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Long-term outcomes after definitive radiotherapy with modern techniques for unresectable soft tissue sarcoma

Benoît Allignet, Waisse Waissi, Xavier Geets, Armelle Dufresne, Mehdi Brahmi, Isabelle Ray-Coquard, Jean-Yves Blay, Amine Bouhamama, Pierre Meeus, Gualter Vaz, et al.

► To cite this version:

Benoît Allignet, Waisse Waissi, Xavier Geets, Armelle Dufresne, Mehdi Brahmi, et al.. Long-term outcomes after definitive radiotherapy with modern techniques for unresectable soft tissue sarcoma. *Radiotherapy & Oncology*, 2022, 173, pp.55-61. 10.1016/j.radonc.2022.05.020 . hal-04155355

HAL Id: hal-04155355

<https://hal.science/hal-04155355v1>

Submitted on 7 Jul 2023

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Radiotherapy and Oncology

Long-term outcomes after definitive radiotherapy with modern techniques for unresectable soft tissue sarcoma

--Manuscript Draft--

Manuscript Number:	RADONC-D-22-00227R2
Article Type:	Full length article
Section/Category:	Soft Tissue
Keywords:	intensity modulated radiotherapy; stereotactic body radiotherapy; Soft tissue sarcoma; definitive radiotherapy; systemic therapy
Corresponding Author:	Benoît ALLIGNET Centre Léon Bérard: Centre Leon Berard Lyon, FRANCE
First Author:	Benoît ALLIGNET, MD
Order of Authors:	Benoît ALLIGNET, MD Waisse WAISSI, MD, PhD Xavier GEETS, MD, PhD Armelle DUFRESNE, MD, PhD Mehdi BRAHMI, MD, MSc Isabelle RAY-COQUARD, MD, PhD Jean-Yves BLAY, MD, PhD Amine BOUHAMAMA, MD, MSc Pierre MEEUS, MD Gualter VAZ, MD François GOUIN, MD, PhD Coralie MONCHARMONT, MD, MSc Marie-Pierre SUNYACH, MD
Abstract:	<p>Introduction: The use of definitive radiotherapy (dRT) in unresectable soft-tissue sarcomas (STS) is still controversial and recent data are scarce. We report clinical results of this therapeutic option.</p> <p>Methods: We retrospectively included STS patients treated between 2009 and 2020, with dRT for unresectable or with a measurable residual disease after R2 surgery. Response rate, local failure (LF), progression-free survival (PFS) and overall survival (OS) were evaluated.</p> <p>Results: 116 patients with localized/locally advanced STS were treated from 2009 to 2020, with a median age of 71 years (range 18–92). Most tumors were deep-seated (96.6%), grade 2-3 (85.1%), located in the trunk or extremities (74.2%). Helical tomotherapy, volumetric modulated arc therapy, or stereotactic radiotherapy was performed in 39.7%, 19% and 8.6% of patients, respectively. The median equivalent dose in 2 Gy fractions (EQD2) was 60 Gy (IQR 52-65). At first follow-up, 66 (58.9%) and 25 (22%) patients had stable disease and partial response. After a median follow-up of 54.8 months (IQR 40.3-95.4), 3-year LF, PFS and OS were 43.2%, 16.6% and 34%, respectively. Median OS was 21.4 months (95%CI 14-26). The multivariate analysis identified grade 3 and AJCC T3-T4 stage to be associated with both shorter PFS and OS (all $p < 0.001$). Macroscopically incomplete resection and EQD2 ≥ 64Gy were associated with better OS ($p = 0.016$ and $p = 0.007$). Acute and late severe adverse events occurred in 24 (19.7%) and 5 (4.3%) patients.</p> <p>Conclusion: In unresectable STS patients, definitive modern radiotherapy is a safe and effective treatment yielding long term control in selected patients.</p>

HIGHLIGHTS:

- Definitive radiotherapy in unresectable soft tissue sarcoma is controversial.
- Available data are scarce, especially for intensity-modulated radiotherapy.
- One of five patients presented partial response.
- Cumulative incidence of local failures was <50% at five years.
- A third of patients were alive at three years.

Long-term outcomes after definitive radiotherapy with modern techniques for unresectable soft tissue sarcoma

ABSTRACT

Introduction: The use of definitive radiotherapy (dRT) in unresectable soft-tissue sarcomas (STS) is still controversial and recent data are scarce. We report clinical results of this therapeutic option.

Methods: We retrospectively included STS patients treated between 2009 and 2020, with dRT for unresectable or with a measurable residual disease after R2 surgery. Response rate, local failure (LF), progression-free survival (PFS) and overall survival (OS) were evaluated.

Results: 116 patients with localized/locally advanced STS were treated from 2009 to 2020, with a median age of 71 years (range 18–92). Most tumors were deep-seated (96.6%), grade 2-3 (85.1%), located in the trunk or extremities (74.2%). Helical tomotherapy, volumetric modulated arc therapy, or stereotactic radiotherapy was performed in 39.7%, 19% and 8.6% of patients, respectively. The median equivalent dose in 2 Gy fractions (EQD2) was 60 Gy (IQR 52-65). At first follow-up, 66 (58.9%) and 25 (22%) patients had stable disease and partial response. After a median follow-up of 54.8 months (IQR 40.3-95.4), 3-year LF, PFS and OS were 43.2%, 16.6% and 34%, respectively. Median OS was 21.4 months (95%CI 14-26). The multivariate analysis identified grade 3 and AJCC T3-T4 stage to be associated with both shorter PFS and OS (all $p < 0.001$). Macroscopically incomplete resection and EQD2 ≥ 64 Gy were associated with better OS ($p = 0.016$ and $p = 0.007$). Acute and late severe adverse events occurred in 24 (19.7%) and 5 (4.3%) patients.

Conclusion: In unresectable STS patients, definitive modern radiotherapy is a safe and effective treatment yielding long term control in selected patients.

