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Patterns of adjuvant treatment and survival outcomes in stage I uterine carcinosarcoma

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ABSTRACT

Objective: To determine patterns in type and sequence of adjuvant treatment and associated differences in overall survival among women with Stage I uterine carcinosarcoma (UCS).

Methods: Women with stage I UCS from 2000 to 2015 were identified through the National Cancer Institute's Surveillance, Epidemiology and End Results database linked to Medicare-based claims follow-up data through 2016. Data including demographics, co-morbidities, surgical procedure, surgical pathology and type and sequence of adjuvant treatment were collected. The primary study outcome was overall survival (OS) by type and sequence of adjuvant therapy. Cancer specific survival was also analyzed.

Results: A total of 755 women with Stage I UCS were identified. Of these, 56.3% (n = 445) received adjuvant therapy, whereas 43.7% (n = 330) did not. In comparison to no adjuvant treatment, an overall survival benefit was noted with receipt of chemotherapy alone for women with Stage I disease (log rank $p < 0.01$). Pairwise comparisons did not show a benefit in OS of concurrent RT-chemo, sequential RT-chemo, or sequential chemo-RT, over chemotherapy alone ($p > 0.05$ for all). Likewise, radiation alone and no treatment were associated with worse OS compared to chemotherapy alone ($p < 0.001$ for both). Adjusted Cox regression models demonstrated an OS benefit only in the chemotherapy alone cohort for Stage I disease (HR 0.43 95% CI 0.32, 0.60, $p < 0.0001$), as well as for CSS (HR 0.41, 95 %CI 0.26, 0.62, $p < 0.0001$), compared to no treatment.

Conclusions: In comparison to no adjuvant therapy, an overall survival and cancer-specific survival benefit was noted with receipt of chemotherapy alone in Stage I UCS.

1. Introduction

Uterine carcinosarcoma (UCS) is a rare, but aggressive, form of uterine cancer that accounts for<5% of all uterine malignancies (Cantrell et al., 2015). In comparison to other high risk uterine cancers (clear cell, serous and International Federation of Gynecology and Obstetrics Grade 3 endometrioid histologies), early stage (Stage I and II) UCS has a worse prognosis with poorer survival outcomes (Vaidya et al., 2006; Amant et al., 2005). Despite poor outcomes associated with this disease, there is a lack of level I evidence to guide adjuvant treatment in early stage UCS. This is likely attributable to limitations in performing prospective, randomized controlled trials in such a rare disease entity.

Currently, National Comprehensive Cancer Network (NCCN) guidelines allow for a variety of adjuvant treatment modalities following primary surgical treatment with hysterectomy, bilateral salpingo-oophorectomy and staging for early stage UCS. For Stage IA UCS, NCCN adjuvant treatment recommendations range from observation to radiotherapy to combination chemoradiotherapy. Similarly, for Stage IB

Abbreviations: Uterine carcinosarcoma, UCS.

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UCS, NCCN adjuvant treatment recommendations include both systemic chemotherapy and combination chemoradiotherapy (NCCN. National Comprehensive Cancer Network Guidelines for Treatment of Cancer by Site: Uterine Neoplasms. In: NCCN, editor.: NCCN;, 2021).

Data supporting the utilization of adjuvant chemotherapy and radiotherapy in early stage UCS is largely limited to small, retrospective cohort studies. For example, a multi-institutional retrospective cohort study of 111 women with early stage UCS by Cantrell et al. found an improvement in progression free survival with adjuvant chemotherapy when compared to observation or radiotherapy (Cantrell et al., 2012). In comparison, several small retrospective studies have found an association between adjuvant radiation and local control among women with early stage uterine carcinosarcoma, but have not consistently demonstrated an improvement in survival outcomes (Hornback et al., 1986; Chi et al., 1997; Gerszten et al., 1998; Callister et al., 2004).

Given the limited available data to guide adjuvant therapy recommendations among women with early stage UCS, the aim of the current study was to determine if type and sequence of adjuvant treatment is associated with differences in overall survival among women with Stage I UCS. Here we are using an alternative national cancer registry, SEER-Medicare, compared to those previously published, to assess adjuvant treatment and associated differences in overall survival in this population to explore the impact of treatment sequencing on such outcomes. SEER-Medicare merges national cancer registry data with Medicare claims data which captures dates of all treatments rendered as well as surgical, radiation, and chemotherapy details including drugs administered. These details are not available in other databases such as the National Cancer Database. SEER-Medicare also provides a broader patient population than multi-institutional data-sources.

