Impact of Adjuvant Pelvic Radiotherapy in Stage I Uterine Sarcoma

WILLIAM J. MAGNUSON[1], DANIEL G. PETEREIT[2], BETHANY M. ANDERSON[1], HEATHER M. GEYE[1] and KRISTIN A. BRADLEY[1]

[1]*University of Wisconsin Department of Radiation Oncology, Madison, WI, U.S.A.;*
[2]*John T. Vucurevich Cancer Care Institute, Rapid City, SD, U.S.A.*

Abstract. *Background/Aim: The optimal adjuvant therapy for stage I uterine sarcoma remains unresolved and may consist of radiotherapy (RT), chemotherapy, hormonal therapy or observation. We analyzed the impact of adjuvant pelvic RT on overall survival (OS), cause-specific survival (CSS), disease-free survival (DFS), pelvic control (PC) and patterns of failure. Patients and Methods: A retrospective analysis of 157 patients with International Federation of Gynecology and Obstetrics FIGO stage I uterine sarcoma was performed. RT was given postoperatively to a dose of 45-51 Gy in 28-30 fractions. Results: The 5-year OS, CSS, DFS and PC was 58%, 62%, 47% and 72%, respectively. Adjuvant RT significantly improved PC (85% for RT group vs. 64% for non-RT group; p=0.02) but did not impact OS, CSS or DFS. Conclusion: The addition of adjuvant pelvic RT significantly improved PC for patients with stage I uterine sarcoma. As systemic therapies continue to improve, optimal locoregional control may result in improved patient outcomes.*

Uterine sarcomas are rare tumors that comprise only 4-9% of uterine malignancies but cause nearly 30% of deaths from uterine cancer (1, 2). A recent Surveillance, Epidemiology and End Results (SEER) analysis demonstrated that 54% of patients present with stage I disease (3) and a 5-year survival for uterine-confined sarcoma that ranges from 33-68% (1, 4-6) reflecting their aggressive clinical behavior. Due to the rarity of the disease and resultant inability to accrue to phase III randomized controlled trials (6-8), neither radiotherapy (RT) nor chemotherapy has consistently been shown to increase overall survival (OS) and the optimal adjuvant therapy for stage I uterine sarcoma has yet to be elucidated.

Correspondence to: William J. Magnuson, University of Wisconsin Department of Radiation Oncology, 600 Highland Avenue, K4/B100 Clinical Science Center, Madison, WI 53792 U.S.A. Tel: +1 6082638500, Fax: +1 6082639167, e-mail: wmagnuson@uwhealth.org

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The primary treatment for uterine sarcoma is surgical resection with total hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection. While uterine sarcomas have a propensity for early hematogenous spread, local failure following surgery occurs in 24-57% of patients who do not receive adjuvant RT (6, 8, 9) suggesting a need for additional local treatment. RT has been shown to reduce locoregional failures without a consistent OS survival benefit, as distant failure is the predominant pattern of failure (4-6, 9). Despite the high risk of distant metastasis, recurrent pelvic disease can result in significant morbidity with negative impact on quality of life. Unfortunately, adjuvant chemotherapy has also failed to demonstrate an OS benefit in recent prospective randomized trials (7, 8).

From a histological stand-point, uterine sarcomas were initially classified as carcinosarcoma (CS), leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS) and undifferentiated sarcoma (US), with each subtype constituting approximately 50%, 38%, 10% and 2%, respectively (10). However, CS has recently been reclassified as a dedifferentiated or metaplastic form of endometrial carcinoma as it appears to arise from a common stem cell that produces epithelial tumors with a bi-phasic development, which gives rise to its mixed histological appearance (11-13). Despite this re-classification, and because it exhibits much more aggressive behavior than endometrioid carcinoma, CS is still included in most retrospective studies of uterine sarcoma and the 2003 World Health Organization classification. To reflect the different biological behavior, inherent in the different types of uterine sarcomas, the International Federation of Gynecology and Obstetrics (FIGO) adopted a new classification and staging system in 2009. For stage I disease, ESS and LMS are now sub-divided according to tumor size, while CS is still staged in the same manner as endometrial carcinoma.

Although there is a paucity of randomized data investigating the efficacy of adjuvant RT, two large studies containing epidemiologic data have been reported (3, 14). While both studies demonstrated a significant local control benefit to adjuvant RT, the study by Brooks *et al*. also

Table I. *Patients' characteristics*.