Keywords: intensity modulated radiotherapy; stereotactic body radiotherapy; soft tissue sarcoma; definitive radiotherapy; systemic therapy

Introduction

Soft tissue sarcomas (STS) are rare and heterogeneous and account for only 1% of newly diagnosed adult malignancies [1]. Standard treatment for localized STS is surgery while metastatic disease is treated with systemic therapies. The major challenges of STS are their propensity to spread widely and their possible proximity to critical organs. Complete resection cannot be achieved in 15 to 55% of STS, thus leaving a gross residual disease (R2 resection) [2–5]. Mutilating surgery is rarely done, given the prognosis of these patients. In addition, since 42% of sarcoma patients are diagnosed after 65 years of age, some might also be medically unfit for surgery [1].

Current standard of care of unresectable or residual STS is chemotherapy (CT) with or without radiotherapy (RT) [6]. In locally advanced and metastatic STS, the EORTC 62012 trial investigated the addition of ifosfamide to first line doxorubicin [7]. They reported higher overall response rate (ORR; $p < 0.001$) and progression-free survival (PFS; median: 7.4 vs 4.6 months, $p = 0.003$) [7]. However, the ORR remained low (26% versus 14%), and while no improvement in overall survival (OS) was reported an increase in toxicity was described, reaching 46% of febrile neutropenia. A recent publication reported only 10% partial response after neoadjuvant adriamycin-ifosfamide combination [8].

Definitive radiotherapy (dRT) could be a valuable option in these non- or oligo-metastatic situations. Although high dose is required to achieve local control (LC) [9,10] with 3 dimensional-conformal radiotherapy (3D-CRT), progress issued from technical innovations such as image-guided and intensity-modulated radiotherapy (IMRT) enables better target conformation and decreases local failures and adverse events in localized STS [11–13].

Available data are scarce and report clinical outcomes of 3D-CRT or older techniques [9,14,15]. We aimed to evaluate the efficacy and safety of modern dRT in patients with unresectable or R2 resected STS.

Methods and materials

Study population

This retrospective monocentric study included all patients who received dRT for unresectable or R2 resected STS from January 2009 to November 2020. Inclusion criteria were patients of 18 years and older, with a histologically proven STS considered unresectable or who had R2 resected with a measurable gross disease and treated by definitive external beam RT at an equivalent dose in 2 Gy fractions (EQD2; considering alpha beta ratio 4 Gy [16–18]) higher than or equal to 45 Gy. This dose was chosen to include every patient in whom we aimed for medium-term local control and planned to deliver at least 39 Gy in 3 Gy/fraction. Exclusion criteria were R2 resection without measurable residual disease, rhabdomyosarcomas, dermatofibrosarcoma protuberans, desmoid tumors, and multimetastatic diseases. We included patients with oligometastatic disease, defined as 5 or less lesions in 1 or 2 sites among soft tissue, lung, liver, and bones.

Histological diagnosis and grading according to Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)[19] were performed or reviewed by an expert pathologist member of the French Sarcoma Pathological Reference Network (RRePS).

Irradiation technique

A simulation computed tomography (CT) with 2-5 mm thick images was performed in supine position. Customized devices were used to optimize position reproducibility if necessary. Gross tumor volume (GTV) was delineated on the simulation CT or, if performed, on T1-weighted gadolinium enhanced magnetic resonance imaging fused with the simulation CT. A 0-30 mm clinical target volume (CTV) margin was added and edited to major anatomical barriers such as skin, bowels, bones, and major fascial planes. Planning target volume (PTV) margins were 5-10 mm. The prescription was done on the median dose with at least 95% of the PTV covered by 95% of the dose. In case of stereotactic body radiation therapy (SBRT), the CTV and PTV margins were 0 and 3-5 mm, respectively, and the dose was prescribed on the 80%-isodose line.

Follow-up

Patients were monitored with an MRI, or, in case of retroperitoneal sarcomas, an abdominal and pelvic CT. Follow-up also included thoracic CT and clinical examination and was

1 scheduled every 4 months for 3 years, then every 6 months for 2 years and then yearly.
2 Additional rounds of local therapy could be performed in case of limited disease progression.
3 Systemic treatment was initiated in fit patients having: 3 or more growing lesions, new lesions,
4 if additional local therapy was not safely feasible, or according to physician or patient
5 preferences.
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10 *Clinical outcomes*

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12 Clinical outcomes were ORR, local failure (LF), regional recurrence, PFS, OS, systemic
13 treatment free survival (STFS) in patients who had not previously received CT, and adverse
14 events (AE). Response rate was evaluated according to Response Evaluation Criteria in Solid
15 Tumors (RECIST) version 1.1. GTV progression and marginal recurrence were defined as any
16 clinical or radiological RECIST tumor progression, and a soft tissue recurrence less than 5cm
17 away from the GTV, respectively. To assess the usefulness of dRT in achieving local control,
18 LF included both GTV progression and marginal recurrence. Regional recurrence included
19 regional nodal recurrence and soft-tissue recurrence more than 5cm away from the GTV,
20 excluding peritoneal sarcomatosis. STFS was defined as the time from the beginning of RT to
21 the initiation of antineoplastic CT, targeted therapy, immunotherapy, or death from any cause.
22 Acute and late AE (defined as beyond three months after RT completion) were graded
23 according to National Cancer Institute Common Terminology Criteria for Adverse Events
24 (CTCAE) version 4.0.
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39 *Statistical analyses*

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41 Median follow-up was determined using the reverse Kaplan Meier method [20]. Local failure
42 was estimated using cumulative incidence curves and compared using Gray's K-sample test
43 and Fine and Gray models. Introduction of a systemic treatment, development of distant
44 metastasis, or death prior to LF were considered competing risks. PFS, OS and STFS rates were
45 estimated using the Kaplan Meier method from the first day of RT, and comparisons used log-
46 rank test.
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52 Prognostic factors were investigated in univariate and multivariate Cox model analyses.
53 Covariates with trend to statistical significance (p-value <0.15) were included in multivariate
54 analyses. To avoid multi-collinearity with the same indicators, such as CTV volume, tumor
55 size, and American Joint Committee on Cancer (AJCC) T stage, we considered the most
56 statistically significant factor. Significant multi-collinearity was denoted if variance inflation
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1 factor > 2. Two-sided p-value was considered statistically significant if < 0.05. Statistical
2 analyses were performed using R software version 3.5.3 (R Foundation for Statistical
3 Computing, Vienna, Austria).
4

5 The study protocol was reviewed and approved by the institutional ethics committee.
6 Processing of personal data was performed according to French reference methodology n°004
7 of the Informatic and Liberties National Commission (CNIL).
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10 11 **Results**

