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Original Article

Dose volume histogram constraints in patients with soft tissue sarcomas of the extremities and the superficial trunk treated with surgery and perioperative HDR brachytherapy

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ABSTRACT

Background: Wound healing complications (WHC), osteoradionecrosis (ORN), and nerve damage (ND) are common adverse effects in adult patients with soft tissue sarcomas of the extremities and the superficial trunk treated with surgery and perioperative high dose rate brachytherapy (PHDRB) alone or combined with external beam radiotherapy (EBRT).
Rationale: Analysis of the treatment factors contributing to these complications can potentially minimize their occurrence and severity.
Patients: A total of 169 patients enrolled in two parallel prospective studies were included in this analysis. Previously Unirradiated cases (Group 1; n = 139) were treated with surgical resection, 16–24 Gy of PHDRB and 45 Gy of EBRT. Adjuvant chemotherapy was given to selected patients with high-grade tumors. Previously irradiated cases (Group 2; n = 30) were treated with surgical resection and 32–40 Gy of PHDRB without further EBRT.
Methods: Patient factors, tumor factors, surgical factors, PHDRB factors and EBRT factors were analyzed using Cox univariate and multivariate analysis.
Results: In Previously Unirradiated cases, WHC, ORN and ND occurred in 38.8%, 5.0% and 19.4%. Multivariate analysis indicated that WHC increased with CTV size (p = 0.02) and CTV_{2cm3} Physical dose (p = 0.02). ORN increased with $Bone_{2cm3}$ EQD2 $\geq$ 67 Gy (p = 0.01) and ND was more frequent in patients with TV_{100} DVH-based dose (tissue volume encompassed by the 100% isodose) $\geq$ 84 Gy (p < 0.01). In Previously Irradiated cases, WHC, ORN and ND occurred in 63.3%, 3.3% and 23.3%. Multivariate analysis showed that WHC was more frequent in patients with $Skin_{2cm3}$ Lifetime EQD2 $\geq$ 84 Gy (p = 0.01) and ND was more frequent after CTV_{D90} Physical Doses $\geq$ 40 Gy (p < 0.01).
Conclusions: WHC in Previously Unirradiated patients can be minimized by using a more conservative CTV definition together with a meticulous implant technique and planning aimed to minimize hyperdose CTV_{2cm3} areas. In Previously Irradiated patients WHC may be mimimized considering Lifetime EQD2 $Skin_{2cm3}$ doses. ORN can be reduced by using the $Bone_{2cm3}$ EQD2 constraint. ND occurs more frequently in patients with large tumors receiving high treated volume doses, but no specific constraints can be recommended due to the lack of peripheral nerve definition during brachytherapy planning.

Introduction

Surgery followed by adjuvant radiation therapy (RT) is a well-established treatment for soft tissue sarcomas [1–3]. The main adverse effect of the combined modality treatment is the development of wound healing complications (WHC) that occur in 18% to 35% of the cases treated with either postoperative or preoperative external beam radiation therapy [4]. In addition, patients treated

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with adjuvant brachytherapy alone or a combination of brachytherapy and external beam radiotherapy develop WHC in 24 and 34% of the cases, respectively [5,6]. In previously irradiated cases, salvage surgery and reirradiation with external beam radiotherapy or brachytherapy causes major wound complications in 10–80% of the patients [7–9].

In 2019, we published a prospective study to determine the efficacy and toxicity profile of limb-salvage surgery with HDR brachytherapy (PHDRB) combined with EBRT in patients with soft tissue sarcomas of the extremities and superficial trunk [10]. Grade 3 or greater adverse events were observed in 34% of the cases and there was a direct relationship between implant volume (TV_{100}) and adverse events ($p = 0.003$). No specific organ at risk (OAR) constraints were determined since there was not a uniform OAR contouring policy during the study.

The present research project aims to determine DVH constraints of wound healing complications (WHC), osteoradionecrosis (ORN), and nerve damage (ND) through standardized contouring of the OARs (skin, scar, bone) adjacent or included into the Clinical Target Volume (CTV) in a series of 169 patients with soft tissue sarcoma of the extremities and superficial trunk enrolled in two prospective controlled trials of Perioperative High Dose Rate Brachytherapy (PHDRB) conducted in our institution from 2000 to 2018. The development of solid DVH constraints should minimize complications, increase patient comfort, and allow a better integration with other treatment modalities that may be required at the completion of the radiation course.

