



**HAL**  
open science

## Prospective evaluation of intensity-modulated radiotherapy toxicity in extremity soft tissue sarcomas patients: A role for irradiated healthy soft tissue volume?

Rémi Bourdais, Samir Achkar, Charles Honoré, Matthieu Faron, Andrea Cavalcanti, Guillaume Auzac, Carine Ngo, Leila Haddag-Miliani, Benjamin Verret, Sarah Dumont, et al.

### ► To cite this version:

Rémi Bourdais, Samir Achkar, Charles Honoré, Matthieu Faron, Andrea Cavalcanti, et al.. Prospective evaluation of intensity-modulated radiotherapy toxicity in extremity soft tissue sarcomas patients: A role for irradiated healthy soft tissue volume?. *Clinical and Translational Radiation Oncology*, 2021, 29, pp.79-84. 10.1016/j.ctro.2021.05.007 . hal-04504197

**HAL Id: hal-04504197**

**<https://hal.science/hal-04504197>**

Submitted on 22 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

## **Prospective evaluation of intensity-modulated radiotherapy toxicity in extremity soft tissue sarcomas patients: a role for irradiated healthy soft tissue volume?**

*Running title: ESTS IMRT: impact of healthy soft tissue volume*

Rémi Bourdais, MD,<sup>1\*</sup> Samir Achkar, MD,<sup>1</sup> Charles Honoré, MD, PhD<sup>2</sup>, Matthieu Faron, MD,<sup>2</sup> Andrea Cavalcanti, MD,<sup>2</sup> Guillaume Auzac<sup>1</sup>, Carine Ngo, MD,<sup>3</sup> Leila Haddag-Miliani, MD,<sup>4</sup> Benjamin Verret, MD,<sup>5</sup> Sarah Dumont, MD, PhD,<sup>5</sup> Eric Deutsch, MD, PhD,<sup>1,6,7</sup> Axel Le Cesne, MD,<sup>5</sup> Olivier Mir, MD, PhD,<sup>5</sup> Cécile Le Péchoux, MD,<sup>1</sup> Antonin Levy, MD, PhD<sup>1,6,7\*</sup>

1. Department of Radiation Oncology, Gustave Roussy, F-94805, Villejuif, France
2. Department of Surgery, Gustave Roussy, F-94805, Villejuif, France
3. Department of Pathology, Gustave Roussy, F-94805, Villejuif, France
4. Department of Radiology, Gustave Roussy, F-94805, Villejuif, France
5. Department of Medical Oncology, Gustave Roussy, F-94805, Villejuif, France
6. Université Paris-Saclay, F-94270, Le Kremlin-Bicêtre, France
7. Université Paris-Saclay, INSERM U1030, Molecular Radiotherapy, F-94805, Villejuif, France

\*Corresponding authors:

Department of Radiation Oncology, Gustave Roussy, Université Paris-Saclay, F-94805, Villejuif, France. : Tel: +33 (0) 1 42 11 47 57; Fax: +33 (0) 1 42 11 52 53; Email: remi.bourdais@gustaveroussy.fr  
antonin.levy@gustaveroussy.fr

### **Funding**

None.

### **Authors' disclosures of potential conflicts of interest**

The authors indicated no potential conflicts of interest.

Data sharing statement:

Owing to legal and ethical issues, patient level data used in this study are unavailable.

**Prospective evaluation of intensity-modulated radiotherapy toxicity in extremity soft tissue sarcomas patients: a role for irradiated healthy soft tissue volume?**

## **Abstract**

**Aim:** To prospectively assess toxicities of curative-intent intensity-modulated conformal radiotherapy (IMRT) in patients with extremity soft tissue sarcomas (ESTS).

**Methods:** Data from 59 consecutive patients with ESTS between 2014 and 2019 were both retrospectively and prospectively analysed. Toxicity data were collected both by confidential mailed survey (39% completed) and medical charts, and graded according to CTCAE v5.0. Normal tissues dosimetric data (healthy soft tissue segment, joint and bone) were included. The healthy soft tissue segment was created by adding 5 cm on either side of the PTV on CT axial slices, the PTV and bone (and articulation if present) were then removed from the generated volume.

**Results:** IMRT was delivered post-operatively for nearly half of patients (n=24, 41%), preoperatively for 18 (31%) and exclusively for 17 (28%; salvage: 13% or immediately inoperable: 15%). The median total dose delivered to the planned target volume (PTV) was 50.4 Gy (36-68 Gy) and 13 patients (22%) received a boost. With a median follow-up of 27 months (6-94 months), a total of 87 late effects were identified in 44/59 (75%) patients: 89% G1–2, and 11% G3–4. The main G1-2 toxicities were: functional limitation (36%), oedema (29%), gait disorders (20%), neurological disorders (20%) and chronic pain (32%). G3-4 toxicities were pain (n=2), arterial stricture (n=1) and a chronic wound requiring skin graft (n=2). No bone fracture was observed. Quality of life was rated as good or very good in 70% patients who completed the survey. Larger (>3500 cm<sup>3</sup>) healthy soft tissue segment volume was associated with decreased late toxicities (p=0.02). No other predictive factor of toxicity was identified. The 2-year rates of local control, overall survival and recurrence-free survival were 90%, 90% and 64%, respectively.