12 We included 116 STS patients treated between 2009 and 2020 with dRT (details in [Table 1](#)).
13 Median age was 71 years (range 18-92). Most tumors were deep-seated (n=112, 96.6%),
14 FNCLCC grade 2 or 3 (n=91, 85.1%), and located in the trunk or the extremities (n=86, 74.2%).
15 Among the 83 patients (71.6%) with a primary presentation, 16 had R2 surgery with a median
16 pre-RT size of residual disease of 4.2 cm (IQR 2.6-6.2) after being referred in our expert center
17 and within the limits of MRI interpretation in the postoperative situation. These patients were
18 younger (mean 52 vs 69 years; p=0.008) and had smaller tumors (mean 4.5 vs 10.8 cm;
19 p<0.001) than the unresected subgroup. The 63 patients (54.3%) who received neoadjuvant CT
20 had either stable (n=39, 61.9%) or progressive (n=15, 23.8%) disease after neoadjuvant CT and
21 before the start of dRT. They did not present with higher grade tumors (p=0.6), oligometastatic
22 (p=0.09) disease or larger tumors (p=0.08). Those patients begun dRT with a median range of
23 63 days (IQR 32-91) after the last CT cycle. Non-exclusive reasons for non-surgical
24 management were unresectable tumors (n=95, 81.9%), patients unfit for surgery (n=18, 15.5%),
25 or patient's refusal for major surgery or amputation (n=11, 9.4%).
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41 Median maximal tumor diameter at diagnosis was 7 cm (IQR 4-12). Among the 106
42 patients treated in non-stereotactic conditions, 27 (25.5%) were treated using 3D-CRT, with a
43 median EQD2 and GTV volume of 55 Gy and 414cc, respectively. Otherwise, intensity-
44 modulated techniques were performed (median EQD2 and GTV volume of 60 Gy and 336cc),
45 mostly using helical tomotherapy (n=47, 40.5%). Median dose and EQD2 were 58 Gy (IQR
46 50-64 Gy) and 60 Gy (IQR 53-65 Gy), respectively. Four patients with subcutaneous tumors
47 received highly hypofractionated treatment (range 4-8 Gy per fraction).
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54 SBRT was performed in 10 patients (8.2%) with a median GTV volume of 180cc.
55 Radiation fractionations were 35 Gy delivered in 5 daily fractions (n=5), or 3 to 5 fractions of
56 6 Gy (n=3). Dose was always prescribed on the 80%-isodose line (n=10).
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1 The median follow-up was 54.8 months (IQR 40.3-95.4). While most patients had stable
2 disease (n=66, 58.9%), ORR was 22% (n=25). Thirty-one (26.7%) patients had no evidence of
3 local or distant recurrence at death or last follow-up, after a median follow up of 41.7 months
4 (range 2.2-131.6). Among the 85 relapses, 23 (27.1%) were local-only, 2 (2.4%) regional-only,
5 28 (24.1%) distant-only, and 32 (27.6%) had both distant and locoregional relapses. Regional
6 recurrences were nodal (n=1) or in the same limb but more than 5 cm away from GTV (n=2).
7 Most of local failures were primary GTV progression (n=50, 92.6%) whereas 4 (7.4%) were
8 marginal. Median time to LF was 7.2 months (range 1-56) in the 50 patients with GTV
9 progression. The 3-year and 5-year cumulative incidence of LF were 43.2% and 46.5%,
10 respectively (Fig.1). Three-year LF in limb, trunk, and retroperitoneal STS patients was 36.3%,
11 47.3%, and 43.5%, respectively. Fifty two of the 57 local recurrences (91.2%) occurred within
12 2 years after RT. EQD2 \geq 64 Gy and neoadjuvant CT were not significantly related to LF
13 (p=0.45 and p=0.83) (Table 2).
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23 Median PFS and OS were 8.4 (95%CI 6.5-13.9) and 21.4 months (95%CI 14-28.1), with
24 a 3-year rates of 16.6% and 34%, respectively (Fig.2). Ten patients were alive 5 years after dRT
25 (grade 2-3 liposarcomas, n=3; myxoid liposarcomas, n=2; low-grade fibromyxoid sarcomas,
26 n=2; malignant peripheral nerve sheath tumors, n=1; undifferentiated pleomorphic sarcomas,
27 n=1; malignant solitary fibrous tumors, n=1) yielding a 5-year OS of 18%. Median OS in
28 patients with unresected primary, R2 resected primary and unresected recurrent tumor was 18.3
29 (95%CI 13.5-28.1), 34.5 (95%CI 13.0-Not reached) and 16.9 (95%CI 13.0-43.4) months,
30 respectively (Fig.3). In univariate and multivariate analyses, FNCLCC grade 3 and T3-T4
31 stages were associated with shorter PFS and OS (all p<0.001), while R2 resection and EQD2 \geq
32 64Gy were correlated with better OS (p=0.016 and p=0.007, respectively) (Table 2 and Table
33 3). In univariate analysis, other parameters significantly associated with both shorter PFS and
34 OS were low Karnofsky index and GTV size \geq 200 cc. Neoadjuvant CT and the presence of
35 oligometastases were not significantly correlated with PFS (p=0.28 and p=0.85, respectively)
36 nor OS (p=0.92 and p=0.92, respectively) (Kaplan-Meier curves in Appendix).
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49 Among the 61 (52.6%) patients who had subsequent treatments, 17 (27.9%) had first
50 received at least one local therapy for locally progressive or oligorecurrent disease [surgery
51 (n=7); RT (n=6); interventional radiology (n=4)]. At first progression, the other 44 patients
52 (72.1%) received systemic treatments. In patients who had not received prior CT, median STFS
53 was 14.0 months (95%CI 11-25.3), with a 3-year rate of 31.3% (see in Appendix). This result
54 was not significantly different in patients who have received neoadjuvant treatment [median
55 9.8 months (95%CI 7.3-20.2), p=0.25]. Overall, 38 patients (32.8%) never received systemic
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1 treatment in their clinical course. No clear data was available to record which were too unfit
2 and therefore never eligible for CT. One of the 11 patients who refused major surgery recurred
3 locally and underwent amputation.
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5 Acute grade 3 AE occurred in 24 (19.7%) patients and were mostly radiation dermatitis
6 (n=13, 11.1%) and pain (n=8, 6.8%) (see in Appendix). No complication required amputation.
7 One patient presented grade 3 femoral fracture 15 months after the end of RT. Four (3.4%)
8 patients presented late grade 3 pain possibly related to RT, whereas no late grade 3 edema,
9 fibrosis nor neuropathy was reported. One death was considered as possibly related to RT. One
10 quadriplegic patient after a previous trauma died because of an infection of a sacral tumoral and
11 perineal pressure ulcer one month after treatment was completed.
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19 **Discussion**

