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A retrospective assessment of outcomes of chemotherapy-based versus radiation-only adjuvant treatment for completely resected stage I–IV uterine carcinosarcoma

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Abstract

Purpose—To determine the progression-free survival (PFS) and overall survival (OS) in a cohort of patients who received either platinum-based chemotherapy with or without radiation therapy (pelvic or WAI), or RT alone.

Methods—Memorial Sloan-Kettering Cancer Center (MSKCC) electronic medical records from 8/1/1995 to 10/3/2007 were reviewed for patient age, diagnosis date, type of primary surgery, residual disease at the completion of primary surgery, FIGO stage, treatment details, dates of progression and death, and site(s) of first recurrence. PFS and OS by stage (I/II v III/IV) and by treatment type (chemotherapy with or without RT v RT alone) were determined using landmark analyses 8 weeks after surgery. Patients who received chemotherapy with or without RT (pelvic or abdominal) or RT alone (pelvic or abdominal) were included in the analysis. Both groups were allowed to have received IVRT.

Results—Forty-nine patients met study criteria. Thirty-eight/49 patients received chemotherapy: 23/38 (60.5 %) received PC; 7/38 (18.4 %) received ifosfamide-platinum; 8/38 (21.0 %) received other chemotherapy. FIGO stage was: I = 15 (31%); II = 5 (10%); III = 21 (43%); IV = 8 (16%). Three-year PFS for the entire cohort was 24%. Three-year OS for the entire cohort was 60%. Three-year median PFS time for the entire cohort was 15 months (95%CI: 11–25 months). Three-year median OS time for the entire cohort was 67 months (95%CI: 23–89 months). Three-year PFS for stages I–II was 43% v 14% for stages III–IV (HR = 1.98 [0.9–4.33]); *P* = 0.082. Three-year OS for stages I–II was 68% v. 55% for stages III–IV (HR = 1.26 [0.47–3.41]); *P* = 0.648. Three-year PFS for chemotherapy with or without RT was 35% v 9 % for RT alone (HR = 1.74 [0.79–3.85]); *P* = 0.164. Three-year OS for chemotherapy with or without RT was 66% v 34% for RT alone (HR = 2.02 [0.77–5.33]); *P* = 0.146.

Conclusions—Our study corroborates GOG 150 results, and shows that paclitaxel-carboplatin appears to be a reasonable option for adjuvant therapy of completely resected uterine

carcinosarcoma. The role of adjuvant RT in addition to chemotherapy warrants further investigation.

Introduction

Carcinosarcoma (CS) of the uterus is a rare, aggressive malignancy with a great capacity for metastasis. Uterine sarcomas represent approximately 4% of all invasive uterine cancers with an annual incidence rate of < 2 per 100,000 females (1, 2). Surgical stage at diagnosis is the most important prognostic factor, but the prognostic significance of cell type, grade, mitotic count of sarcomatous component, and depth of myometrial invasion is unknown (4, 5, 6). Uterine carcinosarcomas have a high propensity for pelvic and paraaortic lymph node involvement, and the optimal initial management includes surgical staging consisting of total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), lymph node dissection (LND), resection of any gross intra-abdominal disease, and sampling of peritoneal washings (7).

Optimal initial management in CS has been investigated, and as yet, no consensus exists. GOG 150 was a randomized phase III trial of WAI v CIM as post-surgical treatment for stages I–IV CS. In this study, patients with stages I–IV primary CS of the uterus or cervix who underwent a TAH, BSO, and optimal tumor debulking to < 1cm of residual disease were eligible. Peritoneal cytology and lymph node dissection were optional. Patients who received prior chemotherapy and/or radiation therapy, or who had a concomitant malignancy (other than non-melanoma skin cancer) within 5 years of uterine CS diagnosis were ineligible. Patients were randomized to WAI v CIM chemotherapy, and treatment had to begin within 8 weeks following surgery. This study required 11 years to meet accrual goals. After adjusting for stage and age, the recurrence rate at 5 years was 21% lower for CIM v WAI (relative hazard [RH] = 0.789, 95% confidence interval [CI]: (0.530–1.176), $P = 0.245$, 2-tail test). The death rate was 29% lower for CIM v WAI (RH = 0.712, 95% CI: 0.484–1.048, $P = 0.085$, 2-tail test) (3).