	RT group (n=72; 46%)	Non-RT group (n=85; 54%)	Total (n=157)
Median age (range)	54 (38-71)	56 (35-75)	55 (35-75)
Histology			
Carcinosarcoma	39 (54%)	24 (28%)	63 (40%)
Endometrial stromal sarcoma	8 (11%)	23 (27%)	31 (20%)
Leiomyosarcoma	25 (35%)	38 (45%)	63 (40%)
Chemotherapy	11 (15%)	23 (27%)	34 (22%)
Lymph node dissection	18 (25%)	30 (35%)	48 (31%)
Follow-up (years)			
Median (range)	4 (0.5-20.5)	3.6 (0.5-12.6)	3.8 (0.5-20.5)

RT, Radiotherapy.

reported an OS benefit (3). However, studies of this nature are unable to adequately detail RT technique, dose of RT delivered, selection criteria for administering RT or if chemotherapy was given. Due to the heterogeneous manner in which these patients were treated, the outcomes must be interpreted with caution. To add to the body of literature on uterine sarcomas, we retrospectively analyzed our experience with regard to the impact of adjuvant pelvic RT on OS, cause specific survival (CSS), disease-free survival (DFS), pelvic control (PC) and patterns of recurrence in patients with stage I uterine sarcoma treated at a single institution.

Patients and Methods

After Institutional review board approval, the medial records of patients with FIGO stage I uterine sarcoma treated at the University of Wisconsin Carbone Cancer Center between April 1969 and July 2012 were reviewed. Only patients treated with curative intent were included. Patients who received definitive RT or vaginal cuff brachytherapy (alone or with external beam RT) were excluded to remove a potentially confounding variable. The remaining 157 patients treated with curative intent were analyzed (Table I).

All patients were retrospectively staged according to the 2009 FIGO staging system for uterine sarcoma. Patient records were reviewed to determine pattern of recurrence (pelvic, distant or both), site of recurrence within the pelvis, complications and survival. Any recurrence above the pelvis (defined as superior to the lumbosacral angle) was considered a distant recurrence. Toxicity was reported using the Radiation Therapy Oncology Group (RTOG) scale and only toxicities ≥ grade 3 were reported (15).

Treatment. All patients underwent surgical resection of the primary tumor, consisting of total abdominal hysterectomy bilateral salpingo-oophorectomy surgery (TH-BSO) with peritoneal washings and a lymph node dissection was performed in 30% of patients. Adjuvant RT alone was administered to 46% of patients. Chemotherapy alone was administered to 16% of patients and chemotherapy prior to adjuvant RT to 6% of patients. Due to either physician or patient preference, 32% of patients were observed.

The majority (92%) of patients receiving adjuvant RT were treated with a four-field technique targeting the entire pelvis to a dose of 45-51 Gy in 1.7-2.0 Gy fractions. A minority (8%) of patients received a hypofractionated course of 30 Gy in 10 fractions, followed by 20 Gy in 8 fractions to provide logistical convenience for patients traveling a significant distance to the treatment facility. RT was delivered with 4-18 MV photons.

Statistical analysis. Kaplan-Meier estimates were used for each clinical end-point. The data points for OS, CSS, DFS and PC were measured from the time of definitive surgery to the time of event. OS was defined as the time of death due to any cause. CSS was defined as a death from disease, a treatment-related complication or any unknown cause within 5 years of treatment and deaths due to other causes were censored from the analysis. DFS was calculated as the time interval to any pelvic or distant failure. PC was defined as the absence of disease within the pelvis. Patients were censored at the date of the last follow-up visit or death.

For statistical comparisons both within histological subtype and for all subtypes combined, we employed Cox proportional hazards (PH) models. These models were used not only to compute *p*-values but also to obtain hazard ratios (HR) and their associated 95% confidence intervals (CI). Cox modeling allowed us to fit stratified models by which we could obtain an overall estimate of the effect of RT while allowing for different baseline hazard rates within the three histologic subtypes. Unless otherwise noted, all estimates of hazard ratios, their associated confidence intervals and *p*-values are based on the stratified Cox PH model. The statistical analyses were performed using SPSS (Statistical Package for Social Sciences, version 21.0, Chicago, IL, USA).