2. Methods

A retrospective cohort study was completed. Subjects who were diagnosed with uterine carcinosarcoma from 2000 to 2015 were identified through the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database linked to Medicare-based claims follow-up data through 2016. The SEER-Medicare linked database provides Medicare claims-specific information for patients captured within SEER. (SEER-Medicare Linked Database, 2020) By utilizing Medicare claims-based information, real-time practice and receipt of treatments, including timing and sequencing of both radiation and chemotherapy, is captured.

The primary outcome for this study was overall survival based on vital statistics data provided by SEER. Secondary outcomes included cancer-specific survival. The exposure was defined as the modality and sequence of post-operative adjuvant therapy initiated within 6 months of the index date. The index date was defined as the date of primary surgical treatment based on Medicare claims for hysterectomy. In the absence of a Medicare claims date for hysterectomy, the SEER based diagnosis date was used to define the index date. For either radiotherapy or chemotherapy, at least two or more sequential claims were required to attribute receipt of therapy. If only one claim was identified in the adjuvant time frame, patients were not included as receiving radiotherapy or chemotherapy based on likely minimal clinical impact of the aforementioned therapy. Methodology to capture treatment information is available via a prior publication (Ko et al., 2020). Subjects were followed until death or last follow-up through 12/31/2016.

Data including demographics, co-morbidities, surgical procedure, surgical pathology and adjuvant treatment were collected. Baseline co-morbidities were identified during the twelve months preceding the diagnosis of uterine carcinosarcoma by utilizing the Charlson-Deyo Klabunde comorbidity score as drawn from ICD to 9 and ICD-10 codes (Klabunde et al., 2000). Inclusion criteria included: 1) age $\geq$ 65; 2) diagnosis of Stage I uterine carcinosarcoma (2009 International Federation of Gynecology and Obstetrics staging system) as identified by SEER histology codes of 8950/3, 8951/3, 8980/3, 8981/3 and 8982/3; and 3) active participation in Medicare for the 12 months preceding and following a uterine carcinosarcoma diagnosis. Exclusion criteria included: 1) diagnosis of more than one malignancy in SEER; 2) diagnosis of endometrial cancer by autopsy or death certificate only; and 3) enrollment in Medicare for disability or end stage renal disease.

Receipt of radiation therapy (RT) was identified by an RT claim initiated within 6 months of the index date. The end date of RT was identified when a gap of $>$ 65 days elapsed since the last RT claim with the end date designated as the last RT claim prior to this gap. Data on all modalities of RT were collected, including general radiation therapy, intensity modulated radiation therapy, 3D-specific radiation protocols, stereotactic body radiation therapy, cyberknife, brachytherapy and interstitial therapy (Ko et al., 2020).

Chemotherapy administration was identified utilizing chemotherapy claims initiated within 6 months of the index date (Ko et al., 2020). Data on chemotherapy administration was collected without restriction to the specific drug used. The start date for chemotherapy was defined as the first date of a procedure claim for administration or prescription of chemotherapy. The end date of chemotherapy was defined as the last claim for chemotherapy administration or prescription after the index date with an interval between claims of $\leq$ 65 days. If an interval of $>$ 65 days existed between chemotherapy claims, the last chemotherapy claim prior to the gap defined the chemotherapy end date and the chemotherapy given outside the 65 day gap was identified as a new line of chemotherapy.

Subject receipt of modality and sequence of adjuvant therapy were categorized as follows (Ko et al., 2020). Subjects without RT or chemotherapy claims within 6 months of the index date were categorized as receiving no adjuvant therapy (no adjuvant therapy). Subjects with initiation of RT claims, but no chemotherapy claims, within 6 months of the index data were categorized as receiving RT only (RT only). Those subjects with initiation of chemotherapy claims, but no RT claims, within 6 months of the index date were categorized as receiving chemotherapy only (chemo only). Subjects with both chemotherapy and RT claims within the same time interval (i.e. chemotherapy procedure or prescription claims occurring between the start and end date of adjuvant RT claims or vice versa) initiated within 6 months of the index date were characterized as receiving concurrent chemoradiation (concurrent chemo-RT). Those subjects fulfilling the criteria for concurrent chemo-RT followed by additional chemotherapy claims within $\leq$ 65 days of completion of concurrent chemo-RT were characterized as receiving concurrent chemo-RT followed by chemotherapy (concurrent chemo-RT followed by chemo). Subjects who received both chemotherapy and RT with a RT completion date prior to initiation of chemotherapy claims within 6 months of the index date were defined as receiving sequential RT-chemotherapy (sequential RT-chemo). Those who received both chemotherapy and RT with a chemotherapy completion date prior to initiation of RT claims within 6 months of the index date were defined as receiving sequential chemotherapy-RT (sequential chemo-RT). Sandwich chemoradiation was defined as those subjects that received chemotherapy followed by RT initiation within $\leq$ 65 days of the chemotherapy end date followed by re-initiation of chemotherapy within $\leq$ 65 days of the RT end date (sandwich). Per SEER-Medicare restrictions on sample size, data specific to aforementioned classifications with less than eleven subjects were not reported. (Supplement Table 1).

