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Original Article

Clinicopathological characteristics, treatment and outcomes in uterine carcinosarcoma and grade 3 endometrial cancer patients: a comparative study

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ABSTRACT

Objective: Uterine carcinosarcoma (UCS) shared the same staging system with endometrial carcinoma in the International Federation of Gynecology and Obstetrics 2009. The aim of the present study was to compare the clinicopathological and prognostic characteristics between UCS and grade 3 endometrioid endometrial carcinoma (G3EC).

Methods: A retrospective analysis of 60 UCS and 115 G3EC patients with initial treatment at the Department of Gynecology in the Fudan University Shanghai Cancer Center between February 2006 and August 2013. Chi-square analysis was used to compare differences between variables. Prognostic factors were determined using univariate/multivariate analysis, and the survival rates were assessed using the Kaplan-Meier method. The Cox regression model was used to assess the independent prognostic factor.

Results: UCS had significantly worse overall survival (OS) compared with G3EC. Carcinosarcoma subtype was an independent factor (hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.0 to 5.8; p=0.039), stratified based on stage. Compared with G3EC, UCS patients had a greater incidence of ascites fluid (55.0% vs. 15.7%, p<0.001) and adnexal involvement (20.0% vs. 8.7%, p=0.048) and larger median tumor volume (4.6 cm vs. 4.0 cm, p=0.046). Subgroup analysis of the prognostic factors revealed that UCS patients exhibited worse OS than G3EC patients in such specific subgroups as patients at younger ages, with postmenopausal status, without ascites fluid, with early stage diseases, without vagina invasion, without lymph node metastases and receiving adjuvant chemo/radiotherapy. Adjuvant radiotherapy with chemotherapy was predictive of better survival in UCS patients compared with chemotherapy or radiotherapy alone (5-year OS, 71.0% vs. 35.8%, p=0.028). Multivariate Cox regression revealed that tumor mesenchymal component (HR, 4.6; 95% CI, 1.4 to 15.8; p=0.014) was an independent prognostic factor for UCS, whereas advanced stages (HR, 5.9; 95% CI, 1.0 to 33.9; p=0.046) and ascites fluid (HR, 5.1; 95% CI, 1.1 to 22.7; p=0.032) were independently correlated with poor prognosis for G3EC patients.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Conclusion: The distinctions in both clinicopathological and prognostic characteristics between UCS and G3EC suggest that this subtype should be treated separately from high-risk epithelial endometrial carcinoma.

Keywords: Grade 3 Endometrioid Endometrial Carcinoma; Multivariate Analysis; Univariate Analysis; Uterine Carcinosarcoma

INTRODUCTION

Uterine carcinosarcomas (UCSs), also called malignant mixed Müllerian tumors (MMMTs) of the uterus, are a rare but aggressive form of endometrial cancer, comprising both malignant epithelial and mesenchymal components. The mesenchymal component is either homologous or heterologous. Homologous sarcoma comprises tissue that is native to the Müllerian duct, such as endometrial stromal sarcoma, fibrosarcoma or leiomyosarcoma. Cartilaginous, osteosarcomatous, liposarcomatous, and rhabdomyosarcomatous differentiations are commonly observed in heterologous elements. Although UCS accounts for less than 5% of all uterine malignancies, the 5-year overall survival (OS) rate for this subtype is extremely low, ranging from 10% to 47% [1-3].

UCS was traditionally classified in the sarcoma category because of the sarcomatous component. However, molecular and genetic research has demonstrated that UCS is distinct from sarcoma, and the carcinomatous component induces the observed tumor aggressiveness and metastasis. Recent data have suggested that the origin of UCS is monoclonal, and UCS should be best categorized as a de-differentiated uterine carcinoma rather than as a sarcoma [4,5]. Furthermore, evidence showed that UCS metastasizes via the lymphatic system instead of the blood system, which is the primary pattern of spread in sarcoma subtypes. As a result, the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging guidelines suggest that UCS should be staged according to carcinomas of the endometrium [6].

MATERIALS AND METHODS

In the present study, we performed a retrospective analysis including 60 UCS and 115 grade 3 endometrioid endometrial carcinoma (G3EC) consecutive patients who underwent primary surgery between February 2006 and August 2013 at Fudan University Shanghai Cancer Center. Patients who underwent secondary cytoreductive surgery were excluded. Informed consent was obtained from all individual participants included in the present study. Gynecologic pathologists reviewed all pathological slides to confirm the diagnosis.

We retrospectively collected demographic and clinicopathological data from the medical records, which included age at diagnosis, parity, menopause state, body mass index (BMI), presence of ascites fluid, tumor stage, family history of malignancy, pretreatment cancer antigen 125 serum level, tumor size, myometrial invasion, lymph-vascular space involvement (LVSI) and nerve invasion, and lymph node metastasis.

The data on surgical procedures and adjuvant treatment were also analyzed. Twenty-three UCS and 38 G3EC patients with stage IIIc-IVb diseases received cytoreductive surgery.

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Optimal cytoreduction was defined as tumors with the maximal diameter of the largest residual tumor nodule measuring less than 1 cm at the completion of the primary operation. OS was evaluated and defined as the time between the dates of diagnosis and death by the tumor or the last follow-up visit.

