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Does adjuvant radiation therapy increase loco-regional control after optimal resection of soft-tissue sarcoma of the extremities?

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Abstract

Adjuvant radiotherapy (RT) is routinely recommended for most soft-tissue sarcomas (STS) of the extremities. However, its impact on local control is not clearly established after wide complete excision. We performed a retrospective analysis of patients who underwent wide resection in our institution (first or second resection in cases of incomplete surgery) and either did or did not receive adjuvant RT. All histological specimens of patients operated upon between 1975 and 1996 were carefully analysed and only patients with free tumour margins (ftm) were retained for the analysis. The histopathological classification was as follows: minimal resection (mR) (ftm <10 mm) and optimal resection (oR) (ftm $\geqslant 10$ mm). There were 133 patients with a median age of 44 years (range 16–88 years). The median tumour size was 6 cm (range 1–20 cm) with 28, 44 and 28% of stage I, II and III lesions, respectively. 93 patients (70%) were reoperated upon and residual tumour was found in 55% of the patients (51/93). 69 patients (17 oR and 52 mR) received adjuvant RT and 64 patients did not (54 oR and 10 mR). Other patient characteristics (age, tumour size, stage, deep-seated lesion, histoprognostic grade, adjuvant chemotherapy) were similar in both the RT and no-RT groups. Median follow-up was 10 years (3–25 years). The 5- and 10-year local relapse-free survival rates were 78 and 71%, respectively. 33 patients relapsed locally: 11 in the RT group and 22 patients in the control group ($P=0.01$). In the univariate analysis, adjuvant RT was correlated with relapse-free survival, while tumour grade and tumour margin status were correlated with overall survival. The multivariate analysis demonstrated a favourable impact of RT and negative influence of malignant fibrous histiocytoma (MFH) on local relapse-free survival; the tumour grade was correlated with overall survival. RT had a positive influence on local control exclusively in patients with mR resection ($P=0.005$) and in patients with residual tumour cells after re-excision ($P=0.001$). RT had no influence on 5- and 10-year overall survival. The 5- and 10-year overall survival for the entire population were 77 and 67%, respectively. Optimal resection seems to be the best predictive parameter for a favourable outcome in localised STS. Adjuvant RT is indicated after mR resection and for residual tumour after definitive surgery, but its role after oR resection (primary resection or no residual tumour after re-excision) should be evaluated in a prospective randomised trial.

Keywords: Soft-tissue sarcoma; Radiotherapy; Surgery; Prognostic factors

1. Introduction

Treatment strategies for soft-tissue sarcoma (STS) have gradually evolved over the past few decades. There has been a trend away from amputation towards conservative treatments because of comparable local control rates [1–4]. Limb-sparing surgery with radiation therapy is now widely accepted as standard treatment for most primary STS of the extremities and this combined modality approach is used routinely in many centres [1,5–8] and selectively in others [9,10]. As radiotherapy was found to enhance local control after resection of STS, it was often delivered after initial surgery without ascertaining the quality of the resection. Consequently, a high

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proportion of patients referred for adjuvant treatments had probably received irradiation after incomplete initial surgery (persistent macroscopic or microscopic tumour). The results of multicentric randomised trials or retrospective monocentric studies evaluating the impact of both postoperative radiotherapy and/or chemotherapy were therefore often controversial and conclusions had to be interpreted with caution.

Re-excision at the primary tumour site is a relatively new concept, developed exclusively in referral centres that manage such tumours. This strategy is supported by the high incidence of residual tumour cells found after re-resection performed in patients initially operated upon in a non-specialist centre [8,11–14] and seemed to have a favourable impact on 5-year disease-free survival in a recent retrospective study [11]. The careful histological analysis of tumour margins on the operative specimen is another relatively new concept. The prognostic value of tumour margins on the operative specimen has been suggested by a large retrospective study in patients with extremity sarcoma [15]. The probability of achieving greater tumour control after surgical resection was demonstrated to be dependent on obtaining negative tumour margins even with the adjunction of radiotherapy [5,7,15–18]. Patients with positive tumour margins are at an increased risk not only of developing a local recurrence [15,19,20], but also have a poorer survival [7,9,15,20,21]. This emphasises the need to obtain negative margins before considering adjuvant treatments.

