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Scientific Article

Combined Adjuvant Chemotherapy and Radiation Therapy Improves Disease-Free Survival for Uterine Serous Cancer

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Abstract

Purpose: Uterine serous carcinoma (USC) is a rare but aggressive endometrial cancer histology. We reviewed outcomes for patients with USC to identify the best adjuvant treatment strategy.

Methods and Materials: We retrospectively identified 162 patients with The International Federation of Gynecology and Obstetrics (FIGO) stage I-IVA USC treated at our institution. Baseline characteristics, treatment details, clinical outcomes, and toxicity data were recorded.

Results: Median follow-up was 3.4 years (0.3-26 years). A variety of adjuvant therapy strategies were employed: 14% no adjuvant therapy, 28% radiation alone, 15% chemotherapy alone, and 43% combined chemotherapy and radiation. Distant metastasis was the most common type of recurrence (37% at 5 years). For patients with stage I-IVA disease, there were no significant differences in outcomes by treatment type. For patients with stage I-II disease (70% of the cohort), disease-free survival was significantly higher after chemotherapy (alone or with radiation therapy, $P = .005$) and after combined chemotherapy and radiation compared with all other treatments ($P = .025$). Toxicity outcomes were favorable, with minimal grade 3 and no grade 4 or 5 events.

Conclusions: Patients with USC experience high rates of recurrence and mortality. Distant metastasis is the most common pattern of failure for all stages. For patients with early-stage disease, combined chemotherapy and radiation improves 5-year disease-free survival compared with either single adjuvant treatment alone or no adjuvant treatment. The relatively large group of patients with USC included in this study may account for our ability to detect this improvement whereas clinical trials have failed to do so, possibly owing to the relatively small percentages of patients with USC enrolled.

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Introduction

Uterine cancer represents the most common gynecologic malignancy in the United States. Estimates predict 65,620 new cases and 12,590 deaths in 2020, with an

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approximate 5-year overall survival (OS) rate of 81%.[1] Uterine serous carcinoma (USC) is an aggressive subtype of endometrial cancer that portends a poor prognosis, even compared with other aggressive histologies such as clear cell or grade 3 endometrioid adenocarcinoma. Specifically, USC comprises only 10% of endometrial cancers but accounts for 39% of deaths.[2] The 5-year disease-specific survival for women with USC is lower than that of other aggressive histologies (55% for USC, 68% for clear cell, and 77% for grade 3 endometrioid), a difference that remains significant even for patients with stage I-II disease (74% USC, 82% clear cell, and 86% grade 3 endometrioid).[2]

Patients with USC are often excluded from or underrepresented in clinical trials for patients with endometrial cancer.[3-5] As such, it is difficult to ascertain the optimal treatment strategy. In several trials for patients with high-risk endometrial cancer, subgroup analyses of patients with USC have not shown a significant treatment effect owing to the relatively small percentages of patients enrolled with this histology.[6-8] Risk factors for recurrence for patients with early stage USC include greater than 50% myometrial invasion, positive peritoneal washings, cervical stromal invasion, and lymphovascular space invasion.[9-11] However, even women with the most favorable stage disease are at high risk of recurrence without adjuvant therapy.[12]

Despite the poor survival rates for USC relative to other endometrial cancer histologies, outcomes for these patients have improved over time as changes in the management of these patients have been adopted, suggesting an efficacy of new treatments such as systemic therapy.[13] According to an National Cancer Database analysis, since 1998, the use of adjuvant chemotherapy (CT) and vaginal brachytherapy (VBT) have increased, whereas the use of pelvic radiation therapy (RT) (external beam RT; EBRT) has decreased.[14] CT is generally recommended for USC given the high rates of distant spread; however, the role of RT is unclear.[15] Evidence regarding the role of RT in this disease is conflicting, with some studies failing to show a benefit whereas others have demonstrated improved outcomes with the addition of RT.[9,14,16-20]

Given the lack of evidence guiding selection of adjuvant therapies for USC treatment, we retrospectively examined our institutional outcomes of patients with USC and compared outcomes by adjuvant treatment strategy.

Methods and Materials

Patient population

In this retrospective study, we evaluated patients treated at a single institution diagnosed with stage I-IVA endometrial cancer with serous histology (either pure serous or with a mixed component), established pathologically by endometrial biopsy and/or hysterectomy. Because the percent serous component was not always reported for patients who had mixed histologies, no "threshold" or minimum percentage serous component was set for inclusion. Rather, all patients who had any serous component were included. Patients with distant metastases at the time of diagnosis were excluded. Patients were required to have a minimum of 6 months of follow-up. This study was approved by our hospital's institutional review board.

