Radiotherapy and Oncology 135 (2019) 91–99

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Long-term results of Perioperative High Dose Rate Brachytherapy (PHDRB) and external beam radiation in adult patients with soft tissue sarcomas of the extremities and the superficial trunk: Final results of a prospective controlled study

Marta Gimeno [a], Mikel San Julián [b], Mauricio Cambeiro [a], Leire Arbea [a], Paola Jablonska [a], Marta Moreno-Jiménez [a], Santiago Amillo [b], Javier Aristu [a], Fernando Lecanda [c], Rafael Martinez-Monge [a,*]

[a] Department of Oncology; [b] Department of Orthopedic Surgery, Clínica Universitaria de Navarra; and [c] Department of Solid Tumors and Biomarkers, Center for Applied Medical Research University of Navarra, Pamplona, Spain

ARTICLE INFO

Article history:
Received 13 November 2018
Received in revised form 4 February 2019
Accepted 13 February 2019
Available online 19 March 2019

Keywords:
Soft tissue sarcomas
Perioperative
High dose rate
Brachytherapy
External beam radiation therapy

ABSTRACT

Background: To analyze toxicity, patterns of failure, and survival in 106 adult patients with soft tissue sarcomas of the extremity and the superficial trunk treated in a prospective controlled trial of combined Perioperative High Dose Rate Brachytherapy (PHDRB) and external beam radiotherapy (EBRT).
Methods: Patients were treated with surgical resection and 16 Gy or 24 Gy of PHDRB for negative or close/positive margins, respectively. EBRT (45 Gy) was added postoperatively. Adjuvant chemotherapy was given to selected patients with high-grade tumors.
Results: The median follow-up was 7.1 years (range, 0.6–16.0). Grade ≥3 adverse events were observed in 22 patients (20.8%), and grade ≥4 events in 14 patients (13.2%). No grade 5 events were noted. Multivariate analysis (p = 0.003) found that Grade ≥3 toxic events increased with increasing implant volume (TV_{100}). Local control, locoregional control, and distant control rates at 5 and 10 years were 89% and 87%, 82% and 80% and 75% and 69%, respectively. Multivariate analysis (p = 0.024) found that positive margins correlated with decreased local control. Disease-free survival and overall survival rates at 5 and 10 years were 64% and 59% and 73% and 62%, respectively. In multivariate analysis, disease-free survival rates decreased with increasing tumor size (p = 0.0001) and inadequate margins (p = 0.024), and overall survival decreased with increasing tumor size (p = 0.001) and male gender (p = 0.039).
Conclusions: The combination of conservative surgery, high-dose PHDRB, and EBRT produces adequate function and local control in the majority of patients with soft tissue sarcomas of the extremities and the superficial trunk, including a substantial percentage of cases with positive margins. Patients with larger tumors are at a higher risk of complications, treatment failure, and cancer-related death and require an individualized treatment approach.

Adjuvant radiotherapy is a well established treatment component in the conservative management of soft tissue sarcomas. The National Comprehensive Cancer Network guidelines recommend that postoperative irradiation be considered in the majority of the patients after resection of localized soft tissue sarcomas of the extremities and the superficial trunk. When brachytherapy alone is used, 45 Gy of low-dose rate (LDR) or high-dose rate (HDR equivalent) brachytherapy are recommended for patients with negative margins. In patients with positive margins, a combination of 50 Gy of external beam radiation (EBRT) and 16–20 Gy of LDR brachytherapy or the high-dose rate (HDR) equivalent is advised [1]. This range of radiation doses produces 5-year locoregional control rates in 75–90% of patients [2–15].

Higher radiation doses (>60 Gy) have shown improved local control in patients with positive margins in some retrospective studies [16]; therefore, dose escalation is generally advised in patients with inadequate resections. In this setting, the smaller treatment volume generated by the brachytherapy implants is probably advantageous in terms of reduced long-term toxicity compared with to that seen with an EBRT boost [17].

In 2000, we initiated a prospective study to determine the toxicity profile and efficacy of dose escalation with combined perioperative HDR brachytherapy (PHDRB) and EBRT in patients with soft tissue sarcomas of the extremities and superficial trunk. Treatment

* Corresponding author at: Department of Oncology, Clínica Universidad de Navarra, University of Navarre, Avda Pío XII s/n, Pamplona, Navarre, Spain.
E-mail address: rmartinezm@unav.es (R. Martinez-Monge).

https://doi.org/10.1016/j.radonc.2019.02.011
0167-8140/

protocol included higher than conventional doses for patients with negative margins (EQD2 = 62.9 Gy) and close/positive margins (EQD2 = 72.3 Gy). An initial report with 60 patients and a median follow-up of 4.1 years was published in 2011 [18]. The present report updates the former experience and includes additional patients and an extended follow-up.

Materials and methods

Eligibility criteria

From October 2000 to May 2016, 106 adult patients (median age, 47 years; range, 21–83) presenting with primary soft tissue sarcomas of the extremities or the superficial trunk ($n = 89$) were treated with a conservative macroscopic surgical resection, PHDRB, and EBRT. Patients with unirradiated locally recurrent sarcomas ($n = 17$) were also included. Patients selected for PHDRB included those cases that based on preoperative physical and imaging presented a high probability of undergoing a marginal resection. Patients with incomplete gross resections (R2) were excluded from this analysis. Metastatic workup included Computed Axial Tomography (CT) scans of the chest and upper abdomen in all cases. Positron Emission Tomography (PET) Scan was performed at the discretion of the treating physician. Previously irradiated patients were treated under a separate protocol that is not reported here. IRB approval was obtained and all patients gave written informed before study entry. A detailed description of patient and tumor characteristics is presented in Table 1.

