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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Proposal for a Risk-Based Categorization of Uterine Carcinosarcoma

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ABSTRACT

Purpose. To propose a categorization model of uterine carcinosarcoma (UCS) based on tumor cell types (carcinoma and sarcoma) and sarcoma dominance.

Methods. This secondary analysis of a prior multicenter retrospective study examined 889 cases of UCS with available histologic evaluation. Based on survival outcome, cases were clustered into three groups: low-grade carcinoma with nondominant homologous sarcoma [type A, $n = 96$ (10.8%)], (1) low-grade carcinoma with heterologous sarcoma or any sarcoma dominance and (2) high-grade carcinoma with nondominant homologous sarcoma [type B, $n = 412$ (46.3%)], and high-grade carcinoma with heterologous sarcoma or any sarcoma dominance [type C, $n = 381$ (42.9%)]. Tumor characteristics and outcome were examined based on the categorization.

Results. Women in type C category were more likely to be older, obese, and Caucasian, whereas those in type A category were younger, less obese, Asian, and nulligravid (all $P < 0.01$). Type C tumors were more likely to have metastatic implants, large tumor size, lymphovascular space invasion with sarcoma cells, and higher lymph node ratio, whereas type A tumors were more likely to be early-stage disease and small (all $P < 0.05$). On multivariate analysis, tumor categorization was independently associated with progression-free survival (5-year rates: 70.1% for type A, 48.3% for type B, and 35.9% for type C, adjusted $P < 0.01$) and cause-specific survival (5-year rates: 82.8% for type A, 63.0% for type B, and 47.1% for type C, adjusted $P < 0.01$).

Conclusion. Characteristic differences in clinicopathological factors and outcomes in UCS imply that different underlying etiologies and biological behaviors may be present, supporting a new classification system.

Uterine carcinosarcoma (UCS) is a rare type of high-grade endometrial cancer, however the proportion of UCS has been gradually increasing among endometrial cancer in the USA, exceeding 5% in recent years.[1] Histologically, UCS contains both carcinoma and sarcoma components in the uterine tumor site, with the sarcoma element being dedifferentiated from the carcinoma component.[2,3] Both the carcinoma and sarcoma components have important prognostic implications pertaining to treatment response and survival in women with UCS.[4]

Additionally, the dominant tumor component has been shown to be a salient tumor factor in UCS. A recent analysis showed that the dominant pattern in the uterine tumor, either carcinoma or sarcoma, is an independent predictor of survival in UCS.[4] In this analysis, sarcoma dominance had the largest impact on survival among the uterine tumor factors in UCS.[4] Type of sarcoma dominance (homologous vs heterologous) also impacts survival.[5]

UCS is understudied due to its rarity and the complexity of the tumor factors (carcinoma, sarcoma, and dominant component), making it difficult to interpret the true effects of histological components on survival. For UCS, it is hypothesized that the carcinoma component is the main driver of tumor progression, and the sarcoma component and sarcoma dominance are secondary factors, altering tumor behavior. However, the association between combination patterns of these three tumor factors and survival of UCS has not been examined.

The objective of this study is to examine the clinicopathological pattern and survival based on carcinoma, sarcoma, and dominant components in UCS, with the goal of proposing a risk-based categorization model of UCS.

MATERIALS AND METHODS

Eligibility Criteria

We utilized the previously organized database from a large multicenter retrospective study to conduct this secondary analysis. Previously, we examined consecutive women with stage I–IV UCS who underwent primary hysterectomy-based surgical treatment in 26 institutions between 1993 and 2013 (906 cases).[4–11] Institutional review board approval was obtained at each participating site. By querying this database, we examined cases with information available concerning all three tumor factors (carcinoma and sarcoma types, and dominant component).

Clinical Information

Among eligible cases, we abstracted information for patient demographics, tumor characteristics, surgical performance, postoperative treatment type, and survival. Patient demographics included age, race/ethnicity, country, body mass index (BMI, kg/m^2), pregnancy history, history of tamoxifen use, history of pelvic irradiation, and preoperative cancer antigen 125 (CA-125, IU/L) levels. Surgical performance included residual disease at the end of surgery.