Several studies on patients with primary STS treated with surgery alone suggested that radiotherapy could be avoided in a sub-group of patients in whom the surgical definition of wide resection is based on a very meticulous assessment of the tumour margins [22–26]. This hypothesis has recently been highlighted by a randomised trial comparing postoperative radiotherapy with surgery alone. A similar outcome was observed in both treatment arms when patients who underwent radical surgery had adequate free tumour margins (at least 10 mm around the tumour) [27]. Since both the acute and long-term side-effects of radiotherapy are not negligible [28,29], better selection of patients likely to benefit from radiotherapy is needed.

In order to better determine which patients should be considered for adjuvant treatment after wide resection and those in whom surgery alone would suffice, we retrospectively analysed histological and clinical data of patients older than 15 years with soft tissue sarcoma of the extremities.

2. Patients and methods

From 1 January 1975 to 31 December 1996, 1110 patients older than 15 years with extremity STS were referred to the Institut Gustave Roussy (IGR). To meet inclusion criteria for the final analysis, patients had to have had (1) primary and localised STS, (2) histological analysis of tumour margins on the operative specimen after definitive surgery (initial or second resection within 3 months) performed in our institution, and (3) had to have undergone a wide *en-bloc* resection according to the Enneking classification [30]. Patients who had undergone a R2 resection (macroscopic residual disease), a R1 resection (microscopic residual disease, positive margins) and patients with unknown tumour margins, with incomplete information on the margin status of the entire operative specimen, or with free tumour margins <1 mm were excluded from the analysis. In addition, patients who had received induction chemotherapy before surgery and patients with osteosarcoma, Ewing's sarcoma/primitive neuroectodermal tumour, embryonal rhabdomyosarcoma, dermatofibrosarcoma protuberans and fibromatosis were excluded from the analysis.

The operative specimen was examined in all selected cases by the pathologist who specified the histological type/subtype, histoprognostic grade, size and the status of the tumour margins. The histological type was based on the Enzinger and Weiss classification [31]. The histoprognostic grade was determined by evaluating tumour differentiation, the mitotic count and necrosis [32]. Free tumour margins (ftm) were defined as minimal if margins in one section were less than 10 mm (mR for minimal resection, 1–9 mm) or optimal if margins were $\geqslant 10$ mm all around the tumour (oR for optimal resection).

2.1. Patient characteristics

133 patients were retained for the analysis. There were 73 men and 60 women with a median age of 44 years (range 16–88 years). The median tumour size was 6 cm (range 1–20 cm). According to the TNM classification, 51 patients (38%) were classified as having stage T1 disease, 80 (60%) T2, and 2 (2%) Tx. According to the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging classification, 36 patients (27%) were classified as having stage I disease, 55 (41%) stage II, 36 (27%) stage III. The disease stage was unknown in six patients (5%). The most common histological type diagnosed was malignant fibrous histiocytoma (MFH) (40 patients) followed by synovial sarcoma (28 patients). The histological grade was 1 for 25 patients (19%), 2 for 51 patients (38%), 3 for 53 patients (40%) and unknown for 4 patients (3%). Regarding the location, 17 lesions (13%) were superficial and 116 (87%) were deep-seated tumours. Thirty-seven tumours were located in the upper extremity and 92 in the lower extremity. All patients had undergone maximal conservative surgery.

