Multimodality therapy for uterine serous carcinoma and the association with overall and relapse-free survival

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Objective To identify prognostic factors for overall survival (OS) and relapse-free survival (RFS) for patients with uterine serous carcinoma.

Methods From January 1, 2000 to January 1, 2010, 44 patients with uterine serous carcinoma were analyzed to determine prognostic and predictive factors for OS and RFS using the Kaplan-Meier product-limit method and log-rank tests.

Results Median follow-up was 4.1 years, median OS was 4.2 years, 2-year OS was 83% and decreased to 48% at 5 years. Two-year RFS was 82% and decreased to 75% at 5 years. Age, stage, tumor size, tumor not arising from a polyp, parametrial involvement, lymphovascular invasion, and no adjuvant treatment were prognostic factors associated with shorter OS. Higher-stage and parametrial involvement were prognostic factors associated with shorter RFS. Combined adjuvant chemotherapy and radiation therapy was significantly associated with longer OS rates.

Conclusions Adjuvant chemotherapy and radiation therapy as well as tumors arising from a polyp are associated with increased overall survival in patients with uterine serous carcinoma. Early-stage disease is associated with increased relapse-free and overall survival. Adjuvant chemotherapy with a platinum and paclitaxol-based regimen and radiation therapy should be attempted in patients with uterine serous carcinoma.

Endometrial cancer is the most common gynecologic malignancy and the fourth most common cause of cancer among women in the United States, with more than 40,000 cases and approximately 8,000 deaths annually.[1] Uterine serous carcinoma is a rare subtype of endometrial carcinoma that comprises 10% of cases but accounts for 40% of deaths.[2] Patients with uterine serous carcinoma present with more advanced stages of cancer and have high-risk pathologic features that result in relapse and poor overall prognosis.[1] Several studies suggest a role for adjuvant therapy, including chemotherapy (CT) and radiation therapy (RT), but there is no consensus on the optimum adjuvant therapy. Current National Comprehensive Cancer Network guidelines recommend either CT with or without tumor-directed radiation therapy or whole abdominal RT with or without vaginal brachytherapy (VB) for uterine serous carcinoma with myometrial invasion that has been adequately debulked with surgery. The purpose of this retrospective study was to examine our institutional experience and to assess the clinical, pathological, and treatment factors that affected overall survival (OS) and relapse-free survival (RFS) rates for patients with uterine serous carcinoma.

Method and materials

Patient population

Records from 429 endometrial cancer patients treated with total hysterectomy and bilateral salpingo-oophorectomy at our institution from January 1, 2000 to January 1, 2010 were retrospectively reviewed. From those patients, 62 patients with uterine serous carcinoma were identified for

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inclusion in this study. Inclusion criteria required receiving treatment for the primary cancer at our institution. Exclusion criteria included incomplete pathological or treatment data and unknown stage of disease. In all, 18 patients were removed because of incomplete treatment data, leaving a total of 44 patients for inclusion in this analysis. Patient information was retrieved from hospital and departmental medical records. Surgical pathological specimens were reviewed again by a single pathologist. The 2010 International Federation of Gynecology and Obstetrics staging system was used for reporting. The study was approved by the institutional review board.

Treatments

All of the patients had undergone a total hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection. Patients who were treated with chemotherapy received a combination of carboplatin and paclitaxol-based regimen. Patients treated with pelvic external beam RT received 180 cGy for 25 treatments, typically with a four-field technique. External beam RT (EBRT) was administered daily for 5 days a week. Patients who had been treated with VB received 7 Gy prescribed at the vaginal surface administered weekly for 3 fractions with a cylinder using high dose rate iridium-192.