Standard descriptive statistics were employed to describe demographic, clinical, pathologic, and treatment variables. Continuous variables were reported as median (interquartile range) and categorical variables were reported as frequencies (percent). Chi-square and Kruskal-Wallis tests were utilized to compare categorical and continuous characteristics, respectively, between patient groups. Survival curves were estimated using the Kaplan-Meier method and log rank tests were performed to compare survival differences. Multivariable Cox regression models were used to compare both unadjusted and adjusted relative hazard ratios of survival and their 95% confidence intervals. All

statistical tests were two-sided and differences were considered statistically significant at $p < 0.05$. SAS version 9.4 was used for all analyses (SAS Institute, Cary, NC). Institutional Review Board exemption (Protocol# 824875, May 2016) was granted by the University of Pennsylvania.

3. Results

A total of 755 women with Stage I were identified (Table 1). Among these women, 43.7% (n = 330) received no adjuvant therapy, 24.8% (n = 187) received RT only and 19.7% (n = 149) received chemo only. Additionally, a smaller subset received variations of chemoradiation, including 6.8% (n = 51) concurrent chemo-RT, 2.0% (n = 15) sequential RT-chemo and 3.0% (n = 23) sequential chemo-RT.

Of patients who received chemotherapy (n = 238), 73% received carboplatin (n = 173), 69% received paclitaxel (n = 164), 6.7% received docetaxel (n = 16), 5.5% received doxorubicin (n = 13), and 8% received cisplatin (n = 19). By treatment modality, chemotherapy-only patients primarily received a carboplatin doublet (76%), most commonly combined with paclitaxel (69.8%), or docetaxel (10.1%). Similarly, 71% of concurrent RT-chemotherapy and 86% of sequential chemotherapy-RT patients received a carboplatin/paclitaxel doublet. As for sequential RT-chemotherapy, the small sample size revealed scattered distributions across agents including carboplatin, paclitaxel, cisplatin, and doxorubicin.

Radiation administration varied within each adjuvant therapy arm. For those receiving radiation-only, 44% received EBRT, 16% VB, and 38.5% EBRT + VB. For concurrent RT-chemotherapy, the majority (52%) received combination EBRT + VB, compared to 23% EBRT and 23% VB. For sequential RT-chemotherapy, the majority (86%) received EBRT only, and 13% combination EBRT + VB. In contrast, for sequential Chemotherapy-RT, the majority (60%) received VB only, followed by 25% EBRT and 8% EBRT + VT.

Among women with Stage I uterine carcinosarcoma, younger women were more likely to receive adjuvant treatment (62.8% in age 40–69 vs 60.4% in age 70–79 vs 41.0% in age ≥ 80; $p < 0.01$). Women diagnosed in later years were more likely to receive adjuvant therapy (59.3% of those diagnosed between 2009 and 2015 vs 52.3% diagnosed between 2000 and 2008; $p < 0.0001$). There was a trend towards less receipt of adjuvant therapy with lower income (50.0% with income <$40,000, compared to 57.5% with income $40,000 to <$55,000, 63.0% with income $55,000 to <$75,000 and 55.7 % with income >$75,000; $p = 0.056$). Those being treated in the Northeast (61.7%) were most likely to receive adjuvant therapy compared to the other areas of the country, 52.6% in the Midwest, 55.4% in the South and 54.0% in the West; $p = 0.012$). Women with Stage I uterine carcinosarcoma who underwent lymphadenectomy were also more likely to receive adjuvant therapy than those who did not undergo lymphadenectomy (60.0% vs 44.1%, $p = 0.001$). There were no significant differences between race and receipt of adjuvant treatment among women with Stage I uterine carcinosarcoma (Table 2).

Table 1
Stage I uterine carcinosarcoma patients according to sub-stage and type of adjuvant therapy received. Cells with counts < 11 are reported in suppressed fashion according to NCI SEER-Medicare data use agreement guidelines.