Of a total number of 133 patients, 47 (35%) were referred to the IGR with the tumour intact and 86 (65%) after an initial resection has been performed elsewhere. 93 patients were reoperated upon to obtain wider margins (all patients operated upon in another centre and 7 patients who had initially undergone surgery at the IGR) and residual tumour cells were discovered in the operative specimen in 55% of them (51/93). After definitive surgery, 71 patients (53%) were classified as oR and 62 (47%) as mR. The decision of whether to irradiate these patients was taken by a multidisciplinary committee comprising a surgeon, a pathologist, a radiation oncologist, and a medical oncologist. 69 patients (52%) received postoperative radiotherapy (RT) after surgical resection and 64 (48%) did not. Patient characteristics were equally balanced between the two treatment groups, except for the histological subtype and the tumour margin status (Tables 1 and 2). As expected, the majority of patients with residual tumour cells (36/51) and mR margins (52/62) received adjuvant RT, whereas patients with oR margins (54/71) did not. In addition, RT was delivered more frequently for synovial sarcomas than for liposarcomas (Table 2).

Table 1
Distribution of clinical characteristics by treatment arm—RT versus no-RT

	RT ($n=69$) no. (%)	No-RT ($n=64$) no. (%)
Median age (years)	42	45
Gender		
Male	38 (55)	35 (55)
Female	31 (45)	29 (45)
Median tumour size (mm) (range)	60 (10–200)	65 (10–180)
Depth		
Superficial	9 (13)	8 (13)
Deep-seated	60 (87)	56 (87)
Size (cm)		
T⩽5	29 (42)	22 (34)
T>5	40 (58)	40 (62)
AJCC/UICC stage (%)		
I	21 (30)	15 (23)
II	24 (35)	31 (48)
III	23 (33)	13 (22)
Grade (%)		
1	9 (13)	16 (25)
2	27 (39)	24 (37)
3	32 (46)	21 (33)
Resection margins		
oR (⩾10 mm)	17 (25)	54 (16)
mR (<10 mm)	52 (75)	10 (84)
Postoperative CT		
Yes	10 (14)	11 (17)
No	59 (86)	53 (83)

T, tumour; CT, chemotherapy; RT, radiotherapy; oR, optimal resection; mR, minimal resection; AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer.

Our postoperative RT technique has been previously described in Ref. [33]. Most patients (57/69) were treated by megavoltage external-beam photons, 9 with brachytherapy implants and 3 with a combination of techniques appropriate for each site. Individual immobilisation devices were used for reproducible positioning. Postoperative RT was delivered at a median dose of 50 Gy (range 36–65 Gy). The limits of initial field margins varied, but they were at least 5 cm around the tumour bed. RT was initiated as soon as the wound had healed and was delivered within 8 weeks of surgery or after the last chemotherapy cycle, if adjuvant chemotherapy had been planned. Care was taken to avoid circumferential limb irradiation.

Adjuvant chemotherapy was delivered to 21 (16%) patients (equally balanced in both groups) and consisted of the CYVADIC regimen (cyclophosphamide, vincristine, doxorubicin and dacarbazine) in 13 patients, doxorubicin plus ifosfamide in 6 patients, and doxorubicin plus dacarbazine and cyclophosphamide in 2 patients.

2.2. Statistical analysis

Patient and treatment characteristics are presented using descriptive statistics. Analysis of variance, the Chi^2 test or Fisher's exact test were used to compare patient baseline characteristics according to adjuvant treatment (RT versus no RT). The endpoints for the statistical analysis were overall survival, local recurrence and metastasis. Survival curves, the local recurrence-free interval, and the metastasis-free interval were calculated from the date of the diagnosis and were estimated using the Kaplan–Meier method (Bio Medical Data Program) [34]. For survival curves, all deaths were considered as events. For the local recurrence-free interval, only the first local recurrence was considered as an event; when patients died without a local recurrence

Table 2
Distribution of histological subtypes by treatment group

Histological subtype	RT ($n=69$) no. (%)	No-RT ($n=64$) no. (%)
MFH	22 (32)	18 (28)
Synovial sarcoma	22 (32)	6 (9)
Liposarcoma	6 (9)	17 (27)
Leiomyosarcoma	3 (4)	4 (6)
Fibrosarcoma	3 (4)	4 (6)
Unclassified	8 (12)	10 (16)
Chondrosarcoma	0 (0)	1 (2)
Malignant schwannoma	1 (1)	1 (2)
MPNST	3 (4)	1 (2)

MFH, Malignant Histio-Fibrosarcoma; MPNST, malignant peripheral nerve sheath tumour.