Treatment technique

We identified a total of 162 patients who met the above criteria. All patients underwent total hysterectomy and bilateral salpingo-oophorectomy (TH-BSO) with surgical staging. Surgery was done either via open approach or laparoscopically. Adjuvant treatment details and follow-up information were recorded, along with the rates of genitourinary (GU), gastrointestinal (GI), and gynecologic toxicities. Adjuvant treatment groups included no adjuvant therapy (NAT), chemotherapy only (CT), radiation therapy only (RT), or combined CT and RT (CRT). Twenty-two (14%) patients received NAT.

One hundred fourteen patients (71%) received adjuvant RT, which included VBT, whole pelvic EBRT, whole abdominal and pelvic irradiation (WAPI), or a combination of these. Patients who were treated with EBRT received a median dose of 45 Gy to the pelvis (range, 25-53 Gy). Those treated with WAPI received a median dose of 30 Gy to the abdomen (range, 13.5-30 Gy). Patients treated with VBT alone received a median dose of 30 Gy (range, 21-30 Gy) in 6 fractions (range, 3-6).

Ninety-four patients (58%) received adjuvant CT. The most common CT agents used were carboplatin and paclitaxel, given for a total of 6 cycles every 3 weeks. CT was either given sequentially with radiation therapy (before or after) or given in a sandwich fashion with radiation therapy (3 cycles CT, then RT, then an additional 3 cycles of CT).

Follow-up

Surveillance was performed in accordance with published national guidelines.[21] Standard follow-up consisted of a history and physical examination every 3 months for the initial 2 years after treatment, then every 6 months for the next 3 years, then annually. Surveillance imaging was ordered at the discretion of the treating physician.

Clinical outcomes

Local recurrence (LR), regional recurrence (RR), distant metastases (DM), OS, and disease-free survival (DFS) were calculated for all patients and separately for

patients with stage I-II disease according to Kaplan-Meier.

Statistical analysis

Clinical outcomes were analyzed using Student's unpaired *t* tests for continuous variables and Pearson's χ^2-tests for categorical variables among groups. Analyses of OS, cancer specific survival, DFS, LR, RR, and DM were calculated and compared using the Kaplan-Meier method. Acute (less than or equal to 6 months post-RT) and chronic (greater than 6 months post-RT) GI/GU/gynecologic toxicities were graded according to Common Terminology Criteria for Adverse Events v4.0.[22] Findings were considered statistically significant if the *P* value was $< .05$, and all statistical tests were 2-sided. Statistical analyses were performed with Statistical Package for the Social Sciences version 24.0 (IMB, Armonk, NY).

Results

Baseline characteristics

The patient cohort consisted of 162 patients with USC treated at our institution from 1975 through 2018, for whom complete treatment records were available. The median follow-up time after definitive treatment was 3.4 years (range, 0.3-25.8 years). The median age at diagnosis was 68 years (range, 38-91 years). The median tumor size at recurrence was 3.8 cm (range, 0-13 cm) (Table 1).

Because our analysis was limited to patients with serous histology, most patients had grade III disease; however, for a few patients with mixed histologies, the overall tumor grades were reported as grade I (2 patients, 1%) or grade II (14 patients, 9%). Fifty-five patients (34%) had mixed histologies with a serous component, and the remaining 107 patients (66%) had pure serous carcinomas. Of those with mixed histologies, the serous component (measursed as a percentage) was not reported for 33 patients. For the remaining 22, the percent serous component ranged from 10% to 99% (median 30%). Tumor grade was unavailable or was listed as "unknown" for 7 patients with mixed histologies and for 15 patients with pure serous carcinoma.

Patients presented with a variety of stages; however, the majority (57%) had The International Federation of Gynecology and Obstetrics (FIGO) stage I (40% IA and 17% IB) disease. Thirteen percent of patients had FIGO stage II disease. The second most common stage group was stage III disease (28% overall; 6% IIIA, 1% IIIB, and 21% IIIC). Most stage III patients had pathologically positive pelvic or peri-aortic lymph nodes (14% and 5%, respectively). Only 2% of patients had FIGO stage IVA disease. There were no patients with stage IVB disease, as patients with metastatic disease at diagnosis were excluded. Lymphovascular space invasion was present in 50% of patients.