Tumor characteristics abstracted were carcinoma type, sarcoma type, sarcoma dominance, cancer stage, tumor size, depth of myometrial tumor invasion, lymphovascular space invasion (LVSI), and pelvic/paraaortic lymph node status [rate of metastasis among staged cases, and lymph node ratio (LNR) among metastatic cases]. Postoperative treatment types included use of postoperative chemotherapy and/or radiotherapy. Survival outcomes were abstracted for progression-free survival (PFS) and cause-specific survival (CSS).

Histopathology Evaluation

In all the cases, archived histopathology slides for hematoxylin–eosin stains and immunohistochemistry stains, if available, were reviewed at each institution. Pathologists were blinded to clinical information. In a comprehensive evaluation, carcinoma type, sarcoma type, sarcoma dominance, and LVSI cell types were assessed as described previously (Supplementary Method).[4]

Tumor Factor-Based Categorization

Among 906 cases of UCS in the database, there were 889 cases with available information regarding histologic component and sarcoma dominance. We first plotted the crude PFS results based on the combination patterns of carcinoma type, sarcoma type, and sarcoma dominance (Supplementary Fig. S1). Based on the survival outcomes, these eight groups were further clustered into three independent categories (Table 1).

In this pilot exploratory study, we termed these three categories as type A, B, and C tumors for the purpose of convenience. Type A tumors are defined as low-grade carcinoma with nondominant homologous sarcoma. Type B tumors are defined as (1) low-grade carcinoma with heterologous sarcoma or any sarcoma dominance or (2) high-grade carcinoma with nondominant homologous sarcoma. Type C tumors are defined as high-grade carcinoma with heterologous sarcoma or any sarcoma dominance (Table 1).

Study Definition

Obesity was defined as BMI $\geq$ 30 kg/m^2. We reclassified cancer stage based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) definition. Low-grade carcinoma (grade 1–2 endometrioid) and high-grade carcinoma (grade 3 endometrioid, serous, clear cell, undifferentiated, and mixed) were defined based on a prior study.[4] Similarly, sarcoma types were grouped as homologous (endometrial stromal sarcoma, leiomyosarcoma, fibrosarcoma, and undifferentiated sarcoma) or heterologous (rhabdomyosarcoma, osteosarcoma, chondrosarcoma, and liposarcoma).[4]

LVSI types were grouped based on presence of sarcoma cells within the lymphatic or vascular capillary, as described previously (carcinoma alone, sarcoma with or without carcinoma, and none).[4] LNR was defined as percent proportion of lymph nodes containing tumor cells among resected lymph nodes. PFS was defined as the time interval between hysterectomy and first recurrence/progression of disease or death due to UCS. CSS was defined as the time interval between hysterectomy and death due to UCS.

TABLE 1 Proposed grouping criteria based on tumor factors

Carcinoma type	Sarcoma type	Dominant component	No.	2-Year PFS (%)	5-Year PFS (%)	Proposed categorization
Low-grade	Homologous	Carcinoma	96 (10.8%)	77.0	70.1	Type A
Low-grade	Homologous	Sarcoma	65 (7.3%)	57.4	47.4	Type B
Low-grade	Heterologous	Carcinoma	40 (4.5%)	54.1	54.1	
Low-grade	Heterologous	Sarcoma	52 (5.8%)	55.5	48.8	
High-grade	Homologous	Carcinoma	255 (28.7%)	59.2	47.5	
High-grade	Homologous	Sarcoma	110 (12.4%)	47.5	41.5	Type C
High-grade	Heterologous	Carcinoma	134 (15.1%)	45.5	32.6	
High-grade	Heterologous	Sarcoma	137 (15.4%)	48.2	35.3	

Risk stratification based on three tumor factors: carcinoma component, sarcoma component, and sarcoma dominance