(21/39), they were considered as censored data at the time of their death. For the metastasis-free interval, only the first metastasis was considered as an event; when patients died without metastasis (5/39), they were considered as censored data at the time of their death. The Rothman method was used to derive 95% confidence intervals (95% CI) for overall 5- and 10-year survival rates, 5- and 10-year local recurrence rates, and 5- and 10-year metastasis rates. The log-rank test was used to compare the curves [35]. The final study date was 1 March 2000. A multivariate analysis was performed using the Cox proportional hazards method with the stepwise option (BMDP) [36].

2.3. Follow-up

Upon completion of curative therapy, patients were followed-up initially at 4-monthly intervals for 2 years, bi-annually during the next 3 years and yearly thereafter. Follow-up studies included a thorough clinical examination, a chest X-ray and/or computed tomography (CT) and more recently, magnetic resonance imaging (MRI) of the primary site. The median duration of follow-up from the date of diagnosis was 10 years (range 3–25) for all patients; it was 9 years (range 3–24) for all living patients.

3. Results

3.1. Local control

The 5- and 10-year local recurrence rates were 22% (95% CI 16–30) and 29% (95% CI 21–39), respectively, for the whole series of patients. 33 patients developed a local recurrence: 11 among the 69 irradiated patients and 22 among the 64 treated with surgery alone. The time to the first local relapse varied between 4.4 months and 163 months after the diagnosis (median of 20 months). All but 5 local recurrences (61, 81, 96, 134 and 163 months) occurred less than five years after surgery.

The results of the univariate analysis are shown in Table 3. The only factor clearly related to local control was adjuvant RT ($P=0.01$). The 5- and 10-year local recurrence rates were 31% (95% CI 21–43%) and 39% (95% CI, 26% to 54%), respectively, for no-RT patients and 14% (95% CI 7–25%) and 19% (95% CI 11–33%) for patients who received RT (Fig. 1). There was a trend towards an improved local control according to the tumour depth. The 5-year local control rates were 94 and 75% for superficial and deep-seated sarcomas, respectively ($P=0.06$). In addition, the 5-year local control rates were 64% for MFH and 83% for all other histological subtypes combined ($P=0.07$).

Other factors explored such as tumour size (<5 versus $\geqslant 5$ cm), grade, adjuvant chemotherapy, the final tumour margin status (minimal versus optimal ftm), age ($\geqslant 50$ versus <50 years), treatment period (1975–1989 versus 1990–1996) and re-excision were not statistically significant for local control.

Only significant parameters in the univariate analysis were retained for the multivariate analysis. No adjuvant RT ($P=0.008$) and the MFH histological type ($P=0.02$) were independently correlated with an increased recurrence rate. In patients with a MFH, a significant difference was observed between the two treatment groups in favour of radiation therapy ($P=0.002$). Eleven recurrences arose in 18 patients

Table 3
Univariate analysis of predictors of local recurrence (5 and 10 year recurrence free rate)

	No. of patients Total (%)		5-year (%)	10-year (%)	Log-rank *P* value
Tumour size					
T1 ($\leqslant 5$ cm)	51	(39)	84	72	0.41
T2 (>5 cm)	80	(61)	75	72	
Grade					
1	25	(19)	88	88	0.23
2	51	(39)	74	67	
3	53	(40)	75	64	
Tumour depth					
Superficial	17	(13)	94	94	0.06
Deep-seated	116	(87)	75	68	
Margin status					
mR (ftm <10 mm)	62	(47)	80	77	0.53
oR (ftm $\geqslant 10$ mm)	71	(53)	76	68	
Histological subtype					
MFH	40	(30)	64	52	0.07
Liposarcoma	23	(17)	81	70	
Synovial sarcoma	28	(21)	80	80	
Others	41	(31)	88	82	
Radiotherapy					
Yes	69	(52)	86	81	0.01
No	64)	(48)	69	61	