Table 1
Patient and tumor characteristics.

	n	%
Gender		
Male	71	67.0
Female	35	33.0
Histology type		
Angiosarcoma	1	0.9
Chondrosarcoma	2	1.9
Dermatofibrosarcoma protuberans	1	0.9
Epithelioid sarcoma	5	4.7
Fibrosarcoma	15	14.2
Hemangiopericytoma	1	0.9
Leiomyosarcoma	10	9.4
Liposarcoma	25	23.6
Malignant fibrous histiocytoma	21	19.8
Malignant schwannoma	2	1.9
Pleomorphic sarcoma	7	6.6
Synovial sarcoma	12	11.3
Solitary fibrous tumor	1	0.9
Undifferentiated sarcoma	3	2.8
Histology grade		
Low grade	37	34.9
High grade	69	65.1
Tumor largest diameter (cm)		
Mean: 8.1		
Range: 0.5–30.0		
AJCC stage 7th edition		
Ia	1	0.9
Ib	15	14.2
IIa	24	22.6
IIb	7	6.6
III	40	37.7
IV	2	1.9
Recurrent disease	17	16.0
Tumor location		
Extremities	80	75.5
Upper	24	22.6
Lower	56	52.8
Superficial trunk	26	24.5

Treatment protocol

Patients were treated with surgical resection and implantation of catheters for PHDRB. In the present protocol surgical margins equal to or greater than 10 mm were classified as negative, and any negative margin of less than 10 mm was classified as close. The brachytherapy dose was 4 Gy b.i.d. (interfraction interval of at least 6 h) × 4 (16 Gy total dose) for negative margins and 4 Gy b.i.d. × 6 (24 Gy total dose) for close/microscopically positive margins (Table 2). The brachytherapy dose was prescribed to the implant minimum target dose (MTD) as per ICRU No. 58 recommendations [19] from 2000 to 2006 and to the $CTVD_{90}$ (Minimal Dose received by 90% of the Clinical Target Volume) from 2006 onwards. Radiation treatment was completed with EBRT (45 Gy in twenty-five 1.8 Gy daily fractions) 4–5 weeks after the surgical procedure if healing was adequate. Total radiation doses equivalent to standard fractionation regimens delivered with 2 Gy daily fractions and calculated with the linear quadratic formulation without time correction (i.e., $BED = nd[1 + d/(\alpha/\beta)]$) [20] for the ICRU No. 58 MTD or $CTVD_{90}$ were 62.9 Gy for negative margins and 72.3 Gy for close/positive margins.

In addition, some patients with high-grade tumors were treated with adjuvant chemotherapy consisting of doxorubicin (20 mg/m^2/d) and ifosfamide (1.5 g/m^2/d, with mesna uroprotection) during three consecutive days every four weeks for three to six courses.

Brachytherapy technique and dosimetry guidelines

A detailed description of the implantation techniques used has been described previously [18]. Briefly, the surgical and the radiation oncology teams used preoperative physical and imaging, surgical findings, frozen sections where necessary, and gross examination of the surgical specimen to jointly determine the Clinical Target Volume (CTV) that, in most cases, corresponded to the entire surgical bed. The boundaries of the CTV were delineated with at least 4 cardinal gold seeds that facilitated brachytherapy treatment planning as well as image guidance for the subsequent external irradiation. The CTV was covered with a set of plastic catheters placed as parallel as possible at 1.0–1.5 mm intervals. In 92 patients (86.8%) the catheters were placed in a single plane

Table 2
Treatment characteristics.

	n	%
Surgical margins CUN[a]		
Negative margins	30	28.3%
Close/Positive margins	76	71.7%
Close	52	49.1%
Positive	24	22.6%
Surgical margins MSKCC[b]		
Negative margins	62	58.5%
Positive margins	44	41.5%
PHDRB dose		
16 Gy	31	29.2%
24 Gy	72	67.9%
Other	3	2.9%
EBRT dose		
40–50 Gy	99	93.4%
Other	7	6.6%
Chemotherapy		
Concomitant	4	3.8%
Adjuvant	39	36.8%

[a] Margin classification used in the present study as described in the Material and Methods section.
[b] The Memorial Sloan-Kettering Cancer Center classification defines positive margins as microscopically positive margins and negative margins within 1 mm of the inked margin of resection.

and in 14 cases (13.2%) as a double plane (Fig. 1). Catheters were either sutured onto the surface of the surgical bed or inserted no more than 5 mm into the surgical bed to avoid underdosage of the surgical surface. Suction drainage tubes were inserted into the surgical bed in all cases.

A CT scan was performed for verification during the first 48 h after surgery. In single-plane implants, the CTV was a seed-generated volume with a thickness of 5 mm centered on the catheter plane. To account for postoperative edema, expansion of the CTV up to 1 cm beyond the cranial and caudal seeds was allowed. In multiple-plane implants, the CTV included the different planes with a 2–3 mm margin (Fig. 1). Brachytherapy delivery began 1–9 days after surgery (median 5 days). The rest of the brachytherapy parameters are detailed in Table 3.

Study endpoints and statistical analysis

This study was undertaken to determine factors predictive of toxicity, patterns of failure, and survival in a series of patients with soft tissue sarcomas treated with conservative surgery and high-dose radiation delivered with PHDRB followed by EBRT. Toxicities were documented using the Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria [21]. Acute toxicities were defined as those occurring from the date of surgery to 90 days after the completion of the treatment. Toxicities were classified as late if they occurred more than 90 days after the end of the treatment. Patterns of failure were classified as local, locoregional, and distant. Local failure was defined as any tumor regrowth totally or partially encompassed by the 100% isodose line (4 Gy). Any other failure in the anatomical region that was implanted but outside of the 100% isodose line was considered as regional, and any failure elsewhere was considered distant failure.

Patient factors (age, gender), tumor factors (grade, diameter, stage, location), treatment factors (margin status, surgery to brachytherapy gap, duration of brachytherapy, number of channels, treatment volume, dose homogeneity index, concomitant and adjuvant chemotherapy, biological equivalent dose) were analyzed using Cox univariate and multivariate analysis to evaluate correlations with the study endpoints. Numerical variables (i.e, age, TV_{100}, tumor size, etc.) were entered as continuous values and Categorical variables (i.e, stage, etc.) as categorical values.

Table 3
Brachytherapy parameters.

	n
Number of catheters	
Median	6
Range	2–14
Surgery to brachytherapy gap (days)	
Median	4
Range	1–9
Brachytherapy duration (days)	
Median	5
Range	1–9
TV_{100} (cc)	
Mean ± SD	121.2 ± 155.3
Median	73
TV_{150} (cc)	
MEAN ± SD	35.1 ± 46.2
Median	21
DHI[a]	
Mean ± SD	0.69 ± 0.07
Median	0.7

[a] Dose Homogeneity Index = $(TV_{100} - TV_{150})/TV_{100}$.