No. number, *PFS* progression-free survival

TABLE 2 Clinicopathological demographics based on risk stratification

Characteristic	Type A	Type B	Type C	*P* value
Number	*n* = 96	*n* = 412	*n* = 381	
Age (years)	59 (IQR 15)	62 (IQR 14)	65 (IQR 14)	< **0.001**
< 60	49 (51.0%)	148 (35.9%)	95 (24.9%)	
≥ 60	47 (49.0%)	264 (54.1%)	286 (75.1%)	
Race				< **0.001**
Caucasian	16 (17.0%)	120 (29.6%)	139 (37.2%)	
African	1 (1.1%)	28 (6.9%)	50 (13.4%)	
Hispanic	2 (2.1%)	7 (1.7%)	13 (3.5%)	
Asian	73 (77.7%)	243 (59.9%)	163 (43.6%)	
Others	2 (2.1%)	8 (2.0%)	9 (2.4%)	
Country				< **0.001**
USA	24 (25.0%)	171 (41.5%)	223 (58.5%)	
Japan	72 (75.0%)	241 (58.5%)	158 (41.5%)	
BMI (kg/m^2)	22.6 (IQR 5.6)	23.3 (IQR 5.9)	23.9 (IQR 7.2)	**0.008**
< 30	77 (81.1%)	307 (76.6%)	260 (73.7%)	
≥ 30	18 (18.9%)	94 (23.4%)	93 (26.3%)	
Gravida				**0.002**
Nulli	27 (28.4%)	57 (14.1%)	54 (14.8%)	
Multi	68 (71.6%)	346 (85.9%)	310 (85.2%)	
History of tamoxifen use				0.36
No	91 (95.8%)	389 (95.6%)	356 (93.4%)	
Yes	4 (4.2%)	18 (4.4%)	25 (6.6%)	
Prior pelvic irradiation				0.87
No	95 (99.0%)	407 (98.8%)	375 (98.4%)	
Yes	1 (1.0%)	5 (1.2%)	6 (1.6%)	
Preop. CA-125 (IU/L)	20.5 (IQR 28)	22 (IQR 42)	28 (IQR 52)	0.31
< 30	47 (59.5%)	176 (61.3%)	127 (52.9%)	
≥ 30	32 (40.5%)	111 (38.7%)	113 (47.1%)	
Residual disease				0.32
No	86 (91.5%)	355 (89.6%)	318 (86.9%)	
Yes	8 (8.5%)	41 (10.4%)	48 (13.1%)	
Postop. radiotherapy				0.10
No	77 (80.2%)	312 (76.7%)	268 (71.3%)	
Yes	19 (19.8%)	95 (23.3%)	108 (28.7%)	
Postop. chemotherapy				0.40
No	27 (28.1%)	129 (31.7%)	131 (34.7%)	
Yes	69 (71.9%)	278 (68.3%)	246 (65.3%)	
Stage				< **0.001**
I	58 (60.4%)	220 (53.4%)	159 (41.7%)	
II	8 (8.3%)	35 (8.5%)	21 (5.5%)	
III	23 (24.0%)	113 (27.4%)	135 (35.4%)	
IV	7 (7.3%)	44 (10.7%)	66 (17.3%)	
Tumor size (cm)				< **0.001**
< 5	47 (50.0%)	157 (39.7%)	109 (29.1%)	
5–9.9	42 (44.7%)	200 (50.6%)	191 (50.9%)	
≥ 10	5 (5.3%)	38 (9.6%)	75 (20.0%)	
Myometrial invasion				0.22
Inner half	56 (59.6%)	216 (52.4%)	187 (49.6%)	

TABLE 2 continued

Characteristic	Type A	Type B	Type C	*P* value
Outer half	38 (40.4%)	196 (47.6%)	190 (50.4%)	
LVSI				**0.013**
None	46 (50.0%)	153 (39.5%)	148 (42.2%)	
Carcinoma only	41 (44.6%)	187 (48.3%)	143 (40.7%)	
Sarcoma	5 (5.4%)	47 (12.1%)	60 (17.1%)	
PLN metastasis[a]				**0.014**
No	62 (82.8%)	239 (76.1%)	180 (68.4%)	
Yes	12 (16.2%)	75 (23.9%)	83 (31.6%)	
PAN metastasis[a]				**0.007**
No	35 (83.3%)	168 (85.3%)	110 (71.9%)	
Yes	7 (16.7%)	29 (14.7%)	43 (28.1%)	
Lymph node ratio (%)[b]				
PLN	7.6 (IQR 6.4)	11.8 (IQR 28.3)	21.4 (IQR 41.7)	**0.028**
PAN	9.5 (IQR 61.0)	45.0 (IQR 89.1)	50.0 (IQR 80.0)	0.26

Median (IQR) or number (percent per column) is shown. Kruskal–Wallis *H* test or Chi square test for *P* values. Significant covariates are emboldened

IQR interquartile range, *BMI* body mass index, *CA-125* cancer antigen 125, *LVSI* lymphovascular space invasion, *PLN* pelvic lymph node, *PAN* paraaortic lymph node

[a]Examined only staged cases

[b]Examined only positive lymph node cases

Cases without these survival events at last follow-up were censored.