**Conclusion:** Healthy soft tissue segment volume influenced toxicity. Long-term prospective monitoring in a homogeneous population remains critical to assess the impact of IMRT

induced chronic toxicity in ESTS patients. This should ideally lead to a validated normal tissue dose constraint (e.g.: healthy soft tissue segment volume > 3500 cm<sup>3</sup>) to recommend for practitioners to help reduce the late toxicity risk.

**Keywords:** Soft tissue neoplasm, Sarcomas, Radiotherapy, intensity-modulated, Surgery, Toxicity

## **Introduction**

Management of extremity soft tissue sarcomas (ESTS) at risk of local relapse involves limb-sparing surgery associated with perioperative radiation therapy [1-4]. The aim of this approach is to maximize local control while preserving limb function. External beam radiotherapy is usually delivered using a three-dimensional (3D) conformal technique, leading to 90% local control [5, 6]. As the cure rates continue to improve, the incidence and management of long-term consequences are a constant challenge. In ESTS, the accountability of late complications may be difficult to assess given the type and combination of treatments. The development of intensity modulated (IMRT) and imaged guided Radiotherapy (IGRT) has led to the delivery of a homogeneous dose distribution into the tumour bed with maximum sparing of critical organs and subsequently decrease late toxicity [7, 8]. When planning radiotherapy, dose-volume constraint have been applied for bones to limit the risk of fracture [9], but no dose-volume constraints for soft tissues has been established. In the present study, we aimed to prospectively assess toxicities of IMRT delivered for curative-intent in patients with ESTS and to evaluate potential prognostic factors for late toxicity, with a special focus on dose delivered to healthy soft tissues.

## **Patients and Methods**

### *Population, data collection and toxicity assessment*

Data from 59 patients who received IMRT (n=4, 7%), volumetric-modulated arc therapy (n=12, 20%, Elekta<sup>®</sup> VERSA HD) or helical TomoTherapy<sup>®</sup> (n=40, 73%, Accuray, Sunnyvale, CA) for a histologically proven ESTS at our tertiary cancer centre between January 2014 and May 2019, were both retrospectively and prospectively analysed. Patients

treated for abdominal, retroperitoneal, thoracic and cervical localizations or who had metastases at diagnosis were not included in this study. A strictly confidential survey was mailed in 09/2019 to all patients, except to patients with local relapse. The questionnaire was divided into five constructed sections based on items in the Late Effects in Normal Tissues Subjective, Objective, Management and Analytic (LENT SOMA) scoring system: pain, urinary, swelling/oedema, functional limitation/gait disorders, and quality of life (QoL). A blank space was left at the end of the questionnaire for free comments. A total of 20/52 (39%; not sent to patients with local relapse) patients completed and returned the questionnaire. Complications were systematically recorded retrospectively based on the clinical charts, physical examination, and prospectively with delivered surveys throughout the follow-up period, and graded according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0). The follow-up protocol included clinical examinations, MRI and CT every 6 months for 5 years and then yearly for 10 years.

### *Management*

ESTS patients' management at our centre has been previously described [5, 6]. Radiotherapy was delivered in a preoperative, post-operative or exclusive (salvage treatment after a relapse or immediately inoperable ESTS) fashion. IMRT was delivered using daily cone beam CT image guidance and an automated bone matching algorithm. Changes exceeding a 1-cm predetermined threshold lead to potential resimulation and replanning. The radiotherapy dose level was discussed at multidisciplinary board and depended mostly upon the quality of surgery, margin size and type of tissue, as well as timing of irradiation. Sarcoma subtypes, patient age as well as consequences of a possible local recurrence were considered in the decision. Radiotherapy planning generally included modern procedures with immobilization device and the target volume was based on the fused preoperative magnetic resonance

imaging (MRI). Target volume recommendations were previously described [5,6]. A boost to the tumour bed was administered to bring the tumour bed to a dose of 60–66 Gy depending on margins status. Of note, patients who had isolated limb perfusion (ILP) received 45 Gy in 25 fractions, so as to minimize possible sequelae. Raystation® v8 treatment planning system was used.

A healthy soft tissue segment was created by adding 5 cm on either side of the Planning Target Volume (PTV) on computed tomography (CT) axial slices, the PTV and bone (and articulation if present) were then removed from the generated volume (as shown on **Figure 1**). The healthy soft tissue segment volumes receiving a minimum of 5 Gy, 10 Gy, 15 Gy, 20 Gy, 25 Gy and 30 Gy were collected, as well as the mean dose received by this volume. The joints and bones were also delineated. The average dose to the joints, the maximum dose to the bone and the bone volume receiving a minimum of 40 Gy were calculated.