Materials and methods

Eligibility criteria

One-hundred and sixty-nine adult patients with Soft Tissue Sarcomas (STS) of the extremities and superficial trunk treated in a Phase II trial at the Clínica Universidad de Navarra with surgery and adjuvant HDR brachytherapy alone or combined with postoperative external beam (EBRT) irradiation from October 2000 to December 2018 were analyzed. One-hundred and five patients had a primary STS, and sixty-four patients had a recurrent STS. Sixty-seven patients (39.6%) had a non-oncological resection as the first treatment in another center. No patient was treated with preoperative radiotherapy.

Tumor characteristics are shown in Table 1. Exclusion criteria included: 1) head, intraabdominal or visceral STS, 2) treatment with palliative purpose, and/or 3) incomplete clinical and dosimetric information. Median follow-up of for patients alive at the time of this analysis was 7.7 years (range, 0.6–19.6).

Treatment protocol

Previously Unirradiated cases (n = 139) were treated with a combination of functional surgery, PHDRB and postoperative EBRT. Brachytherapy dose was 16 Gy in 4 treatments of 4 Gy b.i.d. for R0 resections and 24 Gy in 6 treatments of 4 Gy b.i.d. for R1 resections followed by 45 Gy of external irradiation in 25 daily treatments with 3DCRT, IMRT or VMAT. Sixty patients (43.1%) received adjuvant chemotherapy with doxorubicin (20 mg/m2/d) and ifosfamide (1.5 g/m2/d).

Previously Irradiated cases (n = 30) were treated with surgery and PHDRB to a dose level of 32 Gy in 8 treatments of 4 Gy b.i.d. for R0 resections and 40 Gy in 10 treatments of 4 Gy b.i.d. for R1 resections without further external reirradiation. Eighteen patients (60%) received adjuvant chemotherapy.

The total physical dose per group as well as the rest of the brachytherapy parameters are shown in Table 2. In all cases, the brachytherapy physical dose per fraction was of 4 Gy b.i.d. (interfraction interval of at least 6 h) prescribed to the implant minimum target dose (MTD) as per ICRU No. 58 recommendations from 2001 to 2006 and to the CTVD90 (minimal dose received by 90% of the clinical target volume) from 2006 onwards.

Table 1
Tumor Characteristics.

	n	%
Tumor Location		
Extremities	145	85.8
Upper leg	65	38.4
Upper arm	37	21.9
Lower leg	28	16.5
Lower arm	15	8.8
Superficial Trunk	24	14.2
AJCC Stage 7th Edition		
Ia	3	1.7
Ib	20	11.8
IIa	24	14.2
IIb	13	7.7
III	44	26
IV	6	3.5
Recurrent	59	34.9
Histology		
Pleomorphic sarcoma	48	28.4
Synovial sarcoma	21	12.4
Myxoid liposarcoma	20	11.8
Fibrosarcoma	20	11.8
Leiomyosarcoma	13	7.7
Dedifferentiated liposarcoma	9	5.3
Aggressive fibromatosis	8	4.7
Well-differentiated liposarcoma	6	3.5
Epithelioid sarcoma	6	3.5
Schwanosarcoma	4	2.4
Rhabdomyosarcoma	3	1.8
Clear cell sarcoma	2	1.2
Solitary fibrous tumour	2	1.2
Extraskeletal Ewing sarcoma	2	1.2
Extraskeletal chondrosarcoma	2	1.2
Alveolar soft part sarcoma	1	0.6
Angiosarcoma	1	0.6
Dermatofibrosarcoma protuberans	1	0.6
Pathological Risk Features		
Skin surface resected[1]	19 cm^2 (range, 0.9–306)	
Tumor largest diameter[2]	7.3 cm (range, 1–30)	
Positive Margin	60	35.5
Close Margin	20	11.8

[1] Average, range.
[2] Average, range.