Statistical analysis

The Kaplan-Meier product-limit method was used to estimate survival distributions, and log-rank tests were used to compare OS and RFS between groups of interest. Survival rates at 2 years and 5 years were estimated. Patients who were still alive were considered to be censored in the OS analysis. Relapses were defined as local (pelvic) or distant metastases. Patients who did not experience a relapse were considered to be censored in the RFS analysis. On finding a significant result with the log-rank test in comparisons with at least 3 groups, Bonferroni-adjusted pairwise multiple comparisons were conducted to determine which groups differed from each other. The following factors were analyzed as categorical or continuous predictors as indicated: age (continuous), race (white, black/Asian), stage (I/II, III/IV), tumor size (continuous), tumor arising from a polyp (yes/no), depth of myometrial invasion (≤ 50% or > 50%), lower uterine segment involvement (yes/no), parametrial involvement (yes/no), cervical involvement (yes/no), lymphovascular invasion (yes/no), positive peritoneal cytology (yes/no), positive lymph nodes (yes/no), and treatment group (no adjuvant therapy, chemotherapy, RT, chemotherapy plus RT).

TABLE 1 Patient, tumor, and treatment characteristics

Characteristic	Percentage of patients
Patient	
Age, mean (SD), y	[70 (9.74)]
Race/ethnicity	
Asian	6.98
Black	44.19
White	48.84
Disease stage	
I	44.19
II	11.63
III	32.56
IV	11.63
Tumor	
Depth of invasion	
≤ 25%	40.48
> 25-50%	23.81
> 50-75%	9.52
> 75%	26.19
Site involvement	
Lower uterine segment	
Yes	39.53
No	60.47
Lymphovascular	
Yes	29.73
No	70.27
Pelvic lymph node	
Yes	25.00
No	75.00
Para-aortic lymph node	
Yes	18.18
No	81.82
Treatment administered	
Chemotherapy	
Yes	70.45
No	29.55
Radiation therapy	
EBRT	54.55
VB	68.18
EBRT+VB	50.00

Abbreviations: EBRT, external beam radiation therapy; VB, vaginal brachytherapy.

Results

Patient, tumor, and treatment characteristics

Clinical and pathological characteristics of the patients are listed in Table 1. Median age at diagnosis was 69 years (interquartile range, 14.5 years). Median follow-up time was 4.1 years (95% CI, 3.4-6.8 years). Adjuvant therapy was received by 42 patients. Of those patients, 10 received chemotherapy alone. Eleven patients received RT alone of which 2 received VB alone, and 9 patients received VB plus EBRT. In all, 21 patients received chemotherapy and RT. Chemotherapy was administered to 10 of 16 patients with stage IA disease, 0 of 3 patients with stage IB disease, 4 of 5 patients with stage II disease, 1 of 1 patient with stage IIIA disease, 1 of 3 patients with stage IIIB disease, 4 of 4 patients with stage IIIC1 disease, 6 of 6 patients with stage IIIC2 disease, and 4 of 5 patients with stage IV disease. EBRT or VB was administered to 14 of 16 patients with stage IA disease, 3 of 3 patients with stage IB disease, 5 of 5 patients with stage II disease, 1 of 1 patient with stage IIIA disease, 2 of 3 patients with stage IIIB disease, 2 of 4 patients with stage IIIC1 disease, 4 of 6 patients with stage IIIC2 disease, and 1 of 5 patients with stage IV disease. VB was administered to 22 of 24 patients who received EBRT.