Table 1 Baseline characteristics for all patients, stage I-IVA (n = 162)

Median age (y)	68 (38-91)
Median follow-up (y)	3.4 (0.3-25.8)
Median tumor size (cm)	3.5 (0-13)
Grade	
I	2 (1%)
II	14 (9%)
III	124 (76%)
N/A	15 (9%)
Unknown	8 (5%)
T stage	
1a	72 (44%)
1b	33 (20%)
2	30 (18%)
3a	13 (8%)
3b	10 (6%)
4a	1 (0.6%)
Unknown	3 (2%)
N stage	
0	109 (67%)
1	23 (14%)
2	8 (5%)
Unknown	22 (14%)
FIGO stage group	
I	93 (57%)
IA	66 (40%)
IB	27 (17%)
II	21 (13%)
III	46 (28%)
IIIA	10 (6%)
IIIB	2 (1%)
IIIC	33 (20%)
IVA	3 (2%)
LVSI	
Yes	81 (50%)
No	72 (44%)
Unknown	9 (6%)
Chemotherapy	
Yes	93 (58%)
No	66 (40%)
Unknown	3 (2%)

Abbreviations: FIGO = The International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion.

Adjuvant treatment

In our patient cohort, 138 patients (85%) received some form of adjuvant therapy. Twenty-four patients (15%) received adjuvant CT alone, and 114 patients (70%) received adjuvant RT with or without CT. Of the patients who received adjuvant RT therapy, 45 (28%) received adjuvant RT alone, and 69 (43%) received adjuvant RT and adjuvant CT. A variety of RT techniques

Table 2 Number (%) of patients receiving each adjuvant treatment type

	No RT	RT (all types)	VBT alone	EBRT + VBT	EBRT alone	WAPI alone	WAPI + VBT
All (n = 162)	48 (30%)	114 (70%)	40 (25%)	19 (12%)	23 (14%)	1 (1%)	31 (19%)
No CT (n = 67)	24 (15%)	45 (28%)	5 (3%)	6 (4%)	5 (3%)	1 (1%)	27 (17%)
CT (n = 93)	24 (15%)	69 (43%)	35 (22%)	13 (8%)	18 (11%)	0 (0%)	3 (2%)

Abbreviations: CT = chemotherapy; EBRT = external beam radiation therapy; RT = radiation therapy; VBT = vaginal brachytherapy; WAPI = whole abdominal and pelvic irradiation.

were employed, and the number of patients who received each RT type with or without adjuvant CT and as a function of cancer stage are shown in Tables 2 and E1, respectively. Forty patients were treated with VBT alone (25%) to a median dose of 30 Gy (range, 21-30 Gy) in 6 fractions (range, 3-6) (Table E2). Twenty-three patients were treated with pelvic EBRT alone (14%) and 19 with pelvic EBRT and VBT (12%). EBRT was given to a median dose of 45 Gy (range, 25-53 Gy) to the pelvis. One patient was treated with WAPI alone (0.6%) and 31 with WAPI and VBT (19%), to a median dose of 30 Gy (range, 13.5-30 Gy) to the abdomen. Seven patients did not receive WAPI but did have extension of their pelvic fields to include the periaortic lymph node basin. One patient received a boost to an area of node-positive disease (64.8 Gy).

Clinical outcomes

With a median follow-up of 3.4 years, 57 patients recurred (locally, regionally, and/or distantly). Fifty-one patients experienced distant metastasis, making it the most common pattern of recurrence. In contrast, 13 experienced local recurrence and 14 experienced regional recurrence. Of these, 8 local and 10 regional recurrences occurred in patients who also had distant metastases (2 of these patients experienced local, regional, and distant failure, whereas the remaining experienced local and distant or regional and distant failure only). One patient experienced both local and regional recurrence without distant recurrence, and 3 patients experienced isolated regional failure. Only 4 patients experienced isolated local recurrence, all of whom were treated with salvage RT (alone or in combination with CT) and had no evidence of disease at the time of last follow-up. For patients who experienced LR, RR, or DM, the median times to recurrence were 1.4, 1.2, and 1.8 years, respectively. The actuarial 5-year recurrence rates were 11%,12%, and 37%, respectively (Table E3).

When our analysis was limited to the 114 patients with stage I-II disease, 31 patients recurred locally, regionally, and/or distantly. Twenty-seven patients experienced distant metastasis, making it the most common pattern of recurrence for early stage patients as well. Nine experienced local recurrence and 4 experienced regional recurrence. For early stage patients who experienced recurrence, the median times to LR, RR, and DM, respectively, were 1.4, 2.9, and 2.1 years. The actuarial 5-year recurrence rates of LR, RR, and DM for these patients were 10%, 5%, and 26% respectively (Table 3).

