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

Rémi Bourdais [a,*], Samir Achkar [a], Charles Honoré [b], Matthieu Faron [b], Andrea Cavalcanti [b], Guillaume Auzac [a], Carine Ngo [c], Leila Haddag-Miliani [d], Benjamin Verret [e], Sarah Dumont [e], Eric Deutsch [a,f,g], Axel Le Cesne [e], Olivier Mir [e], Cécile Le Péchoux [a], Antonin Levy [a,f,g,*]

[a] Department of Radiation Oncology, Gustave Roussy, F-94805 Villejuif, France
[b] Department of Surgery, Gustave Roussy, F-94805 Villejuif, France
[c] Department of Pathology, Gustave Roussy, F-94805 Villejuif, France
[d] Department of Radiology, Gustave Roussy, F-94805 Villejuif, France
[e] Department of Medical Oncology, Gustave Roussy, F-94805 Villejuif, France
[f] Université Paris-Saclay, F-94270 Le Kremlin-Bicêtre, France
[g] Université Paris-Saclay, INSERM U1030, Molecular Radiotherapy, F-94805 Villejuif, France

## ARTICLE INFO

## 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$^3$) 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$^3$) to recommend for practitioners to help reduce the late toxicity risk.

* Corresponding authors at: Department of Radiation Oncology, Gustave Roussy, Université Paris-Saclay, F-94805 Villejuif, France.
  *E-mail addresses:* remi.bourdais@gustaveroussy.fr (R. Bourdais), antonin.levy@gustaveroussy.fr (A. Levy).

## 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® VERSA HD) or helical TomoTherapy® (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, postoperative 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 Fig. 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® 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 assesable for 7 patients because of insufficient material or histology for which grade
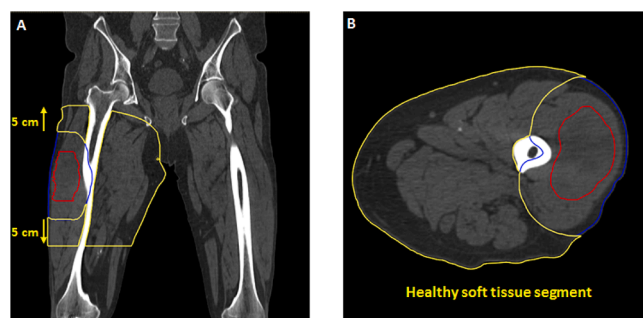


**Fig. 1. Healthy soft tissue segment definition.** Coronal (A) and axial (B) views of a healthy soft tissue segment (yellow), created by adding 5 cm proximally and distally to the Planning Target Volume (PTV: blue) on computed tomography axial slices, the PTV and bone were then removed from the generated volume. Red: Gross Tumour Volume (GTV). *(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)*

**Table 1**
**Patient and treatment characteristics**.

| Characteristics | N=59 |
|---|---|
| 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) |
| Presentation (%) | |
| Planned de novo treatment | 28 (47) |
| Initial woops surgery | 18 (31) |
| Recurrent tumour | 13 (22) |
| Radiotherapy timing (%) | |
| Preoperative | 18 (31) |
| Postoperative | 24 (41) |
| Exclusive | 17 (28) |
| Salvage | 8 (13) |
| Immediately inoperable | 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) |

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 cm3 (87–6094 cm3) and 3911 cm3 (388–14564 cm3), 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 cm$^3$ correlated with a decreased occurrence of late toxicities (p = 0.02). The median healthy soft tissue segment volume was 5207 cm$^3$ (range 388–8477 cm$^3$) in the 15 patients presenting no toxicity vs. 3440 (range 566–14564 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

**Table 2**
**Delayed toxicity**.

| Toxicity | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|
| 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 |
|---|---|---|---|
| Total dose (Gy) | 50.4 (36-68)* | 0.7 | – |
| Boost (N, yes vs no) | 13 vs 46 | 0.5 | NA |
| Timing (N, preop vs postop vs exclusive) | 18 vs 24 vs 17 | 0.6 | NA |
| PTV volume (cm$^3$) | 915 (87–6094)* | 0.34 | – |
| **Healthy soft tissue segment** | | | |
|   Volume (cm$^3$) | 3911 (388–14564)* | 0.046 | Rho: −0.29 |
|   Mean dose (Gy) | 18.62 (5.3–42.5)* | 0.99 | – |
|   $V_{5Gy}$ (cm$^3$) | 2807 (186–10974)* | 0.31 | – |
|   $V_{10Gy}$ (cm$^3$) | 2393 (169–9358)* | 0.31 | – |
|   $V_{15Gy}$ (cm$^3$) | 2054 (138–7878)* | 0.34 | – |
|   $V_{20Gy}$ (cm$^3$) | 1722 (98–6830)* | 0.34 | – |
|   $V_{25Gy}$ (cm$^3$) | 1274 (66–5795)* | 0.31 | – |
|   $V_{30Gy}$ (cm$^3$) | 865 (30–4674)* | 0.32 | – |
|   $V_{5Gy}$/Soft tissue volume (%) | 77 (18–98)* | 0.67 | – |
|   $V_{10Gy}$/Soft tissue volume (%) | 65 (11–95)* | 0.83 | – |
|   $V_{15Gy}$/Soft tissue volume (%) | 54 (10–93)* | 0.98 | – |
|   $V_{20Gy}$/Soft tissue volume (%) | 43 (9–89)* | 0.8 | – |
|   $V_{25Gy}$/Soft tissue volume (%) | 29 (7–89)* | 0.82 | – |
|   $V_{30Gy}$/Soft tissue volume (%) | 21 (1–79)* | 0.96 | – |
| **Bone** | | | |
|   Maximum dose (Gy) | 50.75 (11.42-61.51)* | 0.26 | – |
|   $V_{40Gy}$ (cm$^3$) | 82 (3.5-367)* | 0.24 | – |
| **Joint** | | | |
|   Mean dose (Gy) | 23.87 (0-64)* | 0.38 | – |