Statistical Considerations

The primary objective of this study is to outline the clinicopathological characteristics across type A–C UCS. The secondary objective of this study is to examine the independent association of the tumor categorization with survival.

The Kaplan–Meier method was used to plot survival curves, and the log-rank test was used to assess statistical difference among the curves. In this study, an association of tumor categorization and survival was adjusted for clinicopathological factors in the four models based on a manner of practical treatment intervention for UCS. A Cox proportional hazard regression test was used for this modeling, and the relative magnitude of statistical significance is expressed as hazard ratio (HR) and 95% confidence interval (CI). Stepwise assessments were performed to examine the durability of independent association in each set of the adjustment model.

In the first model, an association of tumor categorization and survival was adjusted for patient demographics. In the second model, the association was further adjusted for surgical performance. In the third model, tumor factors were added to the adjustment model. In the fourth model, postoperative treatment types were added to the third model. The variables and their cut-point in the four models were based on a priori survival factors, as described previously.[4]

Sensitivity analysis was performed to examine the utility of tumor categorization on postoperative treatment response. Among women with stage I–III disease, survival was examined based on postoperative treatment type (none, chemotherapy alone, radiotherapy alone, and both chemotherapy and radiotherapy). These groupings have previously been shown to be possible effective postoperative therapy choices.[12–14]

$P < 0.05$ was considered statistically significant (two-sided hypothesis). Statistical Package for Social Science software (IBM SPSS, version 24.0, Armonk, NY, USA) was used for all analyses. We consulted the STROBE guidelines to describe the results of retrospective observational cohort studies.[15]

RESULTS

The two most common tumor categories were type B ($n = 412$, 46.3%) and type C ($n = 381$, 42.9%), while type A tumor was the least common category ($n = 96$, 10.8%). Patient demographics are presented in Table 2.

Women in the type C category were more likely to be older, whereas those in the type A category were more likely to be younger (median age: type A 59, type B 62, and type C 65 years, $P < 0.001$). Women in the type C

category were more likely to be Caucasian (37.2%), whereas those in the type A category were more likely to be Asian (77.7%) ($P < 0.001$). Women in the type C category were more likely to be obese, whereas those in the type A category were least likely (type A 18.9%, type B 23.4%, and type C 26.3%, $P = 0.008$). Among the three groups, women in the type A category were most likely to be nulligravida (type A 28.4%, type B 14.1%, and type C 14.8%, $P = 0.002$).

Tumor characteristics were examined across the three categories (Table 2). Type C tumors were more likely to be advanced stage, whereas type A tumors were least likely (proportion of stage III–IV disease: type A 31.3%, type B 38.1%, and type C 52.7%, $P < 0.001$). On the contrary, type A tumors were more likely to be confined to the uterus, whereas type C tumors were least likely (type A 60.4%, type B 53.4%, and type C 41.7%, $P < 0.001$). Type C tumors were more likely to be large, whereas type A tumors were least likely (proportion of tumor $\geq$ 10 cm: type A 5.3%, type B 9.6%, and type C 20.0%, $P < 0.001$).

Prevalence of any LVSI was similar across the three categories ($P = 0.15$). However, type C tumors were more likely to have LVSI with sarcoma cells, whereas type A tumors were least likely (type A 5.4%, type B 12.1%, and type C 17.1%, $P = 0.013$). Among staged cases, type C tumors were more likely to have pelvic/paraaortic nodal metastasis, whereas type A tumors were least likely (both $P < 0.05$; Table 2). Moreover, among pelvic nodal metastatic cases, type C tumors had the highest LNR, whereas type A tumors had the lowest (type A 7.6%, type B 11.8%, and type C 21.4%, $P = 0.028$).