The 5-year rate of DFS after definitive treatment was 54% for all patients (stage I-IVA). Median OS was not reached. The 5-year rate of OS was 63%. For patients with early-stage disease, the 5-year rate of DFS was 65%, and 5-year OS was 71%.

Staging and clinical outcomes by treatment type

To examine the effect of FIGO stage on choice of treatment type, the number of patients in each FIGO stage group as well as treatment type were recorded (Table E1). Patients were classified based on whether or not they received any RT or CT and on the number receiving specific RT types, such as VBT alone, pelvic EBRT alone or with VBT, or WAPI. Not surprisingly, patients who received no adjuvant CT or RT were more likely to have early stage disease: of the 24 patients who received no adjuvant CT or RT, 21 had stage I-II disease. However, the groups that received adjuvant CT or RT included both patients with early and advanced stage disease: of the 69 patients who received both (CRT), there were 25 patients with stage IA disease and 20 with stage IIIC disease. Of note, adjuvant treatment recommendations varied by the treating physician.

To investigate the possible effect of treatment type on recurrence and survival, we examined each clinical outcome by each treatment type. Although more than two-thirds of patients received some form of RT, overall, all possible treatment groups were well-represented: 24 patients received no adjuvant therapy, 24 received CT without RT, 45 received RT without CT, and 69 received both CT and RT (Table 2). Although there was a trend toward improved outcomes for patients who received adjuvant therapy over those who received none, there was no significant difference in the rate of LR, RR, DM, recurrence, OS, or DFS among the 4 possible treatment groups (NAT, RT only, CT only, and CRT) at 1, 2, and 5 years for patients with stage I-IVA disease (Table E3).

Because of the heterogeneity of stages within each treatment group (Table E1), we also reported the number of recurrences by treatment type for patients with stage I-II disease only (Table 3). For this group of patients,

Table 3 Clinical outcomes for all patients with stage I-II disease and by treatment group (at 2 y, 5 y)

	All patients	By adjuvant treatment group				
	(n = 114)	NAT (n = 19)	RT only (n = 37)	CT only (n = 18)	CRT (n = 40)	*P* value
LR	6%, 10%	7%, 16%	6%, 10%	12%, 12%	3%, 7%	.815
RR	1%, 5%	0%, 10%	0%, 4%	6%, 6%	0%, 5%	.878
DM	12%, 26%	30%, 44%	4%, 31%	12%, 18%	3%, 19%	.075
OS	92%, 71%	83%, 54%	91%, 71%	89%, 77%	97%, 74%	.085
DFS	80%, 65%	60%, 47%	75%, 59%	78%, 72%	95%, 75%	**.012**

Abbreviations: CRT = combined chemotherapy and radiation therapy; CT = chemotherapy; DFS = disease-free survival; DM = distant metastases; LR = local recurrence; NAT = no adjuvant therapy; OS = overall survival; RR = regional recurrence; RT = radiation therapy.
Bold value indicates statistical significance.

there was a significant difference between the treatment groups in the rate of DFS (Fig 1). The 2-year rates of DFS were 60% for the group that received no CT or RT (NAT), 75% for the RT only group, 78% for the CT only group, and 95% for the CT and RT group; the 5-year DFS rates were 47%, 59%, 72%, and 75% (P = .012). Of note, within the CT and RT group, 5 of the 7 recurrences occurred in patients who received VBT alone. Clinical outcomes for the remaining 48 patients with stage IIIA-IVA disease are shown in Figure E4.

We also compared clinical outcomes for patients with stage I-II disease who received CT versus those who received no CT, regardless of RT. Patients who received CT had improved rates of DM, recurrence, OS, and DFS compared with those who did not (Tables 4 and E5). There was no difference in any outcome for patients with stage I-II disease who received RT (with or without CT) versus those who received no RT. Patients who received both CT and RT had improved DFS compared with those in any other treatment group (CT alone, RT alone, or NAT) (Table 4, Fig 2).

