Postoperative Hypofractionated Volumetric Modulated Arc Therapy with a Simultaneous Integrated Boost for Soft Tissue Sarcomas

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ABSTRACT

Soft tissue sarcomas (STS) are rare neoplasms whose standard treatment combines surgery and radiotherapy. Conventional postoperative radiotherapy regimens involve prolonged treatment courses, which has prompted the exploration of hypofractionated alternatives. The development of advanced techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), together with the use of a simultaneous integrated boost (SIB), allows biologically equivalent doses to be delivered over a shorter period, optimizing dose distribution and reducing irradiation of healthy tissues. We present a retrospective series of 51 patients with STS treated with postoperative hypofractionated radiotherapy delivered in 15 fractions. Acute and late toxicity and oncologic outcomes were evaluated. The results showed satisfactory local control and survival, a low incidence of acute toxicity, and a moderate rate of late fibrosis. These findings suggest that hypofractionation using IMRT/VMAT is a viable therapeutic alternative in selected settings.

Keywords: Intensity-modulated radiotherapy; sarcoma; survival; toxicity.
Level of Evidence: IV

Radioterapia posoperatoria de intensidad volumétrica modulada hipofraccionada con refuerzo simultáneo integrado en sarcomas de partes blandas

RESUMEN

Los sarcomas de partes blandas son neoplasias poco frecuentes cuyo tratamiento estándar combina cirugía y radioterapia. Los esquemas convencionales de radioterapia posoperatoria implican tratamientos prolongados, lo que ha motivado la exploración de alternativas hipofraccionadas. El desarrollo de técnicas avanzadas, como la radioterapia de intensidad modulada y la radioterapia volumétrica, junto con el uso de refuerzo simultáneo integrado, permite administrar dosis biológicamente equivalentes en menor tiempo, optimizando la distribución de dosis y reduciendo la irradiación a tejidos sanos. Se presenta una serie retrospectiva de 51 pacientes con sarcoma de partes blandas tratados con radioterapia posoperatoria hipofraccionada en 15 fracciones. Se evaluaron la toxicidad aguda y tardía, y los resultados oncológicos. Los resultados muestran un control local y una supervivencia adecuados, una baja incidencia de toxicidad aguda y una tasa moderada de fibrosis tardía. Estos hallazgos sugieren que el hipofraccionamiento con radioterapia de intensidad modulada/radioterapia volumétrica constituye una alternativa terapéutica viable en contextos seleccionados.

Palabras clave: Radioterapia de intensidad modulada; sarcoma; supervivencia; toxicidad.
Nivel de Evidencia: IV

INTRODUCTION

Soft tissue sarcomas (STS) account for 1% of all neoplasms in adults.[1,2] The most common sites are the extremities (43%), visceral organs (19%), retroperitoneum (15%), and trunk (10%).[3]

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The histological classification of STS is based on the World Health Organization classification, which has incorporated new entities and updated diagnostic criteria.[4] Prognosis depends on multiple factors.[5] In the absence of radiotherapy, the local recurrence rate is approximately 30%, while the incidence of distant metastases ranges from 30% to 50%.[6]

Standard treatment consists of a combination of surgery and radiotherapy, which has reduced the local recurrence rate to less than 15%.[7]

Postoperative radiotherapy is associated with less acute toxicity but a higher incidence of late toxicity, such as fibrosis, edema, fractures, and joint stiffness.[8,9] Yang et al.[10] compared limb-sparing surgery alone with surgery plus adjuvant radiotherapy in 141 patients with STS (91 high-grade and 50 low-grade). With a mean follow-up of 9.6 years, 10-year local control was significantly higher in the surgery plus radiotherapy group (100% vs. 78%, p = 0.003); among patients with low-grade tumors, however, the difference did not reach statistical significance (95% vs. 68%, p = 0.067). Beane et al.[7] confirmed these findings in a study of 141 patients with STS (both low- and high-grade), with a mean follow-up of 17.9 years, reporting a local recurrence rate of 25% after surgery alone and 1.4% with adjuvant radiotherapy (p = 0.0001).

The standard postoperative dose is 64-66 Gy, administered in 1.8-2.0 Gy fractions over 32 or 33 sessions.[9] Bone fractures occur more frequently in patients receiving high doses (60-66 Gy) than in those receiving 50 Gy (10% vs. 2%).[11]

Regarding overall survival (OS), the data are conflicting. Yang et al.[10] reported no OS benefit with radiotherapy, whereas Kachare et al.,[8] in an analysis of 2606 patients with high-grade extremity STS treated with surgery and radiotherapy, found an OS benefit in both univariate and multivariate analyses.