Treatment	Total = 755	I, NOS	IA	IB	P value
	n (%)	(n = 62)	(n = 475)	(n = 218)	
No adjuvant therapy	330 (43.7)	33+ (53.2)	217+ (45.7)	84+ (38.5)	0.49
RT only	187 (24.8)	18 (29.0)	108 (22.7)	61 (28.0)	
Chemo only	149 (19.7)	<11 (17.7)	94 (19.8)	45 (20.6)	
Concurrent chemo-RT	51 (6.8)	<11 (17.7)	32 (6.7)	17 (7.8)	
Sequential RT-chemo	15 (2.0)	<11 (17.7)	<11 (2.3)	<11 (5.0)	
Sequential chemo-RT	23 (3.0)	<11 (17.7)	13 (2.7)	<11 (5.0)	

Overall survival differences were noted by adjuvant treatment cohort with Stage I uterine carcinosarcoma. Kaplan-Meier survival analyses demonstrated that of all patients who received adjuvant treatment, those receiving only chemotherapy had the longest overall survival (Fig. 1, log rank $p < 0.01$). By type and sequence of adjuvant treatment among women with Stage I uterine carcinosarcoma, 5-year overall survival was longest (69.8%) for those receiving chemotherapy only, followed by 60.6% for sequential chemo-RT and 58.0% for concurrent chemo-RT. Shorter 5-year overall survival was noted among those receiving RT only (45.1%), no adjuvant therapy (43.4%), and sequential RT-chemo (40.0%). In unadjusted cox regression models, those who received only chemotherapy had a 62% reduction in hazards risk of death compared to those who received no therapy (HR 0.38 95% CI 0.28, 0.52), $p < 0.0001$. Additionally, those who received sequential chemo-RT (HR 0.49, 95% CI 0.25, 0.96; $p = 0.038$), concurrent chemo-RT (HR 0.62, 95% CI 0.40, 0.96; $p = 0.031$), and RT only (HR 0.80, 95% CI 0.65, 0.99, $p = 0.043$) demonstrated improved survival compared to receiving no adjuvant therapy. After controlling for age, year of diagnosis, lymph node dissection, charlson score, and geographic region, a survival benefit was only noted in the chemotherapy only cohort (HR 0.44,95% CI 0.32, 0.61, $p < 0.0001$) compared to no adjuvant therapy (Table 3).

Cancer specific survival (CSS) also differed by type of adjuvant therapy received. Patients who received chemotherapy-only had statistically significant improved CSS in unadjusted analyses (HR 0.32, 95 % CI 0.21, 0.49, $p < 0.0001$), and adjusted analyses (HR 0.41, 95 %CI 0.26, 0.62, $p < 0.0001$). All other modalities of adjuvant therapy including radiation-only or combination therapy did not show significantly improved CSS in adjusted analyses (Table 4).

Pairwise comparisons for OS (adjusted for age, year of diagnosis, lymph node dissection, Charlson score, and region) demonstrated that compared to chemotherapy alone, no adjuvant therapy (HR 2.31, 95% CI 1.52, 3.50, $p < 0.0001$) and radiation alone (HR 1.95, 95% CI 1.25, 3.06, $p = 0.0006$) were associated with decreased overall survival. Compared to chemotherapy alone, combination therapy modalities were not associated with improved OS (concurrent RT-chemo HR 1.59, 95% CI 0.82, 3.09, $p = 0.358$; sequential RT-chemo HR 2.31, 95% CI 0.97, 5.52, $p = 0.065$); and sequential chemo-RT HR 1.41, 95% CI 0.55, 3.60, $p = 1.0$). Similarly, pairwise comparisons for CSS in adjusted models showed a significantly decreased survival in patients who received no adjuvant therapy or radiation therapy only compared to chemotherapy alone. Combination therapy demonstrated significantly decreased survival for sequential RT-chemotherapy (HR 3.41, 95% CI 1.19, 9.84, $p = 0.014$) compared to chemotherapy alone. (Supplement Table 2).

4. Discussion

This study demonstrated that women with stage I UCS who received adjuvant chemotherapy had a 5-year overall survival rate of 70%, as opposed to 43% in those who did not receive adjuvant therapy. Of the five modalities of adjuvant treatment evaluated in this study for Stage I uterine carcinosarcoma, only those who received chemotherapy alone demonstrated improved overall survival in comparison to receiving no adjuvant therapy (Fig. 1). Although we did not see a significant survival benefit amongst the combination modalities compared to no treatment, this may be attributed to the relatively small sample sizes of these other comparator groups that received various forms of combination therapy, whether concurrent, sequentially with RT first, or sequentially with CT first (6.8%, 2% and 3%, respectively). Similar findings were noted for cancer-specific survival; patients who received chemotherapy-only had a significantly improved survival compared to no adjuvant therapy (aHR

Table 2
Demographics of stage I uterine carcinosarcoma patients according to type of adjuvant therapy received. Cells with counts < 11 are reported in suppressed fashion according to NCI SEER-Medicare data use agreement guidelines.