Results

A total of 99 complications arising in the high-dose region were observed in 60 of the 106 patients analyzed. The highest RTOG toxicity score observed was grade 3 in 22 patients (20.8%) and occurred at a median of 9 months after surgery. Grade 4 adverse events occurred in 14 patients (13.2%) at a median of 11 months after surgery. No grade 5 complications were observed. The most frequent complication, wound dehiscence, was observed in 25.5% of the cases but was grade 3–4 in only 12.3%. A description of all the toxic events observed, the median time to appearance, and the percentage of grade 3–4 events for each individual complication is shown in Table 4.

In univariate analysis, Grade 3 or greater complications correlated with larger tumor size ($p = 0.004$), primary stage ($p = 0.034$), longer time to loading ($p = 0.018$), and larger TV_{100} ($p = 0.005$) and TV_{150} ($p = 0.014$) values. On multivariate analysis, primary stage ($p = 0.027$) and increased TV_{100} ($p = 0.003$) remained significant.

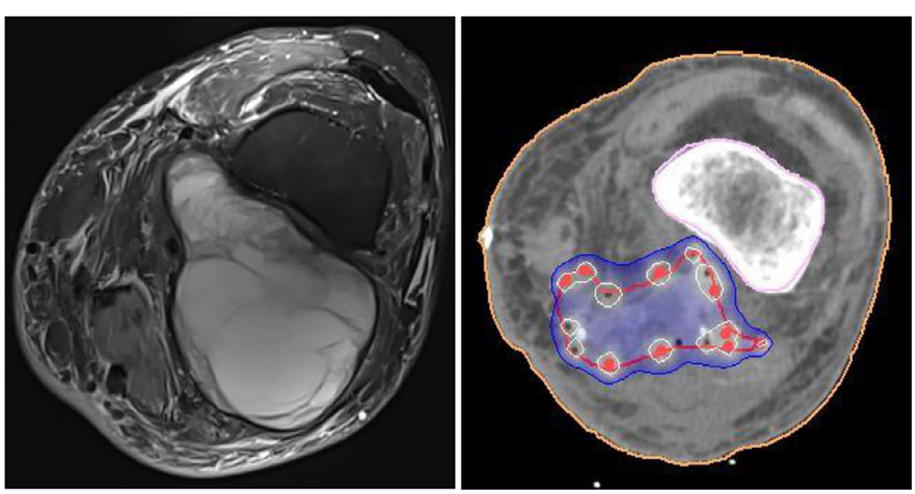


Fig. 1. CTV definition in Multiple Plane Implants. Large tumors (left) leaving significant and irregularly shaped tumor bed cavities usually require multiple-plane implants that are created by covering all aspects of the entire tumor bed surface (right) with catheters. Note that the post-resection CTV is substantially smaller than the GTV due to the collapse of the tumor bed cavity after resection. The after loading catheters appear in the images as red dots, the CTV is delineated in red, the 100% isodose line in yellow, and the 150% isodose line in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Adverse events in the high-dose region.

	N (%)	Time to appearance[a]	RTOG Grade 3–4
Individual events[b]			
Bleeding	2 (1.9%)	13.6	1 (0.8%)
Bone damage	2 (1.9%)	36.8	2 (1.9%)
Edema	6 (5.7%)	4.4	1 (0.9%)
Fibrosis	24 (22.6%)	7.9	5 (4.7%)
Fistula	5 (7.5%)	10.0	5 (4.7%)
Wound	27 (25.5%)	4.4	13 (12.3%)
Necrosis	4 (3.8%)	11.9	4 (3.8%)
Neuritis	14 (13.2%)	16.4	5 (4.7%)
Seroma	11 (10.4%)	2.4	7 (6.6%)
Technical	1 (0.9%)	0	1 (0.9%)
Thrombosis	3 (2.8%)	6.0	3 (2.8%)
Highest grade observed per patient		*n*	%
Grade 0		46	43.4
Grade 1		10	9.4
Grade 2		14	13.2
Grade 3		22	20.8
Grade 4		14	13.2
Grade 5		0	0.0

[a] Time to appearance.
[b] All individual complications observed in the same patient are described.

Grade 4 or greater complications correlated with older age ($p = 0.038$), larger tumor size ($p = 0.016$), and lower limb location ($p = 0.012$). On multivariate analysis, older age ($p = 0.046$) and lower limb location ($p = 0.012$) remained significant.

After a median follow-up of 7.1 years (range, 0.6–16.0) for patients alive at the time of this analysis, 37 patients (34.3%) failed. Eleven patients failed locally (10.4%), all of them with combined regional and/or distant failure (Table 5). Distant failure was the predominant pattern of failure, occurring in 28 patients (18 isolated, 10 combined). The 10-year actuarial local, locoregional, and distant control rates were 87%, 80%, and 69%, respectively.

Local failure increased with positive margins as per the MSKCC classification ($p = 0.024$) and with the number of catheters ($p = 0.007$). MSKCC margins remained statistically significant in the multivariate analysis ($p = 0.024$). Patient with positive margins had a 4.6-fold higher risk of local relapse than patients with negative margins. The 10-year local control rate decreased from 95% in patients with negative margins to 74% in patients with positive margins ($p = 0.013$) as shown in Fig. 2. The number of catheters used had a borderline correlation with local failure in multivariate analysis ($p = 0.06$), suggesting that larger tumor size which required a larger implanted area had a detrimental effect on local control.