According to a randomized trial, postoperative radiotherapy is associated with less acute toxicity than preoperative radiotherapy, but with a higher incidence of late toxicity, such as fibrosis, edema, fractures, and joint stiffness.[9] Bone fractures are more frequent in patients receiving high doses (60-66 Gy) than in those receiving 50 Gy (10% vs. 2%).[11] The standard postoperative dose ranges from 64 to 66, administered in 1.8-2.0 Gy fractions over 32 or 33 sessions.[9]

Radiotherapy techniques have evolved from two-dimensional radiotherapy to computed tomography (CT)-based three-dimensional conformal radiotherapy and, more recently, to intensity-modulated radiotherapy (IMRT).[12] IMRT allows modulation of the radiation beam and sparing of adjacent tissues, particularly bone, because of the conformal shape that can be achieved with the dose distribution. In patients with extremity STS, IMRT has been shown to be feasible and to have a favorable toxicity profile,[12] allowing the dose delivered to bone to be reduced and thereby decreasing the incidence of fractures associated with high radiation doses.[13] These newer techniques make it possible to consider shorter treatment regimens.

The objective of this article is to describe a clinical experience with hypofractionated postoperative radiotherapy using a simultaneous integrated boost (SIB) and to analyze its utility in clinical practice.

Patient Selection

We retrospectively reviewed the medical records of 51 patients diagnosed with STS who were treated at a single institution between January 2017 and October 2024. Data on age, sex, functional status according to the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), histological subtype, tumor location, and disease stage according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system[14] were obtained from the medical records, as were data on surgical treatment and chemotherapy administered.

Patients with STS of the extremities or trunk who had undergone surgery followed by postoperative hypofractionated radiotherapy using IMRT/volumetric modulated arc therapy (VMAT) with an SIB to the tumor site identified on preoperative magnetic resonance imaging (MRI) or CT, as well as adjuvant chemotherapy when indicated, were included.

Patients with retroperitoneal, visceral, or head and neck STS were excluded from the analysis, as were those with stage IV disease or those who had undergone amputation as part of their surgical treatment.

Follow-up was calculated from the first day of radiotherapy to the last in-person or telephone clinical follow-up or the date of death. During treatment, patients were evaluated weekly by the radiation oncologist. Follow-up imaging studies were obtained three months after completion of radiotherapy.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 5.0.[15] Acute toxicity was defined as toxicity occurring during treatment and up to three months thereafter, and late toxicity as toxicity occurring more than three months after treatment.

Local recurrence was defined as recurrence occurring within the previously described irradiated volumes.

Vacuum bags were used for patient immobilization. During virtual simulation, a radiopaque marker was placed over the surgical scar, which was covered with a 0.5-cm-thick synthetic gel (Superflab) or wax bolus of sufficient extent to cover the entire scar. The patient's position was marked on the vacuum bag to ensure accurate reproducibility at each treatment session (Figure 1).