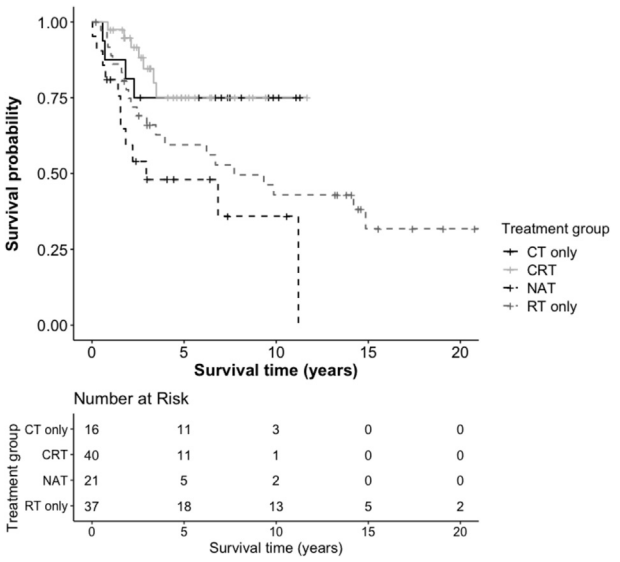

Figure 1 Kaplan-Meier of disease-free survival by treatment group for patients with stage I-II disease.

Specifically, 2-year DFS was 95% for patients who received CRT and 72% for all other groups, whereas 5-year DFS rates were 75% and 60%, respectively.

Clinical outcomes for patients treated with CRT by treatment sequence

Because patients with stage I-II disease treated with CT and RT had improved DFS compared with other treatment groups, we examined the effect of CT and RT sequence for these patients. Twenty-two of these patents (56%) received "sandwich" therapy, or adjuvant CT, followed by RT, followed by additional CT. Seventeen patients (44%) received only adjuvant CT followed by RT. No patient received adjuvant RT before CT or concurrent CRT. There was no significant difference in rates of LR, RR, or DM between patients who received sandwich therapy versus those who did not (Table E6). There was a trend toward improved DFS with sandwich CRT; however, this was not significant (P = .098). There was a significant improvement in OS for patients who received sandwich CRT compared with those who did not (P = .034).

Toxicity

Acute and chronic toxicity data were available for 52 and 45 of the 162 patients included in this study, respectively. The overall incidence of acute grade 2 or higher toxicities was low. The majority of acute toxicities were grade 1, the most common of which was fatigue, which occurred in 23% of patients (Table E7). There were few acute GI and GU toxicities: 1 patient (2%) experienced acute grade 2 urinary incontinence, and the remaining GI and GU toxicities were grade 1. There were 4 grade 2 events: fatigue (2%), urinary incontinence (2%), vaginal infection (2%), and vaginal dryness (2%). There was 1 episode (2%) of acute grade 3 vaginal stenosis. There were no grade 4 or 5 acute toxicities.

The majority of chronic toxicities were also grade 1 events, the most common of which were fatigue (24%), diarrhea (16%), constipation (11%), urinary frequency

Table 4 Outcomes at 2 and 5 y (2 y, 5 y) by CT status, RT status, and combined CRT status for patients with stage I-II disease (n = 114)

	Chemotherapy			Radiation			Chemoradiation		
	No CT (n = 56)	CT (n = 58)	*P* values	No RT (n = 37)	RT (n = 77)	*P* values	Other (n = 74)	CRT (n = 40)	*P* values
LR	6%, 11%	6%, 8%	.660	9%, 13%	4%, 8%	.396	7%, 11%	3%, 7%	.414
RR	0%, 5%	2%, 5%	.948	3%, 7%	0%, 4%	.429	1%, 5%	0%, 5%	.711
DM	19%, 35%	5%, 18%	**.020**	21%, 30%	8%, 25%	.482	17%, 30%	3%, 19%	.087
OS	88%, 66%	95%, 77%	**.038**	86%, 67%	94%, 73%	.472	89%, 69%	97%, 74%	.159
DFS	70%, 55%	89%, 75%	**.005**	69%, 60%	85%, 67%	.256	72%, 60%	95%, 75%	**.025**

Abbreviations: CRT = combined chemotherapy and radiation therapy; CT = chemotherapy; DFS = disease-free survival; DM = distant metastases; LR = local recurrence; OS = overall survival; RR = regional recurrence; RT = radiation therapy.
Bold value indicates statistical significance.

(11%), and vaginal stenosis (20%). Few patients developed chronic grade 2 or higher toxicities: 1 patient developed grade 2 anorexia, 1 patient had grade 2 diarrhea, and 3 had grade 2 urinary incontinence. Twelve patients developed chronic vaginal stenosis: 9 with grade 1 and 3 with grade 2. There was 1 patient with a grade 2 vaginal infection and 1 patient with grade 2 lymphedema in the chronic toxicity period. There were no grade 3, 4, or 5 chronic toxicities.