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23 Surgery is the mainstay of STS. However, in 15 to 55% of patients with a localized disease,
24 the tumor is considered unresectable because of its critical location, or because of the patient's
25 inoperability due to a poor health status [2–5]. In these situations, local control is of main
26 concern to prevent local complications such as pain and bleeding to preserve the patient's
27 quality of life (QoL). We here report a promising ORR of 22% with an acceptable rate of local
28 AE. In contrary, first line CT reported an ORR of 10% and a 13 to 46% febrile neutropenia [7].
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34 With median PFS and OS of 8.4 and 21.4 months, our results are promising and consistent
35 with the literature. Furthermore, we highlight that dRT achieves a 5-year OS of 18%. A median
36 PFS of 5.4-7.3 months was reported in non-metastatic locally-advanced STS treated with CT
37 [21]. After first-line anthracycline-based treatment, median OS was found between 12.8 and 19
38 months [7,21,22] but more than 80% of patients of those series had a metastatic disease.
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66 Our study is the first, to our knowledge, to report a survival benefit in patients who
67 underwent macroscopic incomplete resection compared to unresected ones. Nevertheless, few
68 patients were in this subgroup (n=16), and they presented with younger age. Furthermore, rather
69 than planned cytoreductions, R2 resections are mostly a failed attempt at the complete excision
70 of an initially curable tumor. Previous studies did not evaluate the prognostic value of this
71 parameter [9,24,25]. A recent publication reported that the risks of relapse and death are
72 reduced when surgery is performed in a reference center [23]. With these results, sarcoma
73 multidisciplinary team might discuss debulking surgery in fit unresectable patients, but further
74 prospective and matched comparisons should be performed.
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1 Although dRT may appear as a relevant option in locally advanced STS, recent available
2 data remain scarce. Previous studies reported a 5-year LC of 29-45% [9,15,26,27] and 5-year
3 OS of 25-35% [9,27–29] using photon therapy. With a 5-year LF of 46.5%, our results are quite
4 higher than the previous studies. This may be partly due to our definition of LF. Indeed,
5 previous estimation may have underestimated LC in the presence of competing risks such as
6 metastatic progression or death [30]. On the other hand, our results showed an OS in the low
7 range of previously published results. Age was shown as an important prognostic factor
8 significantly related to OS in STS [31,32]. With a median age of 71 years, our study population
9 contrasts with previous studies having reported younger population aging between 40 and 65
10 years [9,27,33].

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18 Sarcoma radioresistance is an important issue, as we report that GTV progression
19 represented 92.6% of LF. We thus recommend not to use GTV-to-CTV margin in non-resected
20 tumors. Approaches to overcome that radioresistance should be evaluated.

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23 A dose higher than or equal to 64 Gy has been reported to be significantly associated with
24 a better prognosis in patients with positive resection margins [10], unresectable STS [9], and
25 in unresectable bone or soft-tissue sarcoma treated with definitive carbon-ion therapy [34].
26 Escalating dose above 70.4 GyE with carbon-ions did not improve LC nor survival [24].
27 Moreover, severe AE significantly increased from 2-8% to 26-28% when the delivered dose
28 exceeded 68-70 Gy [9,15]. The radiation dose was not significantly associated with LF or PFS
29 in our study, as previously reported with protontherapy [35]. One explanation may be related
30 to the important heterogeneity of radiation dose/fractionation requiring a dose equivalent
31 calculation and thus selecting an alpha/bêta ratio. This unique value of 4 Gy [16,17] does not
32 take into account inter-histotypes variability [18,36]. Clinical radiobiological trials should
33 further evaluate this parameter.

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43 Deliverable irradiation dose and tumor resectability can be limited by the proximity of
44 organs at risk (OAR). Technical innovations such as image-guided, intensity-modulated and
45 stereotactic radiotherapy allow a better sparing of healthy tissue [37] while increasing the
46 delivered dose [38]. In localized STS, IMRT significantly reduced LF (HR=0.46; p=0.02),
47 acute grade ≥ 2 radiation dermatitis (48.7% vs 31.5%; p=0.002) [12] and could possibly
48 decrease femoral fracture rate [13]. Whereas previous publications reporting dRT in
49 unresectable STS mainly evaluated 3D-CRT or older techniques [9,29,39,40], most of our
50 patients received recent IMRT.

