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ORIGINAL ARTICLE

External Beam Radiotherapy Boosted With High Dose Rate Brachytherapy in Completely Resected Uterine Sarcomas. Is This a Treatment Option?

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ABSTRACT

Uterine sarcoma (US) is a relative rare tumor, which accounts for only about 3-5% of all uterine cancers. Aggressive cytoreductive surgery at the time of the initial diagnosis with maximum tumor debulking may lead to a prolonged survival or cure. OBJECTIVE: to identify and review the role of adjuvante external beam radiation therapy (EBRT) associated with high dose rate brachytherapy (HDRB) in the management of patients presenting US with complete resection. MATERIAL AND METHODS: this study is a retrospective analysis of 23 patients with US treated from 10/92 to 03/03, with surgery, external beam radiation therapy (EBRT) and high dose rate brachytherapy (HDRB). The inclusion criteria for study participation included: histologically proven and graded US, completely resection of tumor, Karnofsky status 60–100, absence of significant infection, and recovery from recent surgery. RESULTS: The median age of patients was 62 years (range 39-84); ten-year actuarial disease-free and overall survivals were 42.2% and 63.4%, respectively. On univariate analysis, predictive factors for disease-free survival (DFS) were age at initial presentation (p=0.0268), parity (p= 0.0441), tumor grade (p= 0.0095), cervical or vaginal invasion (p=0.0014) and node dissection at time of surgery (p= 0.0471). On multivariate analysis, the only predictive factor was cervical or vaginal invasion (p= 0.048), hazard ratio of 4.7. CONCLUSION: it is quite likely that neither radiotherapy nor chemotherapy alone will appreciably improve survival in US. If radiation therapy provides better locoregional tumor control, hematogenous metastases will assume an even greater proportion of treatment failures. Unfortunately, our small and heterogeneous group analyzed precludes any definitive conclusions about the impact of HDRB associated to EBRT radiation therapy on recurrence or survival.

Key words: Uterine Sarcoma. High Dose Rate Brachytherapy. Radiation Therapy. Gynecological Cancer.

INTRODUCTION

Uterine sarcoma (US) is a relative rare tumor, which accounts for only about 3-5% of all uterine cancers. In Brazil the incidence of US is underestimated and it is expected to be around 1.7 new cases per 100,000 women 20 years or older.[1]

Current management of US remains unsatisfactory, requiring mainly a surgical treatment. Aggressive cytoreductive surgery at the time of the initial diagnosis, as total abdominal hysterectomy with or without bilateral salpingo-oophorectomy and omentectomy, with maximum debulking of tumor offers the possibility of prolonged survival or cure.[2]

The US has a propensity for local and distant recurrence, even when the disease appears surgically confined to the uterus. The most important prognostic factor in US is the extent of the tumor at the time of diagnosis. The prognostic impact of other factors such as myometrial invasion, menopausal age, age, parity and adjuvant therapy is still being discussed controversially.[3-5]

Although pelvic radiotherapy reduces the rate of pelvic relapses, and responses to chemotherapy have been demonstrated in metastatic disease, adjuvant therapy does not appear to significantly affect survival.[6,7]

The US can be histologically divided into:

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uterine adenosarcoma that is microscopically characterized by a biphasic growth pattern, where by definition, the epithelial component is benign, whereas stromal component typically has the aspect of a low-grade sarcoma, usually an endometrial stromal sarcoma; carcinosarcoma, defined histologically as any tumor of uterine origin composed of carcinomatous and sarcomatous components, made up of cells resembling endometrial stromal cells with only mild cytologic atypia and the low-grade endometrial stromal sarcomas.[8]

The use of brachytherapy to boost external beam radiotherapy (EBRT) after complete resection of US is controversial and scarcely reported in literature.

To identify and review the role of adjuvant pelvic EBRT associated with high dose rate brachytherapy (HDRB) as a boost in the management of patients presenting US with complete resection, we performed a retrospective analysis of patients treated at AC Camargo Hospital, São Paulo, Brazil.

Material and Methods

A retrospective chart review was performed at the Department of Radiation Oncology, A.C. Camargo Cancer Hospital, São Paulo, Brazil, from November, 1992 to March, 2003, and all patients with diagnosis of US were identified during the study period. Patients were staged according to a modification of the International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer.

The initial evaluation for all patients has consisted of history and physical evaluation, including digital rectal exam, chest X-ray, and routine serum laboratory studies (complete blood count, biochemistry panel). The inclusion criteria for study entry included: histologically proven and graded US, completely resection of tumor, Karnofsky status 60–100, absence of significant infection, and recovery from recent surgery.

After a total abdominal hysterectomy with or without bilateral salpingo-oophorectomy, omentectomy and pelvic lymph node dissection, patients were referred to the Department of Radiation Oncology.

