Use of Adjuvant Chemotherapy, Radiation Therapy, or Combined Modality Therapy and the Impact on Survival for Uterine Carcinosarcoma Limited to the Pelvis

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Objective: Clinical outcomes for patients with uterine carcinosarcoma are poor after surgical management alone. Adjuvant therapies including chemotherapy (CT) and/or radiation therapy (RT) have been previously investigated, but the optimal management of this disease remains controversial. The purposes of this study were to analyze the patterns of use of adjuvant CT and RT and to assess the impact on survival of each of these treatment regimens using the National Cancer Data Base.

Methods/Materials: The National Cancer Data Base was queried for patients given a diagnosis of uterine carcinosarcoma confined to the pelvis who underwent total hysterectomy/bilateral salpingo-oophorectomy between 2004 and 2011. Patients were excluded if they survived less than 4 months after diagnosis. Data regarding CT and RT use were collected. Overall survival (OS) was analyzed using the Kaplan-Meier method. Multivariable Cox regression analysis was performed to evaluate the effect of covariates on OS.

Results: A total of 4906 patients were included in this study. Median age was 67 years (interquartile range, 60–75 years). Median follow-up was 28.9 months (interquartile range, 15.4–52.9 months). There were 1777 patients (36.2%) who received no adjuvant treatment, 971 (19.8%) who received CT alone, 1060 (21.6%) who received RT alone, and 1098 (22.4%) who received both RT and CT. The 5-year OS for patients receiving no adjuvant therapy, adjuvant RT alone, adjuvant CT alone, and combined CT and RT were 44.9%, 47.1%, 47.5%, and 62.9%, respectively. On pairwise analysis, combined CT and RT was associated with improved survival compared with all other subgroups ($P < 0.001$). On multivariable Cox regression analysis, combined CT and RT (hazard ratio, 0.50; 95% confidence interval, 0.44–0.57; $P < 0.001$) and CT alone (hazard ratio, 0.78; 95% confidence interval, 0.69–0.88; $P < 0.001$) were significantly associated with improved OS, whereas RT alone was not.

Conclusions: Combination therapy with CT and RT was associated with significantly improved 5-year OS compared with no further therapy, RT alone, or CT alone.

Key Words: Carcinosarcoma, Malignant mixed Mullerian tumor, Endometrial carcinoma, Chemotherapy, Radiation therapy

Received July 7, 2016, and in revised form October 11, 2016.
Accepted for publication November 18, 2016.

(*Int J Gynecol Cancer* 2017;27: 1171–1177)

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ISSN: 1048-891X
DOI: 10.1097/IGC.0000000000001014

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The authors declare no conflicts of interest.

Carcinosarcoma, formerly malignant mixed Mullerian tumor, is a rare subtype of uterine malignancy, representing less than 5% of all uterine neoplasms.[1] It has historically been classified as a uterine sarcoma, but more recent evidence suggests that this disease is best classified as a metaplastic carcinoma rather than a sarcoma.[2] As a result, uterine carcinosarcomas are now classified as carcinomas for staging purposes and within national guidelines.

The primary therapy of uterine carcinosarcoma is total hysterectomy with bilateral salpingo-oophorectomy (TH-BSO). Outcomes after surgery alone have been poor with a high risk of both local and distant relapse.[3] Adjuvant treatment regimens have therefore included systemic chemotherapy, radiation therapy (RT), or both. However, because of the rarity of this disease, there is a paucity of randomized data, and the optimal treatment strategy is debated.

The enthusiasm for adjuvant chemotherapy in the management of this disease was initially tempered after a randomized trial conducted by the Gynecologic Oncology Group (GOG) of adjuvant single-agent doxorubicin for early-stage uterine sarcomas showed no benefit for the addition of chemotherapy.[4] However, multiagent chemotherapy regimens were demonstrated to have efficacy for advanced disease.[5,6] Therefore, the feasibility of multiagent chemotherapy in the adjuvant setting for early-stage patients was evaluated in a phase II trial by the GOG.[7] Using a combination of adjuvant ifosfamide and cisplatin resulted in 2-year progression-free survival and overall survival (OS) rates of 69% and 82%, 7-year progression-free survival and OS rates of 54% and 52%, and an overall 5-year survival rate of 62%.