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58 Unlike photons, deposited dose of charged particles increases with depth until it reaches a
59 maximum, called the Bragg peak [41]. This physical property could be useful to protect nearby
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1 critical OAR while delivering an appropriate dose to unresectable STS. In addition, high linear
2 energy transfer particles such as carbon-ions present valuable radiobiological advantages
3 [42,43] that tend to overcome sarcoma radioresistance. Proton and carbon-ion RT achieve
4 important 5-year LC of 55% and 65-69%, respectively [24,33,35]. However, compared to
5 photon RT, particle-based therapies achieve quite similar 5-year PFS and OS of 24-36%
6 [9,10,14,24,26] and 25-52% [9,10,24,27,28,33], respectively
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10 Neoadjuvant or concurrent radio-chemotherapy could be relevant combinations to increase
11 response rate and limit possible distant micro-metastases. We did not identify the addition of
12 neoadjuvant CT as a prognosis factor, but this may result from a selection bias. In the absence
13 of randomization, appropriate balance in group characteristics cannot be guaranteed, and
14 patients receiving systemic treatment could either have a more aggressive disease or conversely,
15 be more likely to be resected after a partial response. A recent phase III trial evaluated the
16 efficacy of adding oral temozolomide to dRT in 64 STS patients but failed to show a statistical
17 improvement in ORR [44]. This therapeutic combination was previously described by Jakob et
18 al. [45]. Among 15 initially unresectable STS, 7 R0 and 2 R1 resections were finally performed
19 [45]. Other radiosensitizers showed promising results but with AE of concern. Concurrent
20 ifosfamide with dRT achieved a 5-year PFS and OS of both 34% but induced 27% and 22%
21 severe acute hematological and skin complications, respectively [29]. In contrast, in
22 preoperative situations, pazopanib [46] and intratumoral Hafnium oxide nanoparticles [47]
23 achieved promising pathological complete responses with low wound complication rates.
24 Ongoing phase I-II trials are investigating trabectedin (TRASTS; NCT02275286) and olaparib
25 (RADIOSARP; NCT02787642) while a multicenter phase I trial recently reported a median
26 PFS of 6.5 months using concomitant sunitinib [48].
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42 Nowadays, patient-reported outcomes (PRO) and QoL assessments are essential in the
43 oncologic treatment decisions. Innovative endpoints such as STFS [49,50] provide important
44 information in the medical and patient decision-making. Our series experienced a promising
45 median STFS of 14 months, with one third of patients not receiving any systemic treatment.
46 Nevertheless, these results can be biased as some patients may have been too unfit to ever
47 receive CT. Prospective studies would better evaluate this endpoint in more homogeneous
48 samples.
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54 The current work has some limitations. This is a cohort study and could therefore be biased
55 by known or unknown confounders. Furthermore, systemic treatment initiation may be
56 requested by the patient or result from the oncologist decision. However, this series is one of
57 the largest in this treatment population, and the first to evaluate STFS and the influence of
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macroscopic incomplete resection. Moreover, these results contribute to an increase knowledge regarding the contribution of modern radiation techniques in patients with unresectable STS.

Conclusion

In patients with unresectable STS, definitive modern radiotherapy is a safe and an effective treatment yielding long term local control with a third of patients alive at 3 years. Further investigations are necessary to identify patients and histotypes who benefit most from this treatment modality.

1 **Acknowledgements :** We are grateful to Dr Camille ROUKOZ, Sophie KING and Sophie
2
3 DARNIS for their English spell and grammar checking.
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• **Figures:**

1 **Figure 1.** Cumulative incidence of local failure after definitive radiotherapy.
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4 **Figure 2.** Overall survival after definitive radiotherapy.
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9 **Figure 3.** Overall survival according disease presentation.
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• **Appendix:**

14 **Table 4.** Grade 3 to 5 adverse events possibly related to radiation therapy
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19 **Figure 4.** Systemic treatment-free survival in patients who had no prior systemic treatment
20 before definitive radiotherapy.
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25 LMS, leiomyosarcoma; LPS, liposarcoma; MFS, myxofibrosarcoma; MLS, myxoid
26 liposarcoma; UPS, undifferentiated pleomorphic sarcoma
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28 **Figure 5.** Progression-free survival of unresectable STS according to histotype
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32 **Figure 6.** Progression-free survival after definitive radiotherapy according to use of
33 neoadjuvant systemic treatment
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Table 1. Patients and treatment characteristics

Characteristics	Patients (n=116)
Age (years)	71 (57-81)
Sex (n)	
Male	62 (53.4)
Female	54 (46.6)
Karnofsky index (%)	80 (70-100)
Age-adjusted CCI (n)	7 (5-9)
Tumor presentation (n)	
Unresected primary tumor	67 (57.8)
Primary tumor after R2 resection	16 (13.8)
Unresected recurrent tumor	33 (28.4)
AJCC T stage (n)	
T1	23 (19.8)
T2	45 (38.7)
T3	28 (24.1)
T4	20 (17.2)
Oligometastatic disease (n)	17 (14.7)
Deep-seated (n)	112 (96.6)
FNCLCC grade (n)	
Grade 1	16 (14.9)
Grade 2	46 (43)
Grade 3	45 (42.1)
Histologic subtypes (n)	
Dedifferentiated/pleomorphic liposarcoma	35 (30.2)
UPS	18 (15.5)
Leiomyosarcoma	11 (9.5)
Myxoid liposarcoma	9 (7.8)
Myxofibrosarcoma	9 (7.8)
MPNST	7 (6)
Angiosarcoma	7 (6)
Other	7 (6)
Location (n)	
Limb	43 (37.1)
Trunk	43 (37.1)
Retroperitoneum	23 (19.8)
Head and neck	7 (6)
Previous chemotherapy (n)	63 (54.3)
Size (cm)	7 (4-12)
GTV (cc)	348 (126-1232)

Characteristics	Patients (n=116)
Radiotherapy technique (n)	
Helical tomotherapy	46 (39.7)
Conventional 3D-CRT	27 (23.3)
VMAT	22 (19)
IMRT	11 (9.5)
SBRT	10 (8.6)
Radiation dose (Gy)	
Total physical dose	58 (50-64)
EQD2 $_{\alpha/\beta=4}$	60 (52-65)
Non-SBRT	
Fractionation (Gy/fr)	
- 1.8-2.0	82 (77.4)
- 2.5-3.0	20 (18.9)
- 5.0-7.0	4 (3.8)
Overall number of fraction (n)	30 (22-32)
Overall RT time (days)	43 (35-50)
SBRT	
Fractionation (Gy/fr)	
- 6	3 (30)
- 7	5 (50)
- 8	2 (20)
Overall number of fraction (n)	5 (5-5)
Overall RT time (days)	10 (9-14)

Note:

Continuous variables : median (IQR)

Categorical variables : n (%)

3D-CRT, 3-dimensional conformal radiotherapy; CCI, Charlson comorbidity index; FNCLCC, fédération nationale des centres de lutte contre le cancer; GTV, gross target volume; Gy/fr, Gray per fraction; IMRT, intensity-modulated radiotherapy; MPNST, malignant peripheral nerve sheath tumor; SBRT, stereotactic body radiotherapy; UPS, undifferentiated pleomorphic sarcoma; VMAT, volumetric modulated arc therapy

Table 2. Univariate analysis.