Table 5
Patterns of failure.

	n	%
Local failure	11	10.4
Isolated	0	0
Combined	11	10.4
Regional failure	14	13.2
Isolated	5	4.7
Combined	9	8.5
Locoregional failure	18	17.0
Isolated	6	5.6
Combined	12	11.0
Distant failure	28	26.4
Isolated	18	17.0
Combined	10	9.4

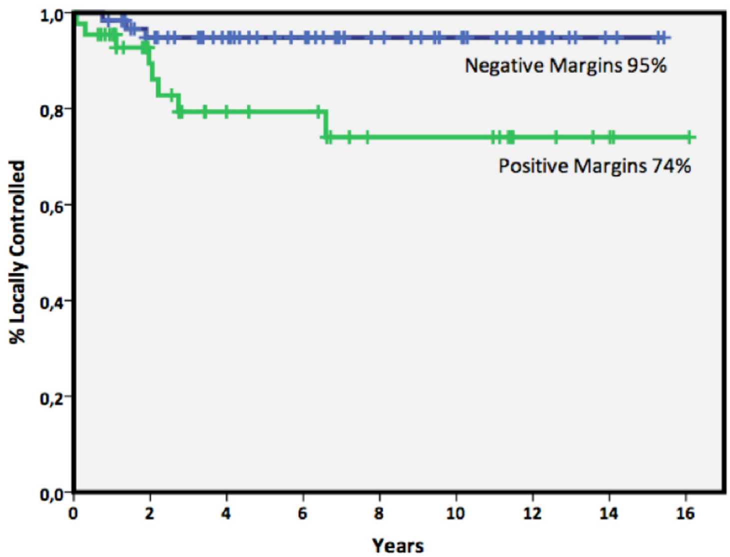
Locoregional failure increased with tumor diameter ($p = 0.003$), positive margins as per the MSKCC classification ($p = 0.014$), positive/close margins as per the CUN classification ($p = 0.045$), and number of catheters ($p = 0.0001$) and was inversely related to the biological equivalent dose ($p = 0.005$). Locoregional failure increased with dose due to the methodology of the study that dictated higher doses for those patients at a higher risk of failure. Number of catheters, a surrogate of tumor size ($p = 0.001$), and positive or close margins as per the CUN classification ($p = 0.036$) remained significant in multivariate analysis. Patients with positive or close margins had an 8.7-fold greater risk of locoregional failure than patients with negative margins. This translates into a 10-year locoregional control rate of 64% for those with close or positive margins, while patients with negative margins had a 10-year locoregional control rate of 90% ($p = 0.009$).

Distant failure increased in male patients ($p = 0.023$) and in patients with larger tumors ($p = 0.001$), positive margins as per the MSKCC classification ($p = 0.029$), positive or close margins as per the CUN classification ($p = 0.015$), number of catheters ($p = 0.023$), concomitant chemotherapy ($p = 0.025$), and adjuvant chemotherapy ($p = 0.01$). Multivariate analysis indicated that patients with larger tumors ($p = 0.005$), positive or close margins as per the CUN classification ($p = 0.05$), and patients receiving adjuvant chemotherapy ($p = 0.016$) had an increased risk of distant metastasis. Patients with tumors of 6 cm or larger had a 3.4-fold greater risk of distant failure than patients with smaller tumors. The 10-year distant control rate in patients with tumors of 6 cm or less was 79.6%; this rate decreased to 61.4% in larger tumors ($p = 0.002$). Patients receiving adjuvant chemotherapy had a 2.6-fold higher risk of distant failure due to the methodology of the study that recommended adjuvant chemotherapy in cases with a higher risk of developing distant metastases.

At the latest follow-up, 72 of the 106 patients (67.9%) remain alive, 66 of them (62.3%) without evidence of disease. Five patients (4.7%) underwent successful salvage treatment after isolated local failure ($n = 3$) or isolated distant failure ($n = 2$). One patient remains alive with disease progression (0.9%) and 28 patients died of disease (26.4%). The 10-year disease-free survival rate was 59%, and the 10-year overall survival rate was 62%.

Disease-free survival rates were poorer among patients with larger tumors ($p = 0.0001$), deeply located tumors ($p = 0.05$), positive margins as per the MSKCC classification ($p = 0.004$), positive or close margins as per the CUN classification ($p = 0.004$), greater number of catheters ($p = 0.0001$), larger TV_{100} ($p = 0.04$) and TV_{150} ($p = 0.05$) values, and delivery of adjuvant chemotherapy ($p = 0.05$). On multivariate analysis, tumor size ($p = 0.0001$) and margins as per the CUN classification ($p = 0.024$) remained statistically significant. Disease-free survival rates at 10 years decreased from 74.5% in tumors of 6 cm or less to 43.5% in larger tumors ($p = 0.0001$; Fig. 3) and from 78% in patients with negative margins to 47% in patients with positive or close margins ($p = 0.007$).

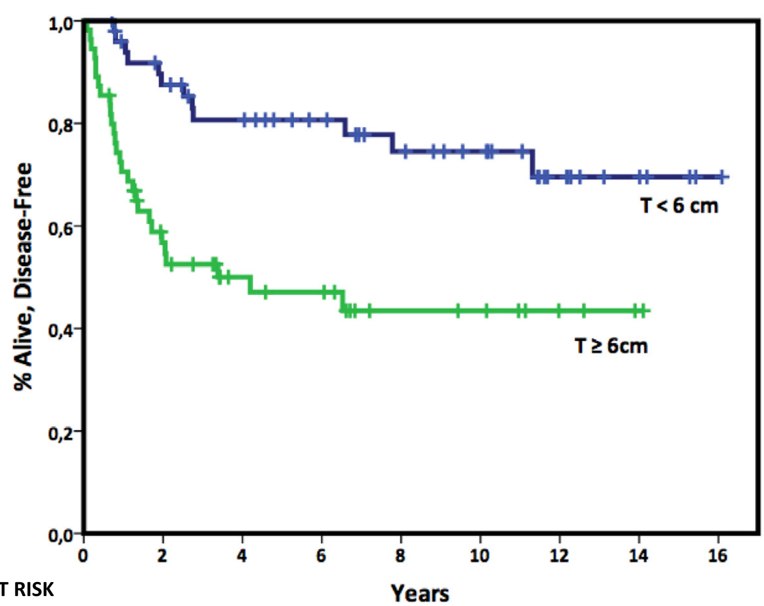
Overall survival rates were lower in male patients ($p = 0.02$), older patients ($p = 0.01$), in patients with larger tumors ($p = 0.0001$), deeply located tumors ($p = 0.05$), positive margins as per the MSKCC classification ($p = 0.02$), positive or close margins as per the CUN classification ($p = 0.02$), greater number of catheters ($p = 0.0001$), and larger TV_{100} ($p = 0.009$) and TV_{150} ($p = 0.02$) values. Tumor diameter ($p = 0.0001$) and gender ($p = 0.039$) were statistically significant in the multivariate analysis. Males had a 2.9-fold greater risk of death than women, and patients with tumors of 6 cm or more had a 2.8-fold greater risk of death than patients with smaller tumors. The 10-year overall survival rate decreased from 75.5% in patients with tumors of 6 cm or less to 48.2% in patients with larger tumors ($p = 0.001$).



