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Matched-pair Analysis for Survival Endpoints Between Women With Early-stage Uterine Carcinosarcoma and Uterine Serous Carcinoma

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Objective: The objective of this study was to compare survival endpoints between women with uterine carcinosarcoma and those with uterine serous carcinoma utilizing matching analysis.

Methods: Patients with stages I to II who underwent hysterectomy at our institution were included in this analysis. Patients with carcinosarcoma were then matched to patients with serous carcinoma based on stage, and adjuvant management received (observation, radiation treatment alone, chemotherapy alone, or combined modality with radiotherapy and chemotherapy. Recurrence-free survival, disease-specific survival, and overall survival were calculated for the 2 groups.

Results: A total of 134 women were included (67 women with carcinosarcoma and 67 with serous carcinoma, matched 1:1). There was no statistically significant difference between the 2 groups regarding 5-year recurrence-free survival (59% vs. 62%), disease-specific survival (66% vs. 67%), or overall survival (53% vs. 57%), respectively. The only independent predictor of shorter recurrence-free survival for the entire cohort was the lack of adjuvant combined modality therapy, while lower uterine segment involvement was the only independent predictor for shorter disease-specific survival. Lack of lymph node dissection and lack of adjuvant combined modality therapy were independent predictors of shorter overall survival.

Discussion: When matched based on stage and adjuvant treatment, our study suggests that there is no statistically significant difference in survival endpoints between women with early-stage carcinosarcoma and serous carcinoma. Adjuvant combined modality treatment is an independent predictor of longer recurrence-free survival and overall survival.

Key Words: endometrial carcinoma, carcinosarcoma, serous, survival, recurrence, matched

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KEY POINTS

- We compared outcomes between uterine carcinosarcoma (CS) and serous carcinoma (USC) using matched analysis.
- When matched, there is no statistically significant difference in survival outcomes between the 2 groups.
- Lack of combined modality therapy and lack of lymph node dissection negatively affected survival outcomes.

INTRODUCTION

USC and CS are rare and aggressive subtypes of endometrial carcinoma constituting 10%[1,2] and 2% to 3%[3,4] of all cases, respectively of women with endometrial carcinoma. Uterine CS is comprised of carcinomatous and a sarcomatous components. Historically, it was felt that CS has intrinsic biology similar to sarcoma than high-grade epithelial tumors. However, it is currently well-known that the 2 different histologic elements may in fact arise from a single malignant epithelial clone.[5,6] Hence, the International Federation of Gynecology and Obstetrics (FIGO) states that uterine CS should be included and staged similarly to endometrial carcinoma.[7]

Patients with uterine CS are thought to have a poor prognosis compared with patients with nonendometrioid carcinoma such as USC. Current literature reported conflicting results of survival endpoints for women with uterine CS compared with those with USC. Few retrospective studies suggest worse outcomes for women with CS compared with other aggressive types of endometrial carcinoma such as USC,[8–12] whereas other investigators reported similar outcomes between the 2.[13,14]

While useful, these aforementioned studies were hampered by various study limitations such as the inclusion of patients with metastatic disease,[9–14] not accounting for various adjuvant management options,[9,10] inclusion of women without a hysterectomy for surgical staging[12,14] and inclusion of some women who were managed with a palliative and not a curative intent.[12] To avoid some of these study limitations, the goal of the current study is to compare survival endpoints in women with early-stage uterine CS to women with early-stage USC using a robust and comprehensive matching analysis.

METHODS

Our study was approved by the Institutional Review Board. Our prospectively maintained database of women with endometrial carcinoma was queried for women with 2009 FIGO stage I to II USC and CS who had undergone a hysterectomy at our institution between January 1990 and December 2019. A total of 228 women were identified. We excluded those with no residual disease in the hysterectomy specimen (n = 12) and those with stage IA and nonmyometrial invasion (n = 18) due to their relatively better reported outcome.[15] We also excluded those with synchronous malignancies (n = 10). We ended up with 188 total patients who fulfilled our inclusion and exclusion criteria before matching

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The authors declare no conflicts of interest.

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(72 women with CS and 116 women with USC). Pathologic diagnosis was confirmed in all included women by gynecologic pathologists.