Variables	LF		PFS		OS		STFS*	
	HR	P-value	HR	P-value	HR	P-value	HR	P-value
Age (per year)	0.99 (0.98-1.01)	0.45	1 (0.99-1.01)	0.79	1.01 (1-1.03)	0.036	1.01 (0.99-1.03)	0.41
Karnofsky index (per 10%)	1.01 (0.85-1.19)	0.92	0.86 (0.76-0.98)	0.025	0.8 (0.7-0.92)	0.001	0.77 (0.63-0.93)	0.007
Previous or concurrent chemotherapy (yes vs no)	0.94 (0.55-1.62)	0.83	1.24 (0.84-1.85)	0.28	0.98 (0.64-1.49)	0.92	-	-
FNCLCC grade (3 vs 1-2)	1.46 (0.99-2.17)	0.058	1.97 (1.46-2.68)	<0.001	1.65 (1.21-2.25)	0.002	1.42 (0.91-2.23)	0.12
AJCC T stage (T3-4 vs T1-2)	1.28 (0.74-2.23)	0.38	1.73 (1.16-2.6)	0.008	2.44 (1.58-3.77)	<0.001	3.06 (1.59-5.87)	<0.001
GTV (\geq 200 vs $<$ 200 cc)	1.6 (0.87-2.93)	0.13	1.71 (1.1-2.66)	0.018	2.32 (1.41-3.82)	0.001	3.24 (1.51-6.95)	0.007
EQD2 (\geq 64 vs $<$ 64 Gy)	1.24 (0.71-2.16)	0.45	0.87 (0.57-1.32)	0.52	0.59 (0.37-0.93)	0.02	0.48 (0.24-0.97)	0.04
Histotype (MLS vs others)	0.83 (0.35-1.96)	0.67	0.76 (0.37-1.57)	0.45	0.6 (0.26-1.39)	0.23	4.21 (0.54-32.6)	0.17
Oligometastatic status (yes vs no)	0.93 (0.52-1.65)	0.80	1.04 (0.6-1.81)	0.85	1.03 (0.58-1.83)	0.92	0.95 (0.29-3.13)	0.93
Presentation								
Unresected 1° tumor	Ref	-	Ref	-	Ref	-	Ref	-
R2 resected 1° tumor	1.56 (0.83-2.91)	0.17	0.56 (0.29-1.06)	0.07	0.42 (0.21-0.85)	0.016	0.30 (0.04-2.01)	0.22

Variables	LF		PFS		OS		STFS*	
	HR	p-value	HR	p-value	HR	p-value	HR	p-value
Unresected recurrence	0.53 (0.25-1.11)	0.091	0.92 (0.58-1.45)	0.72	0.85 (0.53-1.37)	0.51	4.08 (1.49-11.2)	0.006

* In patients who had not received prior systemic treatment

1°, primary; AJCC, American Joint Committee on Cancer; EQD2, equivalent dose in 2 Gy fractions;

FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; GTV, gross tumor volume;

LF, local failure; MLS, myxoid liposarcoma; OS, overall survival; PFS, progression-free survival;