Brachytherapy technique

In brief, the surgical and the radiation oncology teams used the preoperative physical examination and imaging, surgical findings, frozen sections where necessary, and gross examination of the surgical specimen to jointly determine the area to be implanted. Tumor bed margins were delineated with at least 4 cardinal gold seeds. Brachytherapy catheters (PHDRB), as parallel as possible at 10–15 mm intervals, were implanted intraoperatively and tunnelized or sutured onto the surface of the surgical bed. CTV definition evolved from the traditional "entire surgical bed" concept from 2000 to 2011 [11] to a more conservative 2-cm margin around the gold seeds afterwards. The median number of catheters used was of 6 (range, 3–14). Brachytherapy delivery began 4 days after surgery (range, 1–10 days) with a median treatment duration of 4 days (range, 1–9).

Study endpoints and statistical analysis

This study was undertaken to determine DVH Constraints of Wound Healing Complications (WHC), Osteoradionecrosis (ORN)

and Nerve Damage (ND) in a series of adult patients with STS of the extremities and the superficial trunk treated with PHDRB alone or in combination with EBRT. We defined WHC as Bleeding, Edema, Fibrosis, Fistula, Wound infection, Necrosis, Seroma, Thrombosis; ORN as Bone damage and ND as sensitive damage (paresthesias, dysesthesias and anesthesia) and/or motor damage. Patients were seen in regular follow-up visits every 4 months for the first two years, during 6 months during the following 3 years and yearly thereafter. Patients with toxicity had a closer follow-up schedule dictated by the clinical need. Typical follow-up imaging included ultrasound or MRI of the local site and chest X-ray or thoracic CT scan. For special scenarios, such as ORN or ND, plain X-rays, bone CT or electroneurograms were ordered at the discretion of the treating physician.

These constraints were obtained separately for Previously unirradiated (n = 139) and Previously Irradiated patients (n = 30). WHC, ORN and ND were documented using the Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria [12]. 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 brachytherapy treatment. Several dose/volume (CTV_{2cm3}, $CTVD_{90}$) and volume factors (CTV, tissue volume encompassed by the 100% isodose-TV_{100} and tissue volume encompassed by the 150% isodose-TV_{150}) were explored as potential surrogates of normal tissue damage using three different definitions of dose calculation (Physical, EQD2-P and EQD2-DVH). EQD2-P refers to as a 2-Gy equivalent calculation using the prescription isodose while EQD2- DVH uses all the points contained in the entire dose volume histogram. A detailed description of the EQD2-DVH used can be found in Appendix 1. The α/β ratio used in EQD2-P and EQD2-DVH calculations was 3 for late effects. Dose was explored as brachytherapy dose per fraction, as Total Dose per course in those patients receiving brachytherapy and external irradiation and as Total lifetime Dose in those patients who had received prior irradiation. Due to the inherent uncertainty for dose summation, the prescribed external dose was taken as uniformly delivered over the brachytherapy volume in Total Dose per course and Total lifetime Dose calculations. Brachytherapy calculations were performed in all cases without heterogeneity correction.

The impact of the DVH constraints on WHC, ORN and ND was tested in a Binary Logistic Regression that in addition to brachytherapy data also included patient, tumor, and treatment factors. The different variables tested included patient factors (age, gender, diabetes, smoking, BMI), tumor factors (grade, diameter, stage, location, depth), surgical factors (previous "whoops" excision, skin surface resected, wound closure, surgery duration, vascular dissection, bone, wound and nerve complications) and other treatment factors (prior irradiation, combined EBRT, time from surgery, duration of brachytherapy, concomitant and adjuvant chemotherapy, number of channels and dose homogeneity index).

Follow-up to date was done by medical consultation (127 patients) or telephone follow-up (42 patients). All patients gave written informed consent before study entry.

Table 2
Dosimetric Parameters.

	Average ± SD
Physical Dose	
Previously unirradiated	
Surgery + Brachytherapy + EBRT	61.3 ± 13 Gy
Previously Irradiated	
Surgery + Brachytherapy	38.5 ± 4.1 Gy
Treated Volume 100[1] (TV100)	118.8 ± 153.1
Treated Volume 150[2] (TV150)	34.4 ± 45.8
Dose Homogeneity Index[3] (DHI)	0.70 ± 0.06

[1] Tissue volume (in cm^3) encompassed by the the 100% isodose of 4 Gy.
[2] Tissue volume (in cm^3) encompassed by the 150% isodose of 6 Gy.
[3] Dose Homogeneity Index = (TV_{100}-TV_{150})/TV_{100}.