	No adjuvant therapy	RT only	Chemo only	Concurrent chemo-RT	Sequential RT-chemo	Sequential chemo-RT	P value
	(n = 330)	(n = 187)	(n = 149)	(n = 51)	(n = 15)	(n = 23)	
Age (years)							
40–69	87 (26.4)	49 (26.2)	61 (40.9)	19+ (>37.3)	<11 (<68.8)	<11 (<47.8)	<0.0001
70–79	131 (39.7)	89 (47.6)	70 (47.0)	21 (41.2)	<11 (<68.8)	12+ (>52.2)	
≥80	112 (33.9)	49 (26.2)	18 (12.1)	<11 (<21.5)	<11 (<68.8)	<11 (<47.8)	
Race							
White	230 (69.7)	143+ (76.5)	102 (69.9)	30+ (>58.8)	<11 (<68.8)	12+ (>52.2)	0.157
Black	80 (24.2)	32 (17.2)	29 (19.9)	<11 (<21.5)	<11 (<68.8)	<11 (<47.8)	
Other	20 (6.1)	<11 (<5.9)	15 (10.3)	<11 (<21.5)	<11 (<68.8)	<11 (<47.8)	
Charlson-Deyo Klabunde comorbidity score							
0	187 (56.7)	130 (69.5)	97 (65.1)	29+ (>56.9)	<11 (<73.3)	12+ (>52.2)	0.125
1	91 (27.6)	31 (16.6)	32 (21.5)	<11 (<21.6)	<11 (<73.3)	<11 (<47.8)	
2+	52 (15.8)	26 (13.9)	20 (13.4)	11 (21.6)	<11 (<73.3)	<11 (<47.8)	
Year of index date							
2000–2008	155 (47.0)	124 (66.3)	26 (17.5)	<11 (21.5)	<11 (<68.8)	<11 (<47.8)	<0.0001
2009–2015	175 (53.0)	63 (33.7)	123 (82.6)	40+ (>78.4)	<11 (<68.8)	12+ (>52.2)	
Household income ($)							
<40 K	101 (30.6)	50 (26.7)	33 (22.2)	<11 (<21.5)	<11 (<68.8)	<11 (<47.8)	0.056
40 K to < 55 K	79 (23.9)	53 (28.3)	33 (22.2)	16 (31.4)	<11 (<68.8)	<11 (<47.8)	
55 K to < 75 K	64 (19.4)	51 (27.3)	38 (25.5)	12 (23.5)	<11 (<68.8)	<11 (<47.8)	
≥75 K	86 (26.1)	33 (17.7)	45 (30.2)	12+ (>23.5)	<11 (<68.8)	<11 (<47.8)	
Geographic region							
Northeast	80 (24.2)	46 (24.6)	49 (32.9)	16+ (>31.4)	<11 (<68.8)	<11 (<47.8)	0.012
Midwest	45 (13.6)	25 (13.4)	16 (10.7)	<11 (<21.5)	<11 (<68.8)	<11 (<47.8)	
South	79 (23.9)	54 (28.9)	22 (14.8)	13 (25.5)	<11 (<68.8)	<11 (<47.8)	
West	126 (38.2)	62 (33.2)	62 (41.6)	<11 (<21.5)	<11 (<68.8)	12 (52.2)	
LND completed							
No	99 (30.0)	44 (23.5)	21 (14.1)	<11 (<21.5)	<11 (<68.8)	<11 (<47.8)	0.0013
Yes	231 (70.0)	143 (76.5)	128 (85.9)	40+ (>78.4)	<11 (<68.8)	12+ (>52.2)	

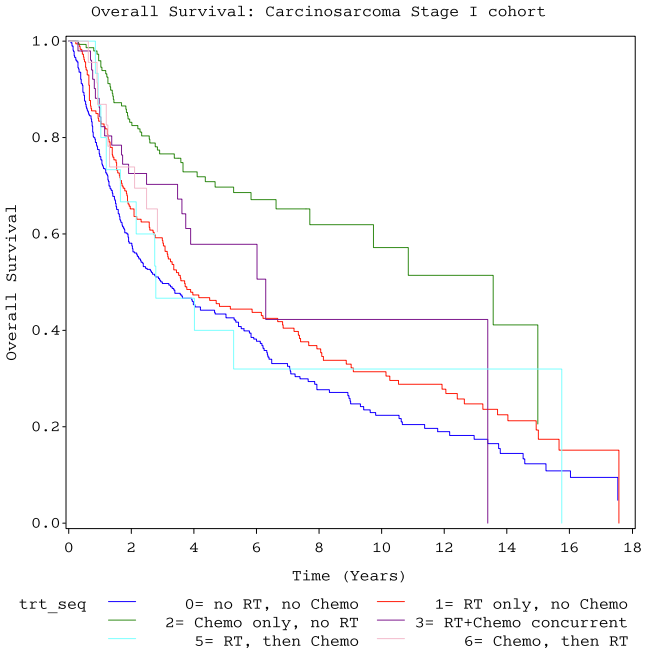

Fig. 1. Overall survival of stage I uterine carcinosarcoma patients according to modality of adjuvant therapy. Only those receiving chemotherapy alone had a significantly improved OS compared to no adjuvant therapy.