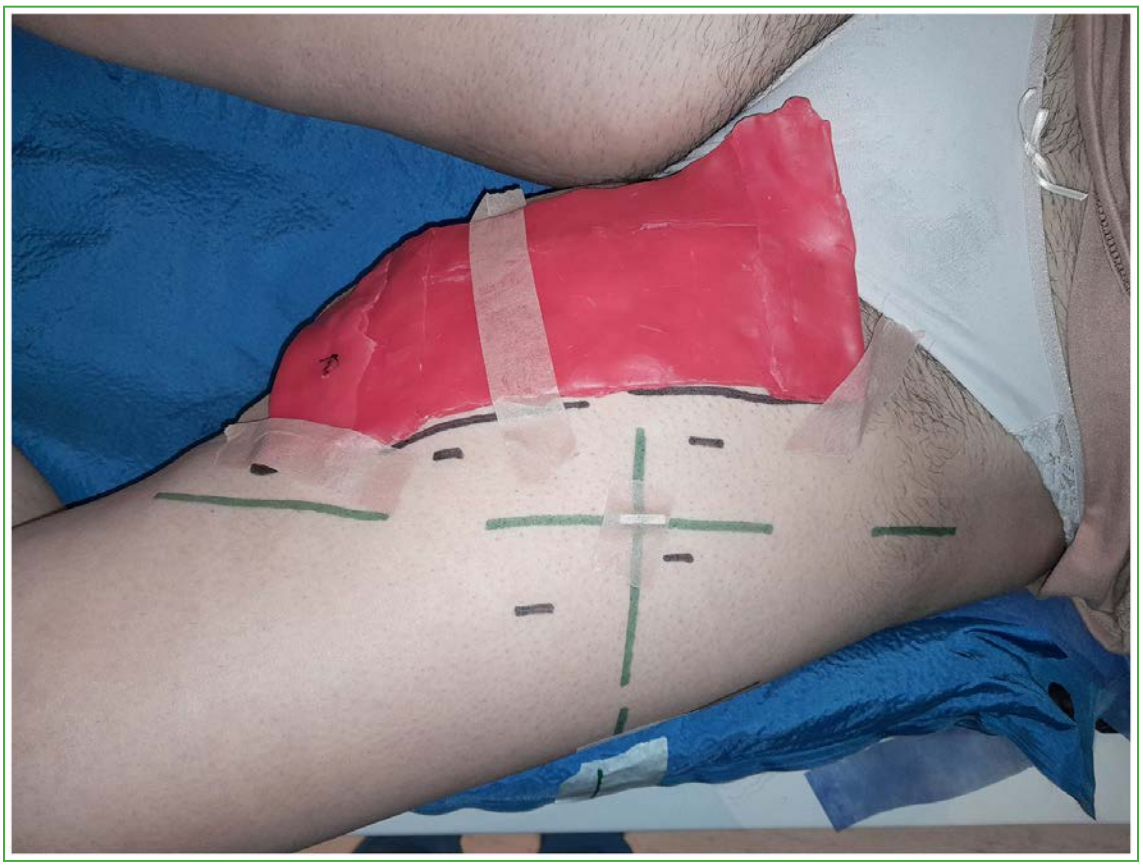

Figure 1. Simulation using a vacuum bag and bolus over the surgical scar. Patient immobilization using a vacuum bag. During virtual simulation, a radiopaque marker was placed over the surgical scar, which was covered with a synthetic gel bolus (Superflab); the marker allows the scar to be delineated.

CT imaging (Somatom GoUp, Siemens) was performed using 3-mm-thick slices and a field of view sufficiently wide to include the patient's entire external contour. CT acquisition included the target volume with margins of at least 5 cm at its superior and inferior ends.

CT images were imported via a DICOM network into the Eclipse treatment planning system, version 15.6 (Varian Medical Systems). Treatment volumes were delineated according to the recommendations published by Hass et al.16 using the simulation CT images and the preoperative MRI images as a guide.

Postoperative radiotherapy was delivered in 15 consecutive fractions at the following doses: tumor bed (SIB), total dose (TD) 48.75 Gy, with a daily dose of 3.25 Gy. The equivalent dose in 2-Gy fractions (EQD2), using

an α/β ratio of 1, was estimated at 64 Gy in patients with negative surgical margins; in patients with positive margins, the TD was increased to achieve an EQD2 of 68 Gy. Clinical target volume 1 (CTV1) received a TD of 43.9 Gy at 2.93 Gy per fraction (EQD2 54 Gy), and CTV2 received a TD of 41.8 Gy at 2.79 Gy per fraction (EQD2 50 Gy).

Planning with IMRT/VMAT

Treatment was delivered using VMAT with 6-MV photon beams, employing two complementary arcs and daily image-guided radiotherapy (Figure 2).