The role of adjuvant RT is more controversial because 2 randomized trials have questioned the benefit of adjuvant RT.[8,9] The GOG conducted a phase III trial randomizing any stage patients with carcinosarcoma after surgery to either adjuvant whole abdominal irradiation or adjuvant chemotherapy. There was a relative 29% lower risk of death in the chemotherapy arm, although this difference did not reach statistical significance.[5] Another phase III trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC)[6] investigated the role of adjuvant pelvic RT for patients with stage I to II uterine sarcoma (including carcinosarcoma, endometrial stromal sarcoma, and leiomyosarcoma). For patients with carcinosarcoma, pelvic RT non-significantly improved local control without affecting OS or progression-free survival.

Given the ongoing controversy regarding the management of these patients, we analyzed the National Cancer Data Base (NCDB) to assess current practice patterns with regard to use of adjuvant chemotherapy, RT, or both for women with uterine carcinosarcoma limited to the pelvis. We also assessed the impact on OS of each of these adjuvant treatment modalities.

MATERIALS AND METHODS

The NCDB is a hospital-based registry that is the joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It is estimated that 70% of all diagnosed malignancies in the United States are captured by facilities participating in this registry and reported to the NCDB. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the de-identified data used in this study. However, they have not verified and are not responsible for the statistical validity or conclusions derived by the authors of this study. Exemption was obtained from the institutional review board before the initiation of this study.

Women who were given a diagnosis of uterine malignant mixed Mullerian tumor or carcinosarcoma (International Classification of Diseases for Oncology, third edition histology codes 8950, 8951, and 8980) with disease confined to the pelvis (International Federation of Gynecology and Obstetrics stages I–IIIC1) between 2004 and 2011 and underwent TH-BSO were included in this study. On the basis of the pathologic extent of invasion coding by the NCDB, women were grouped according to the American Joint Committee on Cancer seventh edition TNM staging. Included stages consisted of pT1-4Nx-1 M0 disease. The NCDB identifies whether any lymph nodes were removed but does not specify whether they were removed from the pelvis, para-aortic nodes, or both. However, the database does stage the patients based on whether positive lymph nodes were from the pelvis or para-aortic region. Therefore, women identified as having pathologic N2 disease (n = 100) were excluded because this represents disease metastatic to the para-aortic lymph nodes. Other nodal involvement was identified as pelvic only, and these women were included. All women had to have complete data regarding the extent of their disease invasion, as well as whether they were treated with RT and/or chemotherapy. In addition, to account for immortal time bias,[10] women who survived less than 4 months after diagnosis were excluded. Data regarding RT and chemotherapy use were collected. Only those who were identified as having received postoperative RT to the pelvis or uterus/cervix regions or brachytherapy were included. Those for whom it was unknown whether chemotherapy was received were excluded, as well as those who received neoadjuvant chemotherapy before surgery.

The sequence of chemotherapy and RT in relation to each other was also derived from the NCDB data, based on the number of days from diagnosis until receipt of their therapies. Patients were identified as received their chemotherapy in relation to their RT as follows: neoadjuvant chemotherapy, concomitant chemoradiation (if the chemotherapy and RT were initiated within 14 days of each other), or adjuvant chemotherapy. Details regarding the chemotherapy agents or number of cycles of chemotherapy delivered are not available from the NCDB.