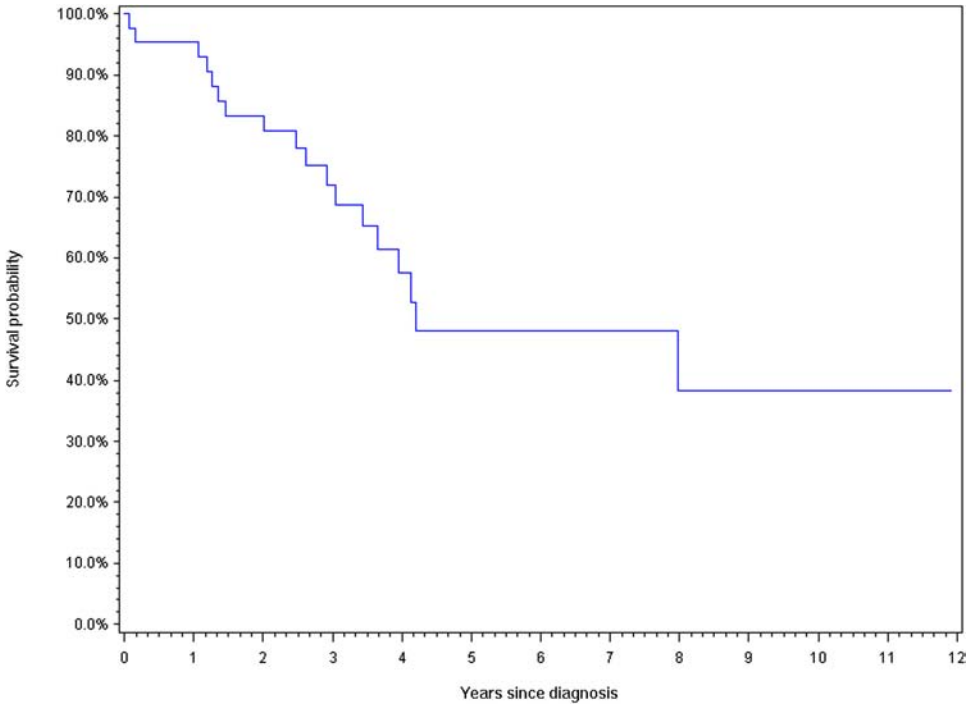

FIGURE 1 Kaplan-Meier overall survival curve.

Overall survival

Median OS for the entire cohort was 4.2 years. OS rates at 2 and 5 years for the entire cohort were 83% and 48%, respectively (Figure 1). Multivariate analysis was not conducted secondary to limited numbers. On univariate analysis, older age, higher stage, larger tumor size, tumor not arising from a polyp, parametrial involvement, lymphovascular invasion, and no adjuvant treatment were associated with a shorter OS rate (Table 2). Patients with stages 1 and 2 disease had significantly improved survival rates at 2 and 5 years compared with patients with stages 3 and 4 disease. There was significant improvement in OS for patients who received a combination of CT and RT (Figure 2). The 5-year overall survival rates were 0%, 38%, 45%, and 61% for patients treated with surgery alone, adjuvant chemotherapy, adjuvant radiation therapy, and combined adjuvant chemotherapy and radiation therapy, respectively.

Relapse-free survival

RFS rates at 2 and 5 years for the entire cohort were 82% and 75%, respectively (Figure 3). A total of 9 patients relapsed of whom 1 was local vaginal recurrence and 8 were distant. Multivariate analysis was not conducted secondary to limited numbers. On univariate analysis, higher stage and parametrial involvement were associated with shorter RFS.

Discussion

Adjuvant therapy for uterine serous carcinoma remains controversial. There is a lack of prospective data that validate types and possible combinations of adjuvant treatment modalities. This retrospective series demonstrates an OS benefit for patients with uterine serous carcinoma treated with adjuvant RT and chemotherapy consisting of a carboplatin-plus-paclitaxol–based regimen.

Age, stage, tumor size, parametrial involvement, lymphovascular invasion, and tumor not arising from a polyp continue to predict for overall survival in concordance with other retrospective studies.[1-5] Depth of myometrial invasion ($\leq$ 50% or $>$ 50%) did not predict for OS. This latter finding is not uncommon because uterine serous carcinoma is frequently found to have lymphovascular inva-

TABLE 2 Log-rank tests for overall and relapse-free survival

Factor	Comparison	OS[a]	RFS[a]
Age	—	0.0056	0.4152
Race/ethnicity	Asian/black, or white	0.6460	0.6315
Treatment	CT, RT, or CT plus RT	0.0001	0.2241
Stage	I/II or III/IV	0.0100	0.0014
Tumor size	—	0.0152	0.0817
Depth of invasion	< 50% or > 50%	0.8770	0.5882
Lower uterine cervical involvement	Yes/no	0.5307	0.1614
Cervix involvement	Yes/no	0.4162	0.3562
Lymphovascular invasion	Yes/no	0.0014	0.0783
Tumor arising from polyp	Yes/no	0.0458	0.1369
Parametrial involvement	Yes/no	0.0020	0.0001
Peritoneal cytology	Positive/negative	0.7079	0.4531
Lymph node involvement	Yes/no	0.7127	0.3565

