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Original Article

Efficacy and Safety of Adjuvant Radiotherapy in Re-excised Soft-tissue Sarcoma After Unplanned Resection

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Abstract

Introduction: The objective of this study was to evaluate the efficacy and safety of adjuvant radiotherapy (aRT) in patients with soft-tissue sarcoma (STS) re-excised after unplanned tumor resection (UPR).

Materials and Methods: From 2000 to 2015, we retrospectively evaluated patients with STS of limb or trunk who underwent post-UPR re-excision in our expert center and received or not aRT.

Results: Median follow-up was 121 months (IQR 94-165). Among the 145 patients, 37 were not treated with aRT (no-RT) and 108 received aRT with a median radiation dose of 50 Gy (IQR 50-60). At 10 years, patients in the aRT and no-RT groups showed a cumulative incidence of local failure (10y-LF) of 14.7% and 37.7%, and a local recurrence-free survival (10y-LRFS) of 61.3% and 45.8%, respectively. Multivariate analysis identified aRT and age ≥70 years as independent predictors of both LF and LRFS, while grade 3 and deep-seated tumor were independent predictors of LRFS. In overall population, 10-year distant metastasis-free survival (10y-DMFS) and overall survival (10y-OS) were 63.7% and 69.4%. In multivariate analyses, age ≥70 years, grade 3, and deep-seated lesion were associated with shorter DMFS and OS. Acute severe adverse events were not significantly increased in aRT group (14.8% vs. 18.1%, $P = .85$) but dramatically increased if radiation dose exceeded 50 Gy (risk ratio 2.96 compared to ≤50 Gy, $P = .04$).

Conclusion: In STS patients re-excised after UPR, 50 Gy aRT was safe and associated with reduced LF and longer LRFS. It seems to be beneficial even in absence of residual disease or in absence of initial adverse prognostic factors.

Key words: soft-tissue sarcoma; unplanned resection; re-excision; adjuvant radiotherapy.

Implications for Practice

In soft-tissue sarcoma patients re-excised after unplanned resection, 50 Gy adjuvant radiotherapy is safe and associated with reduced local failure (LF; HR 0.23) and longer local recurrence-free survival (LRFS; HR 0.47). It seems to be beneficial even in absence of residual disease or in absence of initial adverse prognostic factors. Since a dose higher than 50 Gy tended to decrease LF but without improving LFRS and led to significantly higher rate of acute severe adverse events (23.9% vs. 8%), higher dose may be considered in patients presenting with favorable wound healing.

Introduction

Soft-tissue sarcoma (STS) are rare heterogeneous diseases with an incidence <1 per million per-year.[1] Surgical resection is the mainstay of localized STS management. Because of STS heterogeneity and complexity, prognosis may vary and was shown to be improved in patients with STS treated in expert centers.[2] Unfortunately, 20%-40% of STS patients experienced a non-oncological unplanned resection (UPR)[3-5] leading to shorter distant metastasis-free survival (DMFS; OR 0.56, $P < .001$).[6] Surgical management after UPR has long been under debate. Some authors recommended systematic re-excision[4-6] while others suggested a "wait-and-see"

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approach until detectable local recurrence.[7] Nevertheless, a recent French cohort reported longer local recurrence-free survival (LRFS) and overall survival (OS) in re-excised STS.[8]

After UPR, promising results have been reported using definitive radiotherapy (RT) or preoperative RT.[9,10] American Society for Radiation Oncology (ASTRO) recommendation is that RT be systematically performed before re-excision.[11] Nevertheless, this is based on the results of planned resected patients[12,13] and on a small retrospective study with limited follow-up that exploratory compared preoperative RT (n = 12) to adjuvant or no RT (both n = 11) after UPR.[14] Moreover, while a boost of 10-16 Gy is systematically recommended by ASTRO in post-operative situation, European and French guidelines only recommend this higher dose complement according to the risk of local recurrence.[11,15,16] Therefore, after UPR, RT is often performed in the presence of residual disease, or in case of documented initial adverse criteria identified in planned-resected sarcomas such as surgical margins, size > 5 cm, deep location, and/or high grade.[15-17] The present series aimed to evaluate the efficacy and safety of adjuvant radiation therapy (aRT) in STS patients systematically re-excised after UPR.