### *Statistical analyses*

Follow-up was estimated using the reverse Kaplan-Meier method. Overall survival (OS), disease-free survival (DFS), local relapse (LR), and distant relapse (DR) rates were estimated using the Kaplan Meier method. Survival rates were defined as the time between the date of pathological diagnosis and the first event. Events were: death from any cause for OS, death or tumour relapse for DFS, and death from the treated cancer or after a relapse for cause-specific survival. For the LR and DR rates, death without relapse or a relapse other than the one considered was censored. Survival curves were compared using the log-rank test. For each patient, the total number of late effects was calculated. A composite toxicity score was calculated by summing each toxicity grade per patient. The sum of late effects was compared with the Mann–Whitney test for categorical variables (analysis of variance if more than two



groups), and the Spearman correlation test for continuous numerical values. Analyses were performed using Prism<sup>®</sup> version 5 software and p-values less than 0.05 were considered significant.

## Results

### *Patients and treatments*

The main clinical and treatment characteristics are detailed in **Table 1**. The median age was 60 years (range, 22-89 years), the median initial tumour size was 8 cm (1-40 cm; smallest tumour were those that had local relapse after initial woops surgery) and the most frequent location was the thigh (n=19; 32%). The most frequent histological type was liposarcoma (myxoid: n=9, 15%; dedifferentiated: n=8, 14%). Grade (French grading system) was predominantly 2 (n=22, 37%) and 3 (n=20, 34%). Grade was not assessable for 7 patients because of insufficient material or histology for which grade determination was not applicable (desmoid tumour, angiosarcoma).

Eighteen patients (31%) were referred after incomplete resection (“woops surgery”) and 13 patients (22%) received IMRT for a local recurrence presentation. The majority of patients underwent surgery at our centre (n=42, 71%). IMRT was delivered post-operatively for nearly half of the patients (n=24, 41%), preoperatively for 18 patients (31%) and exclusively for 17 patients (28%; salvage: 13% or inoperable: 15%). Radiotherapy delivered a median total dose of 50.4 Gy (36-68 Gy; preop: 50 Gy; postop: 54 Gy; exclusive: 54 Gy), for a median duration of 39 days (22-89 days). A postoperative boost (median dose of 9 Gy) was delivered to 13 patients (22%) receiving adjuvant irradiation, given limited margin status. For 20 patients (47%), flap reconstructive surgery was performed, planned for 18 patients (43%), unplanned for 2 patients (4%). Histology margins were classified R0 for 30/42 patients (71%),

R1 for 11/42 patients (26%; 5/11 planned R1) and R2 for 1/42 patient (2%, that was a tumour enucleation given amputation patient refusal after ILP). Twelve patients (20%) received pre-operative chemotherapy and 14 patients (24%) received ILP. Of these patients, 11/14 underwent surgery + adjuvant radiotherapy, and 3/14 received exclusive radiotherapy.

### *Toxicity*

The median follow-up was 27 months (range, 6-94 months). Postoperative acute wound injury was observed in 7/42 patients (16.7%), with the need for reintervention in 3/7 patients. Five of these patients had received pre-operative radiotherapy. Late toxicity data is showed in **Table 2**. A total of 87 side effects were observed in 44/59 (75%) patients, including 82 (94%) G1-2 effects in 44 (75%) patients and 5 (6%) G3 effects in 5 (8%) patients. The median number of side effects per patient was 1 (0-6). The median composite toxicity score (sum of toxicity grades per patient) was 1 (0-7). The main toxicities of G1-2 were mobility limitation (35%), oedema (29%), gait disorders (20%), neurological disorders (20%) and chronic pain (32%). G3-4 toxicities were pain (n=2), arterial stricture (n=1) and a chronic wound requiring skin grafting (n=2). No fractures were observed. QoL was rated as good or very good in 14/20 patients (70%) who completed the survey. Most (n=6) patients with decreased QoL results had both mobility limitation (n=5/6) and/or chronic pain (n=5/6).

### *Predictive factors for late toxicity*

Dosimetric data were retrieved for 55/59 (93%) patients and are reported in **Table 3**. The median PTV volume and the median healthy soft tissue segment volume were 915 cm<sup>3</sup> (87-6094 cm<sup>3</sup>) and 3911 cm<sup>3</sup> (388-14564 cm<sup>3</sup>), respectively. The median mean dose delivered to the healthy soft tissue segment was 18.6 Gy (5.3-42.5 Gy). The median maximum dose to the

bone was 50.75 Gy (11.42-61.51 Gy) and the median mean dose to the joint was 23.87 Gy (0-64 Gy).