Results

Patients' characteristics and treatments administered are detailed in Table I. The study sample consisted of 157 patients: 63 LMS, 63 CS and 31 ESS. For the entire cohort, 22% of patients received chemotherapy and 31% had a lymph node dissection. The median follow-up was 3.8 years (range=0.5-20.7).

Survival and pelvic control outcomes. In Table II, we present 5-year Kaplan-Meier estimates for each clinical end-point, as well as HR estimates, their associated 95% CI and *p*-values.

Table II. *Survival and pelvic control*.

	5-year Kaplan-Meier estimates			Subtype-specific Cox PH model	
Overall Survival	RT group	Non-RT group	*p*-Value	HR	95% CI
Carcinosarcoma	63%	49%	0.61	0.81	(0.37, 1.79)
Endometrial Stromal Sarcoma	73%	75%	0.88	0.91	(0.23, 3.45)
Leiomyosarcoma	55%	43%	0.35	0.73	(0.38, 1.41)
Combined	61%	53%	0.41	0.83	(0.53, 1.30)
Cause Specific Survival	RT group	Non-RT group	*p*-Value	HR	95% CI
Carcinosarcoma	66%	62%	0.23	0.82	(0.34, 1.92)
Endometrial Stromal Sarcoma	73%	81%	0.79	1.21	(0.30, 4.86)
Leiomyosarcoma	62%	43%	0.38	0.68	(0.34, 1.36)
Combined	65%	57%	0.33	0.78	(0.48, 1.28)
Disease Free Survival	RT group	Non-RT group	*p*-Value	HR	95% CI
Carcinosarcoma	53%	52%	0.62	0.83	(0.39, 1.74)
Endometrial Stromal Sarcoma	85%	66%	0.21	0.39	(0.09, 1.81)
Leiomyosarcoma	33%	28%	0.29	0.71	(0.37, 1.35)
Combined	49%	45%	0.16	0.74	(0.48, 1.14)
Pelvic Control	RT group	Non-RT group	*p*-Value	HR	95% CI
Carcinosarcoma	79%	58%	0.04	0.37	(0.13, 1.01)
Endometrial Stromal Sarcoma	100%	66%	0.08	0.19	(0.03, 1.53)
Leiomyosarcoma	90%	67%	0.05	0.24	(0.05, 1.08)
Combined	85%	64%	0.01	0.29	(0.14, 0.61)

RT, Radiotherapy.

In this case, the HR reflects the ratio of the risk in the group receiving RT relative to the group not receiving RT.

Pelvic control was significantly improved among patients receiving RT (RR=0.29; 95% CI=(0.14, 0.61); p=0.01). Five-year actuarial pelvic control rates were 85% for the RT group and 64% for the non-RT group (Figure 1). On sub-group analysis, adjuvant RT significantly improved pelvic control for CS (p=0.04) and LMS (p=0.05), though ESS did not reach statistical significance. In the entire cohort, and on sub-group analysis, adjuvant RT did not significantly impact OS, CSS or DFS.

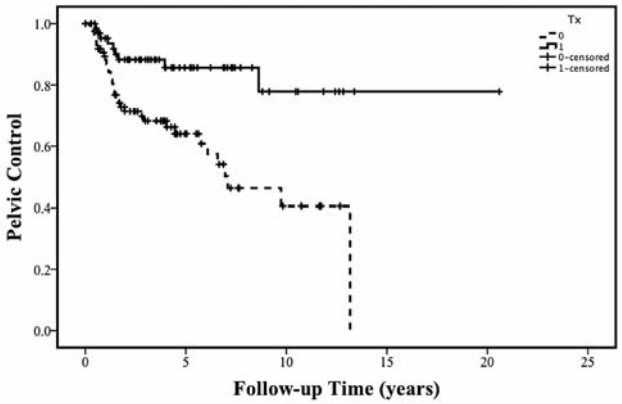

Figure 1. *Kaplan-Meier curve for pelvic control*.

Recurrence patterns. A comparison of the patterns of recurrence between the RT group and the non-RT group is detailed in Table III. Distant metastases developed in 46% of patients overall (57% in the non-RT group *versus* 37% in the RT group). On subgroup analysis, LMS had the highest rate of distant metastases (62%), followed by CS (37%) and ESS (35%).