Patients and Methods

Study Population

Any STS patients with UPR and re-operated at the reference cancer center Léon Bérard, (Lyon, France) between January 2000 and July 2015 were eligible and data were retrospectively collected. Inclusion criteria were patient aged 18 or older; with histologically proven STS of limb or trunk; who underwent unplanned resection in non-expert center; and systematic re-excision in our reference cancer center. Exclusion criteria were second surgery consisting of an amputation; neoadjuvant or adjuvant chemotherapy to limit population heterogeneity; lipoma-like liposarcoma, desmoid tumors, and dermatofibrosarcomas protuberans due to intermediate malignancy; rhabdomyosarcomas; retroperitoneal location; and metastatic disease due to a different standard of care.

Re-excision

MRI of the surgical area and thoracic CT were required before the review of each patient case by a multidisciplinary tumor board (MTB). Re-excision with wide margins was performed by a sarcoma expert surgeon of our reference center. Pathological diagnosis and grading according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) definition[18] was performed by a pathologist of French Sarcoma Pathological Reference Network (RRePS).

Irradiation Technique

Planning computed tomography (pCT) was performed with 2-5 mm thick images in supine position with customized immobilization device if necessary. If performed, pre-operative CT or MRI was fused with pCT to evaluate tumor original location. The surgical bed was delineated based on pre-operative GTV. Clinical target volume (CTV) included the whole surgical bed, clips, drain sites, and scar.[16,17] In case of focal boost, a high-risk CTV was created by expanding the tumor bed by 15 mm axially and 20 mm longitudinally. CTV was edited to major anatomical barriers such as skin, fascial planes, and periosteum. Planning target volume (PTV) was produced expanding CTV isotropically by 7-10 mm. Planned dose was normofractionated from 50 to 66 Gy, depending on initial tumor characteristics, tumor residual disease at re-excision, and skin healing after the 2 surgeries. Indication was based on the presence of residual disease, surgical margins after re-excision, and on initial adverse criteria: size >5 cm, deep-seated lesion, grade ≥2, and high-risk histotypes such as epithelioid sarcoma. Feasibility of RT depended on patient age, performance status, comorbidities, and wound healing after re-excision.

Follow-up

To assess response and toxicity, follow-up included clinical examination, MRI of the limb or trunk, and thoracic CT every 4 months for 3 years, then every 6 months for 2 years, and then once a year.

Clinical Outcomes

Primary outcome was local recurrence-free survival (LRFS). Secondary outcomes included cumulative incidence of LF, DMFS, OS, and tolerance assessed through the rate of severe acute and late adverse events (AE). LRFS was defined from the date of re-excision to the date of any tumor recurrence in the irradiation field, or death from any cause. Cumulative incidence of LF was defined as the time from re-excision to any tumor recurrence at the primary tumor site. DMFS was defined as the time from the date of re-excision to the first documented distant metastasis or death from any cause. Severe AE was defined as grade 3 or more according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 assessed after re-excision.

Statistical Analyses

Categorical and continuous variables were reported as counts (percentages) and median (interquartile range), respectively. Cumulative incidence of LF was estimated using cumulative incidence curves and compared using Gray's K-sample test and Fine and Gray models. The occurrence of distant metastasis or death prior to LF was considered in a competing risk approach. Survival outcomes were estimated by the Kaplan-Meier method from the date of re-excision and differences were compared using the log-rank test. Median follow-up was determined using the reverse Kaplan-Meier method.[19]

Prognostic factors were explored in univariate and multivariate Cox proportional hazards model analyses and included usual known factors: age ≥70 years, myxofibrosarcoma (MFS), or undifferentiated pleomorphic sarcoma (UPS) histotypes, FNCLCC grade 3, deep-seated tumor, and size >5 cm. Covariates with trend to statistical significance (P-value < .10) were included in multivariate analyses. To prevent multi-collinearity if variance inflation factor >2 the most statistically significant factor was considered. Subgroup effects of aRT were explored by performing Cox proportional hazards model analyses, and interactions across subgroups were assessed by interaction tests. Two-sided P < .05 was considered significant. Statistical analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

The requirement for written informed consent was waived, and processing of personal data used the French reference methodology MR004. The study protocol was reviewed and approved by the Centre de Lutte Contre le Cancer Léon Bérard institutional ethics committee, number R201-004-198.