Discussion

As our results indicate, USC is an aggressive histology with poor outcomes. Patients with USC at our institution were treated with a variety of possible combinations of adjuvant therapy: 14% with no adjuvant therapy, 15% with CT alone, 28% with RT alone, and 43% with both CT and RT in varying sequences. Five-year rates of DFS, cancer specific survival, and OS were 54%, 69%, and 63%, respectively. These outcomes are comparable to previously published data on patients with USC.[2] Recurrence was relatively common: overall, the 5-year rate of DFS was 54%, and the vast majority of recurrences were distant, with a 5-year DM rate of 37%. When our analysis was limited to patients with stage I-II disease, 5-year DFS remained relatively poor at 65%, with a 5-year DM rate of 26%. Patients with early-stage disease who received CT had improved outcomes compared with those who did not, similar to other series on patients with USC.[15] Meanwhile, the combination of adjuvant CT and RT significantly improved DFS. However, even for patients with early stage disease who received the most aggressive therapy (combined adjuvant CRT), the 5-year rate of any recurrence was high at 30%, and the majority of recurrences were distant metastases (26%).

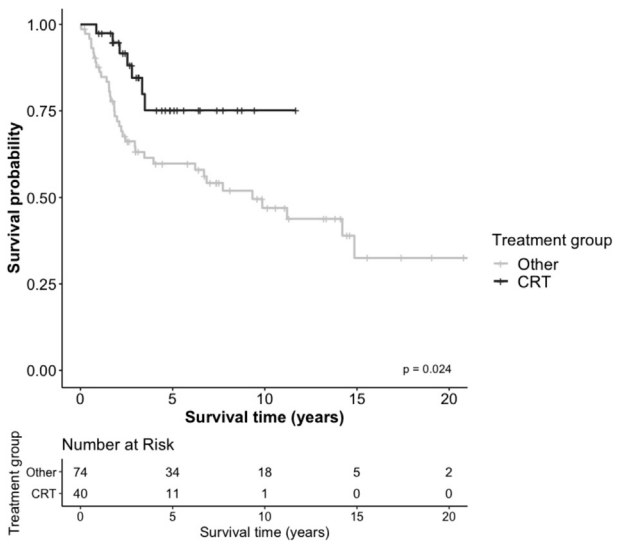

Figure 2 Kaplan-Meier of disease-free survival by combined chemotherapy and radiation therapy status for patients with stage I-II disease.

Patients with USC are frequently excluded from trials or, if they are included, there are typically too few to detect significance on subgroup analysis. Post operative radiation therapy in endometrial carcinoma-3, which tested the addition of concurrent and adjuvant CT to pelvic RT for patients with high-risk disease did include patients with USC; however, they comprised only 16% of the total number of patients enrolled.[6] Those with USC had worse outcomes than patients with other histologies in this trial, with a 5-year OS of 71% and failure-free survival (FFS) of 64% compared with 79% and 72% for the entire cohort, respectively. Subgroup analysis failed to show a significant difference in FFS for patients with USC with the addition of CT at the initial publication of this trial; however, a posthoc survival analysis of the trial with 1 additional year of follow-up showed that after adjustment for stratification factors, patients with USC who received CRT had improved 5-year OS and FFS. Specifically 5-year OS was 71% for those who received CRT and 53% for those who received RT alone.[23] Gynecologic Oncology Group-258, a phase 3 trial testing the addition of RT to adjuvant CT for patients with stage III-IV disease, also included patients with stage I-II USC.[7]

Only 18% of the patients in the study had USC histology, and although this trial showed fewer locoregional relapses (but inferior quality of life and no difference in survival) with the addition of RT, relapse-free survival was not significant for patients with USC on subgroup analysis. Similarly, Gynecologic Oncology Group-249 compared pelvic RT verses VBT plus CT for high-intermediate and patients with high-risk disease, including stage I-II USC, which comprised 15% of the patients in this trial.[8] Again, subgroup analysis failed to show a significant treatment effect by histology, although a disproportionate number of the overall recurrences in this trial were in patients with USC. Finally, in a combined analysis of 2 randomized trials evaluating adjuvant RT with or without sequential CT for women with high-risk endometrial cancer, only 14% of patients had USC histology.[24] Overall, this analysis showed that the addition of adjuvant CT improves progression-free survival; however, subgroup analysis showed no significant benefit for patients with USC.