Paclitaxel-carboplatin has demonstrated high objective response rates in small series patients with advanced uterine carcinosarcoma (15). Paclitaxel-carboplatin is commonly used in both the advanced-disease and the adjuvant setting, despite lack of phase III clinical trial data supporting such use. We aimed to determine whether PFS and OS in a cohort of CS patients who would have met GOG 150 eligibility criteria and received either platinum-based chemotherapy with or without RT (pelvic or WAI) or RT alone (pelvic or WAI) was similar to GOG 150 outcomes, in an era when most patients received paclitaxel-carboplatin (PC) rather than CIM. Both the chemotherapy with or without RT group and the RT alone group were allowed to have received intravaginal radiation therapy (IVRT).

Patients and methods

Patient eligibility

MSKCC electronic medical records from 8/1/1995 to 10/3/2007 were reviewed for patient age, diagnosis date, type of primary surgery, residual disease at completion of primary surgery, stage, treatment (chemotherapy and radiation therapy), dates of progression and death, site(s) of first recurrence and toxic side effects. Only patients meeting GOG 150 eligibility criteria were included in data analysis. Previously untreated patients with stages I–IV CS of the uterus or cervix (without any demonstrable parenchymal hepatic involvement or extra-abdominal distant disease) were eligible. Patients had to have undergone TAH, BSO, and maximal resection of all gross intra-abdominal/pelvic disease, including macroscopically involved paraaortic and pelvic lymph nodes; with no residual disease >1 cm. Peritoneal cytology and LND were optional if there were no intraoperative clinical

manifestations of residual intra-abdominal disease. Patients with an ECOG performance status of 0, 1, and 2 were eligible. Patients who had a concomitant malignancy (other than non-melanoma skin cancer) within 5 years of uterine CS diagnosis were excluded. Treatment had to have been initiated within 8 weeks following the initial surgery.

Patients who received either chemotherapy with or without RT (pelvic or WAI) or RT alone (pelvic or WAI) were included in the analysis. Both groups were allowed to have received IVRT.

WAI radiation treatment was administered per protocol specifications in GOG 150. Eligible patients could have received any form of cytotoxic adjuvant chemotherapy. Patients who received no adjuvant treatment or who received IVRT alone were excluded from the analyses because our aim was to compare outcome differences among patients who were considered to have required some form of adjuvant treatment and who were able to receive it.

A waiver of authorization was obtained and approved by the MSKCC IRB committee prior to conducting this retrospective analysis.

Statistical considerations

Patients were categorized into 2 groups: chemotherapy with or without RT (pelvic or WAI), or RT alone (pelvic or WAI). Stage groups were dichotomized as FIGO stages I and II or stages III and IV.

Sites of first-recurrence were classified as vaginal, pelvic, abdomen, lung, or other distant sites and patients with multiple sites of first recurrence were counted once for each site. Adverse events of treatment were also evaluated and were graded based on the Common Terminology Criteria for Adverse Events v 3.0 (CTCAE).

OS was defined as the time from surgery to either death date or the last follow-up date. Progression-free survival (PFS) was defined as the time from surgery date to either recurrence or death or to the last follow-up date, whichever occurred first. Due to the time-dependent nature of the adjuvant therapy variable, landmark analysis was used at 8 weeks after surgery chosen as the landmark time. The 3-year survival and PFS rates were estimated by the Kaplan-Meier method. The univariate *P*-values in survival analysis were obtained by using the Log-rank test. The hazard ratios were calculated by applying the Cox regression model. All the analyses were performed by using SAS 9.1. *P*-values in Table 2 were obtained using Wilcoxon rank sum test. All other *P*-values were obtained using the Fisher-exact test. Distribution differences between the two treatment groups were checked using Fisher-exact test for the categorical variables and the Wilcoxon rank sum test for the continuous variables.