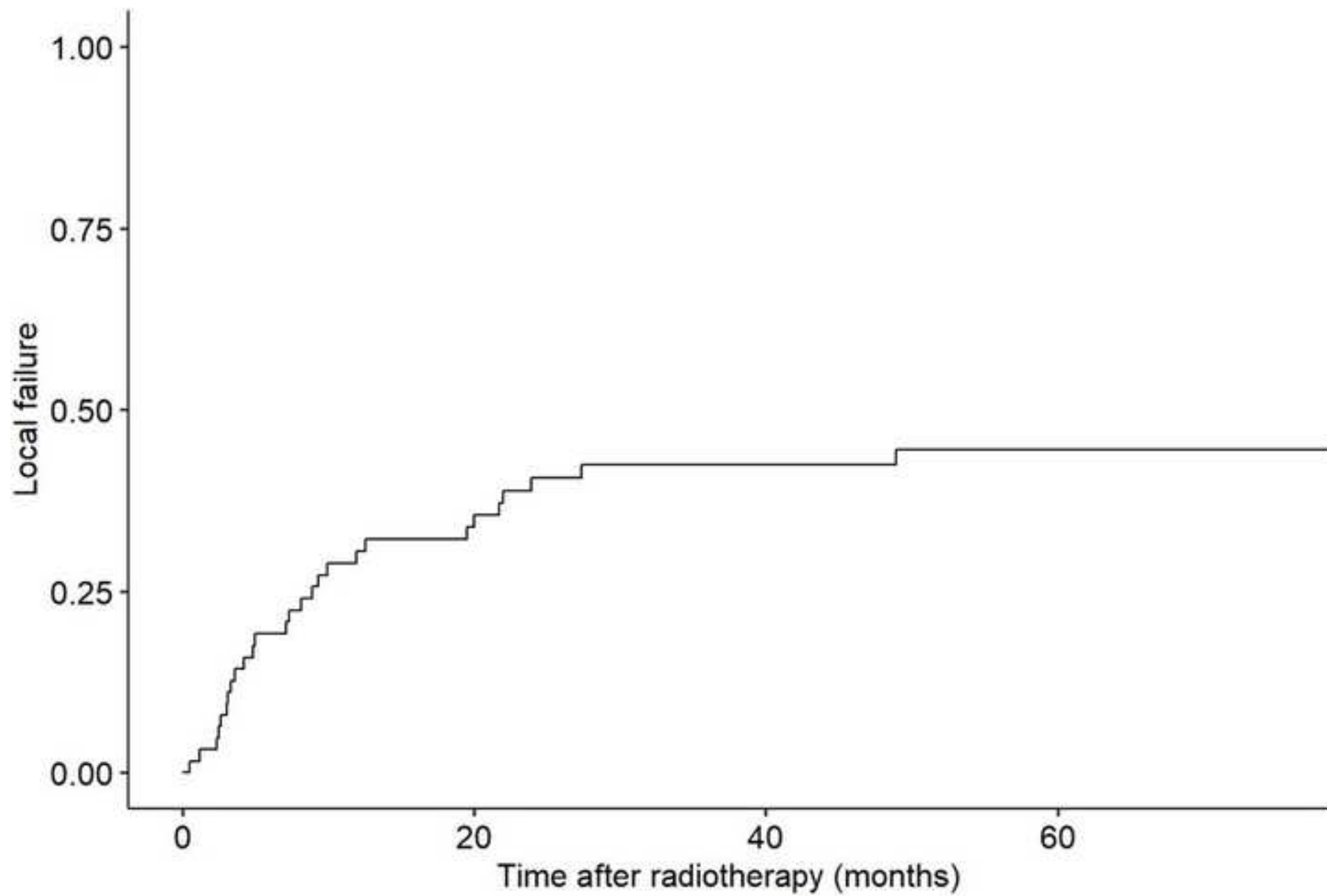
STFS, systemic treatment-free survival

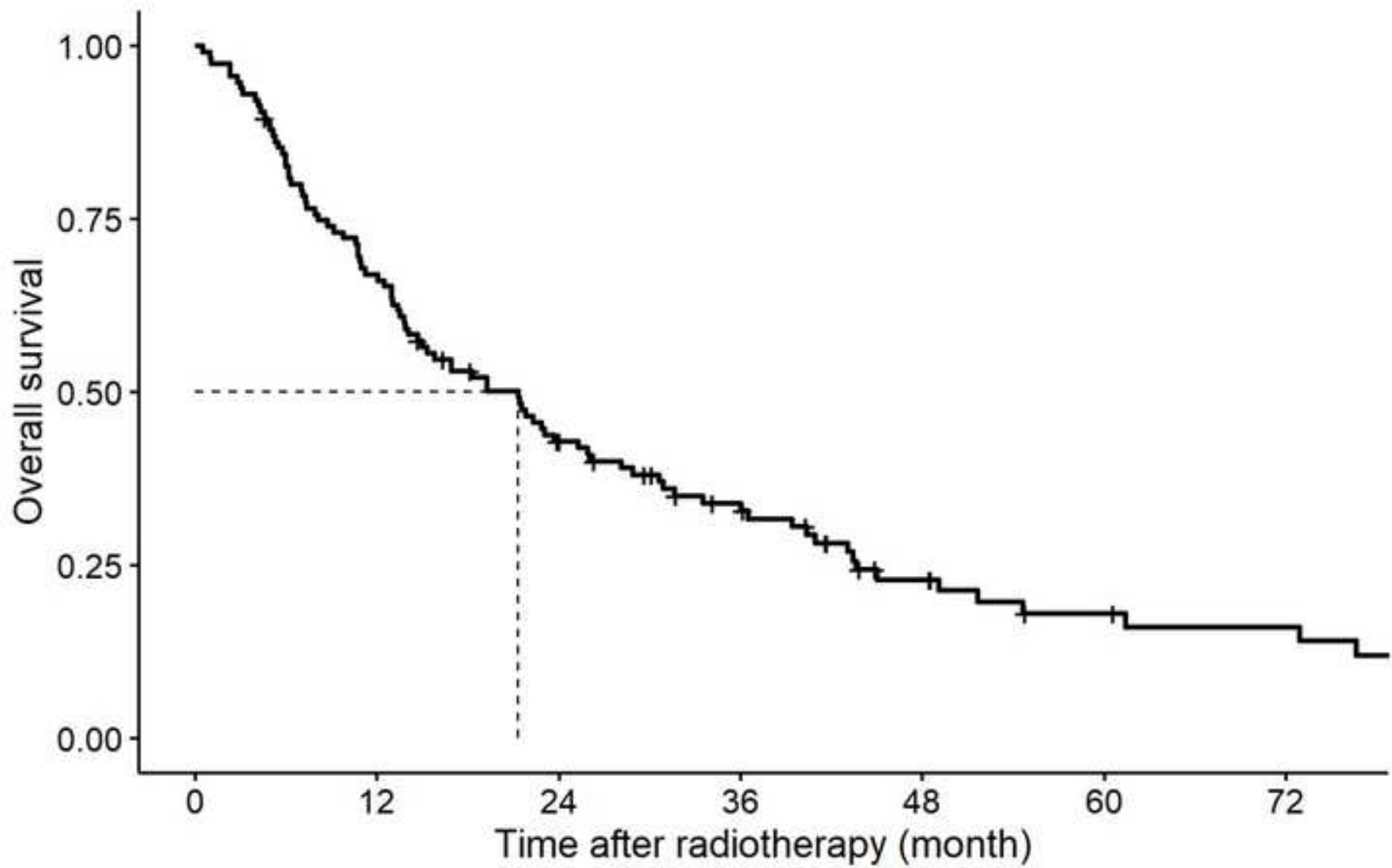
Table 3. Multivariate analysis.

Variables	PFS		OS		STFS*	
	HR	p-value	HR	p-value	HR	p-value
Age (per year)	-	-	1.01 (0.99-1.02)	0.23	-	-
Karnofsky index (per 10%)	0.93 (0.81-1.07)	0.30	0.96 (0.82-1.12)	0.75	0.88 (0.69-1.12)	0.3
FNCLCC grade (3 vs 1-2)	2.64 (1.87-3.73)	<0.001	2.47 (1.72-3.55)	<0.001	2.88 (1.54-5.4)	0.001
AJCC T stage (T3-4 vs T1-2)	2.47 (1.48-4.12)	<0.001	3.63 (2.05-6.43)	<0.001	5.11 (1.86-13.99)	0.002
EQD2 (≥ 64 vs < 64 Gy)	-	-	0.47 (0.28-0.81)	0.007	0.53 (0.20-1.41)	0.2
Presentation						
Unresected 1° tumor	-	Ref	-	Ref	-	Ref
R2 resected 1° tumor	0.61 (0.29-1.25)	0.18	0.35 (0.15-0.82)	0.016	0.47 (0.08-2.75)	0.4
Unresected recurrence	1.42 (0.82-2.44)	0.21	1.24 (0.71-2.17)	0.44	3.85 (1.41-10.48)	0.008