Survival curves were calculated using the Kaplan-Meier method. Kaplan-Meier survival curves were generated, and the survival differences were quantified using the log-rank test (univariate analysis). The Cox regression model (multivariate analysis) was used to analyze independent prognostic factors. Forest plots were introduced as subgroup analyzes for comparing the prognostic differences between these two malignant endometrial carcinomas (EC). Statistical tests were considered significant at $p<0.05$. All analyzes were performed using SPSS ver. 20.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Demographic and clinical features

The median ages of UCS and G3EC patients at diagnosis were 59.5 years (interquartile range [IQR], 53 to 61 years) and 56 years (IQR, 55 to 66 years), respectively, and the values showed statistical significance (p=0.019). Among all patients participating in the present study, 49 UCS patients (81.7%) and 85 G3EC patients (73.9%) experienced menopause, without significant difference (p=0.250). Of the UCS and G3EC patients, the median BMI values were 20.7 kg/m^2 (range, 16.2 to 31.5 kg/m^2) and 22.5 kg/m^2 (range, 15.4 to 33.4 kg/m^2), respectively (p>0.05).

Both UCS and G3EC patients had chief complaints of abnormal vaginal bleeding and/or vaginal discharge. Three UCS (5.0%) and five G3EC patients (4.3%) complained of hypogastric pain; fatigue and anorexia were observed in one UCS patient (1.7%) and three G3EC patients (2.6%). Ascites fluid was observed in 33 UCS and 18 G3EC patients (p<0.001) (**Table 1**).

2. Treatment

Radical/subradical abdominal hysterectomy was the first choice of therapy in all patients with uterine malignancies. Fifty-one UCS patients (85.0%) accepted additional pelvic lymphadenectomy, and 34 patients (56.7%) accepted para-aortic lymphadenectomy when suspected intraoperatively. Among the G3EC patients, 107 patients (93.0%) received pelvic lymphadenectomy and/or omentectomy, and para-aortic lymphadenectomy was conducted in 102 patients (88.7%). Among all of the patients, 23 UCS (45.1%) and 38 G3EC patients (33.0%) had stage IIIc-IVb diseases and received additional cytoreduction surgery, whereas 31 patients (50.8%) received additional extensive surgical procedures, including omentectomy (n=27), appendectomy (n=18), rectum resection (n=1), and peritoneal stripping (n=1). Complete gross resection (R0) was achieved in 36 patients (59.0%), whereas 16 (26.2%) were left with residual diseases, showing tumor nodule diameters of no more than 1 cm, and nine patients (14.8%) were left with residual diseases, showing tumor nodule diameters of more than 1 cm. Patients who accepted complete gross resection had a 3-year OS of 70.1% (SD, 7.9%), and those with gross residual diseases with tumor nodules of ≤1 and >1 cm had a 3-year OS of 45.0% (SD, 13.2%) and 13.3% (SD, 12.3%; p<0.001), respectively. For UCS patients, the 3-year OS rate of the R0 and residual disease groups was 53.7% (SD, 18.7%) and 18.8% (SD, 15.8%), respectively (p=0.030), and the 3-year OS rate

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Table 1. Comparison in clinicopathological characteristics between UCS and G3EC

Characteristic	UCS	G3EC	p-value
Age (yr)	59.5 (35–84)	56 (31–81)	0.019
Menopause status			0.250
Premenopausal	11 (18.3)	30 (26.1)	
Postmenopausal	49 (81.7)	85 (73.9)	
Pretreatment CA-125 level (U/mL)	30.68 (5.0–616.7)	33.41 (7.15–1,974.7)	0.187
Ascite fluid			<0.001
Negative	27 (45.0)	97 (84.3)	
Positive	33 (55.0)	18 (15.7)	
FIGO stage			0.994
I	28 (46.7)	56 (48.7)	
II	9 (15.0)	17 (14.8)	
III	14 (23.3)	25 (21.7)	
IV	9 (15.0)	17 (14.8)	
Tumor volume (cm)	4.6 (0.3–14.0)	4.0 (0.3–11.0)	0.046
Myometrial invasion			0.027
≤1/2	34 (56.7)	45 (39.1)	
>1/2	26 (43.3)	70 (60.9)	
Cervical-stromal involvement			0.638
Positive	25 (41.7)	41 (35.6)	
Negative	35 (58.2)	67 (58.3)	
Adnexal involvement			0.048
Positive	12 (20.0)	10 (8.7)	
Negative	48 (80.0)	98 (85.2)	
Vaginal involvement			0.457
Positive	0	1 (0.9)	
Negative	60 (100)	108 (93.9)	
LVSI			0.247
Positive	21 (35.0)	43 (37.4)	
Negative	35 (58.3)	48 (41.7)	
Lymph node excision	25 (5–65)	24 (3–67)	0.558
Pelvic lymph node			0.513
Positive	10 (16.7)	27 (23.5)	
Negative	38 (63.3)	78 (67.8)	
Para-aortic lymph node			0.615
Positive	4 (6.7)	14 (12.2)	
Negative	34 (56.7)	88 (76.5)	

Values are presented as median (range) or number (%).
CA-125, cancer antigen 125; FIGO, the International Federation of Gynecology and Obstetrics; G3EC, grade 3 endometrioid endometrial carcinoma; LVSI, lymph-vascular space involvement; UCS, uterine carcinosarcoma.

of the R0 group and residual G3EC disease group was 69.6% (SD, 9.6%) and 40.0% (SD, 12.6%), respectively (p=0.088).