Results

A total of 169 patients were included in the study. Pleomorphic sarcoma was the most frequent histological type and stage III and locally recurrent tumors arising in the lower extremities were the predominant presentation (Table 1). Since the analysis has been performed separately for previously unirradiated and previously irradiated patients, the presentation of results will also be done separately (Tables 2 and 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 3. No grade 5 complications were observed.

Previously unirradiated cases

In previously unirradiated cases, wound healing complications (WHC) were observed in 54 of 139 patients (38.8%). Median time to appearance was 9 months. In univariate analysis, WHC were more frequent in tumors greater than 10 cm (p = 0.04) and in tumors located in the lower extremities (p < 0.006). Furthermore, WHC were more frequent in patients with vascular dissection (p < 0.01), perioperative blood transfusion (p = 0.04), CTV larger than 50 cm^3 (p = 0.02) and CTV_{2cm3} total physical dose ≥ 110 Gy (p = 0.02). In multivariate analysis, only CTV larger than 50 cm^3 (p = 0.02) and CTV_{2cm3} dose ≥ 110 Gy (p = 0.02) remained significant and were taken as constraints (Table 4). Patients with CTV and CTV_{2cm3} physical dose values below the constraints had a WHC rate of 13.2%. This figure increased to 44% and 77.8% with one or two values above the constraints, respectively (Fig. 1).

Table 3
Adverse Events in the High-Dose Region.

	n (%)	Time to Appearance[4]	RTOG Grade 3–4 (%)
Previously Unirradiated[5]			
Wound healing complications (WHC)	54 (38.8%)	9	33 (23.7%)
Osteoradionecrosis (ORN)	7 (5%)	59	7 (5.0%)
Nerve damage (ND)	27 (19.4%)	17	12 (8.6%)
Previously Irradiated[6]			
Wound healing complications (WHC)	19 (63.3%)	4	14 (46.6%)
Osteoradionecrosis (ORN)	1 (3.3%)	2	0 (0%)
Nerve damage (ND)	7 (23.3%)	9	2 (6.7%)

[4] Median in months.
[5] All individual complications observed in the same patient are described.
[6] All individual complications observed in the same patient are described.

Table 4
Univariate and Multivariate Analysis for Wound Healing Complications (WHC).

Group	Parameter	Cut-off	Univariate	Multivariate
Previously unirradiated	CTV	50 cm^3	$p = 0.02$	$p = 0.02$
Previously unirradiated	CTV_{2cm3} Physical dose	110 Gy	$p = 0.02$	$p = 0.02$
Previously unirradiated	Tumor Diameter		$p = 0.04$	
Previously unirradiated	Lower Extremity Location		$p = 0.006$	
Previously unirradiated	Blood Transfusion		$p = 0.05$	
Previously unirradiated	Vascular dissection		$p = 0.01$	
Previously Irradiated	$Skin_{2cm3}$ Lifetime EQD2	84 Gy	$p = 0.05$	$p = 0.01$