* In patients who had not received prior systemic treatment

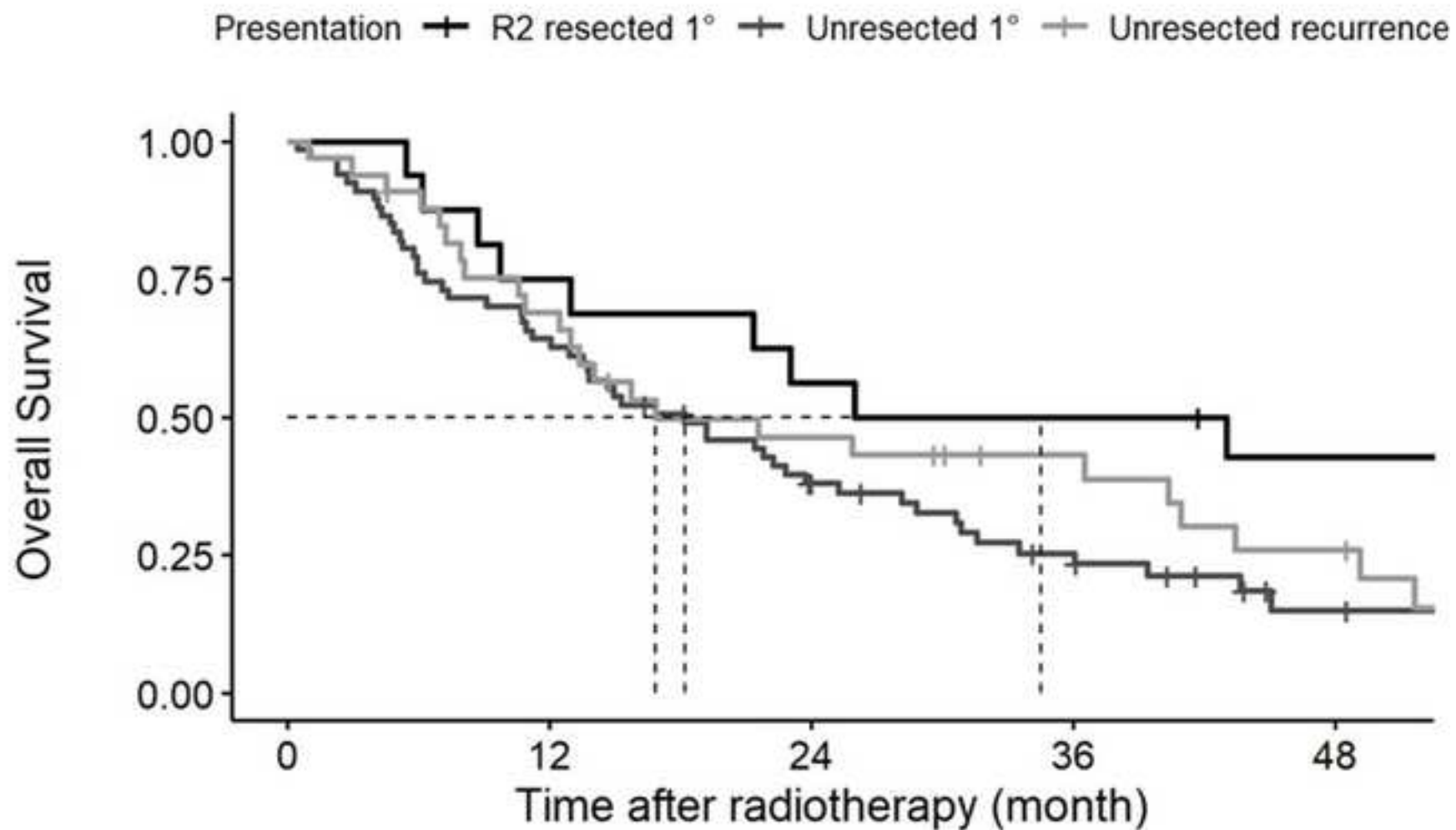
AJCC, American Joint Committee on Cancer; EQD2, equivalent dose in 2 Gy fractions; LF, local failure; OS, overall survival; PFS, progression-free survival; STFS, systemic treatment-free survival





Number at risk

All	116	77	46	31	16	10	8
	0	12	24	36	48	60	72



Number at risk

Unresected 1°	67	43	23	13	4
Unresected recurrence	33	22	14	10	6
R2 resected 1°	16	12	9	8	6
	0	12	24	36	48

Conflict of Interest Statement : The authors have no conflicts of interest to declare.

Funding Sources : None



Long-term outcomes after definitive radiotherapy with modern techniques for unresectable soft tissue sarcoma

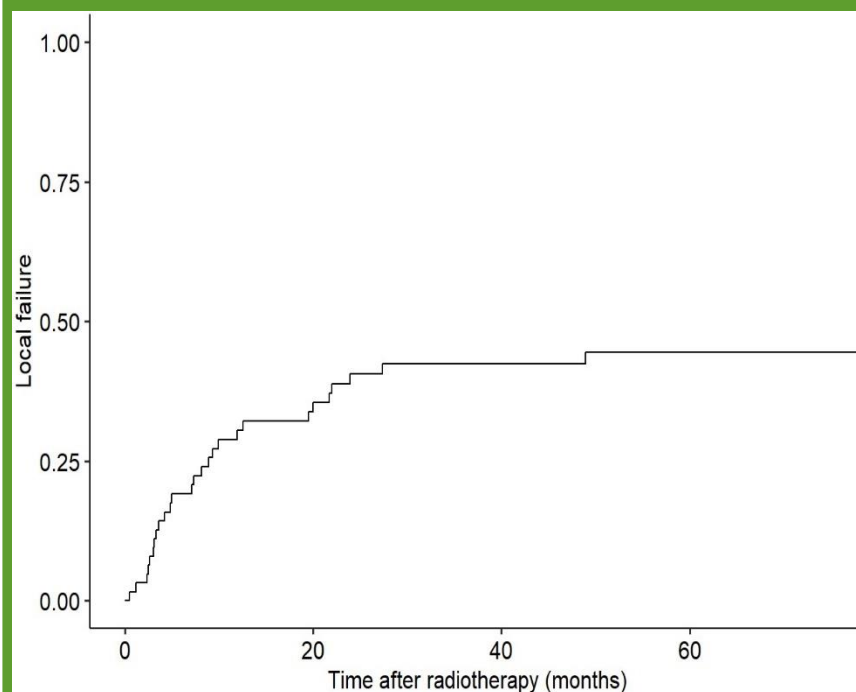


ESTRO

- Definitive radiotherapy in unresectable soft tissue sarcoma is controversial.
- Available data are scarce, especially for IMRT.

- 2009-2020
- 116 patients
- 76.7% treated with intensity-modulated techniques
- 22% partial response

Cumulative incidence of local failure is < 50% at 5 years



One third of patients were alive at 3 years