Adjuvant therapy, including chemotherapy (CT) and radiotherapy (RT), was performed in uterine malignancies. The major CT regimens comprised paclitaxel-carboplatin (n=30), ifosfamide-cisplatin (n=9), doxorubicin (n=11), and others (n=4). Patients receiving carboplatin-paclitaxel and sarcoma-sensitive regimens, including ifosfamide-cisplatin and doxorubicin, had a 5-year OS of 53.2% (SD, 12.9%) and 30.8% (SD, 13.1%), respectively (p=0.020). Among the 57 UCS patients receiving adjuvant therapy, three patients (5.3%) received adjuvant RT, 28 patients (49.1%) received adjuvant CT, and 26 patients (45.6%) received adjuvant CT with RT. The 3- and 5-year OS in patients receiving multimodal therapy were 78.8% and 71.0%, respectively, compared with 59.7% and 35.8% in patients receiving

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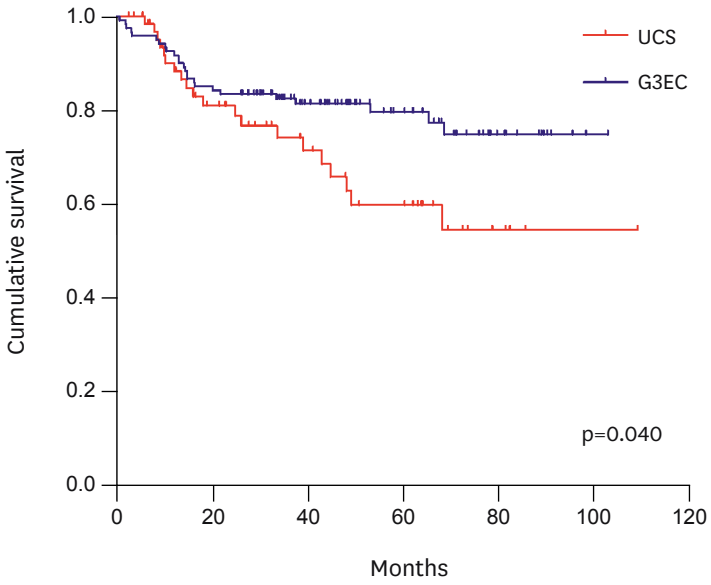

Fig. 1. Overall survival (OS) curve of uterine carcinosarcoma (UCS) and grade 3 endometrioid endometrial carcinoma (G3EC) patients. The 3-year and 5-year OS rate for UCS were 70.5% and 54.2%, 80.0% and 76.8% for G3EC.

adjuvant RT or CT alone, respectively (p=0.028). Among the G3EC patients, 54 patients (47.0%) received adjuvant RT and 59 patients (51.3%) received adjuvant CT. Thirty-seven G3EC patients received RT with CT, but there was no correlation with significantly improved OS.

3. Pathological characteristics

Among all 60 UCS patients, 37 patients (61.7%) were at stage I/II, and 23 patients (38.3%) were at stage III/IV, whereas 73 G3EC patients (63.5%) were at stage I/II, and 42 G3EC patients (36.5%) were at stage III/IV. There was no significant statistical difference between UCS and G3EC patients in stage distribution.

The average diameter of the largest tumors observed in UCS and G3EC patients were 4.6 cm (range, 0.3 to 14.0 cm) and 4.0 cm (range, 0.3 to 11.0 cm), respectively, and these values showed significant statistical differences (p=0.046). Twenty-six UCS (43.3%) and 70 G3EC patients (60.9%) had myometrial invasion ≥1/2, and a significant statistical difference was observed (p=0.027). Adnexal metastasis was observed in 12 UCS (20.0%) and 10 G3EC patients (8.7%; p=0.048).

A heterologous mesenchymal component was observed in 12 patients (20.0%), and a homologous component was observed in 44 patients (73.3%). The 3- and 5-year OS rates for patients with the homologous component were 85.2% and 68.1%, respectively, whereas these rates were 38.9% and 19.4%, respectively for patients with heterologous tumors (log-rank test, p<0.001 for 5-year OS).

4. Overall survival

With a median follow-up period of 49.2 months (range, 2.9 to 110.1 months) for surviving patients, nine G3EC patients (7.8%) were lost to follow-up, and 45 patients died from cancer (20 died from carcinosarcoma and 25 died from G3EC). The 3- and 5-year OS rates were 70.5% and