NUM AT RISK (NUM CENSORED)

NEGATIVE MARGINS	30 (0)	26 (0)	21 (0)	16 (0)	13 (0)	11 (0)	5 (0)	1 (0)	0 (0)
POSITIVE MARGINS	76 (7)	52 (3)	38 (0)	34 (1)	22 (0)	19 (0)	11 (0)	5 (0)	1 (0)

Fig. 2. Actuarial local control according to surgical margins.



NUM AT RISK (NUM CENSORED)

T < 6CM	51 (4)	41 (3)	35 (6)	29 (4)	23 (4)	19 (8)	10 (5)	5 (4)	1 (1)
T ≥ 6 CM	55 (5)	27 (7)	17 (1)	15 (6)	8 (1)	7 (4)	3 (2)	1 (1)	0 (0)

Fig. 3. Actuarial disease-free survival according to tumor size.

Discussion

Toxicity

Overall events

In our study, we found that severe grade 3–4 complications were associated in multivariate analysis with TV_{100} values ($p = 0.003$), lower limb locations ($p = 0.013$), primary stage ($p = 0.027$), and aging ($p = 0.046$). Twenty-two patients (20.8%) included in this study had Grade ≥3 complications, and 14 patients (13.2%) had Grade ≥4 complications that required reoperation. The rate of reoperation observed in our study is similar to the median reoperation rate of 10.0% (range, 0–13.8%) found in the contemporary brachytherapy literature [2–13,15] (Table 6).

TV_{100} ($p = 0.003$) describes the tissue volume encompassed by the 100% prescription isodose and is therefore a surrogate of tumor size, extent of resection, and implant size. A volume effect has also been suggested by the Pohar group [8] who reported an association between increased stage ($p = 0.02$) and acute complications.

Tumor location ($p = 0.013$) also seemed to play a role in the development of complications. In our study, patients with lower limb tumor locations were more likely to develop grade 3 or greater complications than patients with trunk or upper limb tumors. Pohar et al., [8] in a series of 37 patients with soft tissue sarcomas treated with pre- or postoperative external beam irradiation and postoperative LDR or HDR brachytherapy, reported increased acute complications in the management of lesions arising in the lower extremities ($p = 0.008$). In our opinion, the increased risk of complications occurring in lower limb locations was probably due to the presence of larger than average lesions in a functionally active anatomical area.

Primary tumors ($p = 0.027$) showed a greater risk of complications than recurrent lesions in our study. Although this finding is intriguing, a sub-analysis indicated that recurrent tumors were smaller than primary ones (5.4 cm vs. 8.7 cm; $p = 0.007$ *t*-test). Other causes, such as a more cautious closure technique in recurrent cases, may also have contributed to the lower complication rate observed in unirradiated recurrent cases.

Other series have found increased toxicity with higher total irradiation doses [22], and higher brachytherapy doses per fraction [8]. In our study, we found no differences between patients treated at PHDRB doses of 16 Gy or 24 Gy. In addition, the dose per fraction was set at 4 Gy as per protocol, which made dose per fraction analysis impossible.

In our opinion, special precautions aimed at minimizing complications must be taken in older patients, in patients with larger tumors, and those with tumors in lower limb locations. These precautions should include more sophisticated brachytherapy procedures and exhaustive planning aimed at increasing DHI values, as well as more liberal use of reparative surgery in larger tumors.

Specific events

Wound-related events were the predominant complications, occurring in 25.5% of our cases. A recent American Brachytherapy Society consensus report [23] also describes delayed wound healing as the most frequent complication. Similarly, the severe grade 3–4 wound complication rate of 12.3% found in the present study

Table 6
Toxicity in selected brachytherapy series.

Author, year	Follow-up	Radiation mode	*N*	Severe grade 3–4 complications					
				Reoperation	Bone fracture	Neuropathy	Wound	Vascular damage	Amputation
Alektiar, 2000 [24] Sloan-Kettering	>8.0 y	LDR 42–45 Gy	78	10.0%	4.0%	7.0%	19.0%[a]	Not reported	None
Delannes, 2000 [2] Toulouse	4.5 y	LDR 20 Gy + EBRT 45 Gy	58	13.8%	0.0%	5.2%	59.0%	Not reported	None
Alektiar, 2002 [3] Sloan-Kettering	4.5 y	LDR 45 Gy	202	12.0%	3.0%	5.0%	20.0%	Not reported	None
Lazzaro, 2005 [4] Milano	2.8 y	PDR 45 Gy ($n = 18$), or PDR 15 Gy + EBRT 50 Gy ($n = 24$)	42	Not reported	0.0%	0.0%	7.1%	Not reported	None
Livi, 2006 [6] Firenze	4.5 y	LDR 33.7 Gy + EBRT 41 Gy	156	Not reported	4.5%[b]	1.3%	3.7%	Not reported	3.2%
Llacer, 2006 [7] Bordeaux	4.8 y	LDR/PDR 20 Gy + EBRT 46 Gy ($n = 73$), or LDR/PDR alone 45 Gy ($n = 6$)	79	12.7%	4.1%	10.1%	11.4%	2.5%	None
Pohar, 2007 [8] Syracuse	3.9 y 1.4 y	LDR 15–20.5 Gy + EBRT 45–50 Gy HDR 10.2–18 Gy/3–4 Rx + EBRT 45–50 Gy	20 17	Not reported	Not reported	Not reported	30.0% 6.0%	Not reported	None
Laskar, 2007 [5] Tata	3.7 y	HDR 34.5 Gy/LDR 39 Gy, or EBRT 46 Gy + HDR/LDR 23.3 Gy	155	Not reported	0.0%	0.0%	6.0%	Not reported	None
Mierzwa, 2007 [9] Cincinnati	3.3 y	LDR 45 Gy or LDR 25 Gy + EBRT 45 Gy, or LDR 25 Gy + EBRT 45 Gy	43	2.3%	0.0%	4.6%	2.3%	Not reported	2.3%
Muhic, 2008 [10] Copenhagen	3.4 y	PDR 20 Gy + EBRT 50 Gy	39	10.0%	0.0%	0.0%	21.0%	Not reported	None
Beltrami, 2008 [11] Firenze	6.2 y	LDR 35 Gy + EBRT 44 Gy	112	12.5%	2.7%	0.0%	10.0%	Not reported	2.7%
Petera, 2010 [12] Hradec Kralove	3.2 y	HDR40Gy, or HDR24Gy + EBRT 40–50 Gy	45	0.0%	0.0%	2.2%	4.4%	Not reported	None
Itami, 2010 [13] Tokyo	4.1 y	HDR 36 Gy/6Rx	26	7.7%	3.8%	0.0%	11.5%	Not reported	None
Sharma, 2015 [14] New Delhi	3.8 y	HDR 16 Gy + EBRT 50 Gy	52	Not reported	Not reported	Not reported	7.6%	Not reported	None
Current Series, 2018 Pamplona	7.1 y	HDR 16–24 Gy + EBRT 45 Gy	106	13.2%	1.9%	4.7%	12.3%	0.8%	None