Our results show improved outcomes with the use of combined adjuvant CT and RT in patients with early-stage USC. This is consistent with other published data. A retrospective multi-institution review of 55 women with stage II USC showed that patients treated with CT (mostly carboplatin/paclitaxel), with or without RT, had lower rates of recurrence compared with patients treated with RT alone or observation, and none of the patients who were treated with CRT experienced recurrence.[18] In that study, the overall rate of recurrence was 36%, and most recurrences were extra-pelvic, occurred within 2 years, and were not salvageable, which mirrors our findings. Additionally, a meta-analysis comparing the effect of CT alone verses combined CT and RT on OS in women with USC showed that combined CT and RT reduced the risk of death compared with CT alone, and further analysis found a benefit for combined therapy for both early stage and advanced disease.[20] Similarly, 2 retrospective studies of women with USC found a survival benefit for combined therapy with CT and RT for patients with advanced-stage disease[19] and for women with all stages of USC.[25] Limited prospective evidence supports this approach, as a phase II trial of "sandwich" adjuvant pelvic RT and paclitaxel/carboplatin CT for patients with USC showed that this treatment is safe and efficacious.[9] Specifically, they reported a median progression-free survival time of 22 months and median OS of 28 months for patients with stage III and IV disease.

The mechanism for improved survival outcomes with the addition of RT to adjuvant CT for patients with USC is not clear; however, the benefit of RT may be related to reduced rates of pelvic lymph node recurrence. Although not significant, we showed that the 5-year rate of RR was 7% without RT and 4% with RT. A retrospective analysis of patients in the Rare Cancer Network with all stages of USC, including nearly half with stage III and IV disease, showed that the use of RT significantly reduced pelvic recurrence from 29% to 14%.[17] RT dose is also likely to be important, as older RT techniques such as WAPI typically involve a lower dose for abdominal compared with pelvic RT, and WAPI has been shown to be inferior at controlling residual regional disease compared with CT.[26]

Limitations of this study include the retrospective nature of this work. Additionally, we lacked sufficient numbers in each treatment group to compare outcomes by RT treatment types such as pelvic external EBRT, WAPI, or VBT. Similar prior studies have also combined all types of adjuvant RT,[25] making it difficult to draw conclusions about the optimal RT treatment for these patients. Limited exploration of the type of RT most appropriate for these patients is available. However, based on our results showing a trend toward improved outcomes with CRT and the results of randomized trials for high-risk endometrial cancer in general,[6,7] our institutional practice has favored EBRT with or without a VBT boost for all patients with USC with stage IB disease or greater, and VBT alone for those with stage IA disease.

Our results confirm the growing evidence that the addition of adjuvant RT to CT improves outcomes in patients with USC. Although randomized data supporting this approach are lacking, the rarity of this disease makes accrual to clinical trials challenging. Meanwhile, the relatively high rate of DM despite the use of aggressive adjuvant therapy, even in patients with early-stage disease, highlights the need for additional advances for these patients, such as improved surgical techniques[27] and the use of targeted agents like trastuzumab.[28] Finally, inclusion of these patients in larger randomized trials for endometrial cancer is needed, as has been previously suggested,[29] to help improve treatment strategies for this aggressive disease.

Conclusions

In conclusion, USC is an aggressive disease, with relatively high rates of recurrence and mortality. For all stages, DM constituted the vast majority of recurrences. We found that for patients with early-stage disease, combination adjuvant CT and RT improves DFS compared with other adjuvant therapy strategies (NAT, CT alone, or RT alone). This is in contrast to subgroup analyses from clinical trials, where patients with USC make up relatively small percentages of enrolled patients, resulting in the inability to detect significant treatment effects for patients with USC.

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Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.08.013.