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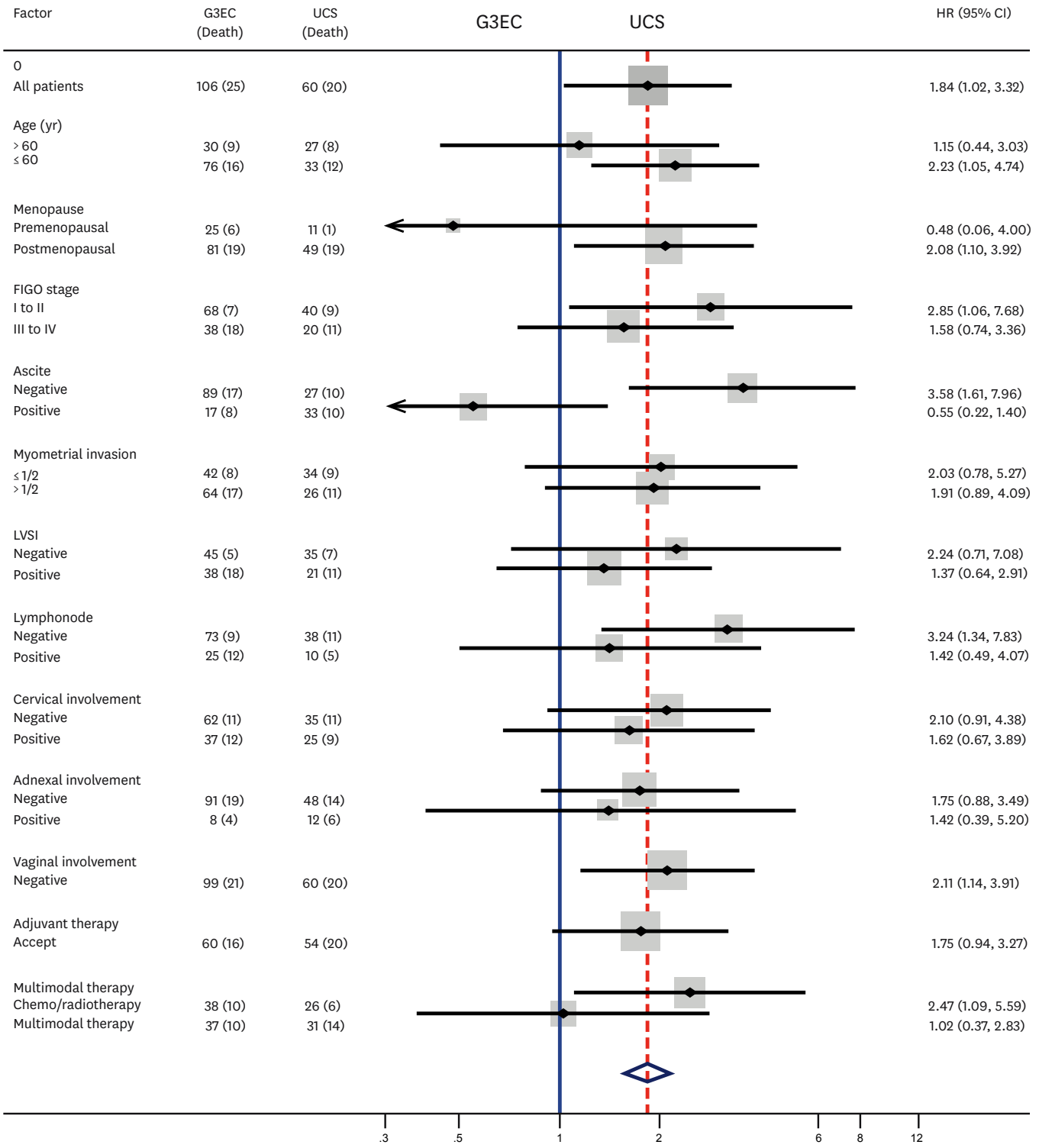

Fig. 2. Subgroup analysis of the prognostic factors between the uterine carcinosarcoma (UCS) and grade 3 endometrioid endometrial carcinoma (G3EC). UCS patients exhibited worse overall survival (OS) than G3EC patients in such specific subgroups: patients who were diagnosed at age less than 60 years (P=0.032), with postmenopausal status (P=0.022), without ascites fluid (P=0.001), tumor with early stage (stage I-II, P=0.035), without vagina invasion (P=0.014), without lymph node metastases (P=0.006), and with adjuvant chemo/radiotherapy (P=0.044).

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Table 2. Multivariate analysis of prognostic factors for overall survival by Cox proportional hazards models

Factor	Hazard ratio	95% CI	p-value
Histological subtype*	2.412	1.044–5.576	0.039
FIGO stage	4.924	1.416–16.596	0.010
Myometrial invasion	1.086	0.386–3.056	0.876
Lymph node metastasis	1.163	0.397–3.411	0.783
Lymph-vascular space involvement	1.099	0.363–3.328	0.868
Tumor volume	0.924	0.782–1.091	0.350
Adjuvant therapy	0.492	0.205–1.184	0.113

FIGO, the International Federation of Gynecology and Obstetrics.
*Histological subtype: comparison between uterine carcinosarcoma and grade 3 endometrioid endometrial carcinoma.

54.2% for UCS patients and 80.0% and 76.8% for G3EC patients (log-rank test, p=0.040 for 5-year OS) (**Fig. 1**), respectively. After adjusting based on FIGO stage, patients with early stage (FIGO I & II) diseases had 5-year OS rates of 67.7% and 92.4% for UCS and G3EC, respectively (log-rank test, p=0.020 for 5-year OS). Patients with advanced stage (FIGO III & IV) diseases had 5-year OS rates of 29.6% and 49.7% for UCS and G3EC, respectively (p=0.421).