Table IV depicts the number of pelvic and vaginal recurrences by treatment group and histology. For the radiotherapy cohort, only 55% of locoregional recurrences were within the pelvis (45% in the vagina) compared to 85% in the pelvis (and 15% in the vagina) for the non-radiotherapy group. Interestingly, there were no vaginal recurrences seen in LMS and 8 of 9 vaginal recurrences were CS.

Table III. *Patterns of recurrence*.

	RT Group			
Pathology	Pelvic only	Distant only	Pelvic + distant	Total recurrence
Carcinosarcoma	3 (7%)	11 (28%)	3 (7%)	17 (42%)
Endometrial Stromal Sarcoma	0%	1 (13%)	1 (13%)	2 (26%)
Leiomyosarcoma	0%	12 (48%)	2 (4%)	14 (56%)
Total	3 (4%)	24 (33%)	6 (8%)	33 (45%)
	Non-RT Group			
Pathology	Pelvic only	Distant only	Pelvic + distant	Total recurrence
Carcinosarcoma	3 (13%)	2 (8%)	7 (29%)	12 (50%)
Endometrial Stromal Sarcoma	2 (9%)	0%	9 (39%)	11 (48%)
Leiomyosarcoma	3 (8%)	5 (40%)	10 (26%)	18 (74%)
Total	8 (9%)	17 (20%)	26 (31%)	51 (60%)

RT, Radiotherapy.

Table IV. *Sites of locoregional recurrence*.

	RT Group				
Pathology	Pelvis	Vagina	Total recurrences	Total patients	Pelvic control
Carcinosarcoma	2	4	6	39	85%
Endometrial stromal sarcoma	1	0	1	8	88%
Leiomyosarcoma	2	0	2	25	92%
Total	5	4	9	72	88%
	Non-RT group				
Pathology	Pelvis	Vagina	Total recurrences	Total patients	Pelvic control
Carcinosarcoma	6	4	10	24	58%
Endometrial stromal sarcoma	10	1	11	23	52%
Leiomyosarcoma	13	0	13	38	65%
Total	29	5	34	85	60%

RT, Radiotherapy.

Toxicity. Adjuvant radiotherapy was well-tolerated with only six (8.3%) late grade 3-4 toxicities observed (5 small bowel obstructions and 1 entero-vesicular fistula). Four out of 6 patients who suffered a late toxicity were treated with the hypofractionated treatment regimen. Excluding these patients, the incidence of grade 3-4 toxicity was 2.8% in patients treated with conventional fractionation.

Discussion

The results of this large retrospective analysis provide further support for the ability of adjuvant RT to improve pelvic control in patients with stage I uterine sarcoma. In comparison to endometrioid carcinoma, uterine sarcoma is characterized by more aggressive behavior with an increased propensity for local recurrence, early dissemination and death. Due to the rarity of the disease and relative paucity of randomized data, the optimal adjuvant therapy for stage I uterine sarcoma remains controversial and has yet to be elucidated. While adjuvant RT has been consistently shown to improve local control (4-6, 8, 9, 14) and a recent chemotherapy trial showed a DFS benefit (7), neither adjuvant radiation therapy nor chemotherapy have consistently improved OS in early stage uterine sarcoma.

The indication for administering adjuvant RT in early-stage uterine sarcoma may be best determined by histological

subtype. EORTC 55874 randomized patients with stage I-II uterine sarcoma to adjuvant RT or observation and found that RT decreased locoregional failures from 40% to 22% (p=0.004) (6). On sub-group analysis, however, the effect was only significant for CS. There was no significant benefit for LMS, whereas the ESS cohort was insufficient to generate a meaningful conclusion. Furthermore, a recent SEER analysis of 1,819 patients with stage I-II CS and 1,088 patients with stage I-II LMS demonstrated that adjuvant RT decreased the risk of death by 21% in CS but did not significantly impact survival in LMS (16). Taken together, these studies underscore the importance of adjuvant RT in early stage CS in improving local control and potentially increasing survival.