All patients were submitted to a course of EBRT, using 4MV to 6MV photons (VARIAN Incorporation, Palo Alto, CA), given in a four-fields "box" technique.

Concurrent or immediately after the end of the course of EBRT, patients were given 4 fractions of weekly HDRB, with 6Gy per fraction, on outpatient basis. The HDRB was performed using either colpostats or vaginal cylinders with diameters ranging from 2.5cm to 4cm. The entire vaginal length treated with HDRB was 2cm in all cases.

Statistical Analysis

Actuarial results were calculated by the Kaplan-Meier method.[9] Chi-square tests were used to assess differences in proportions. Log-rank test was used to compare equality of survivor functions.[10]

Results

The median age of patients was 62 years (range 39-84). The menopausal status was verified, and 18 patients were post-menopausal and 5 pre-menopausal. The median age for menopause onset was 47 years (from 40 to 52), the parity ranging from 0 to 6 (median 2).

All patients have undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without pelvic lymph node dissection. Pelvic lymph node dissection was done in only 17.4% (4) of patients, with a mean of 12 nodes dissected (range 11-14). The clinical stage (CS) and histopathological characteristics are shown in Table 1.

The entire course of prescribed radiotherapy was completed in 91.3% (22) of the patients. The dose prescribed ranged from 40 Gy to 50.4Gy (median 48Gy) given in 20 to 28 daily fractions of 1.6Gy to 2.0Gy. HDRB was given concurrent to EBRT in 12 patients (52.2%). The HDRB for remaining patients started in median interval of 34 days (range 5-99 days) after the completion of EBRT.

The median biological effective dose (BED) calculated for the whole treatment was $91.5Gy_{10}$ (from $85.6Gy_{10}$ to $97.9Gy_{10}$), with a standard deviation of 3.7.

Actuarial 10-year disease-free and overall survivals were 42.2% and 63.4%, respectively (Figure 1).

Table 1 - Pathological Characteristics

Variable	Category	N	%
Clinical	I	17	73.9
Stage	II	4	17.4
	III	2	8.7
Histology	carcinosarcoma	6	26.1
	leiomyosarcoma	4	17.4
	endometrial sarcoma	13	56.5
Tumor	I	10	43.5
grade	II	7	30.4
	III	6	26.1
Myometrial	superficial	13	56.5
invasion	less than half	8	34.8
	more than half	2	8.7
Vaginal /	yes	6	26.1
cervical invasion	no	17	73.9
Nodes	yes	4	17.4
dissection	no	19	82.6
Positive nodes	yes	3	13.0
	no	20	87.0

One patient presented pelvic recurrence one year after the end of the treatment and underwent a second course of salvage HDRB. Three patients presented distant metastases: two to the lungs and liver, and the third presented a paravertebral mass and bone metastasis. All three were referred to systemic chemotherapy, with a mean survival of 12 months (range 4-15). Two patients presented a second primary tumor after completion of treatment, both on the breast, 10 and 12 years after the treatment of the US with conservative surgery, EBRT and chemotherapy.

On univariate analysis, shown in Table 2, the only predictive factors for disease-free survival were age at initial presentation (p=0.0268), parity (p=0.0441), tumor grade (p=0.0095), cervical or vaginal invasion (p=0.0014) and node dissection at time of surgery (p=0.0471). On multivariate analysis the only predictive factor for disease-free survival was cervical or vaginal invasion (p=0.048), with patients with cervical or vaginal invasion presenting a hazard ratio of 4.7 times more chance of dying of disease (Table 3).

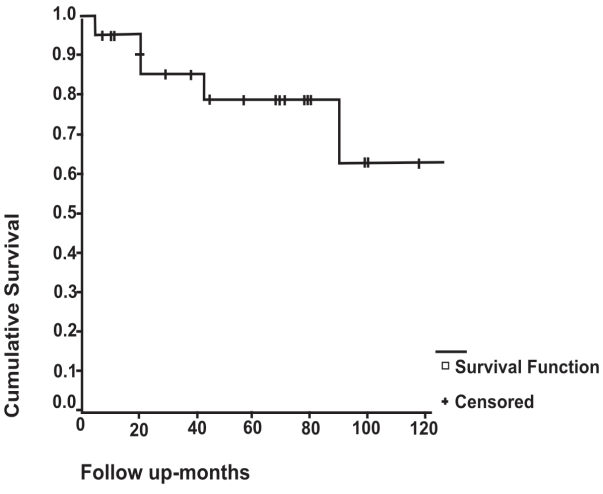

Figure 1- Actuarial overall survival

DISCUSSION

The diagnosis of US generally is based on clinical presentation of these tumors, that is diverse and can come with abnormal uterine bleeding, abdominal pain, pelvic mass, discharge or cervix prominent mass. Other clinical discoveries associated with the presence of US, as obesity and high blood pressure occur in almost 30% of the patients. It is also observed antecedents of pelvic radiation in 5%-10% of the cases. This rare and aggressive form of uterine malignancy is composed by a heterogeneous group of tumors that encompass the mixed Mullerian tumour, leiomyosarcoma and endometrial sarcoma as one entity that presents variable degree of local and distant aggressiveness. Because these tumors are relatively rare, most reports have analyzed all histological subtypes as one entity. The analysis of US is made difficult by the absence of nomenclature standardization, which has contributed to a variety and variability of classifications.[11,12]