The median follow-up time of censored cases was 38.6 (interquartile range, 58.5) months. During the follow-up period, there were 419 survival events recorded. On univariate analysis, tumor category was significantly associated with PFS (5-year rates: type A 70.1%, type B 48.3%, and type C 35.9%, $P < 0.001$; Fig. 1a) and CSS (5-year rates: type A 82.8%, type B 63.0%, and type C 47.1%, $P < 0.001$; Fig. 1b).

On multivariate analysis (Table 3), the type C category was independently associated with decreased PFS (adjusted HR 2.38, 95% CI 1.49–3.78) and CSS (adjusted HR 2.04, 95% CI 1.17–3.53) compared with the type A category after adjusting for patient demographics, surgical factors, tumor factors, and postoperative treatment type (both adjusted $P < 0.05$). Similarly, the type B category was independently associated with decreased PFS and CSS compared with the type A category (both adjusted $P < 0.05$).

Stage-specific survival was examined (Supplementary Table S1). Women with stage I type A tumors had a 5-year CSS rate exceeding 90%, whereas those with stage II–IV type C tumors had nearly 30%. Absolute PFS difference among the three types was 28.5% (range 54.8–83.3%) for stage I disease and 25.5% (range 21.7–47.2%) for stage II–IV disease.

An association between tumor category and postoperative treatment response was examined in women with stage I–III disease (Table 4; Supplementary Table S2). When compared with no adjuvant therapy, chemotherapy alone or chemotherapy with radiotherapy significantly reduced recurrence risk and disease mortality in type B and C

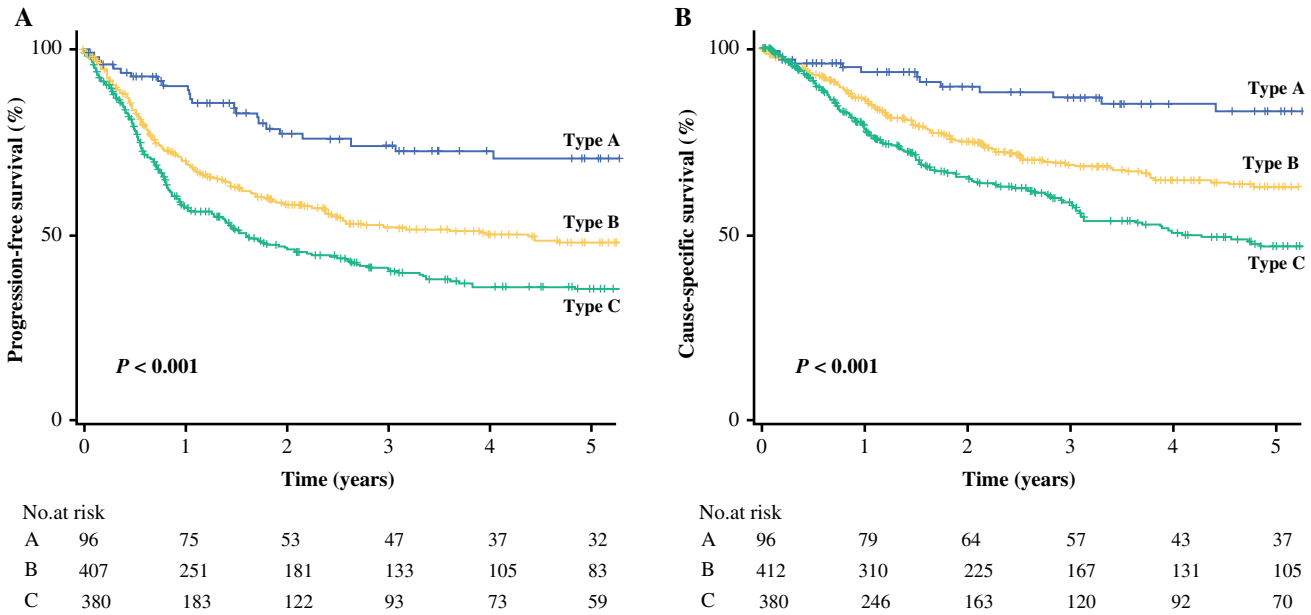

FIG. 1 Survival curves based on risk stratification. Log-rank test for *P* values. Definitions of risk groups are shown in Table 1. **a** Progression-free survival and **b** cause-specific survival