$V_{xGy}$: volume receiving a minimum of xGy; NA: not applicable.

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

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 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 (Fig. 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; Fig. 3).
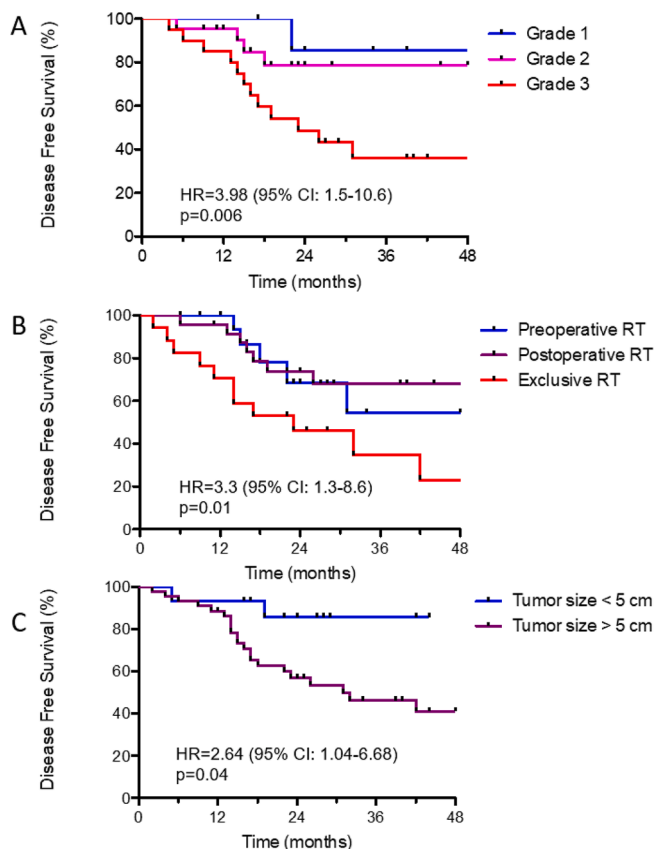


**Fig. 2. Disease-free-survival depending on (A) grade, (B) timing of radiotherapy (RT) and (C) tumour size.**

## 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 cm$^3$) was the only (including clinical, treatment and other dosimetric) variable that
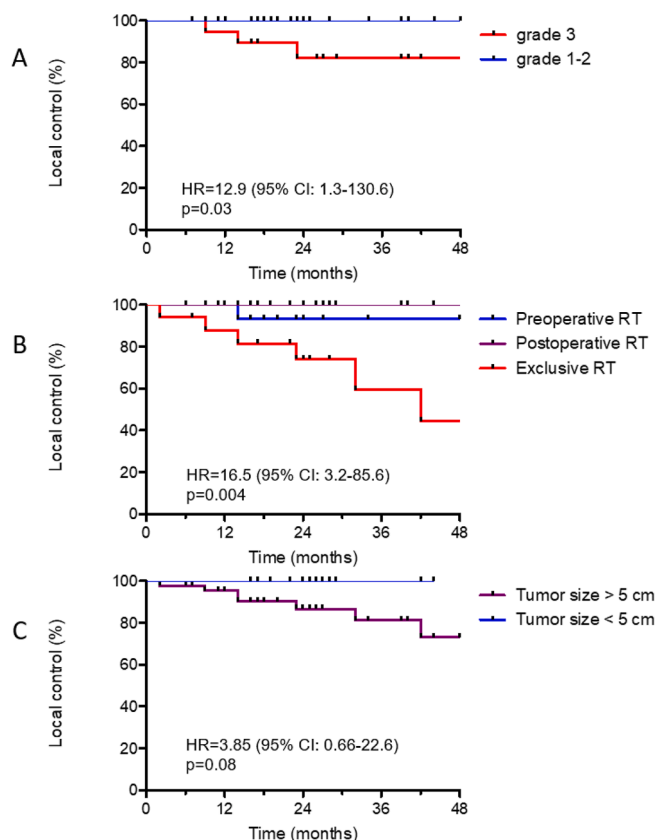
**Fig. 3.** Local control depending on (A) grade, (B) timing of radiotherapy (RT) and (C) tumour size.

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 (Fig. 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 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 cm$^3$, respectively, p = 0.2). Dosimetric constraints associated with bone fracture (V40 > 64%, mean dose to bone > 37 Gy or maximum dose > 59 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 (Figs. 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$^3$) 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 radiosensizers [17,18] and/or surrogate biologic markers of toxicity [16] could lead to mitigate treatments long-term consequences in ESTS patients.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.05.007.

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