[a] Significant wound complications; defined as wound problems requiring operative revision for coverage or threatened limb loss, persistent seroma requiring repeated aspirations and/or drainage, wound separation >2 cm, hematoma >25 ml, and/or purulent wound discharge.
[b] Seven cases (all postmenopausal women) of those treated with LDR + EBRT. Three of them needed amputation. No correlation with dose.

Table 7
Results and treatment characteristics in selected brachytherapy series.

Author, year	F/up, median	Radiation mode	N	% recurrent disease	% positive margins	% close margins	Location	Locoregional control	OS
Delannes, 2000 [2] Toulouse	4.5 y	LDR 20 Gy + EBRT 45 Gy	58	None	36.2%		Extremities & trunk	5 y 89%	5 y 65%
Alektiar, 2002 [3] Sloan-Kettering	5.0 y	LDR 45 Gy	202	None	18.3%	n/a	Extremities	5 y 84%	5 y 70%
Lazzaro, 2005 [4] Milano	2.8 y	PDR 45 Gy (n = 18), or PDR 15 Gy + EBRT 50 Gy (n = 24)	42	23.8%	19.0%	n/a	Extremities 64.9% & trunk	3 y 89%	3 y 83.9%
Laskar, 2007 [5] Tata	3.7 y	HDR 34.5 Gy/LDR 39 Gy, or EBRT 46 Gy + HDR/LDR 23.3 Gy	155	31.0%	5.2%	3.9%	Extremities & trunk	5 y 73%	5 y 73%
Livi, 2006 [6] Firenze	4.5 y	LDR 33.7 Gy + EBRT 41 Gy	156	25.0%	6.5%	n/a	Extremities	5 y 92%	Not reported
Llacer, 2006 [7] Bordeaux	4.8 y	LDR/PDR 20 Gy + EBRT 46 Gy (n = 73), or LDR/PDR alone 45 Gy (n = 6)	79	n/a	45.6%	n/a	Extremities	5 y 90%	5 y 69%
Pohar, 2007 [8] Syracuse	3.9 y 1.4 y	LDR 15–20.5 Gy + EBRT 45–50 Gy HDR 10.2–18 Gy/3–4 Rx + EBRT 45–50 Gy	20 17	0%	15.0% 12.0%	n/a	Extremities	2 y 90% 2 y 78%	2 y 75% 2 y 60%
Mierzwa, 2007 [9] Cincinnati	3.3 y	LDR 45 Gy or LDR 25 Gy + EBRT 45 Gy, or LDR 25 Gy + EBRT 45 Gy	43	21.0%	18.6%	n/a	Extremities & trunk, Retroperitoneal	5 y 88%	3 y 79%
Muhic, 2008 [10] Copenhagen	3.4 y	PDR 20 Gy + EBRT 50 Gy	39	0%	23.0%	43.6%	Extremities & trunk, Retroperitoneal	5 y 83%	5 y 76%
Beltrami, 2008 [11] Firenze	6.2 y	LDR 35 Gy + EBRT 44 Gy	112	23.0%	13.4%		Extremities	8 y 87%	7 y 71%
Petera, 2010 [12] Hradec Kralove	3.2 y	HDR 40 Gy, or HDR24Gy + EBRT 40–50 Gy	45	62.2%	11.1%	22.2%	Extremities & Trunk	5 y 74 %	5 y 70%
Itami, 2010 [13] Tokyo	4.1 y	HDR 36 Gy/6 Rx	26	56.0%	50.0%	50.0%	Extremities & trunk	5 y 78%	5 y 76.5%
Sharma, 2015 [14] New Delhi	3.8 y	HDR 16 Gy + EBRT 50 Gy	52	Not reported	2.0%	Not reported	Extremities & trunk	4 y 100%	55 y 67%
Cortesi, 2017 [15] Bologna	8.3 y	HDR 20 Gy + EBRT 45 Gy	107	58.9%	5.9%	27.1%	Extremities & trunk	5 y 81%	5 y 87%
Current Series, 2018 Pamplona	7.1 y	HDR 16–24 Gy + EBRT 45 Gy	106	16.0%	22.6%	49.1%	Extremities & trunk	16 y 79%	16 y 59%

was similar to the 10.0% (range, 2.3–59.0%) median complication rate found in the brachytherapy literature [2–14,24] (Table 6). Although a shorter time to loading has been traditionally associated with an increase in wound complications [25], we found no such relationship in our study. Moreover, a longer time to loading correlated with an increased rate of grade 3 or greater complications, probably due to the prolonged stay of the catheters. Other authors have found an association between the width of the excised skin (WES) and the rate of wound reoperation [1% (WES <4 cm) vs. 10% (WES >4 cm), p = 0.02], a factor probably related with the size of the tumor [24].