Clinical, pathologic, and demographic details were compared between patients who received no adjuvant therapy, adjuvant RT alone, adjuvant chemotherapy alone, and combined chemotherapy and RT. Patient characteristics were compared via χ^2 test, Fisher exact test, and Mann-Whitney *U* test where appropriate. Kaplan-Meier analyses were performed based on the receipt of any adjuvant treatment. The variables analyzed were those who received no adjuvant chemotherapy or RT, those who received adjuvant RT only, those who received adjuvant chemotherapy only, and those who received both adjuvant chemotherapy and adjuvant RT. Subgroup analysis was performed to compare survival

outcomes by treatment based on pathologic nodal status. A second subgroup analysis of only those who received both chemotherapy and RT was performed to compare survival based on the receipt of external beam RT or brachytherapy. Multivariate Cox regression was also performed to determine the effect of covariables on survival. The variables measured included age (continuous), receipt of adjuvant treatment (no adjuvant treatment, adjuvant RT only, adjuvant chemotherapy only, or adjuvant chemotherapy and RT), grade of disease,[1–3] modified Charlson/Deyo score (0, 1, or ≥2), and race (white, black, other). Data regarding local control and cause of death are not available in the NCDB. Significant values were defined as those with a *P* value of less than 0.05. Statistical analysis was performed using SPSS version 23 (IBM Inc, Armonk, NY).

RESULTS

Patient Characteristics

There were 4906 women included in this study, with a median age of 67 years (interquartile range, 60–75 years). The median follow-up for all women was 28.9 months (interquartile range, 15.4–52.9 months), and the median follow-up for living women was 44.3 months (interquartile range, 26.1–68.4 months). There were 833 women (17.0%) who had no lymph nodes removed, 1430 (29.1%) who had 1 to 10 lymph nodes removed, 2496 (50.9%) who had more than 10 lymph nodes removed, and 147 (3.0%) for whom it was unknown whether lymph nodes were removed. There were a total of 605 women (12.3%) who were identified as having positive nodal disease.

A total of 2158 women (44.0%) received adjuvant RT, 1060 women in the RT-only group and 1098 in the chemo-RT group. For those who received RT, the treatment approaches included external beam RT alone for 1116 women (51.7%), brachytherapy alone for 508 women (23.5%), and external beam RT plus brachytherapy boost for 518 women (24.0%). For 16 women (0.7%), the type of RT provided was not available.

Chemotherapy was used in 2069 women (42.2%). For 971 (46.9%) of these women, chemotherapy was the only adjuvant treatment offered. The remaining 1098 (53.1%) women also received adjuvant RT, consisting of chemotherapy followed by RT for 704 women, concomitant chemoradiation for 103 women, RT followed by chemotherapy for 177 women, and unknown sequence for 114 women. There were 1777 women (36.2%) who did not receive any adjuvant treatment. Table 1 lists several patient characteristics among the different treatment groups.

Overall Survival

We compared the OS among 4 groups of women: those who received no adjuvant therapy, those who received only adjuvant RT, those who received only adjuvant chemotherapy, and those who received both chemotherapy and RT (Fig. 1). The 5-year OS was 62.9% in those who received chemotherapy and RT, which was superior to all other groups on pairwise analysis ($P < 0.001$ for each comparison). The 5-year OS was 47.5% for chemotherapy alone, 47.1% for RT alone, and 44.9% for no adjuvant therapy. On pairwise analysis, there were no differences in survival between those who received RT alone over no adjuvant therapy ($P = 0.30$), those who received

TABLE 1. Patient characteristics

	No Adjuvant Therapy	RT Only	Chemotherapy Only	Chemo + RT	*P*
N	1777	1060	971	1098	
Age, median, y	70	68	65	64	<0.001
Race					0.03
White	1329 (74.8%)	736 (69.4%)	700 (72.1%)	784 (71.4%)	
Black	379 (21.3%)	276 (26.0%)	228 (23.5%)	251 (22.9%)	
Other	69 (3.9%)	48 (4.5%)	43 (4.4%)	63 (5.7%)	
Charlson/Deyo score					0.053
0	1294 (72.8%)	767 (72.4%)	710 (73.1%)	854 (77.0%)	
1	388 (21.8%)	234 (22.1%)	215 (22.1%)	202 (18.4%)	
≥2	95 (5.3%)	59 (5.6%)	46 (4.7%)	42 (3.8%)	
Pathologic T-stage					<0.001
T1a	972 (54.7%)	459 (43.3%)	335 (34.5%)	401 (36.5%)	
T1b	376 (21.2%)	291 (27.5%)	191 (19.7%)	251 (22.9%)	
T2	198 (11.1%)	182 (17.2%)	90 (9.3%)	186 (16.9%)	
T3-4	231 (13.0%)	128 (12.1%)	355 (36.6%)	260 (23.7%)	
Pathologic nodal status					<0.001
Nx-0	1648 (92.7%)	965 (91.0%)	773 (79.6%)	915 (83.3%)	
N+	129 (7.3%)	95 (9.0%)	198 (20.4%)	183 (16.7%)	