0.41, 95 %CI 0.26, 0.62, p < 0.0001).

Forty-Four percent of women diagnosed with stage I UCS did not receive any adjuvant therapy. This aligns with prior studies using NCDB,

Table 3
Overall survival outcomes of stage I uterine carcinosarcoma patients. Unadjusted and adjusted hazard ratios for death are presented. *Models were adjusted for age, year of diagnosis, lymph node dissection, Charlson score, and geographic region.

	uHR (95% CI)	P value	aHR (95% CI) *	P value
Type and sequence of treatment				
No adjuvant therapy	ref	ref	ref	ref
RT only	0.80 (0.65, 0.99)	0.043	0.86 (0.69, 1.06)	0.160
Chemo only	0.38 (0.28, 0.52)	<0.0001	0.44 (0.32, 0.61)	<0.0001
Concurrent chemo-RT	0.62 (0.40, 0.96)	0.031	0.71 (0.45, 1.11)	0.129
Sequential RT-chemo	0.84 (0.46, 1.54)	0.578	1.06 (0.58, 1.967)	0.844
Sequential chemo-RT	0.49 (0.25, 0.96)	0.038	0.62 (0.31, 1.21)	0.160

which reported 36% – 42% of UCS patients receiving no adjuvant treatment. Notably these NCDB studies included patients of all ages and included either patients from stage I only (Seagle et al., 2017), or stage I-III (Wong et al., 2017; Stokes et al., 2018; Rauh-Hain et al., 2015). In our SEER-Medicare population, we found that women who did not receive treatment were generally older, more frequently Black, with higher comorbidity indices, lower income, and resided in the West. This study demonstrates that even with UCS limited to stage I disease, lack of adjuvant therapy portends a poor prognosis, whereby less than half of the women survived 5 years from diagnosis. When possible, adjuvant therapy with systemic chemotherapy should be considered given the significant gain in overall survival. Further efforts should be made to

Table 4
Cancer Specific Survival.

	uHR (95% CI)	P value	aHR (95% CI)*	P value
Type and sequence of treatment				
No adjuvant therapy	ref	ref	ref	ref
RT only	0.97 (0.75, 1.27)	0.839	1.00 (0.76, 1.31)	0.980
Chemo only	0.32 (0.21, 0.49)	<0.0001	0.41 (0.26, 0.62)	<0.0001
Concurrent chemo-RT	0.67 (0.40, 1.12)	0.123	0.82 (0.48, 1.39)	0.459
Sequential RT-chemo	1.14 (0.56, 2.33)	0.711	1.38 (0.67, 2.86)	0.380
Sequential chemo-RT	0.70 (0.34, 1.41)	0.318	0.90 (0.43, 1.85)	0.765

Table 4 Cancer specific survival outcomes of stage I uterine carcinosarcoma patients. Unadjusted and adjusted hazard ratios for death are presented. *Models were adjusted for age, year of diagnosis, lymph node dissection, Charlson score, and geographic region.

ensure factors such as Black race, income, and access, as well as merely older age are not barriers to receipt of adjuvant therapy in patients who would otherwise be suitable candidates for treatment.

Prior studies evaluating adjuvant therapy outcomes among women with early stage uterine carcinosarcoma have included single or multi-institutional studies with mixed outcomes. A multi-institutional study by Dickson et al. found that among a combined cohort of 195 women with Stage I and II uterine carcinosarcoma, just under two-thirds of women received adjuvant treatment. (Dickson et al., 2015). There was a four-fold increased risk of death among women who received no adjuvant therapy in comparison to those that received adjuvant chemotherapy. In comparing adjuvant chemotherapy to combined chemoradiation, they observed an improvement in progression free survival, but not overall survival, among women who received combined modality adjuvant therapy (Dickson et al., 2015). In contrast, a multi-institutional retrospective cohort study of 111 women with early stage uterine carcinosarcoma by Cantrell et al. (Cantrell et al., 2012) found an improvement in progression free survival with adjuvant chemotherapy when compared to observation or radiotherapy, while Kurnit et al. did not find an improvement in overall survival with adjuvant treatment compared to no adjuvant treatment in a single institutional study of early stage uterine carcinosarcoma (Kurnit et al., 2019).