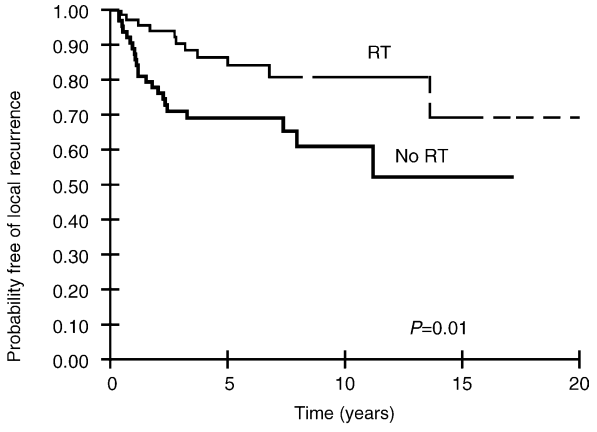

Fig. 1. Local recurrence-free survival for patients who received adjuvant radiation therapy (RT) ($n=69$) versus no radiation therapy (no RT) ($n=64$).

(61%) with this histological type who did not receive RT, whereas only 4 of the 22 patients (18%) relapsed in the RT group.

If all patients are considered, the status of final tumour margins was not a significant predictor of local control. In patients with an oR, there was no significant difference between the RT and the no-RT groups: the 10-year local recurrence rate was 35% (95% CI 48–78%) in the no-RT group and 23% (95% CI 50–92%) in the RT group ($P=0.19$). In contrast, patients with mR fared better if RT had been added: the 10-year local recurrence rate for patients treated with surgery alone and patients treated with combined surgery and RT was 53% (95% CI 25–75%) and 17% (95% CI 8–32%) respectively ($P=0.005$) (Fig. 2).

In addition, the impact of postoperative RT on local control was significant for patients with residual cells after re-excision ($P=0.001$). The 5- and 10-year local control rates were 84 and 84% in the RT group and 46 and 37% in the no-RT group (Fig. 3).

Of the 33 patients who developed a local recurrence, amputation was mandatory in 8 (24%), 3 in the RT group and 5 in the no-RT group. The others underwent conservative resection with or without irradiation (external beam RT or brachytherapy) and chemotherapy.

3.2. Metastases

For the entire population, the 5- and 10-year metastasis rates were 29% (95% CI 22–37%) and 41% (95% CI 32–52%), respectively. The median time to the development of metastases was 22 months (range 3–187 months). Metastases occurred in 37 patients within 5 years after the diagnosis and in 10 patients later on. 17 of these patients (36%) had a local relapse before (14/17) or concomitantly (3/17) with distant metastases (lung involvement in 83% of the cases).

The histoprognostic grade ($P<0.001$), tumour size ($P=0.02$) and depth ($P=0.05$) had a significant impact on the rate of metastases in the univariate analysis. The status of the tumour margins was not significant ($P=0.08$). Only grade was found to be an adverse prognostic factor ($P=0.002$) in the Cox regression. No difference in metastasis-free survival was observed between the RT and no-RT groups.

4. Survival

The 5- and 10-year overall survival rates were 77% (95% CI 69–84%) and 67% (95% CI 57–76%), respectively. The cause of death was disease-related in 34 of the 39 deceased patients. The presence of any recurrence was significantly associated with a lower overall survival rate ($P=0.008$). Among the 33 patients who developed a local recurrence, 20 had distant metastases and 18 died whereas only 27 patients out of the 100 who had no local recurrence developed metastasis and 21 of them died. The tumour grade and margin status were correlated with overall survival in the univariate analysis. High-grade histology was a significant adverse prognostic factor ($P<0.0006$). The 5- and 10-year overall survival rates were 100% and 81% (95% CI 50–95%) for patients with grade 1 tumours, 84% (95% CI 71–92%) and 76% (95% CI 59–87%) for patients with grade 2 tumours, and 58% (95% CI 44–71%) and 50% (95% CI 34–65%) for those with grade 3 tumours. Only the histoprognostic grade (grade 3 versus grades 1 and 2) was statistically significant for survival in the multivariate analysis ($P<0.01$). Patients with a grade 3 tumour had a relative risk of failure of 3.74 (CI 1.86–7.50).