Chemo, chemotherapy; N+, node positive.

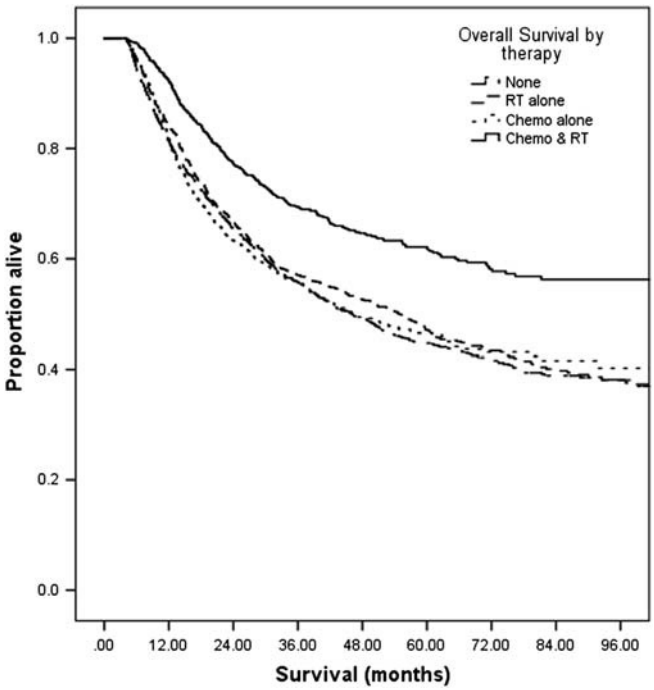

FIGURE 1. Kaplan-Meier curves for OS comparing no adjuvant therapy, adjuvant RT alone, adjuvant chemotherapy alone, and combined chemotherapy and RT.

chemotherapy over no adjuvant therapy ($P = 0.99$), and those who received RT alone or chemotherapy alone ($P = 0.38$).

Subgroup analysis was performed based on pathologic nodal status. For those with node-negative disease, the 5-year OS was 47.9% for no adjuvant therapy, 49.8% for adjuvant RT only, 52.7% for adjuvant chemotherapy only, and 67.5% for adjuvant chemotherapy and RT. On pairwise analysis, only adjuvant chemotherapy and RT was associated with significantly improved survival compared with no adjuvant therapy ($P < 0.001$), whereas adjuvant RT ($P = 0.27$) and adjuvant chemotherapy ($P = 0.17$) were not.

For those with node-positive disease, the 5-year OS was 16.5% for no adjuvant therapy, 27.1% for adjuvant RT only, 34.8% for adjuvant chemotherapy only, and 47.9% for adjuvant chemotherapy and RT. On pairwise analysis, there was no significant difference in survival comparing RT only with no adjuvant therapy ($P = 0.48$). However, adjuvant chemotherapy alone ($P = 0.006$) and adjuvant chemotherapy plus RT ($P < 0.001$) were associated with significantly improved survival.

Finally, subgroup analysis was performed on those who received both chemotherapy and RT stratified by nodal status, to assess for differences in survival based on the type of RT received. For those with node-negative disease, the 5-year OS was 65.2% for those receiving chemotherapy plus external beam RT and 70.4% for those receiving chemotherapy plus brachytherapy ($P = 0.07$) (Fig. 2). For those with node-positive disease, the 5-year OS was 50.5% for chemotherapy plus external beam RT and 31.7% for chemotherapy plus brachytherapy ($P = 0.07$).