Abbreviations: CT, chemotherapy; RFS, relapse-free survival; RT, radiation therapy; OS, overall survival.
[a] Results from log-rank test ($P <$ listed value).

sion, lymph node involvement, and to have spread to intraperitoneal structures even in the absence of myometrial invasion. In addition, numerous retrospective studies have shown rates of extrauterine disease ranging from 37% to 63% among patients with no myometrial invasion.[6]

Randomized trials have investigated the role of chemotherapy in endometrial cancer, including uterine serous carcinoma. The Gynecologic Oncology Group (GOG) 122 trial compared adjuvant whole-abdominal radiation (WAR) therapy with doxorubicin plus cisplatin chemotherapy in patients with advanced stage endometrial cancer. Chemotherapy increased OS and progression-free survival (PFS) for the entire cohort. Serous histology comprised 20% of the cohort. On unplanned subset analysis, chemotherapy did not demonstrate a survival benefit in this cohort of patients, which is hypothesis generating and requires prospective testing.[7] In the GOG 177 trial, the addition of paclitaxel to doxorubicin plus cisplatin (TAP) for patients with advanced endometrial carcinoma demonstrated OS, PFS, and recurrence rate (RR) benefits.[8] Despite the superiority of this 3-drug combination, the 3-day regimen and neurotoxic side effects have limited its use, and carboplatin plus paclitaxel are more commonly used based on review of single-institution studies.[1] All patients who received chemotherapy in our study were treated with a carboplatin-plus-paclitaxol–based regimen. GOG 209, an equivalency trial that compared TAP with paclitaxel plus carboplatin in patients with advanced or recurrent endometrial cancer demonstrated identical PFS and median overall survival did not differ significantly between treatment arms: 38 months with TAP and 32 months with paclitaxol plus carboplatin.[9] Comparison of overall survival in the 2 arms resulted in an adjusted hazard ratio of 1.01 for paclitaxol plus carboplatin compared with TAP. With regard to toxicity, neutropenic fever occurred in 7% of the TAP arm and in 6% of the paclitaxol-plus-carboplatin arm. Other toxic events that were grade 3 or higher that occurred more often with TAP include hematologic and gastrointestinal toxicities.

The benefit of adjuvant chemotherapy in patients with early-stage uterine serous carcinoma has been demonstrated in several large retrospective studies. Fader and colleagues demonstrated a significantly decreased recurrence rate in patients who received adjuvant carboplatin plus paclitaxel compared with no adjuvant chemotherapy in patients with stage I and stage II uterine serous carcinoma.[10,11]

The role of adjuvant RT for endometrial cancer has also been investigated in randomized trials. PORTEC 1 and GOG 99 demonstrated improved local regional control with adjuvant pelvic radiation therapy. The benefit was seen particularly in the high-intermediate risk group in which most of the recurrences occurred at the vaginal cuff.[12,13] These findings led to the trial design of PORTEC 2, which compared pelvic radiation therapy and vaginal brachytherapy in a high–intermediate-risk group. Local and distant failures were low in both arms.[14] Despite these findings for even high-risk groups, the results should not be applied to patients with uterine serous carcinoma. The recurrence patterns with uterine

serous carcinoma are different from even high-grade endometrioid carcinoma and are commonly intraperitoneal for which adjuvant pelvic radiation therapy alone is unlikely to be effective. Given this failure pattern, the GOG investigated whole abdominal radiation in a phase 2 trial in patients with clinical stages I and II uterine serous carcinoma and found a recurrence rate of 37%, with 71% of those recurrences within the treated field.[15] Retrospective analysis for the Surveillance, Epidemiology, and End Results database demonstrated an overall survival benefit for patients with stage I uterine serous carcinoma who were treated with adjuvant RT because of the local control benefit. This benefit did not translate to patients with stage II disease, which suggests the need for adjuvant systemic therapy.[3] Collectively, data from randomized trials and retrospective analyses demonstrate the need for adjuvant radiation therapy to decrease local failures which may translate to a survival benefit. However, given the aggressive nature and failure patterns of uterine serous carcinoma, systemic therapy is also warranted.