Results

Patients' and Treatment Characteristics

Between 2000 and 2015, data from 145 STS patients were collected (Table 1) and included 108 patients having received aRT and 37 patients who had not received RT. The median follow-up was 121 months (IQR 94-165). After re-excision, pathological residual disease was reported in 70 (48.3%) patients. Residual disease was more frequent in elderly patients [risk ratio (RR) 2.19; $P < .001$], MFS ($n = 17/23$, 73.9%), and UPS ($n = 17/21$, 81%) (RR 2.17; $P < .001$), in tumor with higher initial size >5 cm (RR 1.42; $P = .04$) but was not reported to be influenced by FNCLCC grade ($P = .13$) or tumor depth ($P = .24$).

Adjuvant RT was more frequently performed in limb tumors ($P = .01$) and likely to be more frequent if tumor was deep ($P = .055$) or larger ($P = .1$) (Table 1).

In aRT group, all patients received 2 Gy per fraction external beam radiation therapy, mostly using 3-dimensional conformal radiotherapy (3D-CRT; $n = 105$, 97.2%). Median radiation dose was 50 Gy (IQR 50-60), with 46 (42.6%) patients having received a dose higher than 50 Gy (Supplementary Material).

Table 1. Patients and treatment characteristics. Continuous variables are median (IQR); Categorical variables: *n* (%).

Characteristics	No adjuvant RT ($n = 37$)	Adjuvant RT ($n = 108$)	*P*-value
Age	58 (42-69)	56 (42-72)	.76
Gender			.32
Male	23 (62.2%)	57 (52.8%)	
Female	14 (37.8%)	51 (47.2%)	
Karnofsky index	100 (100-100)	100 (100-100)	.22
Body mass index	26 (24-29)	25 (23-28)	.30
Age-adjusted CCI	4 (2-4)	3 (2-5)	.67
Unplanned resection surgical margin			.94
R1	6 (16.2%)	18 (16.7%)	
R2	31 (83.8%)	90 (83.3%)	
Re-excision surgical margin			.75
R0	34 (91.9%)	93 (86.1%)	
Planned marginal excision	2 (5.4%)	9 (8.3%)	
Unplanned R1	1 (2.7%)	6 (5.6%)	
Pathological residual disease at re-excision			.28
Yes	22 (59.5%)	53 (49.1%)	
No	15 (40.5%)	55 (50.9%)	
Tumor size (cm)	6 (1-14)	7 (2-20)	.1
≤5 cm	23 (62.2%)	54 (50%)	
>5 cm	14 (37.8%)	54 (50%)	
Tumor depth			.055
Superficial	20 (54.1%)	39 (36.1%)	
Deep	17 (45.9%)	69 (63.9%)	
Grade			.23
Grade 1	9 (24.1%)	15 (13.9%)	
Grade 2	18 (48.6%)	51 (47.2%)	
Grade 3	10 (27%)	42 (38.2%)	
Histotypes			.45
Myxoid liposarcoma	4 (10.8%)	19 (17.6%)	
Myxofibrosarcoma	4 (10.8%)	19 (17.6%)	
UPS	4 (10.8%)	17 (15.7%)	
Synovial sarcoma	4 (10.8%)	10 (9.3%)	
Leiomyosarcoma	4 (10.8%)	7 (6.5%)	
Dedifferentiated or pleomorphic liposarcoma	4 (10.8%)	6 (5.6%)	
Other	13 (35.1%)	30 (27.8%)	
Location			.01
Limb	27 (73%)	97 (89.8%)	
Trunk	10 (27%)	11 (10.2%)	

Abbreviations: CCI, Charlson comorbidity index; RT, radiation therapy; UPS, undifferentiated pleomorphic sarcoma.