The prognostic value of tumour margins did not reach significance in the multivariate analysis. However, the 5- and 10-year survival rates were 69% (95% CI 56–79%) and 63% (95% CI 49–75%) for mR margins and

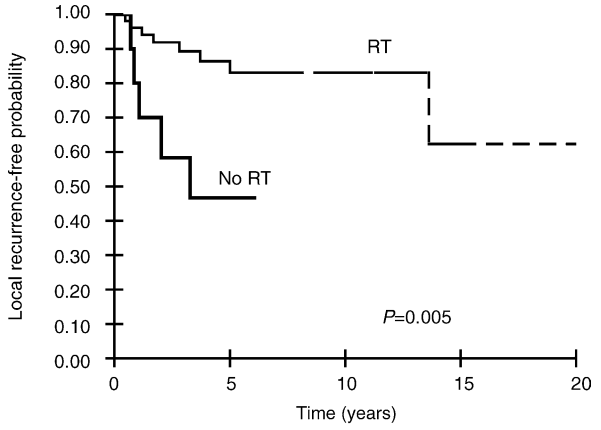

Fig. 2. Local recurrence-free survival for the 62 patients with minimal resection (mR) final margins.

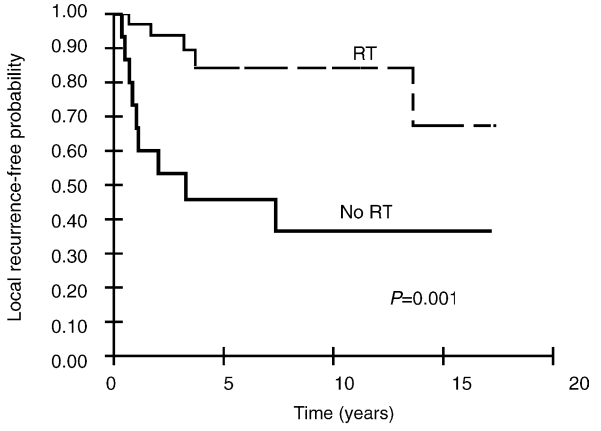

Fig. 3. Local recurrence-free survival for the 49 patients with residual tumour cells (RT, radiotherapy; No RT, no radiotherapy).

85% (95% CI 74–91%) and 72% (95% CI 58–84%) for oR margins, respectively, ($P < 0.04$). Radiation therapy had no influence on overall survival: the 5- and 10-year overall survival rates were 76 and 65% in the no-RT group, 78 and 70% in RT group, respectively ($P = 0.93$).

4.1. Long-term side-effects

Although the median dose of RT delivered was lower than that reported in other series, we observed a substantial rate of RT-related side-effects. 20 patients developed one or more long-term side-effects (29%). Most of these complications were mild or moderate. 11 patients experienced oedema, local sclerosis or moderate impairment of joint movement. Severe fibrosis and lymphoedema occurred in 4 and 1 patient, respectively. 3 patients developed soft-tissue necrosis requiring a skin flap. One patient developed a severe skin reaction during the course of external beam-radiation therapy which had to be interrupted after delivery of 36 Gy. This patient had to have a skin graft. No patients had to be amputated because of treatment-related toxicity.

5. Discussion

Optimising the management of patients with STS continues to be a challenge. In the present study, the 5- and 10-year local recurrence rates were 22 and 29%, respectively, with a median time to recurrence of 20 months. Approximately 80% of these relapses occurred during the first 2 years after the diagnosis. However, local and metastatic recurrences after 5 years accounted for 15 and 21% of cases, respectively. This is in accordance with other reports that emphasised the need for a long-term follow-up in patients with extremity STS since relapses could occur much later [8,17,40–42].