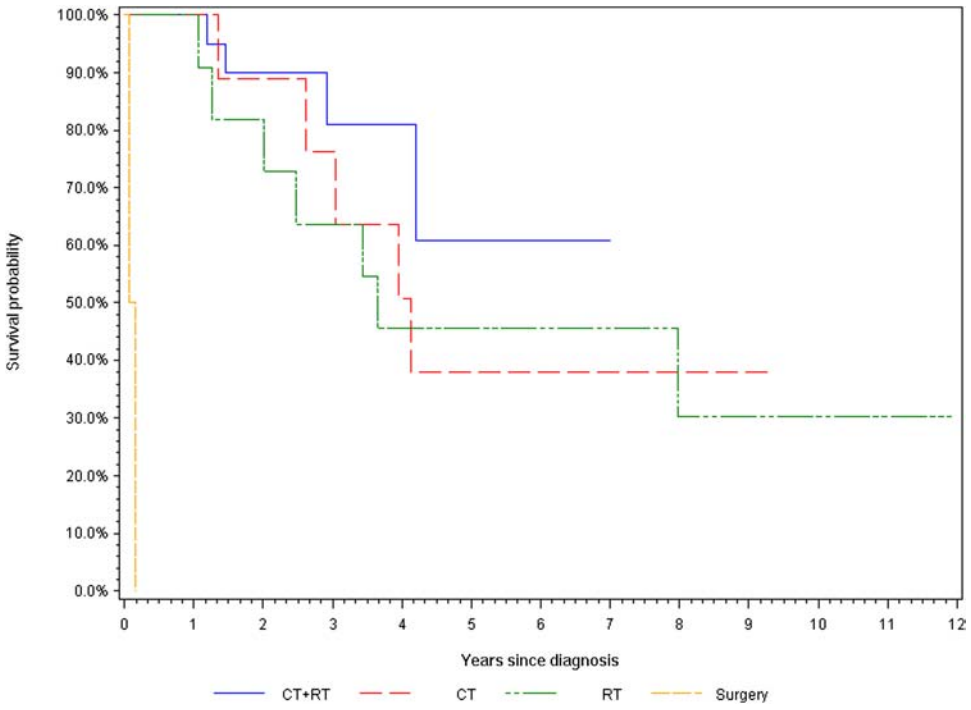

FIGURE 2 Kaplan-Meier overall survival by treatment curve.
Abbreviations: CT, chemotherapy; RT, radiation therapy.