The subgroup analysis of the prognostic factors between the two malignancies was performed (**Fig. 2**). Using a forest graph, we observed that UCS patients presented worse OS than G3EC patients in the following subgroups, showing significant statistical differences: age of <60 years at diagnosis (p=0.032), menopause (p=0.022), absent ascites fluid (p=0.001), tumors with early stages (stage I–II, p=0.035), no vaginal invasion (p=0.014), no lymph node metastases (p=0.006), and adjuvant CT/RT (p=0.044).

5. COX regression analysis

Potential prognostic factors were examined using the multivariate analysis to determine the correlated factors. As shown in **Table 2**, carcinosarcoma histological type (hazard ratio [HR], 2.4; 95% CI, 1.0 to 5.6; p=0.039) and FIGO stage (HR, 4.9; 95% CI, 1.4 to 16.6; p=0.010) were the two independent factors for OS, after adjusting based on myometrial invasion, lymph node involvement, LVSI, tumor volume, and adjuvant CT/RT. These results further suggested that UCS patients have particularly poor outcomes.

To consolidate the results of the present study, the Cox proportional hazards model was also used to evaluate prognostic factors in both UCS and G3EC. Carcinosarcoma patients with advanced stage diseases (p=0.012), adnexal involvement (p=0.021), LVSI and nerve invasion (p=0.005), lymph node metastases (p=0.039), adjuvant RT (p=0.037), and heterologous subtype (p=0.001) exhibited worse OS (**Table 3**). However, only the histological subtype (heterologous vs. homologous subtype, HR, 4.6; 95% CI, 1.4 to 15.8; p=0.014) was identified as an independent prognostic factor for OS in the multivariate analysis (**Table 4**).

G3EC patients with ascites fluid (p=0.003), advanced disease (p<0.001), adnexal involvement (p=0.043), vaginal involvement (p=0.027), LVSI and nerve invasion (p<0.001), and lymph node metastases (p<0.001) were correlated with worse OS (**Table 3**). The multivariate analysis (**Table 5**) revealed that tumor stage (HR, 5.9; 95% CI, 1.0 to 33.9; p=0.046) and ascites fluid (HR, 5.1; 95% CI, 1.1 to 22.7; p=0.032) were independent prognostic factors for OS.

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Table 3. Univariate analysis of factors associated with overall survival in UCS and G3EC

Factor	UCS		G3EC	
	Death	p-value	Death	p-value
Age (yr)				0.210
≤60	33 (12)	0.856	76 (16)	
>60	27 (8)		30 (9)	
Menopause status				0.996
Premenopausal	11 (1)	0.221	25 (6)	
Postmenopausal	49 (19)		81 (19)	
Pretreatment CA-125 level (U/mL)				0.256
≤35	31 (8)	0.053	18 (3)	
>35	20 (11)		20 (7)	
Ascite fluid				0.003
Negative	27 (10)	0.136	89 (17)	
Positive	33 (10)		17 (8)	
FIGO stage				
I	28 (4)	0.012	52 (5)	<0.001
II	9 (5)		16 (2)	
III	14 (7)		24 (10)	
IV	9 (4)		14 (8)	
Tumor volume (cm)				0.841
≤4.5	29 (8)	0.503	61 (15)	
>4.5	30 (11)		27 (6)	
Myometrial invasion				0.262
≤1/2	34 (9)	0.207	42 (8)	
>1/2	26 (11)		64 (17)	
Cervical stromal involvement				0.088
Positive	25 (9)	0.191	37 (12)	
Negative	35 (11)		62 (11)	
Adnexal involvement				0.043
Positive	12 (6)	0.021	8 (4)	
Negative	48 (14)		91 (19)	
Vaginal involvement				0.027
Positive	0 (0)	-	1 (1)	
Negative	60 (20)		99 (21)	
LVSI				<0.001
Positive	21 (11)	0.005	38 (18)	
Negative	35 (7)		45 (5)	
Lymph node metastasis				<0.001
Positive	10 (5)	0.039	25 (12)	
Negative	38 (11)		73 (9)	
Pelvic lymph node metastasis				<0.001
Positive	10 (5)	0.805	24 (12)	
Negative	38 (11)		74 (9)	
Para-aortic lymph node metastasis				0.068
Positive	4 (1)	0.233	13 (8)	
Negative	34 (10)		81 (12)	
Adjuvant radiotherapy				0.322
Accepted	29 (6)	0.037	53 (14)	
Unaccepted	31 (14)		48 (8)	
Adjuvant chemotherapy				
Accepted	54 (20)	0.126	60 (16)	0.225
Unaccepted	6 (0)		41 (5)	
Multimodality therapy				0.763
CT with RT	31 (14)	0.028	37 (10)	
CT/RT	26 (6)		38 (10)	
Mesenchymal component				-
Homologous	44 (9)	<0.001	-	
Heterologous	12 (7)		-	

Values are presented as number (%).
CA-125, cancer antigen 125; CT, chemotherapy; FIGO, the International Federation of Gynecology and Obstetrics; G3EC, grade 3 endometrioid endometrial carcinoma; LVSI, lymph-vascular space involvement; RT, radiotherapy; UCS, uterine carcinosarcoma.