Smaller healthy soft tissue segment volume was associated with the occurrence of late toxicities ( $p=0.046$ ;  $\rho: -0.29$ ). A median healthy soft tissue segment volume  $>3500 \text{ cm}^3$  correlated with a decreased occurrence of late toxicities ( $p=0.02$ ). The median healthy soft tissue segment volume was  $5207 \text{ cm}^3$  (range  $388-8477 \text{ cm}^3$ ) in the 15 patients presenting no toxicity vs.  $3440$  (range  $566-14564 \text{ cm}^3$ ) in the other ones. Others healthy soft tissue (Mean Dose; V5Gy; V10Gy; V15Gy V20Gy; V25Gy; V30Gy), bone (Maximum Dose, V40Gy), and joint (Mean Dose) dosimetric parameters (**Table 3**) were not associated with toxicity occurrence (calculation based on both median and Spearman correlation). Dosimetric parameters did not correlate to specific late toxicity risk (lymphedema, mobility limitation, gait disorder), possibly linked to the limited number of events. Patient and tumour characteristics, treatment period, delivered preoperative treatments (isolated limb infusion, neoadjuvant chemotherapy) and other radiotherapy parameters (timing, total dose, boost, PTV volume...; **Table 3**) were not predictive of the development of overall or individual toxicity. The healthy soft tissue segment volume was not different according to radiation therapy timing (median healthy soft tissue segment volume for preop vs postop vs exclusive radiotherapy of  $4349$  vs  $3838,9$  vs  $3862 \text{ cm}^3$ , respectively,  $p=0.5$ ; preop vs postop patients:  $p=0.2$ ).

#### *Survival data, relapse and prognostic factors*

At the last follow-up, 50 patients (85%) were alive, including 36 patients (61%) without relapse. The 2-year (The median follow-up was 27 months, cf. before) OS rate was 89.9% (95% CI: 77.1-95.7%). Twenty-three patients (39%) had relapsed, including 20 DR (34%) and 7 LR (12%). Four patients had both LR and DR (7%). The 2-year local control and DFS

rates were 90% (95% CI: 78-96%) and 64% (95% CI: 50-76%), respectively (**Figure S1**). Grade 3 (HR=3.98; 95% CI: 1.5-10.6; p=0.006), tumour size > 5 cm (HR=2.64; 95% CI: 1.04-6.68; p=0.04) and the absence of surgery (HR=3.3; 95% CI: 1.3-8.6, p=0.01) were associated with lower DFS rates (**Figure 2**). Predictors of LR were grade 3 (HR=12.9; 95% CI: 1.3-130.6; p=0.03) and the absence of surgery (HR=16.5; 95% CI: 3.2-85.6, p=0.004). A non-significant trend was observed for tumour size > 5 cm (HR=3.85; IC95%: 0.66-22.6; p=0.08; **Figure 3**).

## **Discussion**

In this work, we aimed to prospectively assess toxicity in ESTS patients who received IMRT in real-life practice in a comprehensive cancer centre. IMRT has recently become widely accessible in many radiation oncology centres and two prospective non-randomized studies have shown toxicity reduction with this technique when compared to historical control [7, 8]. Different experiences may not be compared easily given ESTS rarity, specific histological subtypes, and various combined delivered treatments [4, 7, 8, 10, 11]. With a median follow-up of 27 months we identified late effects in 44/59 (75%) patients: 89% G1–2, and 11% G3–4. The rate of limb oedema was lower than previously published (29% here versus 42% in the preoperative IMRT phase II trial [8] and 15-23% G3-4 (depending on the group) in the SR2 trial (3D-radiotherapy only) [4, 12]. It should however be emphasized that oedema rating scale may be difficult to apply (e.g. mild vs. moderate swelling in the commonly accepted Stern's classification [12]). Limbs circumference or volume should ideally be repeatedly assessed all along the follow-up and compared with baseline measures [13]. Mild functional limitation was frequently observed (36%) in this experience and originated from multifactorial causes (joint stiffness, pain, neurological disorders). One limitation is that we

did not use a functional score. Moderate to severe joint stiffness was observed in 18-23% patients in the SR2 trial [4, 12]. We were not able to capture fibrosis in our analysis, an observation that may be underreported in clinical charts (only 2% sclerosis in our previous experience in 414 ESTS patients [5]). In a single-institution phase II prospective study, 9.3% evaluable patients had moderate (grade 2) fibrosis at 2 years, with none rated as severe [8]. Radiological measures, such as ultrasonography quantification using a high-frequency transducer, should be encouraged and evaluated [14].