Cumulative LF

At 10 years, LF in the global population was 21.1% (95% CI, 14.1-28.2), LF in patients treated with aRT was 14.7% (95% CI, 7.8-21.7), and LF in patients with no-RT was 37.7% (95% CI, 21-54.4) (Fig. 1). In univariate analysis, LF was significantly associated with age ≥70 years, MFS or UPS histotypes, and adjuvant RT. LF tended to be higher in presence of residual disease (P = .075, Fig. 2) and in higher tumor size >5 cm (P = .087) (Table 2). Delivering RT dose >50 Gy tended to be associated with a lower rate of LF (P = .082). In multivariate analysis, LF was significantly correlated with adjuvant RT (HR 0.23; P < .001) and age ≥70 years (HR 3.77; P = .003) (Table 2).

LRFS

At 10 years, LRFS in overall population was 57.4% (95% CI, 49.5-66.7), 61.3% (95% CI, 52.3-71.7) in patients with aRT, and 45.8% (95% CI, 31.2-67.2) in patients with no-RT (Fig. 3). The correlation between aRT and LRFS was not significantly different among subgroups, even in patients with absence of residual disease or without initial theoretical RT indication based on initial adverse prognostic criteria (size >5 cm, deep-seated lesion, or grade ≥2, but without considering positive surgical margin) (Fig. 4).

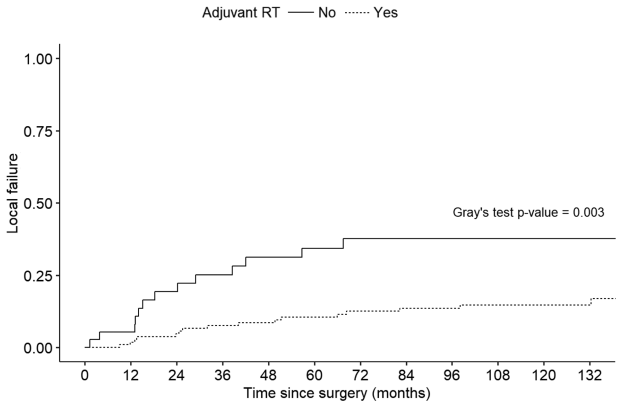

Figure 1. Cumulative incidence of local failure according to adjuvant radiation therapy. Abbreviation: RT, radiation therapy.

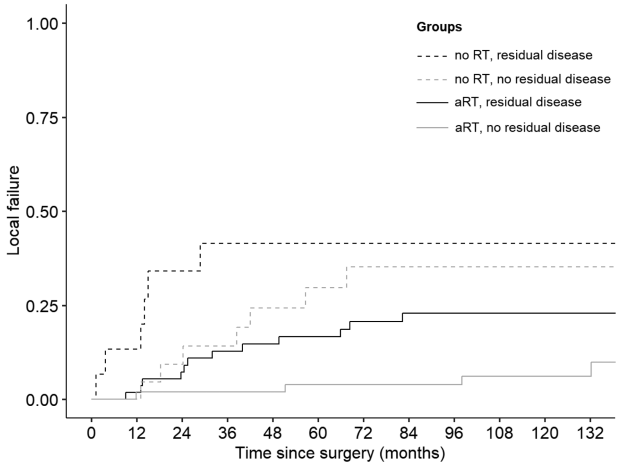

Figure 2. Cumulative incidence of local failure according to residual disease on re-excision specimen and adjuvant radiotherapy. Abbreviations: aRT, adjuvant radiotherapy; RT, radiotherapy.

In univariate analysis, LRFS was correlated with age ≥70 years, residual disease, MFS, or UPS histotypes, size >5 cm, and tended to be longer in patients having received aRT (P = .069) (Table 2). Delivering RT dose >50 Gy was not associated with longer LRFS (P = .19). In multivariate analysis, aRT (HR 0.47; P = .009), age 70 years or older (HR 2.82; P < .001), grade 3 (HR 2.31; P < .001), and tumor depth (HR 1.96; P = .02) were significantly associated with LRFS (Table 2). The presence of pathological residual disease was not an independent prognostic factor of LF or LRFS (P = .66 and .87, respectively).

DMFS and OS

In overall population, 10-year DMFS and OS were 63.7% (95% CI, 55.9-72.5) and 69.2% (95% CI, 61.5-77.8), respectively. In univariate analysis, those 2 endpoints were not related to aRT (P = .33 and P = .83, respectively). In multivariate analysis, factors significantly associated with poorer DMFS and OS were age 70 years or older (HR 2.7, P = .001 and HR 3.17, P < .001, respectively), grade 3 (HR 2.86 and 2.81, both P < .001) and deep-seated lesion (HR 1.9 and 2.07, both P = .03) (Supplementary Material).