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Table 4. Prognostic factors of uterine carcinosarcoma analyzed by Cox proportional hazards models

Factor	Hazard ratio	95% CI	p-value
Mesenchymal component	4.632	1.357–15.816	0.014
FIGO stage	2.087	0.532–8.185	0.291
Lymph-vascular space involvement	2.917	0.853–9.971	0.088
Multimodality therapy	0.332	0.095–1.164	0.085

FIGO, the International Federation of Gynecology and Obstetrics.

DISCUSSION

UCS has been previously categorized as a subtype of uterine sarcoma and was listed among the MMMT (carcinosarcomas) in the 2003 World Health Organization classification of tumors of the female genital tract. UCS has been traditionally classified as a sarcoma subtype, reflecting the presence of a sarcomatous component, invasive tumor spread, and poor survival compared with pure epithelial EC. However, subsequent studies have demonstrated that factors associated with excess estrogen exposure, BMI and the propensity for lymphatic spread were common features of both MMMT and high-grade EC [7]. A similar disease pattern, showing sensitivity to CT in immunohistochemical and molecular studies, has also been reported in studies of UCS and high-grade EM [8-11]. Indeed, the revised FIGO 2009 staging system distinguished UCS from other uterine sarcomas, and classified this disease together with EC, reflecting similar risk factors shared by both neoplasms. Nevertheless, there remain doubts that challenge the same FIGO system in clinical practice.

Although the increased risk of recurrence and mortality is associated with high-risk EC subtypes, there are few studies comparing the MMMT subtype to high-grade EM in large cohorts. In the present study, we reported that patients with carcinosarcoma had worse survival outcomes compared with G3EC patients. When stratified according to stage, similar findings were observed in patients with early- and advanced-stage diseases. After adjusting for other confounding factors, the multivariate analysis revealed that carcinosarcoma subtype was an independent prognostic factor for poor OS. These findings are consistent with those of previous studies, which also reported survival differences between UCS and high-grade EM cases [3,12]. A SEER (Surveillance, Epidemiology and End Results) study reported that high-grade EM cases had significantly better OS than UCS cases after adjusting for age, race, lymph node dissection, stage, and postoperative RT [3]. Similarly, Bland et al. [12] conducted a retrospective study, reporting that UCS patients had a significantly shorter progression-free survival (23 months vs. 57 months, p=0.001) and OS (55 months vs. 92 months, p=0.001) compared with patients with high-grade endometrial cancer. Zhang et al. [13] also recently

Table 5. Prognostic factors of grade 3 endometrioid endometrial carcinoma analyzed by Cox proportional hazards models

Factor	Hazard ratio	95% CI	p-value
Menopause status	1.794	0.483–6.666	0.383
FIGO stage	5.914	1.031–33.903	0.046
Ascite fluid	5.106	1.148–22.706	0.032
Myometrial invasion	0.551	0.141–2.147	0.390
Lymph-vascular space involvement	3.221	0.712–14.580	0.129
Lymph node metastasis	0.930	0.190–4.549	0.929
Adjuvant therapy	0.313	0.087–1.121	0.074

FIGO, the International Federation of Gynecology and Obstetrics.

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reported that UCS patients had significantly worse outcomes (OS, disease-specific survival, and recurrence-free survival) compared with high-grade EC cases.

Whether the behavior of UCS is the same as high-grade EC remains under debate. However, the results of the present study confirmed that UCS exhibits more aggressive behavior and worse outcome than G3EC. To determine which factors might contribute to this distinct behavior, we compared the demographic and clinicopathological features between UCS and G3EC patients. Compared with G3EC, UCS patients were diagnosed at an older age. In addition, a higher incidence of ascites fluid and adnexal involvement and larger tumor volume were demonstrated in carcinosarcoma, indicating that UCS exhibits more aggressive behaviors. In the present study, the propensity for lymphatic spread between UCS and G3EC did not obviously differ ($p>0.05$), and was consistent with previous studies [7,14]. We observed that 16.7% of UCS cases had positive pelvic lymph node involvement and only 6.7% of UCS cases had positive para-aortic lymph nodes, compared with 23.5% and 12.2%, respectively, of G3EC cases. The unifying characteristic in lymphatic spread might reflect the fact that 20% of UCS patients did not have a lymph node examination, compared with 7.8% of G3EC cases, which might have contributed to the low prevalence of positive lymph node involvement in this subgroup.

The present study is unique in that we observed a significant difference in OS between UCS and G3EC patients using subgroup analysis. Although previous studies have reported that UCS patients have poorer survival, only a few studies stratified specific factors in which UCS exhibit worse outcomes compared with high-grade EC. In the following subgroups, including age at diagnosis of less than 60 years, postmenopausal women, negative ascites fluid, stage II tumors, negative vaginal involvement, negative lymph node involvement and adjuvant therapy, UCS patients presented significantly worse outcomes compared with G3EC patients. The specific subgroup analysis could explain why UCS patients had a relatively higher incidence of aggressiveness and modality compared with G3EC patients.