The inclusion of the mixed mullerian tumors (MMT) in the same group can be argued as clinical, histopathological, immunohistochemical, ultrastructural, and molecular. Tissue culture data suggest that most mixed mullerian tumors are monoclonal metaplastic carcinomas rather than a mixture of a carcinoma and a sarcoma.[13]

The current management of US remains unsatisfactory, and neither adjuvant chemotherapy nor radiotherapy has significantly improved survival, but most of these patients receive multimodality therapy with surgery followed by chemotherapy and/or radiotherapy.[14,15] There must be a subgroup of patients that can benefit from adjuvant therapy, as their estimated survival is still very low and prospective randomized trials are almost impossible. The use of adjuvant treatments are almost always a reality. Piver et al. have

Table 2 - Univariate analysis for clinical, histopatological and disease-free survival

Variables		Number	Number censored	Percentage censored	p*
Age in years	< 65	13	12	92.3	0.0268
	> 65	10	5	50.0	
Menopausal status	pre	3	3	100.0	0.4513
	post	20	14	70.0	
Menopause onset	< 47 years	9	8	88.9	0.5775
	> 47 years	14	9	64.2	
Parity	< 3	12	10	83.3	0.0441
	> 3	9	7	77.8	
	unknown	2	0	0.0	
Clinical stage	I	17	12	70.6	0.2307
	II	4	4	100	
	III	2	1	50.0	
Histology	carcinosarcoma	6	2	33.3	0.1427
	leiomyosarcoma	4	4	100.0	
	endometrial sarcoma	13	11	84.62	
Tumor grade	I	10	4	40.0	0.0095
	II	7	7	100.0	
	III	6	6	100.0	
Myometrial Invasion	superficial	13	13	69.2	0,8224
	less than half	8	8	75.0	
	more than half	2	2	100.0	
Cervical / vaginal invasion	yes	6	5	94.0	0.0014
	no	17	1	16.7	
Node dissection	yes	4	2	50.0	0.0471
	no	19	15	78.9	
Node metastasis	yes	3	2	66.7	0.4444
	no	20	15	75.0	
EBRT treatment time	< 60 days	11	8	72.7	0.3102
	> 60 days	12	9	75.0	
Interval EBRT / HDRBT	< 30 days	12	9	75.0	0.4271
	> 30 days	11	8	72.7	
Overall treatment time	< 88 days	13	10	76.9	0.7955
	> 88 days	10	7	70.0	
BED (Gy10)	< 91.5	18	14	77.8	0.3443
	> 91.5	5	3	60.0	

* Log-rank test for equality of survival distributions for age under and over 65. 95% Confidence Interval

Table 3 - Multivariate analysis by Cox Regression Model for clinical, histopatological and disease-free survival

Variable	p	Exp(B)	95% CI for Exp (B)		HR*
			Lower	Upper	
Parity	0.238	0.968	0.917	1.022	1.604
Tumor Grade	0.356	1.532	0.619	3.790	1.127
Myometrial invasion	0.702	0.632	0.061	6.606	0.904
Number of nodes dissected	0.756	0.935	0.610	1.431	0.904
Cervical and / or vaginal invasion	0.048	115.183	1.048	12658.027	4.728

*HR- hazard ratio

reported only an estimated 5-year survival rate of 36% for patients with US.[16]

Histological differentiation between US and the endometrial stromal sarcomas (ESS) is obligatory, as the last one is a rare gynecological malignancy, in which optimal management remains unclear. The ESS is a hormone-sensitive tumor of young women that accounts for less than 0.2% of gynecological malignancies, and most ESS express receptors for estrogen, progesterone, gonadotropin releasing hormone and aromatase.[17]

Pelvic radiotherapy reduces the rate of pelvic relapses, but its association with HDRB is scarce in literature. The median age of our group of patients was 62-year old and conversely to endometrial carcinoma that tends to occur in an older population who has competing causes of death such as heart disease, the relationship between local recurrence versus distant failure and survival has been somewhat unclear.

In our series, only patients submitted to complete resection of tumors were referred to a course of adjuvant radiation therapy, which must have impacted the results, as our 10-year actuarial disease-free and overall survivals rates were 42.2% and 63.4%, respectively. Since local recurrences in pelvis or vagina are not easily handled, we have offered a course of HDRB for all these patients.