Results

Patient characteristics

Patient characteristics are detailed in Table 1. Forty-nine patients were included in study analysis (58 patients were identified; 9 excluded for no treatment or IVRT only; 3 for progression within 8 weeks of surgery). Twenty/49 patients were stages I–II and 29/49 patients were stages III–IV. The median age was 66 years (range 49–76). Histologic subtypes were: 29/49 patients homologous; 20/49 heterologous. Patient race distribution was as follows: 81.6% (40) white, 14.3% (7) Black, 2% (1) Hispanic, 2% (1) other. ECOG performance status range was as follows: 81.6% (40) ECOG 0, 8.2% (4) ECOG 1, 2.0% (1)

ECOG 2, 8.2% (4) unknown. There were no significant differences when comparing distributions of clinical factors between the two groups, as shown in Table 2.

Treatment

Patients received chemotherapy with or without RT or RT alone based on stage, age, presence of nodal metastasis, performance status, and medical co-morbidities. In general, patients with higher stage disease received chemotherapy with or without RT. Those who did not undergo LND received combination chemotherapy and pelvic RT. Patients with early stage disease who underwent LND received chemotherapy and IVRT. Pelvic RT was delivered at a dose of 4500 cGy in patients who were subsequently to receive IVRT at 1500cGy. In one case, 4500 cGy of pelvic RT and 1800 cGy of IVRT was administered. When pelvic RT was administered alone or in combination with chemotherapy, generally a dose of 5040 cGy was delivered. In one case, a patient received 4500 cGy of pelvic RT out of a planned 5040 cGy due to grade II diarrhea. In one case 4500 cGy of RT was administered with chemotherapy. Patients who received chemotherapy and IVRT-only received between 1200–2100 cGy of IVRT. One patient received 3000 cGy WAI and 4890 cGy pelvic RT.

A total of 49 patients met inclusion criteria and received adjuvant treatment for completely resected carcinosarcoma. Thirty-eight of 49 patients received chemotherapy with or without RT [stage I (9/38), stage II (4/38), stage III (17/38), and stage IV 8/38)]. Eleven of 49 patients received RT alone [stage I (6/11), stage II (1/11), stage III (4/11), and stage IV (0/11)]. Only one of the 11 RT-alone patients received WAI.

Among the 38 patients who received chemotherapy, treatment regimens were as follows: 23/38 (60.5 %) received PC; 7/38 (18.4 %) received ifosfamide-platinum; 8/38 (21%) received other chemotherapy (6 received cisplatin only, 1 received carboplatin only and 1 received paclitaxel only).

Adverse Effects of Treatment

The frequency and severity of treatment-related adverse events are summarized in Table 3. Overall, both chemotherapy with or without RT and RT alone were well tolerated. More treatment-related toxicities were noted in the chemotherapy with or without RT group than in the RT alone group. Predominant grade II toxicities in this group included myalgias (7.9%), fatigue (5.3%) and neuropathy (5.3%). One case (2.6%) of treatment-related grade IV acute renal failure occurred in the chemotherapy with or without RT group. Only 1 case (9.1%) of grade II diarrhea occurred in the RT alone group, and no grade III or IV toxicities occurred in this group.

Patterns of first recurrence

Among the 49 patients, 29 recurred within 3 years. Nineteen/38 (50.0%) patients in the chemotherapy with or without RT group, and 10/11 (90.9%) patients in the RT alone group recurred. Of note, the patient who received WAI was among the 10 RT-alone patients who recurred. Although sample size limits generalization, abdominal recurrences appeared to be more common among the RT-alone patients than among the chemotherapy-treated patients: 34.6% of RT-alone patients v 23.7% of chemotherapy-treated patients. When abdominal and lung recurrence were combined extra-vaginal-pelvic recurrences occurred in 90.9% of RT-alone patients v 44.7% of chemotherapy-treated patients. These data are summarized in Table 4.