One of the largest multi-institutional studies to date was conducted by Matsuo et al. of 26 institutions, aggregating 1192 cases of stage I UCS (Matsuo et al., 2017). Similar to our study, the most common adjuvant therapy was chemotherapy alone (41.3%). Overall distant recurrence was the most common recurrence pattern at 28% followed by local recurrence of 13%. Receipt of chemotherapy remained a significant prognostic factor in reducing both distant (5-year cumulative rates 21.2% versus 38.0%, adjusted-HR 0.41, 95% CI 0.27–0.62, $p < 0.001$) and local-recurrence in multivariate adjusted model (8.7% versus 19.8%, adjusted-HR 0.46, 95% CI 0.25–0.83, $p = 0.01$), whereas radiation alone did not. Notably, however, combining radiotherapy with chemotherapy was significantly associated with decreased local-recurrence compared to chemotherapy alone in the presence of multiple risk factors such as high-grade carcinoma elements, sarcoma component dominance, and deep myometrial invasion (5-year cumulative rates, 2.5% versus 21.8%, HR 0.12, 95% CI 0.02–0.90; $p = 0.013$).

Several NCDB studies have also reported on UCS patients and adjuvant therapy associated outcomes, from slightly older years' cohorts. Seagle et al. evaluated 5614 stage I UCS patients from 1998 to 2013 (Seagle et al., 2017). They found that multiagent chemotherapy was associated with decreased hazard of death (HR 0.62, 95% CI 0.54–0.73, $p = 1.1 \times 10(-9)$). Highest five-year survival was observed after brachytherapy and multiagent chemotherapy (74.1% (68.3–80.3%), $P < 2.0 \times 10(-16)$). Several other NCDB based studies have reported upon UCS patients in aggregate, including those from stage I-IV (Rauh-Hain et al., 2015; Odei et al., 2018) or I-III (Wong et al., 2017). Rauh-Jain et al, identified that stage I-II UCS patients receiving combination therapy had significantly improved OS compared to no treatment (HR 0.55, 96 % CI 0.46–0.66, p = not provided), as well as chemotherapy only (HR 0.73, 95% CI 0.60–0.88), whereas radiation alone did not (HR.90, 95% CI 0.80–1.02) (Rauh-Hain et al., 2015). Wong et al identified that combination therapy was associated with improved OS over other subgroups in pairwise analyses, and with improved OS in multivariable adjusted cox-models over no adjuvant therapy (HR, 0.50; 95% CI, 0.44–0.57; $P < 0.001$) (Wong et al., 2017). Neither of these studies however, reported on stage I UCS outcomes in isolate. Results from the above prior published studies are also summarized in Table 5.

The present study has both strengths and limitations. The primary strength of this study is that it captures a national cohort of stage I UCS patients, and reflects real-world practice captured within an NCI cancer registry-Medicare linked population, which provides an alternative population of study in the United States to NCDB or multi-institutional studies. Limitations include lack of recurrence data, lack of information regarding patient and provider-based values, and lack of information to assess functional status. We also do not have information regarding accessibility of treatment. Regardless, this study illustrates that a large proportion of women with stage I UCS do not receive adjuvant therapy, and this is associated with particularly poor prognosis, whether due to patient or provider preferences, clinical factors, or access to care.

Overall, our results add further evidence to the 2021 NCCN treatment guidelines for early stage UCS in support of using systemic chemotherapy, with a demonstrated benefit for both cancer-specific survival and overall survival. As for the equivocal recommendation for inclusion of vaginal brachytherapy by NCCN, our results also align with that, as we did not find a benefit in OS. We recognize, however, that radiotherapy may provide locoregional control and decreased local regional recurrence based on single and multi-institutional studies. Future directions for the management of early stage UCS may include incorporation of a histologic risk-based classification system that accounts for the sarcomatous components and carcinomatous features into determining adjuvant therapy treatments, (Matsuo et al., 2018) as well as molecular characterization of UCS (Cherniack et al., 2017). Efforts to improve offering and receipt of chemotherapy to all eligible patients with stage I UCS should be considered to improve cancer specific survival and overall survival given the aggressive nature of this disease.

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CRediT authorship contribution statement

Lori Cory: Conceptualization, Investigation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Colleen Brensinger:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Robert A. Burger:** Investigation, Writing – review & editing. **Robert L. Giuntoli II:** Investigation, Writing – review & editing. **Mark A. Morgan:** Investigation, Writing – review & editing. **Nawar Latif:** Investigation, Writing – review & editing. **Lilie L. Lin:** Data curation, Funding acquisition, Investigation, Methodology, Writing – review & editing. **Emily M. Ko:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology,

Table 5
Summary of previously published studies.