TABLE 3 Association models for survival outcomes

Adjustment model	Progression-free survival		Cause-specific survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted				
Type A	1		1	
Type B	2.28 (1.48–3.51)	< **0.001**	2.18 (1.30–3.67)	**0.003**
Type C	3.16 (2.05–4.86)	< **0.001**	3.29 (1.96–5.51)	< **0.001**
Patient demographics				
Type A	1		1	
Type B	2.08 (1.35–3.22)	**0.001**	1.97 (1.17–3.33)	**0.011**
Type C	2.79 (1.80–4.33)	< **0.001**	2.89 (1.71–4.88)	< **0.001**
Patient demographics, surgical factor				
Type A	1		1	
Type B	1.96 (1.25–3.06)	**0.003**	1.74 (1.03–2.95)	**0.038**
Type C	2.63 (1.68–4.13)	< **0.001**	2.50 (1.47–4.26)	**0.001**
Patient demographics, surgical factor, tumor factors				
Type A	1		1	
Type B	1.99 (1.26–3.15)	**0.003**	1.86 (1.08–3.20)	**0.025**
Type C	2.54 (1.60–4.03)	< **0.001**	2.35 (1.36–4.06)	**0.002**
Patient demographics, surgical factor, tumor factors, postop. treatment types				
Type A	1		1	
Type B	2.05 (1.30–3.25)	**0.002**	1.84 (1.07–3.18	**0.029**
Type C	2.38 (1.49–3.78)	< **0.001**	2.04 (1.17–3.53)	**0.011**

Cox proportional hazard regression models for HRs and *P* values. Significant covariates are emboldened. Patient demographics included age (< 60 vs ≥ 60 years) and race/ethnicity (Caucasian, African, Hispanic, Asian, and others). Surgical factor included residual disease at surgery (yes vs no). Tumor factors included cancer stage (I, II, III, or IV), tumor size (< 5 vs ≥ 5 cm), depth or myometrial invasion (inner half vs outer half), and lymphovascular space invasion (yes vs no). Postoperative treatment types included radiotherapy (yes vs no) and chemotherapy (yes vs no)

HR hazard ratio, *CI* confidence interval

tumors (both $P < 0.05$). When compared with radiotherapy alone, adding chemotherapy to radiotherapy reduced recurrence risk of type C tumors (HR 0.44, 95% CI 0.22–0.85, $P = 0.015$). When compared with chemotherapy alone, adding radiotherapy to chemotherapy significantly reduced recurrence risk (HR 0.53, 95% CI 0.34–0.85), and disease mortality (HR 0.38, 95% CI 0.21–0.70) in type C tumors (both $P < 0.01$).

DISCUSSION

We previously examined the combination patterns of carcinoma/sarcoma and found that survival outcomes differ based on histology type.[4] We since learned that sarcoma dominance has significant prognostic implications,[4,5] so this current analysis examines the three principal factors in patient outcomes for UCS (carcinoma, sarcoma, and sarcoma dominance).

Prior analysis was limited to evaluation of histologic pattern on chemotherapy response, while the effects of histologic pattern on response to radiation therapy were not investigated.[4] Given that sarcoma cells appear to be sensitive to radiotherapy,[6,16] and that a multimodality approach with chemotherapy and radiotherapy is common in postoperative management of UCS,[17–19] this investigation adds useful information on the role of radiation therapy based on histology and dominant patterns in UCS.

This study found that type A UCS represents a less aggressive tumor, whereas type C UCS exhibits more aggressive behavior. Additionally, patient baseline characteristics were largely different across the three defined types of UCS. Our results show that UCS may be better categorized by histologic type and sarcoma dominance rather than as a single disease entity. We suggest that there may be various underlying etiologies, each with unique background characteristics.