A larger healthy soft tissue segment volume ( $> 3500 \text{ cm}^3$ ) was the only (including clinical, treatment and other dosimetric) variable that correlated with decreased toxicities ( $p=0.02$ ). To our knowledge, this study is the first to explore healthy soft tissue dosimetric parameters to assess long-term IMRT toxicity in ESTS patients (**Figure 1**). This healthy soft tissue segment volume is of importance because it gives more information than the usual “big fields = increased toxicity“. Schematically, patients with a tumour localized within a larger limb segment could develop a lower complication rate, possibly independently of PTV volume. Higher virtual flap/PTV volume overlap was associated with wound healing complication within 120 days of resection in an IMRT phase II study [8]. In the SR2 study, larger field size was a risk factor for subcutaneous fibrosis and joint stiffness [12]. Other dosimetric or radiation therapy parameters (timing, total dose, boost, PTV volume...; **Table 3**) were not predictive of the development of overall or individual toxicity. The healthy soft tissue segment volume was also not different in preop vs postop patients (median of 4349 vs 3838,9  $\text{cm}^3$ , respectively,  $p=0.2$ ). Dosimetric constraints associated with bone fracture ( $V_{40}>64\%$ , mean dose to bone  $>37 \text{ Gy}$  or maximum dose  $>59 \text{ Gy}$ ) have been reported [9]. In ESTS patients receiving IMRT, the dose of irradiation seems to have less impact on fracture [15].

Limitations of this study include the small number of patients and the short median follow-up (27 months). Some dosimetric data (e.g. higher doses parameters such as V40 & V45 and/or healthy soft tissue - GTV) were not captured and could deserve further analyses. Even if an advantage of our study was a prospective toxicity collection including QoL, this analysis is restricted by the small proportion (39%) of patients who completed this survey. As a result, a large amount of the data was collected retrospectively, favouring collection and reporting bias. The study population was also heterogeneous because exclusive irradiation was delivered for 17 (28%; salvage: 13% or inoperable: 15%) patients; those displayed poorer outcomes as compared to patients that received surgery (**Figures 2 and 3**). However patient population and oncologic results (2-year local control and OS rates of 90%) were comparable with the literature [4, 5]. Even if irradiated volumes are more limited, it is admitted that IMRT does not increase the relapse risk as compared to 3D-conformal radiation therapy [8].

## **Conclusion**

The analysis of this single-center series shows comparable oncological results to those from the literature [4]. The toxicity of IMRT was acceptable with mostly grade 1 and 2 effects. We identified a healthy soft tissue segment volume as possible predictive dosimetric parameter of toxicity. This should ideally lead to a validated normal tissue dose constraint (e.g.: healthy soft tissue segment volume > 3500 cm<sup>3</sup>) to recommend for practitioners to help reduce the late toxicity risk. Long-term prospective follow-up in a homogeneous population remains necessary to confirm such findings. This could be of importance given recent results suggesting the interest of preoperative hypofractionation irradiation [16]. Incorporating newer radiosensitizers [17, 18] and/or surrogate biologic markers of toxicity [16] could lead to mitigate treatments long-term consequences in ESTS patients.

## **Funding**

None.

## **Authors' disclosures of potential conflicts of interest**

The authors indicated no potential conflicts of interest.

## **References**

1. Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg* 1982;196:305–15.
2. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol Off J Am Soc Clin Oncol* 1996;14:859–68.
3. Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol Off J Am Soc Clin Oncol* 1998;16:197–203.
4. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002;359:2235–41.
5. Levy A, Bonvalot S, Bellefqih S, Terrier P, Le Cesne A, Le Pécoux C. Is dose de-escalation possible in sarcoma patients treated with enlarged limb sparing resection? *Radiother Oncol* 2018;126:493–8.
6. Bonvalot S, Levy A, Terrier P, Tzanis D, Bellefqih S, Le Cesne A, et al. Primary Extremity Soft Tissue Sarcomas: Does Local Control Impact Survival? *Ann Surg Oncol* 2017;24:194–201.
7. Wang D, Zhang Q, Eisenberg BL, Kane JM, Li XA, Lucas D, et al. Significant Reduction of Late Toxicities in Patients With Extremity Sarcoma Treated With Image-Guided Radiation Therapy to a Reduced Target Volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. *J Clin Oncol Off J Am Soc Clin Oncol* 2015;33:2231–8.
8. O'Sullivan B, Griffin AM, Dickie CI, Sharpe MB, Chung PWM, Catton CN, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer* 2013;119:1878–84.
9. Dickie CI, Parent AL, Griffin AM, Fung S, Chung PWM, Catton CN, et al. Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: relationship to irradiated bone length, volume, tumor location and dose. *Int J Radiat Oncol Biol Phys* 2009;75:1119–24.
10. Levy A, Bonvalot S, Bellefqih S, Vilcot L, Rimareix F, Terrier P, Belemsagha D, Cascales A, Domont J, Mir O, Honoré C, Le Cesne A, Le Pécoux C. Is preoperative radiotherapy suitable for all patients with primary soft tissue sarcoma of the limbs? *Eur J Surg Oncol*. 2014;40:1648-54.