Women with CS were then matched to those with USC strictly based on 2 factors: 2009 FIGO stage and adjuvant management received (observation, chemotherapy alone, radiation treatment [RT] alone, or combined modality treatment [CMT]). The goal was to randomly match 1 woman from the CS group with 1 woman from the USC group, completely blind to patient outcomes. Matched patients were then removed from the potential match pools to ensure that each patient was unique. All women had a hysterectomy with salpingo-oophorectomy with lymph node evaluation ± omentectomy ± peritoneal cytology.

The following variables were analyzed for each patient; age (continuous variable), body mass index at the time of hysterectomy, Charlson Comorbidity Score[16] at time of hysterectomy, 2009 FIGO stage, presence of lymphovascular space invasion, percentage of myometrial invasion, the status of peritoneal cytology examination (negative, positive, or not performed), lower uterine segment involvement, omentectomy (performed or not), lymphadenectomy (performed or not), and number of examined pelvic and para-aortic lymph nodes. In addition, adjuvant management received (observation, chemotherapy alone, RT alone, or CMT) was also analyzed.

In addition to the descriptive comparisons between the 2 study groups such as patient demographics, tumor characteristics and treatments, survival endpoints of recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS) were also calculated from the date of hysterectomy until the date of recurrence, death from cancer, and death from all causes. The Kaplan-Meier curves were created for each study group for RFS, DSS, and OS. The Wilcoxon rank-sum and Fisher exact tests were performed for univariate comparisons. Multivariate analysis was performed with Cox regression model using manual stepwise selection with an entry criterion of P-value <0.1 and stay criteria of P-value <0.05. A P-value <0.05 was considered statistically significant. Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Of the 72 women with CS, 5 patients did not have any match and were therefore excluded from the final analysis. Thus, a total of 134 women were then included in this study (67 women with CS and 67 with USC, matched 1:1).

All women underwent a hysterectomy and oophorectomy. After surgical staging, patients were followed up on a regular basis usually every 3 to 6 months as clinically indicated. Based on gynecologic oncology tumor board recommendations, physicians' and patient's preferences, various adjuvant management were received. This include observation, chemotherapy alone, RT alone, or most commonly CMT. For patients who received pelvic external beam radiotherapy, the median dose was 45 Gy (range: 45 to 50.4 Gy). Vaginal cuff brachytherapy was administered using ^{192}Ir high-dose rate brachytherapy in 3 to 5 fractions to the proximal 3 to 4 cm of the vagina, of which the median dose was 30 Gy in 5 fractions to the vaginal surface using a single channel vaginal cylinder.

TABLE 1. Patients Demographic, Pathologic, and Management Characteristics of Study Cohort

	n (%)		
Variables	**Carcinosarcoma (N = 67)**	**Uterine Serous Carcinoma (N = 67)**	***P***
Age, median (range) (y)	68 (40-90)	69 (51-90)	0.31
Body mass index, median (range)	34.0 (17.0-52.8)	32.7 (21.5-51.5)	0.86
Follow-up, median (range) (mo)	82.4 (12-280)	99.7 (12-334)	0.54
Race			0.47
White	37 (55)	31 (46)	
African American	28 (42)	35 (52)	
Others	2 (3)	1 (1)	
Charlson Comorbidity Score, median (range)	1.0 (0.0-6.0)	1.0 (0.0-8.0)	0.61
2009 FIGO stage			1.00
IA	42 (63)	42 (63)	
IB	16 (24)	16 (24)	
II	9 (13)	9 (13)	
% of myometrial invasion, median (range)	40 (0.1-1.0)	30 (0.1-1.0)	0.15
LN dissection performed	56 (84)	62 (93)	0.11
No. examined LN, median (range)	12 (0.0-47.0)	14 (0.0-56.0)	0.26
Examined para-aortic LNs, median (range)	1 (0.0-20.0)	2 (0.0-29.0)	0.43
Lymphovascular space invasion	29 (43)	19 (28)	0.07
Omenectomy	35 (52)	37 (55)	0.73
Positive peritoneal cytology	10 (15)	11 (16)	0.97
Lower uterine segment involvement	18 (27)	30 (45)	0.03
Overall adjuvant management			1.00
Observation	12 (18)	12 (18)	
RT alone	9 (13)	9 (13)	
Chemotherapy alone	16 (24)	16 (24)	
Combined chemotherapy and RT	30 (45)	30 (45)	
Radiation treatment modality			0.07
Vaginal cuff brachytherapy	25 (64)	27 (69)	
Pelvic external beam	9 (23)	2 (5)	
Combination	5 (13)	10 (26)	

FIGO indicates International Federation of Gynecology and Obstetrics; LN, lymph node; RT, radiation treatment.