Clinically, young Asian women have more favorable UCS tumors (type A), whereas old Caucasian women may have aggressive UCS tumors (type C). Histologically, early-stage type A UCS can have survival almost comparable to that of low-grade endometrial cancer (5-year CSS rate 90.1%), while type B UCS, the most common type (high-grade carcinoma with nondominant homologous

TABLE 4 Progression-free survival based on adjuvant therapy types for stage I–III disease (n = 772)

Characteristic	Versus no treatment		Versus radiotherapy alone		Versus chemotherapy alone	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Type A category						
None	1		0.68 (0.13–3.50)	0.64	1.52 (0.50–4.67)	0.46
Radiotherapy only	1.48 (0.29–7.64)	0.64	1		2.25 (0.48–10.6)	0.31
Chemotherapy only	0.66 (0.21–2.01)	0.46	0.44 (0.09–2.10)	0.31	1	
Both[a]	1.19 (0.28–4.99)	0.81	0.80 (0.13–4.82)	0.81	1.81 (0.48–6.82)	0.38
Type B category						
None	1		1.46 (0.76–2.82)	0.26	1.77 (1.22–2.57)	**0.003**
Radiotherapy only	0.69 (0.35–1.32)	0.26	1		1.21 (0.64–2.28)	0.56
Chemotherapy only	0.57 (0.39–0.82)	**0.003**	0.83 (0.44–1.56)	0.56	1	
Both[a]	0.51 (0.31–0.84)	**0.008**	0.74 (0.36–1.53)	0.42	0.90 (0.56–1.44)	0.66
Type C category						
None	1		1.23 (0.67–2.26)	0.50	1.51 (1.05–2.18)	**0.027**
Radiotherapy only	0.81 (0.44–1.49)	0.50	1		1.23 (0.68–2.23)	0.50
Chemotherapy only	0.66 (0.46–0.95)	**0.027**	0.81 (0.45–1.48)	0.50	1	
Both[a]	0.35 (0.22–0.57)	< **0.001**	0.44 (0.22–0.85)	**0.015**	0.53 (0.34–0.85)	**0.008**

Cox proportional hazard regression models for unadjusted HRs and *P* values. Significant covariates are emboldened

HR hazard ratio, *CI* confidence interval

[a]Both chemotherapy and radiotherapy

sarcoma, 28.7%), and advanced-stage type C tumors belong to a group with much worse survival (5-year CSS rate 33.9%).

Recent molecular analyses have shown that UCS originally arises from endometrial cancer by means of epithelial–mesenchymal transition (EMT) within the tumor, and that the signature of EMT is more prominent in heterologous-type UCS than in the homologous counterpart.[2,3] Further study is warranted to determine what triggers the initiation of EMT in endometrial cancer causing development of UCS; and additionally what role this plays, if any, in causing homologous versus heterologous dedifferentiation. The results of our analysis may be useful in providing a link between basic clinicopathological characteristics and molecular characteristics in UCS.

This study is the first to propose a categorization of UCS utilizing relevant clinical information with a large sample size and comprehensive histopathology review, enhancing the study's quality and reliability. However, this is a retrospective study with the inherent potential for confounding factors missing in the analysis. For example, we lacked information regarding the exact indications for postoperative therapy, introducing the possibility of selection bias. The majority of the study population was Asian, and generalizability to other population needs to be examined.

A major limitation in the interpretation of our results is the lack of central pathology review with predefined criteria (definitions and guidelines utilized for histopathology evaluation). Additionally, interobserver agreement among pathologists has not been validated. Many high-grade endometrial cancers share similar clinicopathological characteristics, making clear diagnosis difficult.[20] This study did not contain a molecular analysis. Given recent analyses of molecular classifications in endometrial cancer,[21] interactions between our histology pattern-based categorization and molecular characteristics are of interest for further exploration.[2,3]

This study proposes a new categorization of UCS that can facilitate communication between clinicians and pathologists with regards to risk stratification. Furthermore, this study elucidates the potential benefits of postoperative therapy with chemotherapy and/or radiotherapy in type B–C UCS. This is particularly applicable in type C UCS, where addition of radiotherapy to chemotherapy seems to have added benefit. As these findings were only demonstrated in retrospective analysis, further study with a prospective design is necessary to confirm this association.

In summary, we showed that UCS may represent several disease entities rather than a single one, and that survival in UCS can vary widely based on tumor characteristics. While UCS is a type of high-risk endometrial cancer, it is paramount to recognize that certain subtypes of UCS behave similarly to low-risk cancers. Our preliminary attempt at UCS classification has led to several useful observations that warrant further validation and investigation.

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