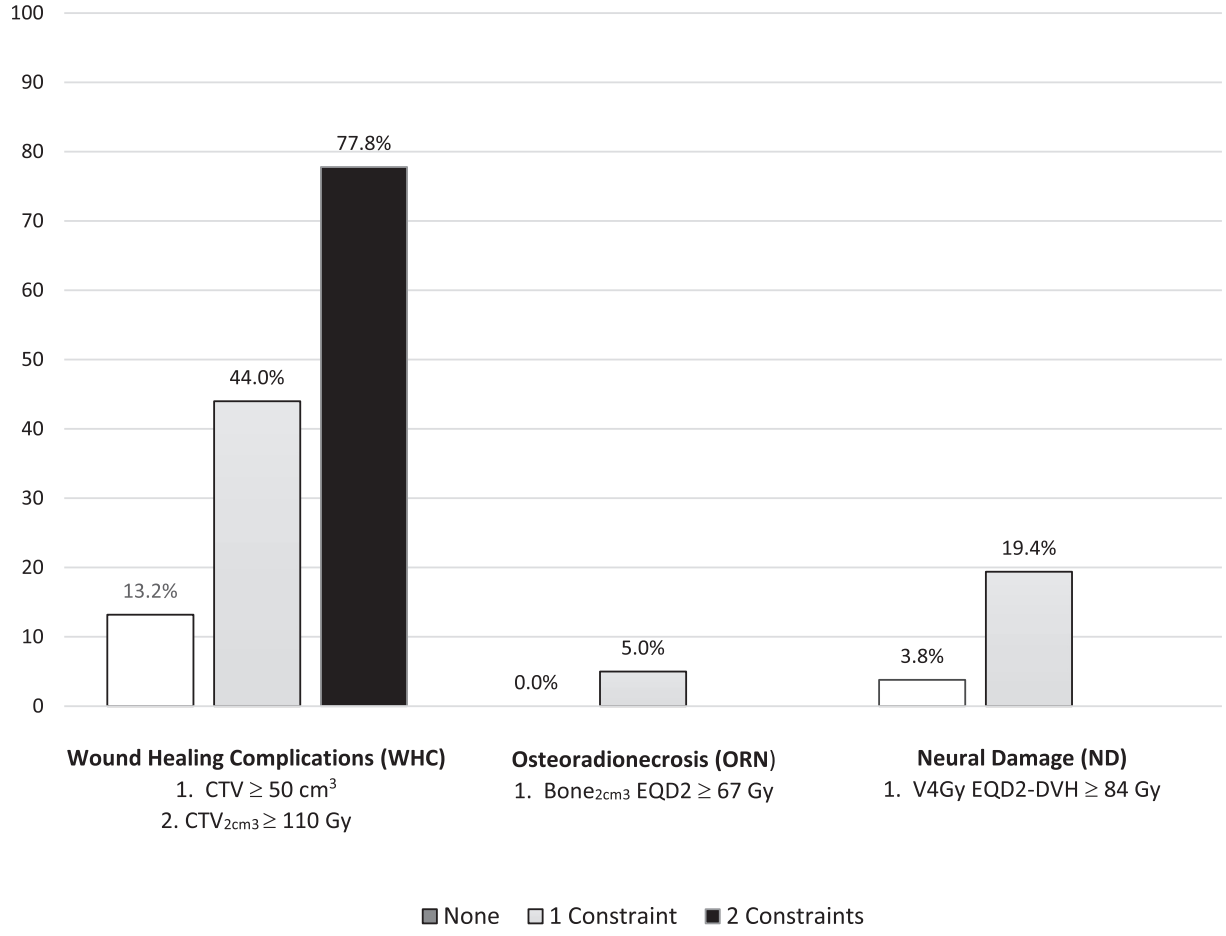

Fig. 1. Previously unirradiated cases. Rate of complications according to the number of constraints not met.

Table 5
Univariate and Multivariate Analysis for osteoradionecrosis (ORN).

Group	Parameter	Cut-off	Univariate	Multivariate
Previously unirradiated	$Bone_{2cm3}$ EQD2	67 Gy	$p = 0.01$	$p = 0.01$

Table 6
Univariate and Multivariate Analysis for nerve damage (ND).

Group	Parameter	Cut-off	Univariate	Multivariate
Previously unirradiated	Tumor Size		$p = 0.02$	
Previously unirradiated	CTV_{2cm3} Physical dose		$p = 0.02$	
Previously unirradiated	V4GyEQD2-DVH	84 Gy	$p = 0.02$	$p = 0.01$
Previously Irradiated	Time from Surgery		$p = 0.02$	
Previously Irradiated	CTV_{D90} Physical Doses	40 Gy	$p = 0.02$	$p = 0.01$

Osteoradionecrosis (ORN) was observed in 7 of 139 patients (5%) with a time appearance of 59 months. In univariate and multivariate analysis, ORN was more frequent when EQD2 $Bone_{2cm3}$ was $\geq$ 67 Gy (p = 0.01) (Table 5).

Nerve Damage (ND) was observed in 27 of 139 patients (19.4%), with a time appearance of 17 months. In univariate analysis, ND was more frequent in tumors > 10 cm (p = 0.02). Also, patients who received V4GyEQD2-DVH $\geq$ 84 Gy (tissue volume encompassed by the 4 Gy isodose and calculated with the EQD2-DVH) had more ND events in univariate (p < 0.01) and multivariate analysis (p < 0.01) (Table 6).