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TABLE 2. Recurrence Patterns of the 2 Study Groups

Variables	n (%) Carcinosarcoma (N = 67)	Uterine Serous Carcinoma (N = 67)	*P*
Cancer recurrence	22 (33)	24 (36)	0.7159
Site of first recurrence			
Isolated vaginal recurrence	2 (9)	3 (13)	1.00
Isolated pelvic recurrence only	1 (5)	2 (8)	1.00
Pelvic and vaginal recurrences	4 (18)	2 (8)	0.16
Para-aortic recurrence without distant	1 (5)	0 (0)	0.77
Any distant recurrence	14 (64)	17 (71)	0.76

Brachytherapy treatments were scheduled once or twice a week. The most common adjuvant chemotherapy regimen received was carboplatin (area under curve = 6) and paclitaxel (175 mg/m^2) given every 21 days. The median number of chemotherapy cycles was 6 (range, 3 to 6).

The median follow-up for the entire study cohort was 99 months (range: 12.0 to 334 mo). Characteristics of the 134 women included in this study are summarized in Table 1. There was no statistically significant difference between the 2 groups regarding patients' demographics, pathologic variables, and extent of surgical staging, except for a higher proportion of women in the USC group with lower uterine segment involvement. In addition, there was no statistically significant difference in recurrence rates or pattern of recurrence between the 2 groups. The most common sites of the first relapse in both groups were lungs (16 patients) and peritoneum (10 patients). Vaginal cuff and pelvic recurrences were significantly lower for those patients who received adjuvant RT with or without chemotherapy (Table 2).

There were no statistically significant differences between women with uterine CS and those with USC regarding 5-year RFS, DSS, and OS. The 5-year RFS was 62% (95% confidence interval [CI]: 0.48-0.73) versus 59% (95% CI: 0.44-0.71) ($P = 0.81$), respectively (Fig. 1). The 5-year DSS was 67% (95% CI: 0.53-0.78) versus 66% (95% CI: 0.51-0.78) ($P = 0.52$), respectively (Fig. 2). The 5-year OS was 57% (95% CI 0.43-0.68) versus 53% (95% CI: 0.39-0.65) ($P = 0.70$), respectively (Fig. 3).

On multivariate analysis, adjuvant multimodality treatment versus observation was the only independent factor for longer RFS. Adjuvant multimodality treatment and lack of lower uterine segment involvement were independent predictors of longer DSS. Lack of lymph node dissection and lack of adjuvant therapy were the only 2 independent predictors of shorter OS. Table 3 summarizes the results of these multivariate analyses including hazard ratios and 95% confidence limits.

DISCUSSION

To the best of our knowledge, this is the first and only study in the literature that used a matched-pair analysis to elucidate the difference in survival outcomes, if any, between women with uterine CS and USC who were treated with similar surgical staging and adjuvant management approaches. In the current study for surgically staged patients with early-stage uterine carcinosarcoma, similar survival endpoints were noted when compared with matched patients with USC. The 5-year RFS was 62% for patients with CS versus 59% for women with USC with $P = 0.81$. Similarly, no statistically significant difference was found in the 5-year DSS or OS between the