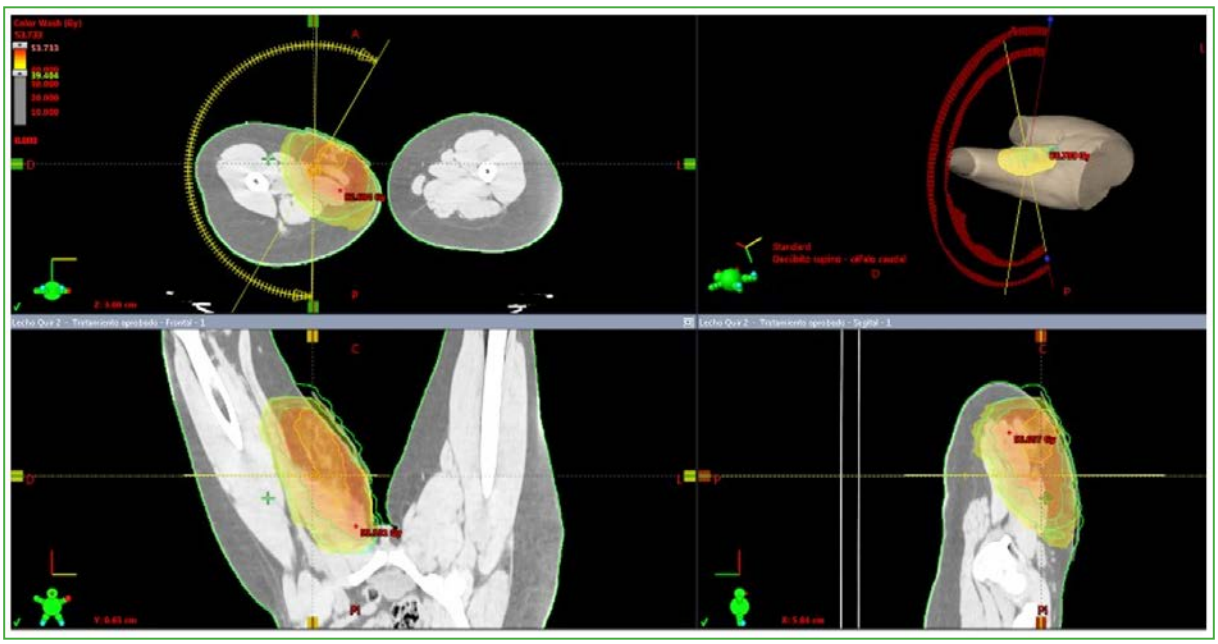

Figure 2. Treatment plan showing dose distribution in the tumor bed of the soft tissue sarcoma of the left thigh. The different isodose lines show coverage of the clinical target volume and its relationship to adjacent healthy tissues on axial, coronal, and sagittal images.

The defined volumes were the tumor bed (SIB), CTV1 (microscopic extension), CTV2 (surgical scar), and the planning target volume (PTV; 5-mm expansion).

Patient-specific quality assurance was performed, including an independent three-dimensional dose calculation using RadCalc v7.3 and portal dosimetry for each arc.

Treatments were delivered using TrueBeam STx or Novalis Tx linear accelerators (Varian Brainlab), both equipped with high-resolution multileaf collimator systems.

All participants provided written informed consent, and the study was conducted in accordance with the ethical principles of the 1975 Declaration of Helsinki.

Statistical Analysis

For descriptive analysis, quantitative variables, such as age, are expressed as mean ± standard deviation and range (minimum–maximum). Categorical variables, such as sex, are reported as absolute frequencies (number of cases) and relative frequencies (percentages).

Survival was estimated using the Kaplan-Meier method,[17,18] with the last day of radiotherapy considered the starting point. The outcomes analyzed were local recurrence-free survival, overall survival (OS), and metastasis-free survival.

Statistical analysis was performed using Statistica software, version 14.1.0.8.

Description of the Cohort

A total of 51 patients (mean age, 55 ± 17 years; range, 18–82) were analyzed, with a mean follow-up of 43 ± 17 months (range, 1.4–100). Twenty-four patients (47.1%) were women and 27 (52.9%) were men. Forty-two (82.4%) had negative surgical margins and nine (17.6%) had positive margins. Seven patients (13.7%) received adjuvant chemotherapy, while 44 (86.3%) did not. The mean interval between surgery and the start of intensity-modulated radiotherapy was 82 ± 44 days (range, 17–226). Tumor locations, listed in order of frequency, are detailed in Table 1.

Table 1. Location of sarcomas (n = 51).

Location of sarcomas	n	%
Lower extremity	28	54.9
Trunk	13	25.5
Upper extremity	10	19.6

The distribution by stage (AJCC 8th edition), as well as tumor grade and size, is shown in Table 2. Mean tumor size was 8.2 ± 5.1 cm (range, 1.3–30.0).

Table 2. Tumor stage, grade, and size (n = 51).

Variable		n	%
Stage			
	IA	2	3.9
	IB	6	11.8
	II	15	29.4
	IIIA	15	29.4
	IIIB	12	23.5
	IV	1	2
Tumor grade			
	I	10	19.6
	II	11	21.6
	III	30	58.8
Tumor size			
	≤5 cm	18	35.3
	>5 cm	33	64.7

Tumor histology is presented in Table 3. Liposarcoma was the most frequent subtype (15 patients, 29.4%), followed by spindle cell tumors (9 patients, 17.6%). Within the liposarcoma group (n = 15), the following histological subtypes were identified: dedifferentiated (5 patients, 33.3%), myxoid (4 patients, 26.7%), pleomorphic (2 patients, 13.3%), and well-differentiated (1 patient, 6.7%).