Previous studies have demonstrated that older age, LVSI, deep myometrial invasion, cervical stromal involvement, and advanced tumor stages represent significant adverse prognostic factors for carcinosarcoma [15,16]. In the present study, UCS patients with advanced stage, adnexal involvement, LVSI and nerve invasion, lymph node metastases, adjuvant RT, and heterologous subtype had a worse OS in the univariate analysis. However, notably, the present study showed that only histological subtype was identified as an independent prognostic factor for OS in the multivariate analysis. We compared the outcomes of UCS patients with homologous elements and heterologous subtype diseases and there was a statistically significant difference in the 5-year OS. There was a statistically significant difference in the 5-year OS survival between the two groups (68.1% vs. 19.4%, $p<0.001$), which was consistent with the results of Hellstrom et al. [17]. A similar result was reported in a study of 42 stage I UCS patients after primary surgery. The presence of heterologous sarcomatous elements is a powerful negative prognostic factor, with a 3-year OS rate of 45% versus 93% in homologous patients ($p<0.001$) [18].

In the absence of standard guidelines specific for UCS, surgery is the mainstay treatment, and the initial recommended surgical treatment is the same for aggressive endometrial cancer: abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal cytology and the removal of pelvic and aortic lymph nodes and omental biopsy. Advanced diseases

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should receive additional cytoreductive surgery. Lymphadenectomy is an important surgical procedure, not only diagnostic, but also therapeutic, for both early and advanced stage diseases. In the present study, the 5-year OS was 54.6% versus 52.5% for UCS patients receiving (n=48) versus patients without lymphadenectomy (n=12). Although no statistical significance was observed (p>0.05), a tendency towards improved survival was seen in patients with lymphadenectomy. Similar results were reported in a SEER retrospective analysis of stage I-III UCS, and Nemani et al. [19] reported that the 5-year OS was 33.4% versus 35.8% for patients with versus without lymphadenectomy, respectively.

Postoperative treatments for UCS have included RT, CT and the combination of CT and RT. The recommended chemotherapeutic regimen, based on retrospective studies, involves platinum-based CT, including carboplatin-paclitaxel or ifosfamide-cisplatin, with less toxicity and improved survival outcome. These results also demonstrated an advantage favoring the use of paclitaxel-carboplatin compared with the cisplatin-ifosfamide combination. Several studies have shown favorable outcomes in carcinosarcoma patients treated with carboplatin-paclitaxel and recommended this regimen as a first-line treatment [20,21]. Radiation therapy is intended to improve local control, particularly in early-stage cancers. Nevertheless, there has been sparse evidence to prove that this treatment extends survival [22,23]. In the present study, we observed that adjuvant RT with CT was predictive of better survival in UCS patients compared with individuals receiving CT or RT alone. Gungorduk et al. [24] conducted a retrospective review of three cancer centers involving 66 UCS patients, noting that adjuvant CT with RT is associated with improved OS compared with CT or RT alone (HR, 3.3; 95% CI, 0.7 to 15.0; p=0.01), consistent with the results of the present study. We collected a larger number of cases and prospective trials warranting the evaluation of the effectiveness of multimodal therapy in UCS patients.

The major strengths of the present study included reliable data from a single cancer center, a large sample size of cases, and adjustments for other prognostic factors. Furthermore, we explored specific prognostic factors via subtype analysis to evaluate potential effect modifications. Potential limitations include the retrospective study design and lack of generalizability to nonsurgical cases, reflecting the inclusion of initial surgical cases in the present analysis.

In conclusion, these data suggested that UCS patients exhibited significant differences in clinicopathological characteristics compared with G3EC patients, and UCS patients had worse outcomes than G3EC patients. Tumor stage was identified as an independent adverse prognostic factor. Given the distinct survival differences shown in the present study, it is reasonable to conclude that UCS should be distinct from endometrial endometrioid carcinomas and regarded as a special subtype of high-risk EC. In addition, future studies should explore the molecular biology of carcinosarcoma not only to increase the current understanding of the carcinogenesis of these tumors but also to identify potential molecule-targeted treatments for use in the treatment of these diseases.

REFERENCES

1. Callister M, Ramondetta LM, Jhingran A, Burke TW, Eifel PJ. Malignant mixed Müllerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. Int J Radiat Oncol Biol Phys 2004;58:786-96.
PUBMED | CROSSREF

