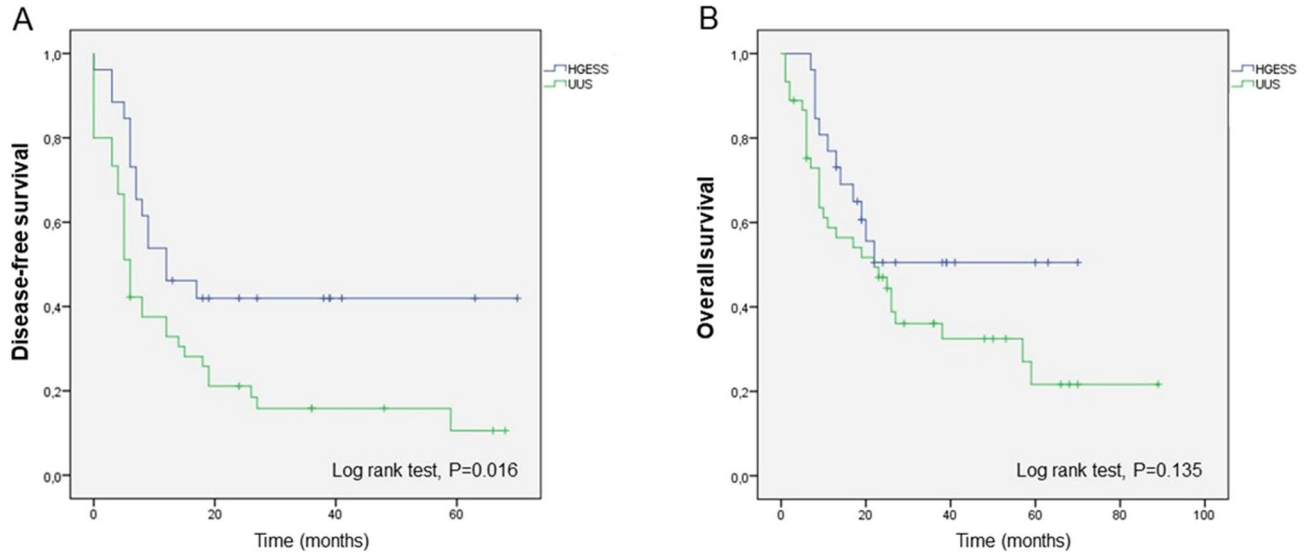

Fig. 1 Survival comparison between high-grade endometrial stromal sarcoma (HGESS) and undifferentiated uterine sarcoma (UUS) **a** Disease-free survival **b** Overall survival

Table 3 Factors associated with progression, recurrence or death for high-grade endometrial stromal sarcoma ($N=26$)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age, years	0.991	0.961–1.021	0.538	–	–	–
Tumor size, cm	1.096	0.954–1.259	0.193	–	–	–
Number of mitoses/10 HPF	1.023	0.959–1.090	0.492	–	–	–
Tumor necrosis (no vs. yes)	1.461	0.314–6.786	0.629	–	–	–
LVSI (no vs. yes)	9.353	2.539–34.457	**0.001**	9.353	2.539–34.457	**0.001**
Lymphadenectomy (no vs. yes)	0.523	0.185–1.474	0.220	–	–	0.210
Omentectomy (no vs. yes)	0.654	0.232–1.841	0.421	–	–	–
FIGO stage				–	–	–
Stage I	1	–	**0.002**	–	–	0.092
Stage II	13.971	3.092–63.122	**0.001**	–	–	–
Stage III	3.640	1.104–12.005	**0.034**	–	–	–
Stage I vs. ≥ II	4.859	1.633–14.455	**0.004**	–	–	–
Adjuvant treatment (no vs. yes)	1.073	0.302–3.805	0.914	–	–	–

HR hazard ratio, *CI* confidence interval, *HPF* high-power fields, *LVSI* lymphovascular space involvement, *FIGO* International Federation of Gynecology and Obstetrics