Progression-free survival and overall survival

At the time of analysis, 18/49 (36.7%) patients had died. The median follow-up for survivors was 26 months and 3-year median OS was 67 months (95%CI: 23–89 months) (Figure 1). Three-year PFS for the entire cohort was 24%. Three-year OS for the entire cohort was 60%. Three-year OS for FIGO stage I–II v III–IV was 68% v 55% (HR = 1.26 [0.47–3.41]); $P = 0.648$ (Figure 2) Three-year OS for chemotherapy with or without RT v RT alone was 66% v 34% (HR = 2.02 [0.77–5.33]); $P = 0.146$. (Figure 3)

The median follow-up for surviving patients without recurrence was 24 months, and 3-year median PFS was 15 months (95%CI: 11–25 months) (Figure 4). Three-year PFS by FIGO stage was 43% v 14% for stages I–II v III–IV (HR = 1.98 [0.9–4.33]); $P = 0.082$ (Figure 5). Three-year PFS by adjuvant treatment type was 35% for chemotherapy with or without RT v 9% for RT alone (HR = 1.74 [0.79–3.85]); $P = 0.164$ (Figure 6).

Discussion

Until recently no randomized phase III data regarding optimal management of uterine carcinosarcoma was available. GOG 150 was a phase III clinical trial of adjuvant WAI versus three cycles of CIM chemotherapy as post-surgical therapy in stages I–IV optimally debulked uterine carcinosarcoma patients. When this study was designed 15 years ago, 3 cycles of CIM therapy were considered an appropriate experimental arm to compare to WAI. GOG 150 failed to show a statistically significant improvement in relapse rate or OS, which was in part felt to be as a result of small sample size and the use of only three cycles of chemotherapy. This study did, however, show that after adjusting for age and stage, the recurrence rate was 21% lower for CIM versus WAI. Additionally, the estimated death rate was 29% lower among the CIM arm (3). This study concluded that the observed differences favor the use of adjuvant combination chemotherapy in the treatment of this rare cancer.

The most effective chemotherapy regimen for CS has not been established. In prior single-agent GOG phase II and III trials, response rates have been as follows: etoposide (7%) (8), topotecan (10%) (9), doxorubicin (10%) (10), cisplatin (18%) (11) and ifosfamide (32%) (12). A GOG phase III trial of ifosfamide with or without cisplatin in advanced or recurrent CS revealed higher objective response rates and longer PFS ($P = 0.02$) with ifosfamide-cisplatin chemotherapy, although no significant survival benefit was found ($P = 0.071$) (13).

GOG 160 was a phase III trial of ifosfamide with or without paclitaxel in advanced or recurrent CS, in which patients received 8 cycles of chemotherapy. This trial revealed response rates of 29% (ifosfamide alone) v 45% (ifosfamide and paclitaxel), and for the first time revealed significantly improved median PFS and OS (3.6 v 5.8 months and 8.4 v 13.5 months, respectively) (14). Currently, the combination of paclitaxel and carboplatin in the treatment of advanced, persistent or recurrent carcinosarcoma patients with measurable disease is being evaluated in a Gynecologic Oncology Group phase II clinical trial (GOG 232B).

Despite paucity of data, paclitaxel and carboplatin chemotherapy is commonly used to treat carcinosarcoma. In our study, 60.5% of patients who received initial chemotherapy were treated with paclitaxel and carboplatin, versus 18.4% who received ifosfamide-platinum. Although not achieving statistical significance due to limited sample size, our results suggest that chemotherapy alone or in combination with RT is associated with longer PFS and OS in patients with stages I–IV CS, compared to treatment with RT alone. Lung and abdominal recurrences were much higher in the RT alone group.

Paclitaxel-carboplatin chemotherapy was well tolerated, with all patients in our cohort able to complete six cycles of therapy. Our study corroborates GOG 150 results, and shows that paclitaxel-carboplatin appears to be a reasonable option for adjuvant therapy of completely resected uterine carcinosarcoma. The role of adjuvant RT in addition to chemotherapy warrants further investigation.

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Fig. 1.
Overall survival cure (N=49).

Fig. 2.
Overall survival stratified by FIGO stage ($N=49$).

Fig. 3.
Overall survival stratified by treatment (N=49).

Fig. 4.
Progression free survival curve (N=49).

Fig. 5.
Progression free survival stratified by FIGO stage ($N=49$).

Fig. 6.
Progression free survival stratified by treatment (N=49).