Previously irradiated cases

WHC were observed in 19 of 30 patients (63.3%), ORN in one case (3.3%) and ND in 7 patients (23.3%). The multivariate analysis showed that WHC were more frequent in patients with Lifetime EQD2 Skin 2 cm3 $\geq$ 84 Gy (p = 0.01) and ND was more frequent with Physical Dose CTVD90 $\geq$ 40 Gy (p < 0.01).

Discussion

Previously unirradiated cases

Wound healing complications

WHC was related to Volume factors (CTV size; p = 0.02) and Dose Volume factors (CTV_{2cm3} Total Physical Dose; p = 0.02) in multivariate analysis. Hence, the use of the CTV size < 50 cm^3 and CTV_{2cm3} values < 110 Gy could potentially decrease the WHC rate from an average of 38.8% to less than 15% (Fig. 1). This complication rate (15%) is similar to that found in the literature for patients treated with surgery alone [13] and is lower than that of patients treated with surgery and preoperative or postoperative radiotherapy in phase III trials [4].

Other volume factors previously described in the literature [1,4,11,14–16] and found to be predictive for WHC in the univariate analysis (Tumor Diameter, Blood transfusion, Lower extremity location and vascular dissection) were all tumor size-related and lost significance against CTV size in the multivariate analysis. However, the rate of rotation and free flap in the first surgery observed in our study was 10%, which remains lower than the median flap rate of 25.5% (18–33%) reported by other series [17–19] without further complications rate.

Since CTV delineation is tumor dependent as well as clinician dependent, several considerations can be made to avoid unnecessarily large CTVs. CTV definition has evolved from the traditional brachytherapy practice in which the CTV was usually defined as the entire surgical bed to more conservative CTV definitions that may be equally useful and less toxic. The American Brachytherapy Society consensus statement for soft tissue sarcoma brachytherapy [20] advices to construct the CVT/PTV with a tumor bed expansion of 2 cm craniocaudally and 1 cm lateral to the tumor bed. Another factor decisively contributing to the CTV size and not well defined so far is the thickness of the CTV [20]. In the absence of solid data indicating at which tissue depth remains the microscopic disease left after surgery, most clinicians will construct the CTV thickness with an expansion of 0.5 to 1.0 cm from the implant plane. Since a CTV thickness of 1.0 cm may be difficult to cover without creating hot spots around the catheters, we advocate the use of a more conservative expansion of 0.5 cm.

With regards, to dose parameters, the literature is scarce. Some reports indicate an increase in WHC with higher Total BED_3 doses when combining EBRT with HDR brachytherapy but no DVH-generated constraints are described [21].

Interestingly, no skin or scar DVH values were found to be predictive of WHC, probably because the contribution of the PHDRB to the total dose to these structures was minimal due to our long-term policy of keeping a minimum of 5 mm between the implant plane and the skin. In fact, the skin was relatively spared in comparison with the CTV dose with median PHDRB $skin_{2cm3}$ Physical doses of 2.8 Gy per fraction (70% of the prescribed dose) and median Total $skin_{2cm3}$ Physical doses of 57.2 Gy. The scar doses were even lower, with median PHDRB $scar_{2cm3}$ Physical doses of 2.2 Gy per fraction (55% of the prescribed dose) and Total $scar_{2cm3}$ Physical doses of 53.4 Gy.

Hence, WHC seems to result mainly from high-dose irradiation of large tissue volumes. In these cases, it may be safer to avoid implantation of postoperative CTVs exceeding 50 cm^3 at with CTV_{2cm3} values higher than 110 Gy. The risk of WHC is 13.2% if both constraints are met. The goal of obtaining a suitable CTV size can only be accomplished through strict case selection. The goal of CTV_{2cm3} values can be achieved using shorter intercatheter spacing (10–12 mm) and meticulous treatment planning to minimize high-dose areas.

Osteoradionecrosis

ORN was related to high-dose irradiation of small bony regions ($Bone_{2cm3}$ EQD2; p = 0.01) in the multivariate analysis. Hence, the use of $Bone_{2cm3}$ EQD2 values < 67 Gy could potentially decrease the ORN rate from an average of 5% to 0% (Fig. 1). $Bone_{2cm3}$ EQD2 should be closely monitored or lowered in cases in which periosteal stripping has been performed [22].