Multivariate Analysis

On multivariate analysis, there remained a significant survival benefit strongly favoring those who received adjuvant chemotherapy and RT (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.44–0.57; $P < 0.001$). The receipt of chemotherapy only was also associated with improved survival on multivariate analysis (HR, 0.78; 95% CI, 0.69–0.88; $P < 0.001$). However, the receipt of RT only was not (HR, 0.91; 95% CI, 0.81–1.01; $P = 0.07$). Increasing age, black race, increasing T-stage, and node-positive disease were all associated with inferior survival, as shown in detail in Table 2.

DISCUSSION

In this analysis of a large hospital-based data set, we found that both adjuvant chemotherapy and adjuvant RT are commonly used after surgical management with hysterectomy for uterine carcinosarcoma, which is in accordance with national guidelines. However, a substantial proportion of patients (36.2%) did not receive any adjuvant therapy. Multimodality therapy with both chemotherapy and RT was associated with the largest improvement in survival with a 50% relative reduction in the risk of death when compared with no additional therapy.

Despite distant relapse being the primary pattern of failure for uterine carcinosarcoma,[3] we found that fewer than half (43%) of the patients in our study received adjuvant chemotherapy. An analysis of the Surveillance, Epidemiology, and End Results (SEER) Medicare database similarly found a low rate of chemotherapy use (15%–18%) in elderly

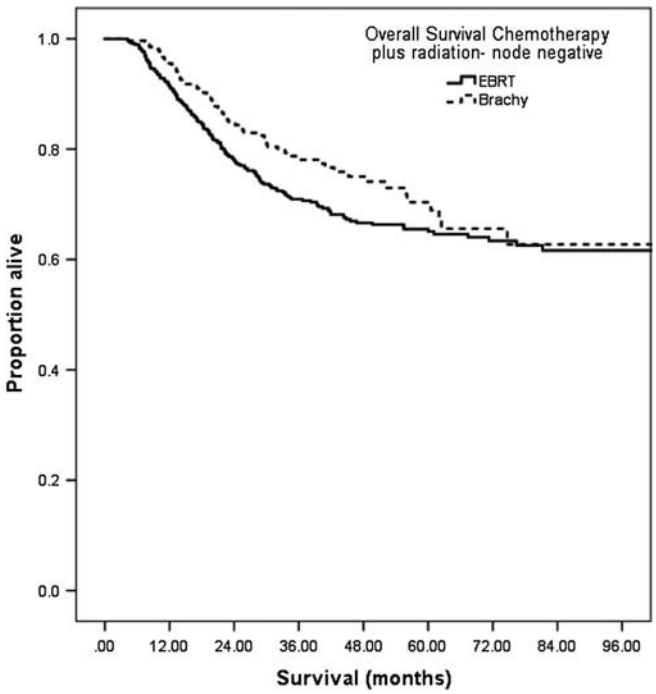

FIGURE 2. Kaplan-Meier curves for OS comparing chemotherapy with external beam RT (EBRT) or brachytherapy (Brachy) for patients with node-negative disease.

TABLE 2. Multivariate analysis for OS

	HR (95% CI)	*P*
Age (continuous), y	1.03 (1.03–1.04)	<0.001
Charlson/Deyo score		
0	1	
1	1.01 (0.91–1.12)	0.86
≥2	1.17 (0.98–1.40)	0.08
Race		
White	1	
Black	1.40 (1.27–1.54)	<0.001
Other	1.04 (0.84–1.28)	0.74
Pathologic T-stage		
T1a	1	
T1b	1.52 (1.35–1.71)	<0.001
T2	2.19 (1.93–2.50)	<0.001
T3-4	3.57 (3.19–4.00)	<0.001
N-recode		
Nx-0	1	
N+	1.33 (1.18–1.50)	<0.001
Treatment		
No adjuvant treatment	1	
Adjuvant RT only	0.91 (0.81–1.01)	0.07
Adjuvant chemotherapy only	0.78 (0.69–0.88)	<0.001
Adjuvant RT + adjuvant chemotherapy	0.50 (0.44–0.57)	<0.001