11. Levy A, Le Péchoux C, Terrier P, Bouaita R, Domont J, Mir O, Coppola S, Honoré C, Le Cesne A, Bonvalot S. Epithelioid sarcoma: need for a multimodal approach to maximize the chances of curative conservative treatment. *Ann Surg Oncol*. 2014;21:269-76.
12. Davis AM, O'Sullivan B, Turcotte R, Bell R, Catton C, Chabot P, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2005;75:48–53.
13. Asdourian MS, Swaroop MN, Sayegh HE, Brunelle CL, Mina AI, Zheng H, Skolny MN, Taghian AG. Association Between Precautionary Behaviors and Breast Cancer-Related Lymphedema in Patients Undergoing Bilateral Surgery. *J Clin Oncol*. 2017 Dec 10;35:3934-3941.
14. Bourcier C, Auperin A, Rivera S, Boisselier P, Petit B, Lang P, et al. Pravastatin Reverses Established Radiation-Induced Cutaneous and Subcutaneous Fibrosis in Patients With Head and Neck Cancer: Results of the Biology-Driven Phase 2 Clinical Trial Pravacur. *Int J Radiat Oncol Biol Phys*. 2019;104:365-373.
15. Folkert MR, Casey DL, Berry SL, Crago A, Fabbri N, Singer S, Alektiar KM. Femoral Fracture in Primary Soft-Tissue Sarcoma of the Thigh and Groin Treated with Intensity-Modulated Radiation Therapy: Observed versus Expected Risk. *Ann Surg Oncol*. 2019;26:1326-1331.
16. Kalbasi A, Kamrava M, Chu FI, Telesca D, Van Dams R, Yang Y, et al. A Phase II Trial of 5-Day Neoadjuvant Radiotherapy for Patients with High-Risk Primary Soft Tissue Sarcoma. *Clin Cancer Res*. 2020;26:1829-1836.
17. Bonvalot S, Rutkowski PL, Thariat J, Carrère S, Ducassou A, Sunyach MP, et al. NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2-3, randomised, controlled trial. *Lancet Oncol*. 2019;20:1148-1159.
18. Gronchi A, Hindi N, Blay JY, Redondo A, Sanfilippo R, Morosi C, et al. Trabectedin and radiotherapy in soft-tissue sarcoma (TRASTS) study: An international, prospective, phase II trial in localized myxoid liposarcoma—A collaborative Spanish (GEIS), Italian (ISG) and French (FSG) group study. *J Clin Oncol* 2020; 38, 15S: 11514 (Abstract #11514)



**Table 1: Patient and treatment characteristics**

<b>Characteristics</b>	<b>N=59</b>
Median age (years)	60 (22-89)
Gender (%)	
Male	33 (56)
Female	26 (44)
Median tumour size at diagnosis (cm)	8 (1-40)
Location (%)	
Upper limb	11 (19)
Lower limb	48 (81)
Histological subtype (%)	
Liposarcoma	17 (29)
Dedifferentiated	8 (14)
Myxoid	9 (15)
Undifferentiated	14 (24)
Myxofibrosarcoma	8 (14)
Leiomyosarcoma	4 (7)
Others	16 (27)
Grade (%)	
1	10 (17)
2	22 (37)
3	20 (34)
Not evaluable	7 (12)
<b>Presentation (%)</b>	
<b>Planned de novo treatment</b>	28 (47)
<b>Initial woops surgery</b>	18 (31)
<b>Recurrent tumour</b>	13 (22)
<b>Radiotherapy timing (%)</b>	
<b>Preoperative</b>	18 (31)
<b>Postoperative</b>	24 (41)
<b>Exclusive</b>	17 (28)
<b>salvage</b>	8 (13)
<b>immediately inoperable</b>	9 (15)
Median dose (Gy, min-max)	50.4 (36-68)
Boost (%)	13 (22%)
Median duration (days)	39 (22-89)
Chemotherapy (%)	
Pre-operative	12 (20)
Post-operative	2 (3)
Isolated Limb Perfusion (%)	14 (24)
Surgery (%)	42 (71)
Surgical margins (%)	
R0	30 (71)
R1	11 (27)
R2	1 (2)
Surgical complications (%)	
Acute wound injury	7 (17)
Reintervention	3 (7)
Flap reconstructive surgery (%)	20 (47)
Planned	18 (43)
Unplanned	2 (4)

**Table 2: Delayed toxicity**

<b>Toxicity</b>	<b>Grade 1 (%)</b>	<b>Grade 2 (%)</b>	<b>Grade 3 (%)</b>	<b>Grade 4 (%)</b>
Oedema	16 (27)	1 (2)	0	0
Fracture	0	0	0	0
Mobility limitation	19 (32)	2 (3)	0	0
Neurologic disorder	10 (17)	2 (3)	0	0
Gait disorder	12 (20)	0	0	0
Chronic pain	14 (24)	5 (8)	2 (3)	0
Vascular complication	1 (2)	0	1 (2)	0
Chronic wound requiring skin graft	0	0	2 (3)	0