Wound doses have not been traditionally recorded in sarcoma brachytherapy; therefore, dose–volume constraints related to skin or wound are not known. A prudent approach would be to report wound doses in all cases in a fashion similar to that used in breast brachytherapy. Although not supported by tradition in sarcoma brachytherapy, the use of multiple implant planes where feasible may be a safe way to decrease high-dose volumes and increase dose homogeneity, as well as to increase the coverage of the tumor bed to more than just the area at the greatest risk of failure. We are currently increasing the number of cases treated with multiple plane implants, especially in larger tumors (Fig. 1).

Other less frequent grade 3–4 complications such as severe neuropathy, bone fracture, vascular damage, or need for amputation occurred in 4.7%, 1.9%, 0.8%, and 0.0% of our patients, respectively. Contemporary literature [2–14,24] reports the rates of severe neuropathy (median 1.7%, range 0–7.0%), bone fracture (median 1.4%, range, 0–4.5%), vascular damage (median 5.5%, range 2.5–0.8%), and amputation (median 0%, range 0–3.2%) similar to those shown in the present report.

When analyzing specific complications, one must bear in mind that these must be understood as multifactorial in origin. For instance, nerve damage has been shown to occur at a rate similar in brachytherapy-treated patients and controls in a phase III trial [24]. In addition, the probability of nerve damage is proportional to the distance to the implant [2]; therefore, implants close to nerves should be managed with special brachytherapy techniques such as the use of a shorter intercatheter distance or the placement of a thin layer of biodegradable material as a spacer. Similarly, Livi et al. [6] have reported that postmenopausal status and number of prior surgeries increased the risk of bone complications in a series of 214 patients treated with postoperative irradiation after radical excision of soft-tissue sarcoma of the limb. Finally, Lin et al. [26] described an association between periosteal stripping and risk of pathological fracture (p = 0.01).

Proper patient selection, meticulous attention to antecedents and prior treatments, as well as appropriate implantation, delineation, and planning are essential to minimize early and late adverse events in sensitive regions.

Outcome analysis

Locoregional failure

After a median follow-up of 7.1 years (range, 0.6–16.0), for patients alive at the time of this analysis, 18 patients (17%) presented with locoregional failure: 6 of them as the only failure

(5.6%), and 12 with synchronous distant metastases (11.0%). Among these 18 patients with locoregional failure, 11 had a local component (10.4%), that was combined in all cases with regional and/or distant tumor foci. The 10-year actuarial local and locoregional control rates were 87% and 80%, respectively.

Multivariate analysis ($p = 0.024$) showed that margin status, as defined by the MSKCC classification, was the only factor predictive of local control. The 10-year local control decreased from 95% to 74% ($p = 0.013$) when the surgical margins were positive. Since the number of patients with positive margins as per the MSKCC classification in our series was 44 (41.5%) and the number of local failures observed was 11 (10.4%), the use of 24 Gy of PHDRB followed by 45 Gy of EBRT may have sterilized at least two thirds of the cases with positive margins.

The importance of margin status on locoregional control has already been emphasized in the contemporary literature [11,15] (Table 7). Beltrami et al. [11] reported on 112 patients treated with surgery, 35 Gy of LDR brachytherapy, and EBRT of 44 Gy. In their study, the local control rate after wide or radical resections was 97% at 3 years; this rate after marginal or intralesional surgery was 80% at 3 years. Other factors reported by other groups to be associated with improved local control such as extremity location [12,15], primary disease [12,15], physical dose >65 Gy [12], or combined PHDRB + EBRT vs. PHDRB alone [12] were not found to be statistically significant in our study.

Distant failure

Distant failure remains the predominant pattern of failure in patients with resected soft-tissue sarcoma. In our study, 26.4% of the patients developed distant metastases, 17% of them as an isolated failure (Table 5). In the multivariate analysis, distant failure was strongly related to tumor size ($p = 0.005$), margin status ($p = 0.05$), and adjuvant chemotherapy ($p = 0.016$). A direct correlation between tumor size and distant metastases has already been shown in the literature. Beltrami et al. [11] reported a correlation between tumor size and systemic control ($p = 0.046$) in a series of 112 patients treated with surgery, 35 Gy of LDR brachytherapy, and 44 Gy of EBRT. They established 5 cm as a reliable cut-off; in our series, the cut-off was set at a maximum tumor diameter of 6 cm.

Survival

The 10-year disease-free survival rate in the present study was 59%. Disease-free survival was related to tumor size ($p = 0.0001$) and margin status ($p = 0.024$) in multivariate analysis. Disease-free survival rates at 10 years decreased from 74.5% in tumors of 6 cm or less to 43.5% in larger tumors ($p = 0.0001$) and from 78% in patients with negative margins to 47% in patients with positive or close margins ($p = 0.007$).

Other authors have found a relationship between improved disease-free survival rates and a number of other factors such as extremity, location, [15] and depth [5].

The 10-year overall survival rate in the present study was 62%. Overall survival was strongly related to tumor size ($p = 0.0001$) and gender ($p = 0.039$) in multivariate analysis. The 10-year overall survival rate decreased from 75.5% in patients with tumors of 6 cm or less to 48.2% in patients with larger tumors ($p = 0.001$). Tumor size has been well-established as a negative prognostic factor in a number of high-quality brachytherapy series [5,27].

Conclusions

The combination of conservative surgery, high-dose PHDRB, and EBRT produces adequate function and local control in the majority of patients with soft tissue sarcomas of the extremities and the superficial trunk, including a substantial percentage of cases with positive margins. Patients with larger tumors are at a higher risk of complications, treatment failure, and cancer-related death and require an individualized treatment approach.

Acknowledgements

This work was supported by the Fondo de Investigaciones Sanitarias to RMM (PI 16/01847). Dr Gimeno and Dr San-Julián equally contributed to this manuscript.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.02.011.