The need for multidisciplinary approaches based on the centralisation of patients with suspected or histologically-confirmed sarcoma has been overemphasised [12,22,42]. Further removal of the surrounding tissue after an unplanned total resection revealed the presence of residual disease in 35–60% of cases [8,11–14] (55% in our study), despite a normal postoperative magnetic resonance imaging (MRI) or CT scan performed in one study [14]. Conflicting results have been reported on the impact of re-excision on both local control and survival, and on the prognostic value of residual tumour cells after definitive surgery [11,12,14,43]. Although some authors [22] have emphasised the importance of referring patients before surgery, others [43] have claimed a significant benefit, in terms of local control and survival, for patients who underwent re-excision after initial surgery elsewhere compared with patients who were referred with an intact tumour or following incisional biopsy. More recently, Lewis and colleagues [11] analysed the impact of re-resection on both local control and survival in a large cohort of patients with primary extremity sarcomas operated upon at the Memorial-Sloan-Kettering Cancer Center (MSKCC). Patients who underwent re-resection after primary resection performed elsewhere had a better survival than patients who underwent a single resection in this referral centre ($P = 0.0001$). Re-resection, however, had no effect on local control as in our study. The precise mechanisms whereby re-excision impacts on survival remain unclear.

However, none of these authors investigated the effectiveness of radiotherapy on local control in this subset of patients. The presence of residual tumour cells was not a poor prognostic factor for overall and local relapse-free survival in our study, despite an unfavourable trend. The analysis of categories of patients who benefit the most from radiotherapy showed that patients with residual tumour cells after definitive surgery who had not received adjuvant radiotherapy fared worse: the 10-year local relapse-free survival after surgery alone was 37% compared with 84% with combined modality treatment ($P = 0.001$). This finding has not been previously reported and may represent a indicator of tumour biological aggressiveness, inadequate initial surgery, tumour rupture during surgical procedures and the absence of *en-bloc* resection. In contrast, postoperative radiotherapy seemed to have less of an impact in patients with no residual tumour cells after definitive surgery.

Although non-randomised trials are open to potential selection bias, our study demonstrated a better probability of local control in patients who underwent radiotherapy in both univariate ($P = 0.01$) and multivariate analyses ($P = 0.008$). These results are consistent with those reported in previous randomised studies [27,44]. Adjuvant radiotherapy therefore improved local control after complete resection of STS. The main purpose of this retrospective study was to identify subgroups of patients who require radiation therapy after careful analysis of tumour margins on the operative specimen after definitive surgery. Besides its favourable impact in the subgroup of patients with residual tumour cells which has already been mentioned, the most significant positive effect of radiotherapy was observed in all patients with minimal tumour margins (mR, ftm < 10 mm). In these patients, the 5-year local control rate was 86% in the RT group compared with 47% in the no-RT group ($P = 0.005$). In patients who had undergone an optimal initial or second resection (oR, ftm > 10 mm), adjuvant radiotherapy appeared to be effective only in cases with residual tumours cells while its impact on patients with no residual tumour cells was less clear.

In this subset of patients and using the same cut-off for tumour margins, Yang and colleagues [27] and Baldini and colleagues [23] found no recurrences in patients

who had a wide local excision. Resection margins exceeding 10 mm significantly decreased the recurrence rate in both low- and high-grade sarcomas. The authors claimed that adjuvant radiotherapy was of questionable benefit for primary sarcoma meticulously treated with limb-sparing surgery with resection margins exceeding 1 or 2 cm in all directions and, in selected anatomical areas, provided close patient follow-up was possible.