Bold values denote statistical significance at the $p<0.05$ level

The recommended surgical treatment of uterine sarcomas is total hysterectomy and BSO and additional resection for extrauterine disease based on disease extent and resectability [4]. The evidence for or against lymphadenectomy is inadequate for the treatment of HGESS and UUS [11, 18]. Seagle et al. reported that 19.8% of patients with HGESS have lymph node metastasis, and omission of lymphadenectomy in that group of patients was an independent adverse prognostic factor [18]. Similarly, Malouf et al. reported that 18% of patients with "*undifferentiated endometrial sarcoma*" have positive nodal status [7]. On the other hand, considering stage as an important prognostic factor [9], although lymph node involvement is expected to be associated with a poorer prognosis, it has been reported that patients without lymphadenectomy had similar survival compared to those with positive nodes [18]. The overall rate of lymph node metastasis was 19.7% (14/71) in our study, which is comparable with those of previous studies [7, 18, 19]. However, when the nodal status was examined with respect to tumor histotype, lymph

Table 4 Factors associated with progression, recurrence or death for undifferentiated uterine sarcoma ($N=45$)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age, years	1.008	0.982–1.034	0.560	–	–	–
Tumor size, cm	1.005	0.951–1.063	0.846	–	–	–
Number of mitoses/10 HPF	0.988	0.962–1.014	0.361	–	–	–
Tumor necrosis (no vs. yes)	0.200	0.022–1.789	0.150	–	–	0.334
LVSI (no vs. yes)	2.512	1.227–5.146	**0.012**	–	–	0.274
Lymphadenectomy (no vs. yes)	0.974	0.426–2.227	0.950	–	–	–
Omentectomy (no vs. yes)	0.828	0.400–1.715	0.612	–	–	–
FIGO stage				–	–	–
Stage I	1	–	**0.048**	–	–	0.681
Stage II	2.264	0.609–8.411	0.222	–	–	–
Stage III	2.345	1.144–4.810	**0.020**	–	–	–
Stage IV	9.831	1.146–84.375	**0.037**			
Stage I vs. ≥ II	2.388	1.182–4.825	**0.015**	–	–	–
Adjuvant treatment (no vs. yes)	0.670	0.313–1.431	0.301	–	–	–

HR hazard ratio, *CI* confidence interval, *HPF* high-power fields, *LVSI* lymphovascular space involvement, *FIGO* International Federation of Gynecology and Obstetrics

Bold values denote statistical significance at the $p<0.05$ level

node positivity rates for HGESS and UUS were found to be as 11.8% and 32.4%, respectively. In contrast with the previous studies [7, 18, 19], we report a higher rate of lymph node positivity with UUS and lower rate with HGESS. This is probably due to the differences in the diagnostic criteria and classification systems used between the current and previous studies, and thereby, due to the histological heterogeneity of the previous studies.

The role of adjuvant therapy for HGESS and UUS is unclear [4, 12]. External beam radiotherapy (EBRT) with or without brachytherapy has been shown to be related with improved DFS and OS in one of the retrospective series [7]. Another study suggested that EBRT may have a role in local–regional control of the disease in patients without residual disease [12]. However, because of the scarcity and heterogeneity of available evidence, it is not possible to draw a definitive conclusion on the survival impact of adjuvant radiotherapy in patients with HGESS or UUS. As the recurrence patterns of patients with HGESS and UUS are reportedly distant and visceral [11, 12], adjuvant chemotherapy may be a reasonable choice particularly in patients with stage ≥ II disease [4]. Although there are no solid data in favor of adjuvant chemotherapy, the combinations of doxorubicin and iphosphamide as well as gemcitabine plus docetaxel have been shown to act against "*high-grade undifferentiated uterine sarcomas*" [20]. When the data from the SARCGYN study are extrapolated to HGESS and UUS [21], it is also possible to suggest adjuvant chemotherapy followed by EBRT as the adjuvant treatment strategy for these tumors [4, 12]. Nonetheless, it is evident that there is an urgent need for better adjuvant treatment modalities given the poor survival outcomes being almost constant for the recent two decades.