References

[1] National comprehensive cancer network. Practice Guidelines in Oncology 2018.
[2] Delannes M, Thomas L, Martel P, Bonnevialle P, Stoeckle E, Chevreau C, et al. Low-dose-rate intraoperative brachytherapy combined with external beam irradiation in the conservative treatment of soft tissue sarcoma. Int J Radiat Oncol Biol Phys 2000;47:165–9.
[3] Alektiar KM, Leung D, Zelefsky MJ, Healey JH, Brennan MF. Adjuvant brachytherapy for primary high-grade soft tissue sarcoma of the extremity. Ann Surg Oncol 2002;9:48–56.
[4] Lazzaro G, Lazzari R, Pelosi G, De Pas T, Mariani L, Mazzarol G, et al. Pulsed dose-rate perioperative interstitial brachytherapy for soft tissue sarcomas of the extremities and skeletal muscles of the trunk. Ann Surg Oncol 2005;12:935–42.
[5] Laskar S, Bahl G, Puri A, Agarwal MG, Muckaden M, Patil N, et al. Perioperative interstitial brachytherapy for soft tissue sarcomas: prognostic factors and long-term results of 155 patients. Ann Surg Oncol 2007;14:560–7.
[6] Livi L, Santoni R, Paiar F, Bastiani P, Beltrami G, Caldora P, et al. Late treatment-related complications in 214 patients with extremity soft-tissue sarcoma treated by surgery and postoperative radiation therapy. Am J Surg 2006;191:230–4.
[7] Llacer C, Delannes M, Minsat M, Stoeckle E, Votron L, Martel P, et al. Low-dose intraoperative brachytherapy in soft tissue sarcomas involving neurovascular structure. Radiother Oncol 2006;78:10–6.
[8] Pohar S, Haq R, Liu L, Koniarczyk M, Hahn S, Damron T, et al. Adjuvant high-dose-rate and low-dose-rate brachytherapy with external beam radiation in soft tissue sarcoma: a comparison of outcomes. Brachytherapy 2007;6:53–7.
[9] Mierzwa ML, McCluskey CM, Barrett WL, Lowy A, Sussman J, Sorger J. Interstitial brachytherapy for soft tissue sarcoma: a single institution experience. Brachytherapy 2007;6:298–303.
[10] Muhic A, Hovgaard D, Mork Petersen M, Daugaard S, Hojlund Bech B, Roed H, et al. Local control and survival in patients with soft tissue sarcomas treated with limb sparing surgery in combination with interstitial brachytherapy and external radiation. Radiother Oncol 2008;88:382–7.
[11] Beltrami G, Rudiger HA, Mela MM, Scoccianti G, Livi L, Franchi A, et al. Limb salvage surgery in combination with brachytherapy and external beam radiation for high-grade soft tissue sarcomas. Eur J Surg Oncol 2008;34:811–6.
[12] Petera J, Soumarova R, Ruzickova J, Neumanova R, Dusek L, Sirak I, et al. Perioperative hyperfractionated high-dose rate brachytherapy for the treatment of soft tissue sarcomas: multicentric experience. Ann Surg Oncol 2010;17:206–10.
[13] Itami J, Sumi M, Beppu Y, Chuman H, Kawai A, Murakami N, et al. High-dose rate brachytherapy alone in postoperative soft tissue sarcomas with close or positive margins. Brachytherapy 2010;9:349–53.
[14] Sharma DN, Deo SV, Rath GK, Shukla NK, Bakhshi S, Gandhi AK, et al. Perioperative high-dose-rate interstitial brachytherapy combined with external beam radiation therapy for soft tissue sarcoma. Brachytherapy 2015;14:571–7.
[15] Cortesi A, Galuppi A, Frakulli R, Arcelli A, Romani F, Mattiucci GC, et al. Adjuvant radiotherapy with brachytherapy boost in soft tissue sarcomas. J Contemp Brachytherapy 2017;9:256–62.
[16] Delaney TF, Kepka L, Goldberg SI, Hornicek FJ, Gebhardt MC, Yoon SS, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. Int J Radiat Oncol Biol Phys 2007;67:1460–9.
[17] Nielsen OS, Cummings B, O'Sullivan B, Catton C, Bell RS, Fornasier VL. Preoperative and postoperative irradiation of soft tissue sarcomas: effect of radiation field size. Int J Radiat Oncol Biol Phys 1991;21:1595–9.

[18] San Miguel I, San Julian M, Cambeiro M, Fernandez Sanmamed M, Vazquez-Garcia B, Pagola M, et al. Determinants of toxicity, patterns of failure, and outcome among adult patients with soft tissue sarcomas of the extremity and superficial trunk treated with greater than conventional doses of perioperative high-dose-rate brachytherapy and external beam radiotherapy. Int J Radiat Oncol Biol Phys 2011;81:e529–39.
[19] International commission on radiation units and measurements. Dose and volume specification for reporting interstitial therapy. ICRU report 58. Bethesda, MD: International commission on radiation units and measurements, 1997.
[20] Douglas BG, Fowler JF. The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation. Radiat Res 1976;66: 401–26.
[21] Late effects consensus conference: Rtog/eortc. Radiother Oncol. 1995;35:5-7.
[22] Aronowitz JN, Pohar SS, Liu L, Haq R, Damron TA. Adjuvant high dose rate brachytherapy in the management of soft tissue sarcoma: a dose-toxicity analysis. Am J Clin Oncol 2006;29:508–13.
[23] Naghavi AO, Fernandez DC, Mesko N, Juloori A, Martinez A, Scott JG, et al. American brachytherapy society consensus statement for soft tissue sarcoma brachytherapy. Brachytherapy 2017;16:466–89.
[24] Alektiar KM, Zelefsky MJ, Brennan MF. Morbidity of adjuvant brachytherapy in soft tissue sarcoma of the extremity and superficial trunk. Int J Radiat Oncol Biol Phys 2000;47:1273–9.
[25] Ormsby MV, Hilaris BS, Nori D, Brennan MF. Wound complications of adjuvant radiation therapy in patients with soft-tissue sarcomas. Ann Surg 1989;210:93–9.
[26] Lin PP, Schupak KD, Boland PJ, Brennan MF, Healey JH. Pathologic femoral fracture after periosteal excision and radiation for the treatment of soft tissue sarcoma. Cancer 1998;82:2356–65.
[27] Alekhteyar KM, Leung DH, Brennan MF, Harrison LB. The effect of combined external beam radiotherapy and brachytherapy on local control and wound complications in patients with high-grade soft tissue sarcomas of the extremity with positive microscopic margin. Int J Radiat Oncol Biol Phys 1996;36:321–4.