**Table 3: Radiation therapy/dosimetric parameter and correlation with the toxicity composite score**

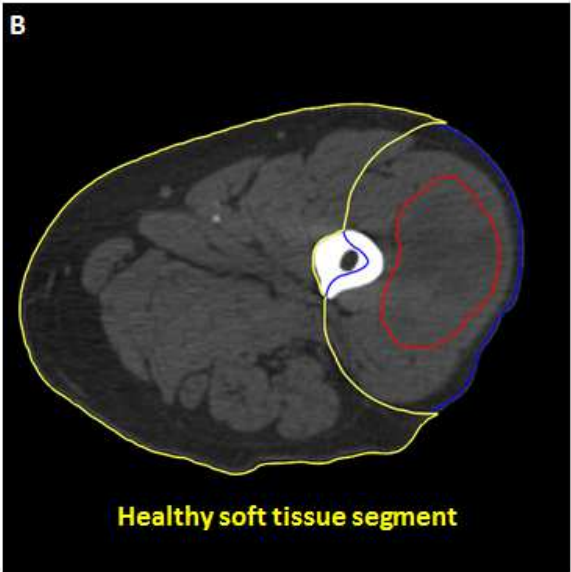
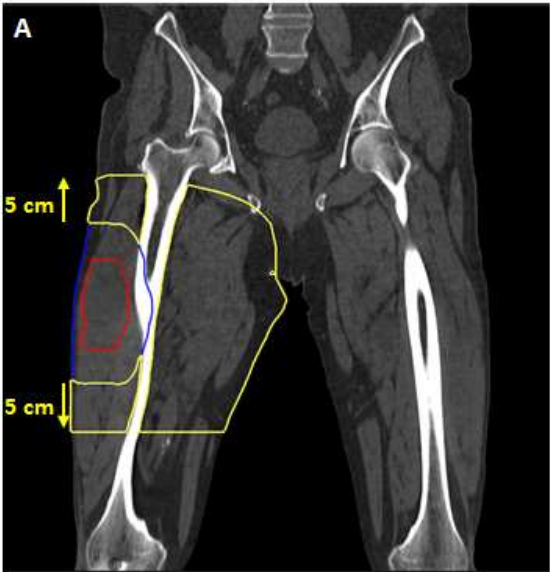
Parameter	Median (min-max)	p-value	Spearman correlation
<b>Total dose (Gy)</b>	50.4 (36-68)*	0.7	-
<b>Boost (yes vs no)</b>	13 vs 46	0.5	NA
<b>Timing (preop vs postop vs exclusive)</b>	18 vs 24 vs 17	0.6	NA
<b>PTV volume (cm<sup>3</sup>)</b>	915 (87-6094)*	0.34	-
<b>Healthy soft tissue segment</b>			
<b>Volume (cm<sup>3</sup>)</b>	3911 (388-14564)*	0.046	Rho: -0.29
<b>Mean dose (Gy)</b>	18.62 (5.3-42.5)*	0.99	-
<b>V<sub>5Gy</sub> (cm<sup>3</sup>)</b>	2807 (186-10974)*	0.31	-
<b>V<sub>10Gy</sub> (cm<sup>3</sup>)</b>	2393 (169-9358)*	0.31	-
<b>V<sub>15Gy</sub> (cm<sup>3</sup>)</b>	2054 (138-7878)*	0.34	-
<b>V<sub>20Gy</sub> (cm<sup>3</sup>)</b>	1722 (98-6830)*	0.34	-
<b>V<sub>25Gy</sub> (cm<sup>3</sup>)</b>	1274 (66-5795)*	0.31	-
<b>V<sub>30Gy</sub> (cm<sup>3</sup>)</b>	865 (30-4674)*	0.32	-
<b>V<sub>5Gy</sub>/Soft tissue volume (%)</b>	77 (18-98)*	0.67	-
<b>V<sub>10Gy</sub>/Soft tissue volume (%)</b>	65 (11-95)*	0.83	-
<b>V<sub>15Gy</sub>/Soft tissue volume (%)</b>	54 (10-93)*	0.98	-
<b>V<sub>20Gy</sub>/Soft tissue volume (%)</b>	43 (9-89)*	0.80	-
<b>V<sub>25Gy</sub>/Soft tissue volume (%)</b>	29 (7-89)*	0.82	-
<b>V<sub>30Gy</sub>/Soft tissue volume (%)</b>	21 (1-79)*	0.96	-
<b>Bone</b>			
<b>Maximum dose (Gy)</b>	50.75 (11.42-61.51)*	0.26	-
<b>V<sub>40Gy</sub> (cm<sup>3</sup>)</b>	82 (3.5-367)*	0.24	-
<b>Joint</b>			
<b>Mean dose (Gy)</b>	23.87 (0-64)*	0.38	-

V<sub>xGy</sub>: volume receiving a minimum of xGy; NA: not applicable.