Adverse Events

Severe acute AE was observed in 16 (14.8%) patients treated with aRT and in 6 (18.1%) patients who did not receive RT (P = .85). In the former group, non-exclusive acute grade 3 AEs were mainly radiation dermatitis (n = 9, 8.4%) and pain (n = 4, 3.7%). Acute toxicity dramatically increased when dose exceeded 50 Gy (23.9% vs. 8%; RR 2.97, P = .043). Three (2.8%) patients experienced at least one severe chronic AE in the aRT group versus none in the no-RT group (P = .72). These severe sequelae included grade 3 fibrosis, pain, and femoral fracture (n = 1), and grade 4 skin necrosis after a dose of 50 Gy (n = 1). No complication required an amputation. No death possibly related to treatment was reported.

Discussion

In patients with STS for whom a re-excision was performed in an expert cancer center after initial UPR, aRT is associated with reduced LF and better LRFS. To the best of our knowledge, our series is the first to report this association. After a median follow-up of 10 years, re-excision followed by aRT achieved promising long-term results with 10 year-LF (10y-LF) of 14.7%, and LRFS, DMFS, and OS at 10 years of 61.3%, 63%, and 69.4%, respectively. Whereas the place, timing, and dose of RT remain unclear in STS patients after UPR, our results are consistent with the scarcely available literature.[9,14,20] After RT alone, Kepka et al reported in patients not re-excised 10y-LC, distant control, and OS of 86%, 80%, and 65%, respectively.[9] In patients treated with RT before a second surgery, Jones et al reported valuable long-term disease control, with 5y-LC, RFS, and OS of 95%, 86%, and 94%, respectively.[20] Saeed et al reported longer PFS in irradiated patients after UPR.[14] They also reported longer PFS in case of preoperative RT, nevertheless they exploratory compared it to adjuvant alone (n = 5), adjuvant post-re-excision (n = 6), or no RT (n = 11) pooled together.[14] Furthermore, their median follow-up was only 2.8 years, and their sample size was limited (n = 34). The pre- or post-operative setting of RT may therefore be discussed according to the local practice of the department and the surgeons.[12,13]

Table 2. Univariate and multivariate analyses of prognostic factors for LF and LRFS.

	LF				LRFS			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	HR	*P*-value	HR	*P*-value	HR	*P*-value	HR	*P*-value
Adjuvant RT (yes vs. no)	0.33 (0.16-0.69)	.003	0.23 (0.10-0.52)	<.001	0.61 (0.35-1.04)	.069	0.47 (0.27-0.83)	.009
Age (≥70 y vs. <70 y)	4.43 (2.14-9.17)	<.001	3.77 (1.55-9.16)	.003	3.63 (2.61-6.1)	<.001	2.82 (1.57-5.08)	<.001
Histotype (MFS or UPS vs. other)	2.06 (1-4.24)	.005	2.19 (0.97-4.94)	.06	2.15 (1.29-3.58)	.003	1.59 (0.9-2.81)	.11
Residual disease (yes vs. no)	1.93 (0.92-4.08)	.075	0.82 (0.34-1.97)	.66	1.99 (1.2-3.29)	.007	1.05 (0.57-1.97)	.87
Grade (3 vs 1-2)	1.33 (0.8-2.23)	.27	—	—	2.29 (1.6-3.28)	<.001	2.31 (1.57-3.4)	<.001
Depth (Deep vs superficial)	1.15 (0.55-2.41)	.7	—	—	1.68 (0.98-2.87)	.06	1.98 (1.12-3.5)	.019
Size (≤5 cm vs. >5 cm)	0.52 (0.25-1.1)	.087	0.5 (0.22-1.11)	.09	0.46 (0.28-0.77)	.003	0.68 (0.39-1.21)	.2

Abbreviations: LF, local failure; LRFS, local recurrence-free survival; MFS, myxofibrosarcoma; RT, radiation therapy; UPS, undifferentiated pleomorphic sarcoma.