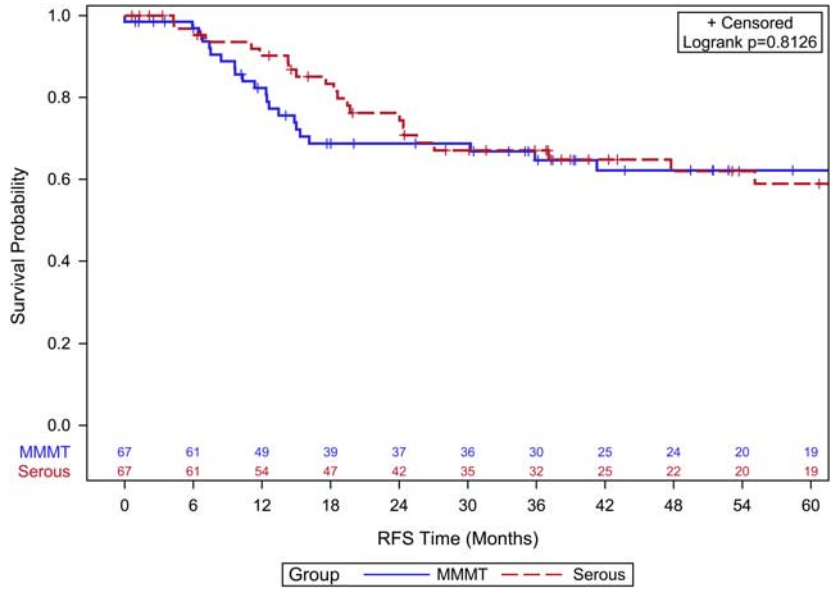

FIGURE 1. RFS for the study cohort based on histology. MMMT indicates malignant mixed Müllerian tumor; RFS, recurrence-free survival. full color online

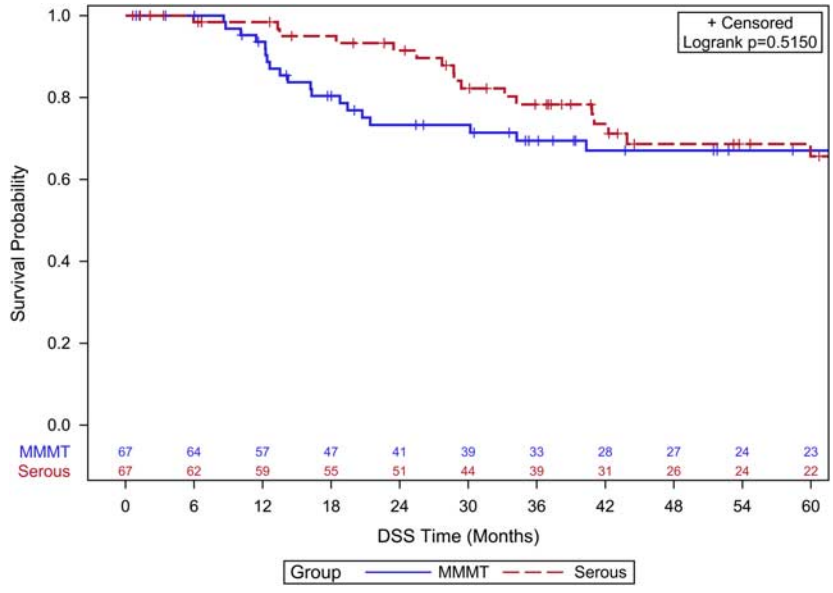

FIGURE 2. DSS for the study cohort based on histology. DSS indicates disease-specific survival; MMMT, malignant mixed Müllerian tumor. full color online

2 groups. In addition, the pattern of the first recurrence was similar and mainly distant (including peritoneal) metastases in both group in more than two third of the patients.

It is important to note that it is difficult to compare our findings directly to previously published data given our unique matched analysis methodology. The only study that only included patients with early-stage disease reported worse survival outcomes for women with uterine carcinosarcoma compared with USC.[8] Interestingly, when the investigators of this study focused at a subset of patients who received similar adjuvant multimodality treatments, they reported no statistically significant difference in RFS, DSS, or OS endpoints in agreement with our findings and conclusion. In agreement with other investigators, the site of first recurrence in both groups was mainly systemic to the lungs, peritoneum, and other distant sites[8,13] highlighting the need for optimizing systemic therapy and identifying novel therapeutic targets.[17,18] Of note, in a phase II prospective study, women with USC with overexpression of HER2/neu demonstrated improved progression-free survival with the addition of trastuzumab to carboplatin and paclitaxel chemotherapy.[17]

Using a matched-pair analysis based on patient's FIGO stage and adjuvant management, we were able to create 2 matched groups of women with early-stage CS and USC based on adjuvant management received and FIGO stage. Accounting for adjuvant therapy is a critically important prognostic variable as one adjuvant approach could be prognostically better compared with other approaches as reported by several investigators for women with USC[19–21] and women with uterine CS.[22–24]