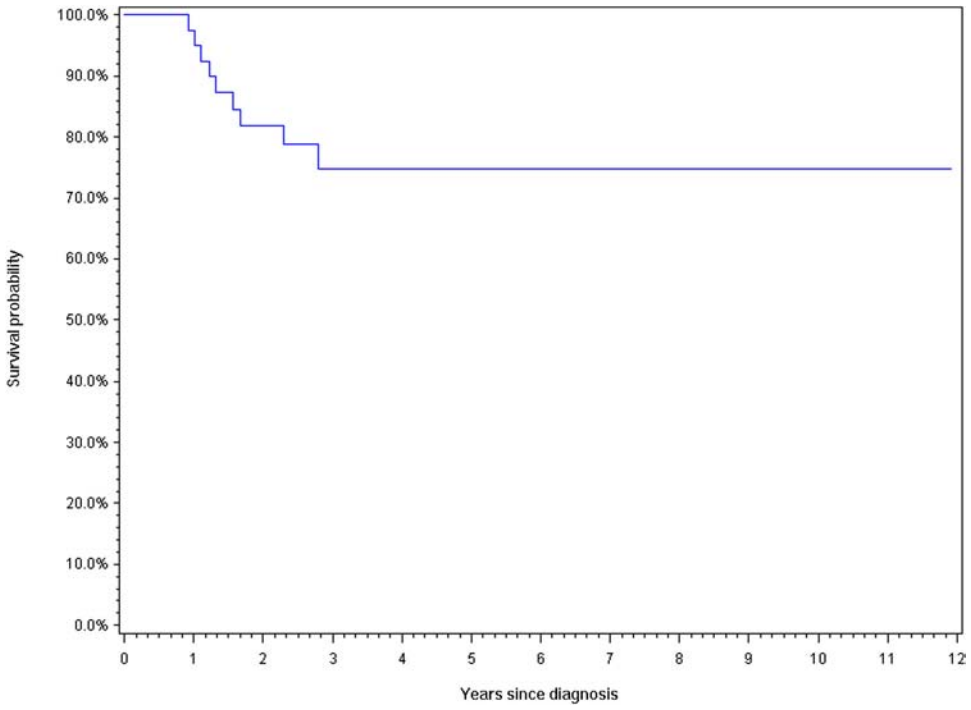

FIGURE 3 Kaplan-Meier relapse-free survival curve.

Although there is a lack of evidence from randomized studies to show benefit in combined modality adjuvant therapy, several retrospective studies have shown that there is a benefit. Vishwanathan and colleagues reported on 135 patients with stages I-IV uterine serous carcinoma and demonstrated an overall survival benefit for patients who were treated with paclitaxel-platinum chemotherapy and a relapse-free survival benefit for patients treated with external beam radiation therapy plus chemotherapy. Despite this apparent benefit, the relapse rate for patients who were treated with radiation

plus chemotherapy was 36%.[4] Kiess and colleagues studied 41 patients with stages I and II uterine serous carcinoma who were treated with adjuvant carboplatin-plus-paclitaxel chemotherapy and intravaginal radiation, and reported the 5-year disease-free and overall survival rates at 85% and 90%, respectively. Although there were no vaginal recurrences, pelvic, para-aortic, and distant recurrence rates were 9%, 5%, and 10%, respectively.[5] Although our study demonstrates an overall survival benefit with the addition of adjuvant radiation therapy and chemotherapy, there remained a relapse rate of 19% mainly at distant sites. These findings suggest that combined radiation therapy and modern chemotherapeutic agents have improved overall survival rates, but that newer agents need further investigation to decrease distant relapse and further extend survival rates.

We acknowledge the limitations of this single institution, retrospective case series and the limited number of patients for extensive subgroup and multivariate analysis secondary to the rarity of uterine serous carcinoma. The advantages of this study are the independent review of each pathological specimen, the completeness of pathological and treatment data, and the uniformity of chemotherapeutic agents that were used. Although our study is the first to report that uterine serous carcinoma tumors arising from a polyp are associated with increased overall survival, we caution its use as a predictive factor in guiding therapy. Given the lack of prospective data addressing optimum therapy for early-stage uterine serous carcinoma, the GOG is currently enrolling patients from various sites, including our institution. The randomized phase 3 GOG 249 study is evaluating whether 3 cycles of carboplatin plus paclitaxel in combination with vaginal brachytherapy is equivalent to pelvic RT in high-risk, early-stage endometrial cancer (including uterine serous carcinoma). In addition, the GOG 258 study is comparing cisplatin plus tumor-volume–directed radiation followed by carboplatin plus paclitaxel with carboplatin plus paclitaxel alone for optimally debulked advanced endometrial carcinoma.

Conclusion

Adjuvant chemotherapy and radiation therapy as well as tumors arising from a polyp are associated with increased overall survival in patients with uterine serous carcinoma. Early-stage disease is associated with increased relapse-free and overall survival. Adjuvant chemotherapy with a carboplatin and paclitaxol-based regimen and radiation therapy should be attempted in patients with uterine serous carcinoma.

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