In our analysis, predictive factors for disease-free survival were age at initial presentation (p=0.0268), parity (p=0.0441), tumor grade (p=0.0095), and node dissection at time of surgery (p=0.0471). Conversely Geller et al. reported on 28 patients with US, 19 low-grade and 9 high-grade, treated between 1972 and 2003.There was no significant difference in overall survival for patients with local versus advanced disease (p=0.53) or in overall survival for those who underwent lymphadenectomy and those who did not (p=0.92). Fifty percent of patients received postoperative radiation with no difference in disease-free or overall survival (p=0.68 and p=0.53).[18] Le has also reported data from 32 patients with US in which 84% had disease confined to the uterus at the time of evaluation. Patients with high-grade sarcomas, deep myometrial invasion, or gross pelvic metastatic disease were offered adjuvant pelvic irradiation. The overall 5-year survival was 38% for this group of patients. He has also observed no statistically significant difference in the progression-free or overall survival in the radiated group compared to the expectantly treated group.[19]

Gerszten et al.[20] in a retrospective review of 60 patients receiving definitive therapy for US have observed that 48,3% of patients were treated with adjuvant radiotherapy, and it has significantly reduced the local recurrence rate from 55% (17 patients) to 3% (1 patient), with no impact on distant recurrence and survival rates in stage III patients. They have also observed that increasing CS and depth of myometrial tumor invasion were negatively associated with overall survival and disease-free survival, but without impact on local recurrence rates. The only predictive component of local recurrence was the nuclear grade of the epithelial component (p=0.0592). They have reported that the relative risk of local recurrence of unirradiated patients versus irradiated patients was 17.54 (p=0.0055) after adjusting for nuclear grade of the epithelial component.[20] By contrast, Sartori et al.[21] have reported that for initial stages postoperative radiation did not improve 5-year disease-free survival and survival curves in patients with advanced disease treated with cisplatin-containing regimens or with doxorubicin (without cisplatin)-containing regimens were overlapping.

A European study by Jereczek et al.[12] evaluating 42 patients with US has reported that 37 patients had previously been operated and 16 had adjuvant postoperative radiotherapy, 2 chemotherapy and chemotherapy and irradiation in one. Treatment failure occurred in 7 out of 14 patients who received adjuvant radiotherapy and in 12 out of 17 treated without irradiation. Median survival time in both groups was 26 months. Survival for the whole series ranged from 2 months to 19 years (median 26 months) and was not related to tumor type. Actuarial two- and five-survival rates were 54% and 30%, respectively.

The role of radiotherapy is greater for mixed mullerian tumors than for leiomyosarcomas for two reasons. First, MMT have greater rates of pelvic and peritoneal failures following surgery. Part of 20% of the patients with clinical stage I or II MMT has

surgical stage III or IV disease with nodal or peritoneal dissemination.[5]

We have verified that only 17.4% of our patients underwent lymphadenectomy. Golf et al.[22] reported in 1993 that pelvic lymph node dissection was done in only 30% of patients, as lymphadenectomy has not been shown to be therapeutically or prognostically significant.

Murphy et al.[23] have published the outcome and patterns of failure of 38 women with ressected US (clear-cell tumors). Adjuvant therapies were as follow: 5 none, 22 had pelvic EBRT, 2 only vaginal brachytherapy , and 7 both EBRT and brachytherapy. With a median 36.5-month follow up, they have observed a 5-year actuarial disease-free survival of 38.5%. No correlation has been seen between relapse and stage, myometrial invasion, cytology, cervical extension, or involvement of extrauterine sites.

Chemotherapy use as adjuvant setting is somewhat appealing, but it is also scarce in literature. Hensley et al.[24] in a recent paper reported a 53% response rate in 34 patients with uterine and pelvic, retroperitoneal, or gastrointestinal leiosarcoma, using gemcitabine and docetaxel. Three patients (9%) had a complete response, and median duration of response was 5.6 months.

It is quite likely that neither radiotherapy nor chemotherapy alone will appreciably improve survival. In fact, if radiation therapy provides better locoregional tumor control, hematogenous metastases will assume an even greater proportion of treatment failures. A logical next step will be to test the combination of more optimal radiotherapy and chemotherapy against the best treatment arm of GOG Protocol number 150.[25]

Unfortunately, our small and heterogeneous analyzed group and the absence of a control treated with EBRT alone preclude any definitive conclusions about the impact of HDRB associated to EBRT radiation therapy on recurrence or survival, even on patients with cervical or vaginal invasion.

Although abdominal failures are common in women with MMT and unusual in the other histological types, translation of higher radiation dosage to cure is still to be proven, as majority of failures have a distant component. Until effective systemic therapy is developed, the prognosis of US with any dissemination beyond the uterus will remain poor.

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