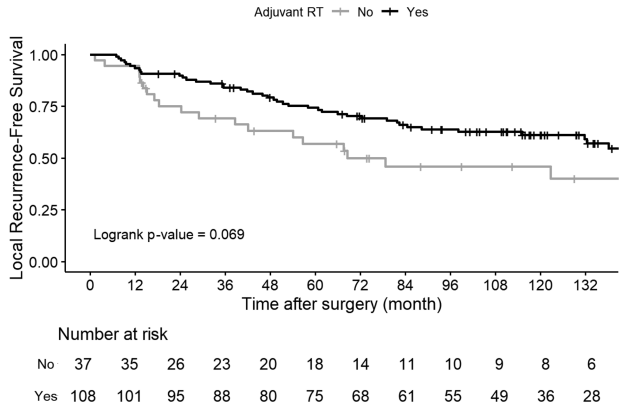

Figure 3. Local recurrence-free survival according to adjuvant radiotherapy (RT).

While surgery is the mainstay in the management of patients with STS and a major prognostic factor for OS[2] almost 20%-40% of patients still undergo inappropriate surgery.[3-5] Many authors recommend systematic re-excision after UPR,[4,5] while some other suggest a "wait-and-see" approach until detectable local recurrence.[7] Revision surgery is more challenging in the absence of target, especially in the absence of pre-UPR MRI. Nevertheless, a recent cohort report that systematic re-excision was related to longer OS, LRFS, and recurrence-free survival (all HR < 0.5, $P < .001$).[8]

Despite encouraging results in such salvage situation, a first appropriate surgery in an expert center remains the best treatment. Compared to planned resections, patients re-excised after UPR have lower distant control ($P < .001$) and tend to experience more LF (OR 1.36; $P = .1$).[6] Indeed, discussions in experienced MTB are associated with longer LRFS and RFS (HR 1.8 and 1.2, respectively; both $P < .001$).[21] Moreover, surgery in expert center is associated with longer LRFS, RFS, and OS (HR 0.65, 0.84, and 0.68, respectively; all $P < .001$).[22]

In post-UPR management, the risk of residual disease should be considered. Available data reported a risk of residual disease in 40%-70% re-excision specimens after UPR,[4,10,20] more frequently observed in MFS and dermatofibrosarcoma protuberans.[10] We report similar findings, with residual tumor in 48% of the cases, more frequently observed in MFS/UPS and in patients aged over 70 years (both HR > 2 and $P < .001$). We can hypothesize that initial surgery may be more conservative in elderly patients than in younger patients. On the other hand, the higher frequency of residual disease observed in MFS and UPS may be related to their infiltrative growth pattern along vascular or fascial plane, as observed in 25%-70% cases[23-25] and leading to R1 resections even in planned patient resections.[24,26,27] Since age >70 years and MFS/UPS are also associated with higher LF and shorter LRFS, systematic re-excision might be discussed if safe and feasible in these patients. In contrast, residual disease did not remain an independent prognostic factor, and may translate tumor aggressiveness in elderly patients or specific histotypes at higher risk of LF.[21,22]

The prognostic value of aRT after re-excision did not differ between subgroups since *P*-values for interaction were not significant. aRT benefit to re-excised STS patients whenever feasible, even in absence of residual disease or in absence of initial adverse prognostic factors. It should be noted that UPR is also a critical risk factor of LF[2,6,22] which may be sufficient to establish an indication of aRT.

In re-excised patients, aRT reported acceptable severe AE rate. Manoso et al reported 24% of wound complications and 18% of late wound healing after adjuvant therapy (CT or RT).[10] Consistently, Jones et al reported 25% peri-operative wound healing complications after preoperative RT before re-excision.[20] In our series, severe acute AEs were reported in 14.8% of the patients treated with aRT, without significant difference with the patients not receiving aRT. This lower rate should be interpreted with caution and may be related to adequate adjuvant timing of RT[23] in patients who presented favorable wound healing. The absence of additional toxicity