http://doi.org/10.3802/jgo.2016.27.e18

2. Vorgias G, Fotiou S. The role of lymphadenectomy in uterine carcinosarcomas (malignant mixed mullerian tumours): a critical literature review. Arch Gynecol Obstet 2010;282:659-64.
PUBMED | CROSSREF
3. Bansal N, Herzog TJ, Seshan VE, Schiff PB, Burke WM, Cohen CJ, et al. Uterine carcinosarcomas and grade 3 endometrioid cancers: evidence for distinct tumor behavior. Obstet Gynecol 2008;112:64-70.
PUBMED | CROSSREF
4. Fujii H, Yoshida M, Gong ZX, Matsumoto T, Hamano Y, Fukunaga M, et al. Frequent genetic heterogeneity in the clonal evolution of gynecological carcinosarcoma and its influence on phenotypic diversity. Cancer Res 2000;60:114-20.
PUBMED
5. Schipf A, Mayr D, Kirchner T, Diebold J. Molecular genetic aberrations of ovarian and uterine carcinosarcomas: a CGH and FISH study. Virchows Arch 2008;452:259-68.
PUBMED | CROSSREF
6. Prat J. FIGO staging for uterine sarcomas. Int J Gynaecol Obstet 2009;104:177-8.
PUBMED | CROSSREF
7. McCluggage WG. Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. Int J Gynecol Cancer 2002;12:687-90.
PUBMED | CROSSREF
8. Benito V, Lubrano A, Arencibia O, Andújar M, Alvarez E, Medina N, et al. Clinicopathologic analysis of uterine sarcomas from a single institution in the Canary Islands. Int J Gynaecol Obstet 2009;107:44-9.
PUBMED | CROSSREF
9. Powell MA, Filiaci VL, Rose PG, Mannel RS, Hanjani P, Degeest K, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. J Clin Oncol 2010;28:2727-31.
PUBMED | CROSSREF
10. Abargel A, Avinoach I, Kravtsov V, Boaz M, Glezerman M, Menczer J. Expression of p27 and p53: comparative analysis of uterine carcinosarcoma and endometrial carcinoma. Int J Gynecol Cancer 2004;14:354-9.
PUBMED | CROSSREF
11. Zelmanowicz A, Hildesheim A, Sherman ME, Sturgeon SR, Kurman RJ, Barrett RJ, et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors. Gynecol Oncol 1998;69:253-7.
PUBMED | CROSSREF
12. Bland AE, Stone R, Heuser C, Shu J, Jazaeri A, Shutter J, et al. A clinical and biological comparison between malignant mixed müllerian tumors and grade 3 endometrioid endometrial carcinomas. Int J Gynecol Cancer 2009;19:261-5.
PUBMED | CROSSREF
13. Zhang C, Hu W, Jia N, Li Q, Hua K, Tao X, et al. Uterine carcinosarcoma and high-risk endometrial carcinomas: a clinicopathological comparison. Int J Gynecol Cancer 2015;25:629-36.
PUBMED | CROSSREF
14. Felix AS, Stone RA, Bowser R, Chivukula M, Edwards RP, Weissfeld JL, et al. Comparison of survival outcomes between patients with malignant mixed mullerian tumors and high-grade endometrioid, clear cell, and papillary serous endometrial cancers. Int J Gynecol Cancer 2011;21:877-84.
PUBMED | CROSSREF
15. Galaal K, Kew FM, Tam KF, Lopes A, Meirovitz M, Naik R, et al. Evaluation of prognostic factors and treatment outcomes in uterine carcinosarcoma. Eur J Obstet Gynecol Reprod Biol 2009;143:88-92.
PUBMED | CROSSREF
16. Vance S, Yechieli R, Cogan C, Hanna R, Munkarah A, Elshaikh MA. The prognostic significance of age in surgically staged patients with type II endometrial carcinoma. Gynecol Oncol 2012;126:16-9.
PUBMED | CROSSREF
17. Hellström AC, Tegerstedt G, Silfverswärd C, Pettersson F. Malignant mixed müllerian tumors of the ovary: histopathologic and clinical review of 36 cases. Int J Gynecol Cancer 1999;9:312-6.
PUBMED | CROSSREF
18. Ferguson SE, Tornos C, Hummer A, Barakat RR, Soslow RA. Prognostic features of surgical stage I uterine carcinosarcoma. Am J Surg Pathol 2007;31:1653-61.
PUBMED | CROSSREF
19. Nemani D, Mitra N, Guo M, Lin L. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. Gynecol Oncol 2008;111:82-8.
PUBMED | CROSSREF

20. Otsuki A, Watanabe Y, Nomura H, Futagami M, Yokoyama Y, Shibata K, et al. Paclitaxel and carboplatin in patients with completely or optimally resected carcinosarcoma of the uterus: a phase II trial by the Japanese Uterine Sarcoma Group and the Tohoku Gynecologic Cancer Unit. Int J Gynecol Cancer 2015;25:92-7.
PUBMED | CROSSREF

21. Takano T, Otsuki T, Tokunaga H, Toyoshima M, Utsunomiya H, Nagase S, et al. Paclitaxel-carboplatin for advanced or recurrent carcinosarcoma of the uterus: the Japan Uterine Sarcoma Group and Tohoku Gynecologic Cancer Unit Study. Int J Clin Oncol 2014;19:1052-8.
PUBMED | CROSSREF

22. Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer 2008;44:808-18.
PUBMED | CROSSREF

23. Makker V, Abu-Rustum NR, Alektiar KM, Aghajanian CA, Zhou Q, Iasonos A, et al. A retrospective assessment of outcomes of chemotherapy-based versus radiation-only adjuvant treatment for completely resected stage I-IV uterine carcinosarcoma. Gynecol Oncol 2008;111:249-54.
PUBMED | CROSSREF

24. Gungorduk K, Ozdemir A, Ertas IE, Gokcu M, Telli E, Oge T, et al. Adjuvant treatment modalities, prognostic predictors and outcomes of uterine carcinosarcomas. Cancer Res Treat 2015;47:282-9.
PUBMED | CROSSREF

http://doi.org/10.3802/jgo.2016.27.e18