Author	Data-source and subjects	Stage and sample size	Median Follow-up	PFS/Recurrence	OS	Summary
Cantrell (2012) (Cantrell et al., 2012)	Multi-insti. Chemo only (26%), RT only (20%), chemoRT (14%), none (40%).	I-II (n = 111)	37 mo (range 1–174)	Chemo dichotomous comparison (aHR 0.28, 95% CI 0.12, 0.64, p = 0.003)	Chemo dichotomous comparison (aHR 0.35, 95 %CI 0.12, 1.04, p = 0.058)	Limited sample size required comparison of chemo (Y/N) only. Chemo demonstrated benefit for PFS but not OS.
Rauh-Hain (2015) (Rauh-Hain et al., 2015)	NCDB. chemo only (22.4%), radiation only (20.7%), chemoRT (17.0%), None (39.9%).	I-IV (n = 10,609) (stage I = 2997)	28 mo	Not available	Stage I-II Chemo only v. none (aHR 0.73, 95 %CI 0.60–0.88) ChemoRT v. none (aHR 0.55, 95 %CI 0.46–0.66)	In stage I-II UCS, chemo alone or chemoRT improved OS vs none; whereas radiation alone did not.
Dickson (2015) (Dickson et al., 2015)	Multi-insti. Chemo (17.6%), RT (19.7%), chemoRT (22.9%), none (39.9%).	I-III (n = 303) (stage I-II = 195)	31 mo (range 1–160)	Early stage: chemoRT v. none (aHR 0.43, 95% CI 0.19–0.95, p = 0.04)	Early stage: chemoRT v. none (aHR 0.94, 95% CI 0.34–2.65, p = 0.91)	In stage I-II UCS, chemoRT improved PFS but not OS. No improved PFS or OS with CT only or RT only v. none.
Matsuo (2017) (Matsuo et al., 2017)	Multi-insti. Chemo (41%), RT (8.4%), chemoRT (15.8%), none (34%).	I (n = 443)	35.2 mo (range 0.1–211.2)	Recurrence (Distant 62%; local 21%; both 16%) DFS chemo vs none (aHR 0.50, 95 %CI 0.35–0.71, P < 0.001) Local recurrence chemo vs. none (adjusted-HR 0.46, 95 %CI 0.25–0.83, P = 0.01) Distant recurrence chemo vs none (adjusted-HR 0.48, 95 %CI 0.33–0.71, P < 0.001)	OS chemo vs none (aHR 0.30 95 %CI 0.19–0.47, P < 0.001)	59% of population were Asian. Only Chemo alone in multivariable analyses showed improved DFS, OS, and local and distant recurrence benefit.
Seagle (2017) (Seagle et al., 2017)	NCDB. Multiagent chemo (21.6%) v. none (71.8%).	I (n = 5314)	54.7 mo (IQR 20.7–80.3)	Not available	Multi-agent chemo v. none (aHR 0.62, 95 %CI 0.54–0.73, p = 1.1×10^{-9})	Multiagent chemo improved OS, however single agent chemo did not.
Wong (2017) (Wong et al., 2017)	NCDB. Chemo only (19.8%), RT only (21.6%), chemoRT (22.4%), none (36.2%).	I-IIIC1 (n = 4906) (stage I = 3276)		Not available	Chemo only v. none (aHR 0.78, 95% CI 0.69–0.88; p < 0.001) ChemoRT v. none (aHR 0.50, 95% CI 0.44–0.57; P < 0.001)	Chemo alone and chemoRT improved OS vs none; Whereas radiation alone did not. Pairwise comparisons demonstrated chemoRT improved OS over chemo alone.
Odei (2018) (Odei et al., 2018)	NCDB. Chemo (50.5%) vs chemoRT (49.5%)	I-IV (n = 3538)	27.7 mo	Not available	ChemoRT v. chemo (aHR 0.67, 95% CI 0.55–0.81, p < 0.01)	Combination chemoRT demonstrated improved OS over chemo alone.
Kurnit (2019) (Kurnit et al., 2019)	Single-inst. Chemo (9.3%), WPRT (15.7%), VBT (14.3%), chemo VBT (15.7%), chemo WPRT (9.3%); none (37%)	I-II (n = 140)	39.1 mo (range 95 %CI 2.9–297.4)	Unadjusted: no modality was significantly improved over none.	Unadjusted: no modality was significantly improved over none.	Limited sample size precluded multivariable analysis.

Table 5 Summary of selected larger previously published studies assessing impact of adjuvant therapy in uterine carcinosarcoma. Abbreviations: Chemo = chemotherapy; RT = radiation; ChemoRT = combination chemotherapy and radiation; mo = month; WPRT = whole pelvic radiation therapy; VBT = vaginal brachytherapy; none = no adjuvant therapy; single-insti = single institutional study; multi-insti = multi-institutional study; NCDB = National Cancer Data Base.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2022.100930.

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