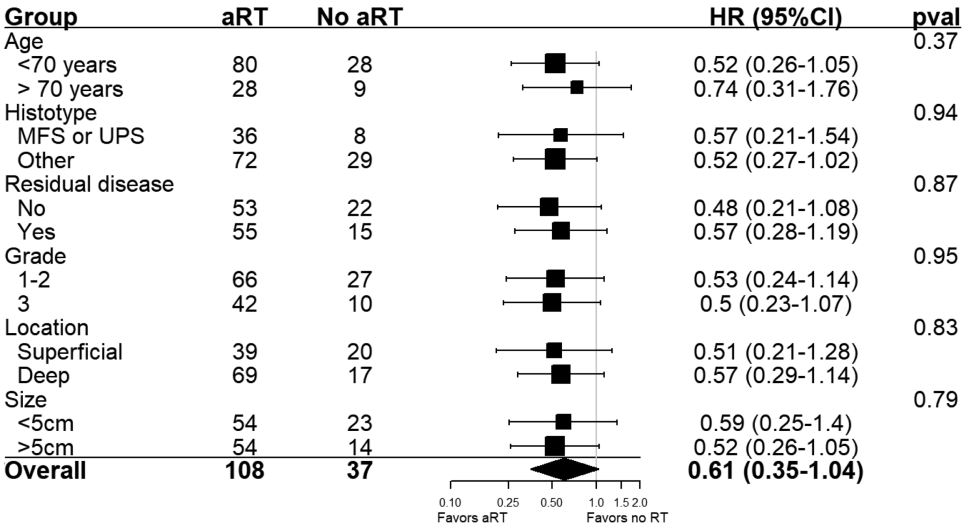

Figure 4. Subgroup analysis and local recurrence-free survival. HR, with upper CI limit below 1 favors aRT, and lower CI limit above 1 favors NoaRT (n = 145). *P*-values for interaction across subgroups. Abbreviations: aRT, adjuvant radiotherapy; MFS, myxofibrosarcoma; UPS, undifferentiated pleomorphic sarcoma.

of RT may be related to an adequate selection of patients who may benefit from this treatment without unacceptable morbidity.

In absence of second surgery after UPR, Kepka et al. reported RT doses ranging from 51 to 88 Gy, and some patients were treated twice daily,[9] whereas in pre-re-excision setting Jones et al delivered 50-50.4 Gy.[20] Saeed et al delivered doses recommended by ASTRO of 50 Gy and 60 Gy in pre- and post-operative situations, respectively.[14] The ASTRO recommends a systematic boost of 10-16 Gy when RT is performed after surgery.[11] On the other hand, European and French guidelines recommend discussing this higher dose according to the risk of local relapse, based on patient age, tumor presentation and histotype, and surgical margins.[15,16] In our series, the median normofractionated adjuvant dose was 50 Gy (IQR 50-60). Since a dose higher than 50 Gy tended to decrease LF but was not associated with improved LFRS and led to a significantly higher rate of acute severe AE (23.9% vs. 8%), higher dose may be considered in patients presenting with favorable wound healing. This novel finding may be due to technical improvements in RT planification and dose delivery.[28] Indeed, while recommendations are mainly based on studies published before 2005, our patients were performed MRI that could have improved target definition,[29] and benefited from daily image-guided radiotherapy.

The present series has some limitations, mainly related to retrospective data collection. Moreover, a selection bias is that we included only patients referred and re-excised in a reference center. Even if this series showed that aRT seems to benefit all subgroups, large CIs are reported due to limited subsample sizes. However, our median follow-up of 10 years and our sample size of 145 patients are significant. Moreover, further validation with larger prospective trials is unlikely. Indeed, the rarity of the disease and a still too heterogeneous management of STS patients preclude clinical trial development in this setting. To the best of our knowledge, these results are the first to highlight a correlation between adjuvant RT of 50 Gy, LF and LRFS in post-UPR re-excised STS patients.

Conclusion

In STS patients re-excised after UPR, adjuvant RT of 50 Gy is safe and may be associated with reduced LF and longer LRFS. It seems to be beneficial even in absence of residual disease or in absence of initial adverse prognostic factors.

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Conflict of Interest

Jean-Yves Blay received research support from Pharmamar, Bayer, GSK, Roche, and Deviphera. The other authors indicated no financial relationships.

Author Contributions

Conception/design: B.A., P.P., M.P.S. Provision of study material or patients: All authors. Collection and/or assembly of data: B.A., P.P., F.I., M.-P.S. Data analysis and interpretation: All authors. Manuscript writing and final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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