Nerve damage

ND was related to Dose Volume factors (V4GyEQD2-DVH; p = 0.02) in the multivariate analysis. Hence, the use of V4GyEQD2-DVH values < 84 Gy could potentially decrease the ND rate from an average of 19.4% to 3.8% (Fig. 1). Literature described that Neurovascular bundle involvement is safely treated with LDR, as long as cumulative doses to the structure do not exceed 90 Gy [23]. While specific OARs were analyzed for WHC (CTV, TV, Skin, Scar) and ORN (Bone), ND could not be associated with any specific OAR due to the lack of peripheral nerve imaging during brachytherapy planning. Hence, only indirect estimations can be made reflecting a greater ND rate in those patients receiving large doses (cut-off set at 84 Gy) at treatment volumes (V4Gy) rather than target volumes (CTV). Future plans include to mark intraoperatively the main nerve pathways adjacent to the implant so that they can be contoured during planning or move to MRI planning as in other brachytherapy locations such as prostate, gynecological, etc.

Progress in the avoidance of ND requires the adoption of accurate contouring of neural structures adjacent to the CTV via intraoperative delineation or MRI planning.

Previously Irradiated cases

WHC was more frequent in cases with Lifetime EQD2 Skin 2_{cm3} $\geq$ 84 Gy (p = 0.01), and therefore, immediate, or staged reconstruction seems a plausible option in patients with recurrent soft tissue sarcoma after prior irradiation in whom additional skin doses are required.

ND was more frequent in previously irradiated patients receiving Physical Doses to $CTVD_{90} \geq$ 40 Gy (p < 0.01). Therefore, precaution should be used when placing implants close to nerves in previously irradiated cases. These patients may better 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 [10].

Finally, we could not make any dosimetric recommendation to minimize ORN in previously irradiated patients due to the small number of cases in this particular scenario.

Proposal

Previously unirradiated cases

WHC seems to result mainly from high-dose irradiation of large tissue volumes. In these cases, we recommend avoiding implantation of postoperative CTVs exceeding 50 cm^3 with CTV_{2cm3} values greater than 110 Gy. The risk of WHC keeping both constraints is 13.2%.

ORN results mainly from high-dose irradiation of small bony regions. In Unirradiated patients, we recommend limiting the irradiation of the $Bone_{2cm3}$ to 67 Gy. The risk of ORN in that scenario is 0%.

Progress in the avoidance of ND requires the adoption of accurate contouring of neural structures adjacent to the CTV via intraoperative markers/delineation or MRI planning.

Previously irradiated cases

The recommendations are limited by the small number of cases in this patient scenario and no statement is possible. However, it seems prudent to limit the Lifetime EQD2 Skin 2 $_{cm3}$ to 84 Gy and the Physical Doses to $CTVD_{90}$ to 40 Gy.

Finally, it must be acknowledged that the study contains several limitations that may hamper the widespread applicability of the proposed constraints. First, the assumption of EBRT dose homogeneity may not be the case in a substantial number of patients, specially nowadays where more inhomogeneous external radiation dose plans are used. Also, the use of the classical RTOG criteria for the assessment of complications may differ in some cases from the more widely accepted CTCAE and this may difficult the comparison of data with more recent series. Finally, the small sample size of the previously irradiated cohort and its inherent heterogeneity may render the constraints obtained less applicable for this patient subset.

Conflict of interest statement

The authors whose names are listed in this paper certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Appendix 1. EQD2 DVH calculation

Using the differential DVH, the 2 Gy equivalent uniform dose can be calculated as shown in (1).

$$eudHDR2Gy = -\frac{\ln\sum_{i=1}^{m} v_i Sf(n,d_i)}{\alpha\left[1+\frac{2Gy}{(\alpha/\beta)}\right]}$$

In equation V is the volume considered, α y α/β the radiobiological parameters and (d_i, v_i) are the dose and volume values of each of the voxels of the differential DVH.

Please note that in equation stands for the cell survival fraction as per the LQ model for a volume v_i receiving a dose d_i as shown in (2).

$$Sf(v_i,d_i) = e^{-and_i\left[1+\frac{d_i}{(\alpha/\beta)}\right]}$$

where in equation n is the numbers of fractions.

The model used does not account for cell repopulation due to the extreme hypofractionation used in brachytherapy.

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