References

1. Howlader N, Noone AM, Krapcho M, et al. Seer cancer statistics review, 1975-2016, National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2016. Accessed November 1, 2019.
2. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. *Br J Cancer*. 2006;94:642-646.
3. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. Portec study group. Post operative radiation therapy in endometrial carcinoma. *Lancet*. 2000;355:1404-1411.
4. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (portec-2): An open-label, non-inferiority, randomised trial. *Lancet*. 2010;375:816-823.
5. Wortman BG, Bosse T, Nout RA, et al. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: Evaluation of the pilot phase of the portec-4a trial. *Gynecol Oncol*. 2018;151:69-75.
6. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (portec-3): Final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:295-309.
7. Matei D, Filiaci V, Randall ME, et al. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. *N Engl J Med*. 2019;380:2317-2326.
8. Randall ME, Filiaci V, McMeekin DS, et al. Phase III trial: Adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer. *J Clin Oncol*. 2019;37:1810-1818.
9. Frimer M, Miller EM, Shankar V, et al. Adjuvant pelvic radiation "sandwiched" between paclitaxel/carboplatin chemotherapy in women with completely resected uterine serous carcinoma: Long-term follow-up of a prospective phase 2 trial. *Int J Gynecol Cancer*. 2018;28:1781-1788.
10. Tate K, Yoshida H, Ishikawa M, et al. Prognostic factors for patients with early-stage uterine serous carcinoma without adjuvant therapy. *J Gynecol Oncol*. 2018;29:e34.
11. Zhong X, Wang J, Kaku T, et al. Prognostic factors of uterine serous carcinoma-a multicenter study. *Int J Gynecol Cancer*. 2018;28:1138-1144.
12. Mandato VD, Torricelli F, Palomba S, et al. Uterine papillary serous carcinoma arising in a polyp: A multicenter retrospective analysis on 75 patients. *Am J Clin Oncol*. 2019;42:472-480.
13. Mahdi H, Han X, Moulton L, et al. Trends in survival of patients with uterine serous carcinoma from 1988 to 2011: A population-based study. *Int J Gynecol Cancer*. 2017;27:1155-1164.
14. Cham S, Huang Y, Tergas AI, et al. Utility of radiation therapy for early-stage uterine papillary serous carcinoma. *Gynecol Oncol*. 2017;145:269-276.
15. Sagae S, Susumu N, Viswanathan AN, et al. Gynecologic cancer intergroup (GCIG) consensus review for uterine serous carcinoma. *Int J Gynecol Cancer*. 2014;24:S83-S89.
16. Havrilesky LJ, Secord AA, Bae-Jump V, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. *Gynecol Oncol*. 2007;105:677-682.
17. Goldberg H, Miller RC, Abdah-Bortnyak R, et al. Outcome after combined modality treatment for uterine papillary serous carcinoma: A study by the rare cancer network (rcn). *Gynecol Oncol*. 2008;108:298-305.
18. Fader AN, Nagel C, Axtell AE, et al. Stage II uterine papillary serous carcinoma: Carboplatin/paclitaxel chemotherapy improves recurrence and survival outcomes. *Gynecol Oncol*. 2009;112:558-662.
19. Holman LL, Pal N, Iglesias DA, et al. Factors prognostic of survival in advanced-stage uterine serous carcinoma. *Gynecol Oncol*. 2017;146:27-33.
20. Lin Y, Zhou J, Cheng Y, et al. Comparison of survival benefits of combined chemotherapy and radiotherapy versus chemotherapy alone for uterine serous carcinoma: A meta-analysis. *Int J Gynecol Cancer*. 2017;27:93-101.
21. Nadeem R, Abu-Rustum M, Sarah Bean M, Kristin Bradley M, et al. *Uterine Neoplasms, version 1.2020*. NCCN Clinical Practice Guidelines in Oncology; 2020. Available at: https://www.nccn.org/about/permissions/reference.aspx. Accessed October 7, 2020.
22. Cancer Therapy Evaluation Program Common Terminology for Adverse Events, version 3.0, DCTD, NCI, NIH, DHHS. http://ctep.cancer.gov; 2006.
23. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (portec-3): Patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. *Lancet Oncol*. 2019;20:1273-1285.
24. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. *Eur J Cancer*. 2010;46:2422-2431.
25. Viswanathan AN, Macklin EA, Berkowitz R, et al. The importance of chemotherapy and radiation in uterine papillary serous carcinoma. *Gynecol Oncol*. 2011;123:542-547.
26. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A gynecologic oncology group study. *J Clin Oncol*. 2006;24:36-44.
27. Basaran D, Bruce S, Aviki EM, et al. Sentinel lymph node mapping alone compared to more extensive lymphadenectomy in patients with uterine serous carcinoma. *Gynecol Oncol*. 2020;156:70-76.
28. Fader AN, Roque DM, Siegel E, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. *J Clin Oncol*. 2018;36:2044-2051.
29. McMeekin DS, Filiaci VL, Thigpen JT, et al. The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: A gynecologic oncology group study. *Gynecol Oncol*. 2007;106:16-22.