The quality of margins on the operative sarcoma specimen has been demonstrated to be correlated with local control in most studies [6,7,10,15,20,23,26,37,45–47]. During the previous decades, the tumour margin status was not rigorously defined and documented in the pathology report and decision-making concerning adjuvant therapies was based on surgical margins designated as wide, marginal or incomplete. However, this surgical definition varied according to the investigators whose comparisons of results concerning the efficacy of perioperative treatments were inconclusive and often controversial. Furthermore, most of these studies were heterogeneous in terms of tumour sites (included trunk wall [10,23] and head and neck sites [10,16,29,48]), tumour status (local relapse [15,16,48], metastatic disease [10,16,29]), surgical procedures (intralesional surgery [10,29,43,48,49], radical [10,16,43,49], amputation [10,15,43]) and perioperative chemotherapy [10,43,49]. The originality of our study is that it focused exclusively on primary sarcomas of the extremities, that were completely resected with histologically-proven free tumour margins, and a long-term follow-up. Only studies that included a homogeneous selection of sarcomas can allow homogeneous conclusions to be drawn. For instance, small STS of less than 5 cm in diameter or stage II-B STS, that are completely resected with wide margins, irrespective of the histoprognostic grade, appear to be at a low risk for recurrence and death, and adjuvant radiotherapy does not appear to decrease the risk of local recurrence [24,50]. Patients included in this retrospective analysis were treated over a period of 20 years. This is why we decided to retain both high- and low-grade sarcomas and all tumour sizes and all tumour locations (superficial versus deep-seated) for the analysis. However, the number of patients would be too small to allow a statistical analysis in subgroups of these parameters. This retrospective analysis seems to demonstrate that the quality of tumour margins may be more important than the histological grade, tumour size and tumour location for better local control in resected sarcomas of the extremities.

In order to achieve optimal margins and subsequently avoid pointless, potentially toxic loco-regional treatment, we advocate re-excision whenever possible in patients in whom surgery was not initially envisaged. This applies to patients in whom the completeness of resection was dubious and optimal free tumour margins could not be determined. Introducing MRI in the work-up and the development of modern surgical techniques (carefully planned biopsy, wide *en-bloc* resection of the entire tissue compartment harbouring the tumour avoiding rupture of the tumour pseudocapsule, systematic excision of any previous incision site, biopsy tract, or drain tract with the definitive resection and reconstructive procedures such as vascular by-pass grafts, muscle flaps, or skin grafts...) has enhanced the probability of local control. Furthermore, the remarkable advances in histopathology techniques including immunohistochemistry, cytogenetic analysis and the newly identified prognostic factors should help us obtain a more reproducible definition of tumour margins and allow us to validate the prognostic significance, if any, of detectable residual tumour cells after re-excision.

A specific histological subtype has rarely been identified as an independent risk factor in STS. In a report from the MSKCC of documented clinico-pathological prognostic factors in 1041 patients with extremity sarcomas, malignant peripheral-nerve sheath tumour was significantly correlated with an increased risk of local relapse in the multivariate analysis [15]. In contrast, liposarcoma seems to be predictive of better local control ($P = 0004$) compared with tumours of other histological subtypes [7]. In our study, MFH was more commonly associated with local recurrence and relapses were significantly associated with the absence of radiotherapy ($P = 0.002$). These findings were already reported in a study of 216 patients with primary non-metastatic MFH in which the absence of radiotherapy was the only adverse factor for recurrence-free survival in the multivariate analysis [21]. However, we cannot draw definitive conclusions concerning this issue because MFH is a heterogeneous disease whose histogenetic origin is no longer considered accurate [40,51]. There is still an great proportion of patients with poorly-differentiated histology and/or unclassified sarcoma that are categorised in the MFH subtype [52]. In addition, the retrospective selection of tumours with available and complete information on surgical margins may account for the high and low rates of MFH and leiomyosarcoma, respectively, in this series.

Identifying subgroups of patients in whom radiotherapy is beneficial and those in whom radiotherapy could be avoided is a real challenge for oncologists faced with the management of these rare tumours during the coming decades. The extent of tumour margins is decisive in the choice of the initial loco-regional treatment options. Since the indication for adjuvant radiotherapy seems to be strongly dependent on this factor, careful measurement of margins is critical. According to the results of this study, radiation therapy seems to be indicated for minimal margins at repeat excision, but its role after optimal resection requires further well-controlled studies. This retrospective analysis emphasises the need for a randomised study to

determine the efficiency of adjuvant radiotherapy in extremity sarcomas, initially resected with modern surgical techniques and based on final tumour margins (ftm $\geqslant$10 mm) or after re-excision with no residual tumour cells.

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