N+, node positive.

women (≥65 years old) with stage I to II uterine carcinosarcoma.[11] Because this was a retrospective review of a hospital-based registry, we are unable to ascertain the reasons patients did not receive adjuvant chemotherapy. Patient age and overall health may have played an important role because we found that patients not receiving chemotherapy were older than those who did receive chemotherapy (median age, 69 vs 65 years). Other unmeasured patient factors or physician biases may have also contributed.

Interestingly, we found that adjuvant RT was used in 43.9% of the patients and more frequently than chemotherapy (42.2%). Previous analyses of the SEER database have reported a similar rate of adjuvant RT use, ranging from 37% to 50%.[12–14] There are only 2 randomized trials examining the role of adjuvant RT for patients with uterine carcinosarcoma. In the GOG-150 trial, 206 surgically staged patients with stage I to IV uterine carcinosarcoma were randomized to either whole abdominal irradiation (30 Gy to the whole abdomen followed by 19.8- to 20-Gy pelvic boost) or multiagent cisplatin/ifosfamide/mesna chemotherapy for 3 cycles.[8] The authors reported a nonstatistically significant trend toward lower recurrence rate and improved survival in favor of the chemotherapy arm. The EORTC conducted a phase III study to evaluate the role of adjuvant pelvic radiotherapy in patients with stage I to II uterine sarcoma treated with TH-BSO.[9] This trial included 224 patients randomized to either no additional therapy or pelvic RT (50.4 Gy in 28 fractions). Approximately 41% of patients had carcinosarcoma, and for these patients, there was a nonstatistically significant trend toward improved local control without a survival benefit in favor of the pelvic RT arm.

Population-based studies have also failed to clarify the role of adjuvant RT. Wright et al[13] analyzed 1819 patients with stage I to II uterine carcinosarcoma from the SEER database. They found that adjuvant RT reduced the relative risk of death by 21%. A separate analysis of the SEER database conducted by Smith et al[14] included 2461 patients with stage I to IV disease. They found that adjuvant RT was associated with improved OS (5-year OS, 42% with RT vs 33% without RT; $P < 0.001$) and uterine-specific survival (56.7% with RT vs 50.7% without RT, $P < 0.001$). On subgroup analysis, however, this benefit in uterine-specific survival was limited only to patients with stage IV disease. It is unclear whether these patients with stage IV disease included women with distant metastatic or locally advanced disease or both. Finally, a third analysis of the SEER data set included 1855 patients with stage I to III disease.[12] The authors did not detect a significant association between RT and OS. A previous analysis of the NCDB also failed to detect any significant impact on survival from the addition of RT (HR, 0.90; 95% CI, 0.80–1.02) for patients with stage I to IV uterine carcinosarcoma.[15] However, the results of this previous NCDB study are difficult to interpret because, unlike our analysis, it did not exclude patients with metastatic disease or para-aortic nodal involvement, those who did not undergo surgery, and those who may have received RT to sites other than the pelvis. Moreover, the authors did not exclude patients with immediate postoperative mortality, which has been previously demonstrated to impact on the survival analysis of postoperative therapies.[10] In contrast, our current analysis demonstrated that the use of adjuvant RT was associated with a 9% absolute improvement in 5-year OS among the patients with disease confined to the pelvis, although this benefit did not remain statistically significant on multivariate analysis. These data collectively suggest that RT alone may be beneficial but not sufficient for adjunctive therapy in treating uterine carcinosarcoma.