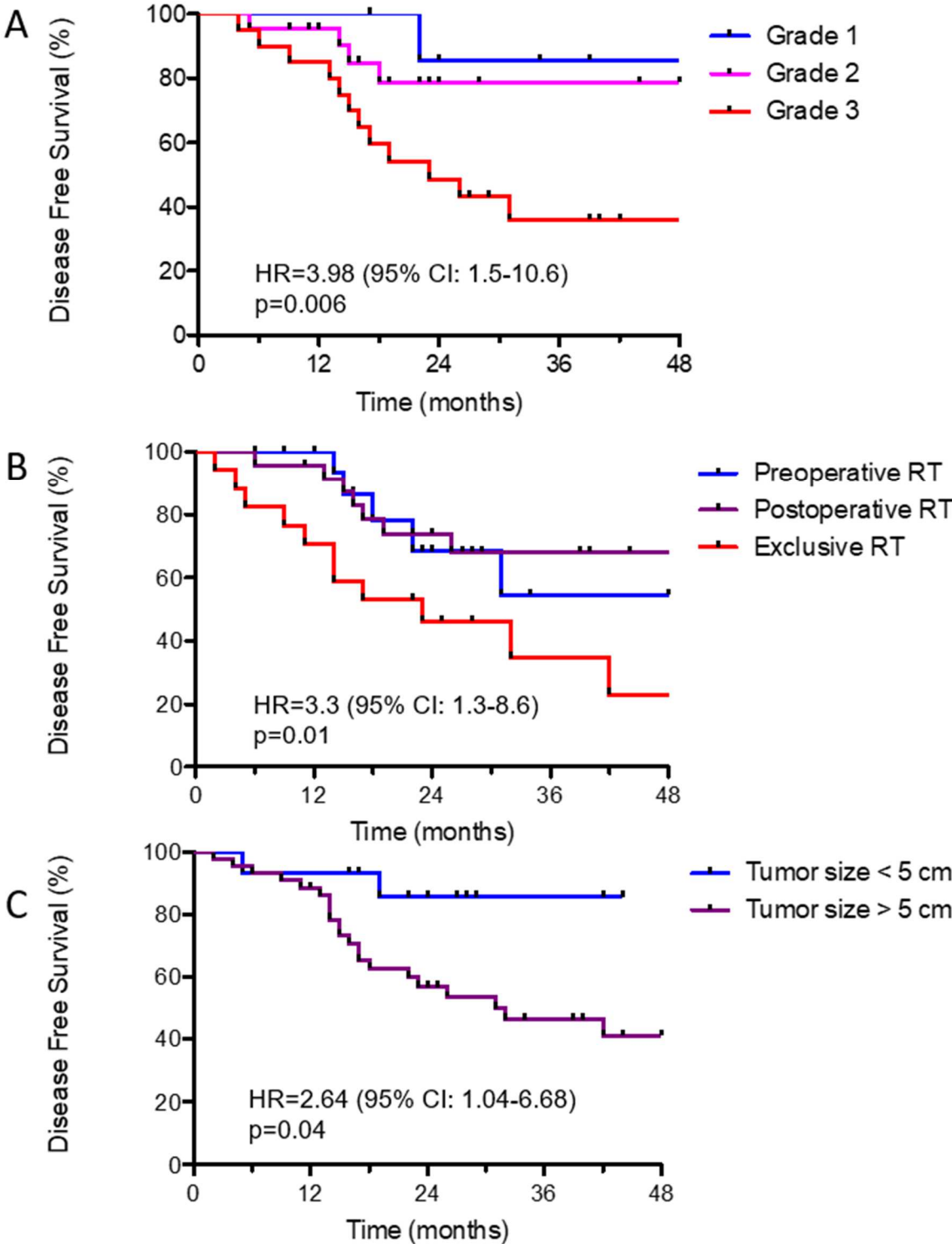
\* Spearman correlation test for continuous numerical values, the median is provided only for information.

**Figure 1: Healthy soft tissue segment definition.**

Coronal (A) and axial (B) views of a healthy soft tissue segment (yellow), created by adding 5 cm proximally and distally to the Planning Target Volume (PTV : blue) on computed tomography axial slices, the PTV and bone were then removed from the generated volume. Red : Gross Tumour Volume (GTV)



**Figure 2: Disease-free-survival depending on (A) grade, (B) timing of radiotherapy (RT) and (C) tumour size.**



**Figure 3: Local control depending on (A) grade, (B) timing of radiotherapy (RT) and (C) tumour size.**