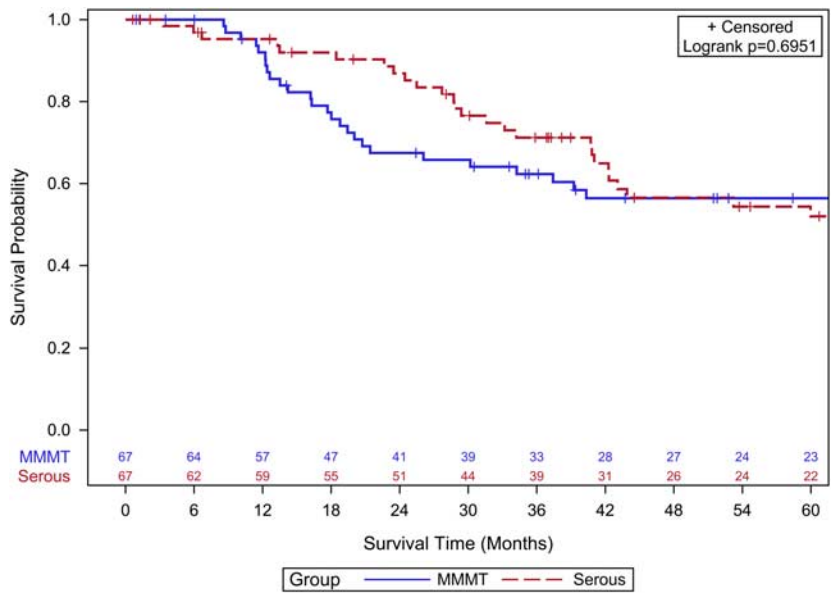

FIGURE 3. Overall survival for the study cohort based on histology. MMMT indicates malignant mixed Müllerian tumor. full color online

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TABLE 3. Multivariate Analysis for Survival Endpoints for the Study Cohort

	Recurrence-free Survival			Overall Survival			Disease-specific Survival		
Variables	**HR**	**95% CI of HR**	***P***	**HR**	**95% CI of HR**	***P***	**HR**	**95% CI of HR**	***P***
Age	NA	NA	NA	1.00	0.97-1.04	0.85	NA	NA	NA
Body mass index	0.97	0.93-1.02	0.19	NA	NA	NA	NA	NA	NA
Charlson Comorbidity Index	NA	NA	NA	1.10	0.94-1.29	0.23	NA	NA	NA
Deep myometrial invasion	2.81	0.65-12.17	0.17	1.91	0.70-5.23	0.21	NA	NA	NA
No lymph node dissection	NA	NA	NA	2.44	1.17-5.11	0.02	2.23	0.92-5.40	0.08
No LUS involvement	0.58	0.30-1.15	0.12	NA	NA	NA	0.36	0.19-0.70	0.003
FIGO stage IA vs. II	0.36	0.11-1.19	0.09	NA	NA	NA	NA	NA	NA
FIGO stage IB vs. II	0.37	0.12-1.18	0.09	NA	NA	NA	NA	NA	NA
Adjuvant CT alone vs. CMT	1.71	0.68-4.28	0.25	1.16	0.53-2.53	0.72	1.20	0.50-2.84	0.69
Observation vs. CMT	3.04	1.24-7.49	0.02	2.65	1.29-5.42	0.01	2.82	1.29-6.20	0.010
Radiation treatment alone vs. CMT	0.32	0.07-1.39	0.13	1.35	0.56-3.22	0.51	0.41	0.09-1.82	0.24

CI indicates confidence interval; CMT, combined modality treatment; CT, chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LUS, lower uterine segment; NA, not applicable.

Our study also demonstrated that adjuvant combined modality was an independent predictor of OS and RFS in the entire study cohort and should be strongly considered.[25,26] While some investigators argued against including women with uterine CS in studies of endometrial carcinoma,[27] our results suggest that inclusion of patients with uterine CS may be allowed in studies involving patients with uterine nonendometrioid carcinoma since surgical staging and adjuvant therapies is practically similar.

Our study has limitations inherent to its single-institution retrospective design. The patients cohort included in this study span over 30 years, during which the treatment protocols has changed. Despite the limitations, we believe that our study is unique since we used our large prospectively maintained database of >3300 women with endometrial carcinoma. This database is regularly updated and audited with full data on patterns of recurrence. In addition, the matched-pair analysis used here accounted for major prognostic factors adding more credibility to our results. With the evolving role of genomics and molecular markers in women with endometrial cancer,[28] the prognostic utility of these innovative markers would certainly help in the decision-making process regarding the management of women with these rare tumors.

CONCLUSIONS

When matched based on FIGO stage and adjuvant treatments, our study suggests there is no statistically significant difference in RFS, DSS, or OS between women with early-stage carcinosarcoma and USC. The most common site of tumor recurrence is systemic highlighting the need for optimizing systemic therapy by incorporating innovative systemic agents in the multimodality adjuvant management.

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