Because nearly 25% of the women with uterine carcinosarcoma will develop pelvic relapse after adjuvant chemotherapy alone,[8] these patients may potentially benefit from multimodality therapy using both chemotherapy and RT. In our analysis, combined chemotherapy and RT was associated with the highest 5-year survival of 62.9%, which was significantly higher than the corresponding survival rate of patients treated with no adjuvant therapy, chemotherapy alone, or RT alone. Several retrospective studies have previously reported encouraging results with the use of combined modality therapy. A multicenter study by Dickson et al[16] included 303 patients with stage I to III uterine carcinosarcoma who underwent observation, adjuvant chemotherapy, adjuvant RT, or multimodal therapy (chemotherapy and RT) after primary surgery. For patients with early-stage disease (stages I–II), combined modality therapy was found to improve progression-free survival (adjusted HR, 0.43; $P = 0.04$) but

not OS (adjusted HR, 0.94; $P = 0.91$) compared with adjuvant chemotherapy alone. For patients with stage III disease, there were nonsignificant trends toward improved progression-free survival (adjusted HR, 0.53; $P = 0.09$) and OS (adjusted HR, 0.58; $P = 0.20$) with combined modality therapy compared with chemotherapy alone. A separate multicenter study reported by Guttman et al[17] included 118 patients with stage I to II uterine carcinosarcoma treated with observation, chemotherapy, RT, or combined chemotherapy and RT after primary surgery. Combination therapy was associated with significantly improved OS compared with observation (HR, 0.31; $P < 0.05$), RT alone (HR, 0.34; $P < 0.05$), or chemotherapy alone (HR, 0.34; $P < 0.05$). A small prospective phase II trial used a regimen consisting of ifosfamide-based chemotherapy for 3 cycles followed by pelvic RT followed by 3 additional cycles of chemotherapy.[18] This "sandwich" approach yielded promising results with mean disease-free survival of 18 and 15.7 months for early- and advanced-stage patients, respectively. Our findings complement these data and support the use of combined modality therapy as an effective adjuvant regimen.

We found that approximately 17% of women in our study did not undergo lymph node sampling or dissection. There is currently no clear consensus on the indications for and therapeutic value of routine lymphadenectomy for the treatment of uterine carcinosarcoma.[19] Two randomized trials addressing the role of routine lymphadenectomy for early-stage endometrial carcinoma have failed to demonstrate a survival advantage for routine lymphadenectomy over standard surgery.[20,21] However, the applicability of these trials to women with uterine carcinosarcoma is limited because less than 1% of the study populations had carcinosarcoma. A SEER analysis of women specifically with carcinosarcoma found that lymphadenectomy was associated with significantly improved survival compared with no lymphadenectomy.[12] Our findings suggest that most practitioners favor performing at least a lymph node sampling, if not a complete lymph node dissection.

The major strength of our study is the large sample size, with nearly 5000 patients included in this analysis. Contrary to the previously mentioned SEER studies, we included only the patients with disease confined to the pelvis (N2 and M1 patients were excluded) and those who received RT only to the primary site. However, we also recognize several important limitations to our analysis. The NCDB does not encode information on patterns of failure and cause of death. The previously mentioned EORTC trial indicated that RT may improve locoregional control, which is presumably the mechanism by which RT may improve survival, but this cannot be established by our analysis. Because the NCDB is a hospital-based registry, there is no central pathology review. Detailed chemotherapy data, including which agents were administered and for how many cycles, are not encoded in the NCDB. Although the optimal chemotherapeutic regimen has yet to be identified, known active agents include paclitaxel, carboplatin, cisplatin, and ifosfamide. Finally, the NCDB does not provide additional information regarding the extent of the surgical staging performed during surgery. For example, we do not know whether peritoneal biopsies and omentectomy were also performed, which may have identified intra-abdominal disease.

In conclusion, we found that both chemotherapy and RT are commonly used adjunctive therapies for the treatment of uterine carcinosarcoma. Chemotherapy alone, as well as combination chemotherapy with RT, was associated with improved OS. Our findings support the use of adjuvant chemotherapy with or without RT, as suggested by national guidelines. Multimodality therapy including both chemotherapy and RT warrants further prospective investigation.

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