Due to the increased propensity for distant hematogenous spread, the role of adjuvant RT in early stage LMS is less clear. While EORTC 55874 showed similar rates of total local failures in LMS, adjuvant RT decreased the rate of isolated local failures from 14% to 2% (6). Similar to the EORTC trial, a SEER analysis by Sampath *et al*. demonstrated that adjuvant RT decreased the rate of local recurrence from 16% to 2% in LMS (14). In two recent pathologic studies, tumor size >5 cm and mitotic index ≥10 mitoses/high power field were shown to be prognostic in stage I LMS and allowed for separation into risk groups with significant differences in prognosis (17, 18). Therefore, one approach may be to administer adjuvant RT in patients with tumor size <5 cm and lower mitotic index as the resultant lower probability of distant metastases renders local control more important.

While histological grade is the most prognostic factor in determining outcome in ESS, the role of adjuvant RT is uncertain because most studies do not stratify outcomes by grade (19, 20). However, a recent study by Li *et al*. demonstrated that adjuvant RT decreased the probability of pelvic recurrence from 43% to 6% (p=0.007) and identified high grade ESS and deep myometrial invasion in low-grade ESS as risk factors for recurrence (21). While the site of first recurrence for LMS is predominantly distant, a recent study of 105 patients with ESS showed isolated pelvic recurrences to be the most common pattern of failure, thus emphasizing the importance of adjuvant RT in those with the aforementioned risk factors (22).

Due to the propensity for distant metastatic spread in uterine sarcoma, chemotherapy has been shown to be a more efficacious adjuvant therapy than RT and improves outcomes when given prior to RT (7, 8). GOG 150 included patients with optimally debulked stage I-IV uterine CS without extra-abdominal spread who were randomized to cisplatin, ifosfamide and mesna (CIM) or whole abdominal radiation (WAI) (8). After adjusting for age and stage, the estimated death rate was 29% lower for patients in the CIM arm (p=0.08) as was the risk for late toxicity. Vaginal recurrences were higher in the CIM arm and abdominal recurrences were greater in the WAI arm, while other sites showed similar rates of failure. A recently completed trial randomizing 81 patients with FIGO stage I-III uterine sarcoma to doxorubicin, ifosfamide and cisplatin (AIP) followed by RT *versus* RT-alone reported a 14% improvement (p=0.05) in 3-year DFS with AIP chemotherapy prior to RT *versus* RT alone (7).

Substantial progress in improving OS has been observed in patients with advanced, persistent or recurrent uterine sarcoma due to improved systemic therapies. GOG 21 randomized patients with stage III-IV uterine sarcoma to adriamycin with or without dimethyl-triazeno-imidazole-carboxamide (DTIC) and found a response rate (RR) of 20-30% with an OS of only 7.7 months (23). More recently, GOG 161 evaluated the efficacy of ifosfamide (with or without paclitaxel) in patients with stage III or IV uterine CS and found a RR of 45% and OS of 13.5 months in the combination arm (24). GOG 87L assessed the effectiveness of gemcitabine plus docetaxel as first-line treatment in metastatic LMS and reported a RR of 53% and an OS of 16.1 months (25). Further investigation of chemotherapy agents continues. GOG 261 is randomizing patients with newly-diagnosed stage I-IV, persistent or recurrent CS to paclitaxel and carboplatin or to paclitaxel and ifosfamide. GOG 250 is evaluating docetaxel, gemcitabine and G-CSF with or without bevacizumab in patients with advanced or recurrent LMS.

This series of patients with stage I uterine sarcoma, treated at a single institution, is one of the largest in the literature and provides further support for the ability of adjuvant RT to improve pelvic control. However, there are limitations to this study. First, it is a retrospective analysis and carries with it the biases of retrospective analyses. Second, the statistical power for each histological subtype is limited because of the relatively small numbers of each particular histology. Third, we are unable to assess the impact of unmeasured confounding factors on treatment and outcome. Finally, each gynecologic oncologist had slightly different treatment philosophy on the role of adjuvant treatment.

In conclusion, the outcomes of patients with stage I uterine sarcoma remain poor and the optimal adjuvant therapy has yet to be elucidated as neither pelvic RT nor chemotherapy have consistently shown an OS benefit. The ability of pelvic RT to decrease the probability of local recurrence can improve quality of life by preventing the physical and psychological morbidity associated with a pelvic recurrence. Furthermore, as improvements in systemic therapies decrease distant failure rates, optimal locoregional control may result in improved patient outcomes.

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