Table 3. Tumor histology (n = 51).

Histology	n	%
Liposarcoma	15	29.4
Spindle cell sarcoma	9	17.6
Leiomyosarcoma	8	15.7
Undifferentiated pleomorphic sarcoma	8	15.7
Fibromyxoid sarcoma	5	9.8
Epithelioid sarcoma	2	3.9
Synovial sarcoma	2	3.9
Fibrosarcoma	1	2.0
Malignant peripheral nerve sheath tumor	1	2.0

Early Toxicity

Grade 1 radiation dermatitis occurred in 37 patients (72.5%), grade 2 in 12 (23.5%), and grade 3 in two (4.0%). Grade 1 edema occurred in 15 patients (29.4%) and grade 2 in one (1.9%), while 35 (68.7%) did not develop this complication. Surgical scar complications (infection) occurred in two patients (4%).

Late Toxicity

Late toxicity was assessed in 49 of the 51 patients. Grade 1 scar fibrosis was observed in 30 patients (61.2%), grade 2 in 10 (20.4%), and grade 3 in one (2.0%), while eight (16.3%) had no fibrosis. Grade 1 edema was detected in 20 patients (40.8%) and grade 2 in two (4.1%). Twenty-two patients (44.9%) had skin changes consistent with post-radiation hyperpigmentation. One patient sustained a bone fracture one year after completing radiotherapy.

Survival

Local recurrence-free survival was 97.9 ± 2.1% at 12 months, 94.6 ± 3.8% at 24 months, and 89.6 ± 6.0% at 48 months (Figure 3A). The OS rate was 97.7 ± 2.2% at 12 months, 95.4 ± 3.2% at 24 months, and 87.3 ± 6.2% at 48 months (Figure 3B). Metastasis-free survival was 87.5 ± 4.8% at both 12 and 24 months and 77.3 ± 6.9% at 48 months (Figure 3C).

DISCUSSION

The results suggest that hypofractionated postoperative radiotherapy using IMRT/VMAT provides adequate local control and survival rates, with an acceptable toxicity profile. In the study by Wang et al.,[19] 80 patients with STS of the extremities and trunk were treated with IMRT in 25 fractions, with equivalent doses of 66 to 70 Gy to the tumor bed, depending on margin status. Similarly, Bourdais et al.[20] evaluated 59 patients treated with postoperative IMRT in 25 fractions, with doses ranging from 60 to 66 Gy adjusted according to the type of resection.

Unlike these conventional regimens, patients in our series received radiotherapy in 15 fractions, maintaining a similar equivalent dose but with a shorter treatment course.