Table 1

Patient characteristics

Patient Demographics	N (=49 patients)	%
Vital Status		
Alive	31	60
Dead	18	40
Recurrence Status		
Recurred	29	60
Not Recurred	20	40
Age at Diagnosis, years		
Median (Mean)	66 (65)	
Range	49–76	
FIGO Stage		
I	1	2.0
IA	1	2.0
IB	10	20.4
IC	3	6.1
IIA	2	4.1
IIB	3	6.1
IIIA	8	16.3
IIIC	13	26.5
IVA	2	4.1
IVB	6	12.2
Histologic Sub-Type		
Homologous	29	59.2
Heterologous	20	40.8
Race		
White	40	81.6
Black	7	14.3
Hispanic	1	2.0
Other	1	2.0
ECOG Performance Score		
0	40	81.6
1	4	8.2
2	1	2.0
Unknown	4	8.2

Table 2

Patient characteristics by treatment type

Patient Demographics	Chemotherapy±RT±IVRT	RT alone	P-value
Number of Patients	38	11	
Age at Diagnosis, years			0.952
Median (Mean)	64.8 (66)	65.5 (64)	
Range	49–76	57–77	
FIGO Stage			0.097
I/II	13 (34.2%)	7 (63.6%)	
III/IV	25 (65.8%)	4 (36.4%)	
Histologic Sub-Type			0.320
Homologous	24 (63.2%)	5 (45.5%)	
Heterologous	14 (36.8%)	6 (54.5%)	
Race			0.400
White	32 (84.2%)	8 (72.7%)	
Non-white	6 (15.8%)	3 (27.3%)	
ECOG Performance Score (4 unknown)		0.258	
0		33 (91.7%)	7 (77.8%)
1, 2 or unknown	3 (8.3%)	2 (22.2%)	

Abbreviations: Chemotherapy±RT±IVRT, chemotherapy plus or minus radiation therapy (pelvic or WAI) plus or minus intravaginal radiation therapy; RT alone, radiation therapy alone (pelvic or WAI)

Table 3

Toxicity by treatment type

Toxicity	Chemotherapy±RT±IVRT (n= 38 patients)					RT alone (n= 11 patients)				
	Grade					Grade				
	1	2	3	4		1	2	3	4	
Anorexia	2	0	0	0	0	0	0	0	0	0
Constipation	8	1	0	0	0	0	0	0	0	0
Cystitis	1	1	0	0	0	2	0	0	0	0
Diarrhea	4	1	0	0	0	1	1	0	0	0
Dyspareunia	1	0	0	0	0	0	0	0	0	0
Fatigue	22	2	0	0	0	3	0	0	0	0
Myalgias	5	3	0	0	0	0	0	0	0	0
Nausea/Vomiting	6	1	0	0	0	0	0	0	0	0
Neutropenia	1	0	0	0	0	0	0	0	0	0
Peripheral neuropathy	9	2	0	0	0	0	0	0	0	0
Proctitis	0	0	0	0	0	2	0	0	0	0
Pulmonary	2	0	0	0	0	0	0	0	0	0
Renal	0	0	0	0	1	0	0	0	0	0

Abbreviations: Chemotherapy±RT±IVRT, chemotherapy plus or minus radiation therapy (pelvic or WAD) plus or minus intravaginal radiation therapy; RT alone, radiation therapy alone (pelvic or WAD); n = total number of cases in each group

Table 4

Patterns of first recurrence

Site(s) of recurrence *	Chemotherapy±RT±IVRT	RT alone
	(n= 38)	(n= 11)
Vagina	1 (2.6%)	1 (9.1%)
Pelvis	9 (23.7%)	2 (18.2%)
Abdomen	9 (23.7%)	4 (36.4%)
Lung	8 (21.1%)	6 (54.5%)
Other distant sites	0 (0%)	1(9.1%)

Abbreviations: Chemotherapy± RT±IVRT, chemotherapy plus or minus radiation therapy (pelvic or WAI) plus or minus intravaginal radiation therapy; RT alone, radiation therapy alone (pelvic or WAI); n = total number of cases in each group

* Some patients had multiple sites of recurrence