Despite extensive surgery and adjuvant therapies, the prognosis is still poor in HGESS and UUS, with the 5-year OS rate ranging from 25 to 31% [9, 12]. Tanner et al. reported the median progression-free survival and OS for 21 patients with "*high-grade undifferentiated uterine sarcoma*" as 7.3 months and 11.8 months, respectively [5]. The corresponding figures were 9.7 months and 23 months, respectively, in another single-institutional study including 30 patients with "*undifferentiated endometrial sarcoma*" treated over a period of 30 years [7]. In the most recent study including 39 patients with localized HGESS or UUS from the French Sarcoma Group, the median DFS and OS were 23 and 32 months, respectively [9]. In the current study, when considering all patients together, the median DFS and OS were 8 months (95% CI 5.67–10.32) and 23 moths (95% CI 16.15–29.84) respectively, nearly identical to those reported by Malouf et al. [7]. However, when we analyze tumor histotypes separately, the median DFS for HGESS and UUS was 12 months and 6 months, respectively. While the median OS was not reached in HGESS group, it was 22 months in the UUS group. Based on our results, patients with UUS had a significantly poorer DFS than those with HGESS ($p=0.016$) although OS did not differ between HGESS and UUS ($p=0.135$).

Prognostic factors associated with HGESS and UUS have not been distinctly determined as there are no consistent data due to the scarcity of those tumors. The present study revealed LVSI as the sole independent prognostic factor for patients with HGESS. According to our findings, HGESS

patients with LVSI are 9.3 times more likely to have refractory/progressive disease, recurrence or death. Contrarily, we found no statistically significant independent prognostic factor for patients with UUS. Similarly, Gynecologic Cancer InterGroup (GCIG) reported no evident prognostic factor for "*high-grade undifferentiated sarcoma*" [12]. Even FIGO stage has been reported to have no prognostic significance, [5, 7, 11, 12] as well as the American Joint Committee on Cancer classification [22]. However, some other studies reported various prognostic factors for decreased OS or DFS including adjuvant radiotherapy [7], adjuvant chemotherapy [9], FIGO stage [9], performance status [9], LVSI [9], age [18], tumor size [18], omission of lymphadenectomy [18], positive margins [18], mitotic activity (> 25 mitoses/10 HPF) [23], and prominent necrosis [24].

The reader certainly should note the limitations of the current study including the lack of a central pathology review, the nature of the study being both multicenter and retrospective, and the inevitable variation among those multiple centers in the decision-making processes and the selection of patients for different adjuvant therapies. It is undeniable that a comprehensive central pathology review would have been beneficial; however, the cases enrolled in the presented study are reflective of the "real-world" diagnoses and practices. Unfortunately, the majority of our patients did not undergo molecular testing, but for almost all cases, the morphological and immunohistochemical characteristics were sufficiently straightforward and adequate to make an accurate pathological diagnosis. On the other hand, the study has notable strengths that include relatively high number of enrolled patients with HGESS and UUS, the surgeries having been performed by gynecologic oncologists, and a study interval in which modern treatment applications of medical oncology and radiation oncology existed.

Conclusion

UUS is a more aggressive tumor than HGESS. Although both histotypes have comparable OS, patients with UUS have a significantly poorer DFS than those with HGESS. While no significant independent predictor of prognosis was found for UUS, LVSI was found to be the sole independent prognostic factor for HGESS, with patients 9.3 times more likely to experience refractory/progressive disease, recurrence or death. The findings should be validated in further studies involving larger number of patients.

Author contribution AA: protocol/project development, supervision. MT: data collection or management. NB: data collection or management. GK: data collection or management. MG: data collection or management. TS: data collection or management. OO: data collection or management, manuscript editing. TT: data collection or management, data analysis, manuscript editing. IY: data collection or management, data analysis. MMM: protocol/project development, manuscript writing, supervision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest and nothing to disclose.

Ethical approval This study has been approved by the Ethics Committee of the Saglik Bilimleri University, Ankara City Hospital (Date: 06/01/2020, Decision no.: 10). This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all patents.

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