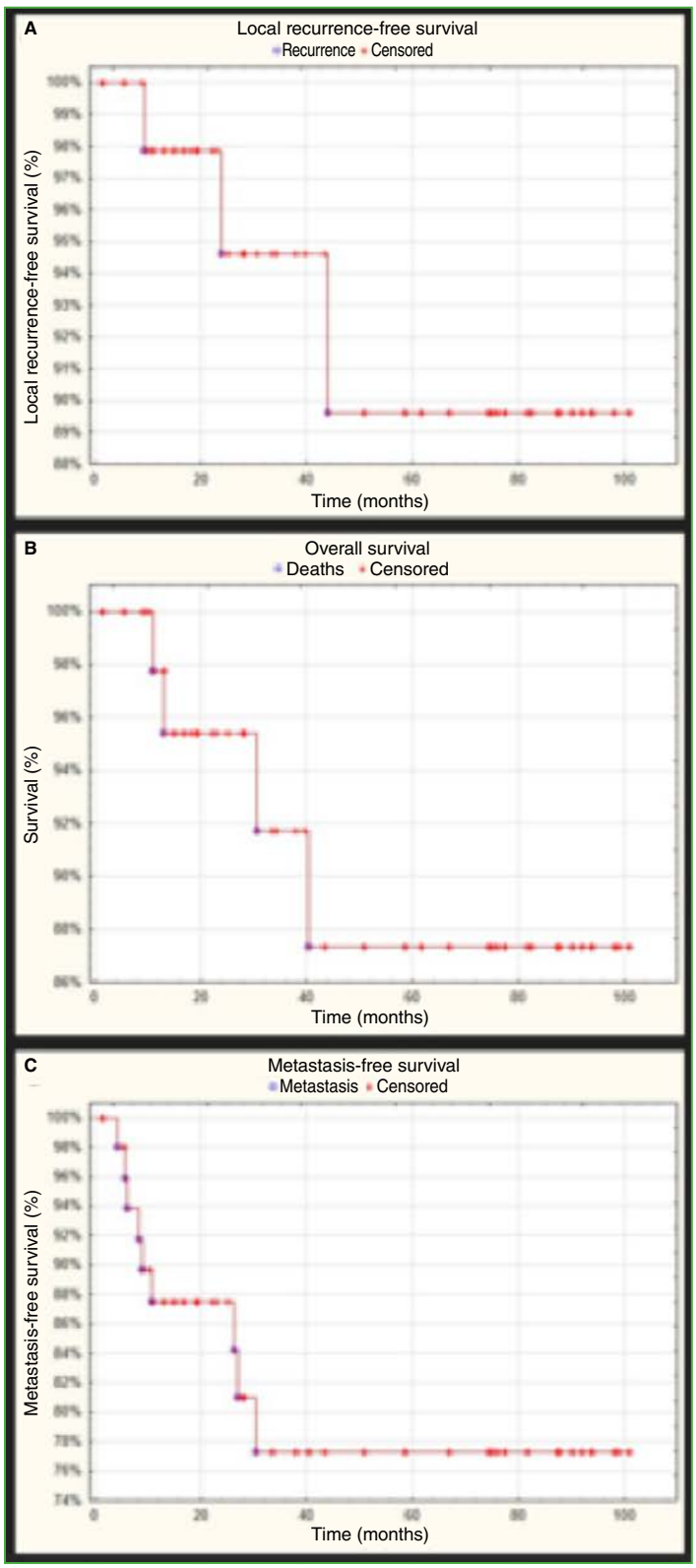

Figure 3. A. Local recurrence-free survival. Local control of 89.6% up to 100 months. **B.** Overall survival. Declines occurred before 40 months, followed by stabilization at 87.3% after 40 months. **C.** Metastasis-free survival. Most events occurred before 30 months, followed by stabilization at 77.3% thereafter.

Regarding acute toxicity, grade 2 and grade 3 radiation dermatitis occurred in 23.5% and 4.0% of patients, respectively; grade 2 or higher edema occurred in 1.9%, and wound-healing complications in 4%. Regarding late toxicity (n = 49), grade 2 or higher fibrosis occurred in 22.4% and grade 2 or higher edema in 4.1%. Wang et al.[19] reported a single case of grade 3 radiation dermatitis with a wound complication and an incidence of limb edema of 17.6%, with no fractures attributable to radiation. Similarly, Bourdais et al.[20] reported edema (29%) and chronic pain (32%) as the most frequent acute toxicities, with no bone fractures. Di Brina et al.[21] evaluated 109 patients treated with three-dimensional conformal radiotherapy (n = 38) or VMAT (n = 71) over 33 days and reported grade 2 fibrosis in 11.3%, with no fractures. Seddon et al.,[22] in a study of 53 patients treated with postoperative IMRT over 30–33 days, reported grade 2 or higher fibrosis in 10.8% and a single fracture.

Taken together, these three studies describe postoperative radiotherapy regimens administered primarily in 25–33 fractions using IMRT or VMAT, with relatively high rates of acute edema and a lower incidence of grade 2 or higher late fibrosis, with no radiation-induced fractures.[19-21]

Regarding oncologic outcomes in our study, local recurrence-free survival, OS, and metastasis-free survival rates at 48 months were 89.6%, 87.3%, and 77.3%, respectively. Consistent with these findings, the corresponding 48-month rates reported by Wang et al.[19] were 92.9%, 87.4%, and 81.2%, while Mills et al.[23] reported rates of 100%, 86%, and 68%, respectively, in patients treated with postoperative IMRT in 28 fractions.

CONCLUSIONS

Despite the limitations inherent to a retrospective study, the findings suggest that hypofractionated postoperative radiotherapy with IMRT/VMAT and SIB is a safe, effective, and efficient alternative for the adjuvant treatment of STS, with a low toxicity profile, the ability to avoid or reduce radiation dose to bone, and favorable oncologic outcomes.

Statement on the Use of AI

The use of artificial intelligence applications was limited to 3% of the work; ChatGPT® was used for grammatical correction of some texts.

Conflicts of interest: The authors declare no conflicts of interest.

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