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Original Article

Local relapse of soft tissue sarcoma of the extremities or trunk wall operated on with wide margins without radiation therapy

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Abstract

Background: The quality of surgical margins is the most important factor affecting local control in soft tissue sarcoma (STS). Despite this, there is no universally accepted consensus on the definition of an adequate surgical margin or on which patients should be offered radiation therapy. This study focuses on local control and its prognostic factors in patients with trunk wall and extremity STS.

Methods: Adult patients with a final diagnosis of trunk wall or extremity STS referred to a single tertiary referral centre between August 1987 and December 2016 were identified from a prospective institutional database. Patients were treated according to a protocol instituted in 1987. The classification of surgical margins and indications for radiation therapy were based on anatomy and strict definition of surgical margins as metric distance to the resection border. Local treatment was defined as adequate if patients received either surgery with wide margins alone or marginal surgery combined with radiation therapy. Margins were considered wide if the tumour was excised with pathological margins greater than 2.5 cm or with an uninvolved natural anatomical barrier. After treatment, patients were followed up with local imaging and chest X-ray: 5 years for high-grade STS, 10 years for low-grade STS.

Results: A total of 812 patients were included with a median follow-up of 5.8 (range 0.5-19.5) years. Forty-four patients had a grade 1 tumour: there were no instances of recurrence in this group thus they were excluded from further analysis. Five-year local control in the 768 patients with grade 2-3 STS was 90.1 per cent in patients receiving adequate local treatment according to the protocol. Altogether, 333 patients (43.4 per cent) were treated with wide surgery alone and their 5-year local control rate was 91.1 per cent. Among patients treated with wide surgery alone, deep location was the only factor adversely associated with local relapse risk in multivariable analysis; 5-year local control was 95.3 per cent in superficial and 88.3 per cent in deep-sited sarcomas (hazards ratio 3.154 (95% c.i. 1.265 to 7.860), P = 0.014).

Conclusion: A high local control rate is achievable with surgery alone for a substantial proportion of patients with STS of the extremities or superficial trunk wall.

Introduction

Surgical resection with a negative margin is the mainstay of treatment for localized soft tissue sarcoma (STS) of the extremities and trunk wall. Consensus guidelines by the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) recommend (neo) adjuvant radiation therapy (RT) for most patient groups[1,2]. According to Pisters *et al.*[3] only selected patients with T1 primary STS should be treated with R0 resection alone. The benefit of RT has been demonstrated in two randomized prospective trials[4,5], which both showed that the local recurrence rate is reduced by RT for STS treated with limb-sparing surgery. In 1998, Yang *et al.* reported results from a study in which 141 patients with extremity STS eligible for limb-sparing surgery were randomized to receive or not to receive postoperative external beam RT[4]. RT reduced the risk of local recurrence in both high-grade and low-grade tumours. However, the risk of local recurrence was small even without RT (3/23) in patients with high-grade tumours resected with a wide (greater than 10 mm) margin or having no tumour in the re-resection specimen. In the second randomized study, 164 patients were randomized to receive or not to receive brachytherapy in addition to complete resection of STS[5]. Patients with high-grade lesions had significantly higher 5-year local control after brachytherapy (89 *versus* 66 per cent, $P =$ 0.0025), whereas brachytherapy had no impact on local control in patients with low-grade lesions ($P = 0.49$). In this study, 72 per cent of the 72 patients resected with a microscopically negative margin without brachytherapy achieved local control. Unfortunately, no further analyses on margin width were reported.

Several non-randomized studies have indicated that local control can be achieved in STS with surgery even without RT if adequate surgical margins are obtained[6,7]. Presently, however,

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there is no international consensus on what constitutes an adequate margin for STS patients treated with surgery alone[8,9]. A margin of 10 mm was proposed by Baldini *et al*.[7], whereas Bilgeri *et al*.[9] suggested 5 mm to be adequate. Narrower margins are generally accepted if the tumour has been operated on with an intact anatomical barrier (for example a fascia/pleura/periosteum). RT may affect limb function and can cause chronic or delayed side-effects[3,10]. Accurate estimation of relapse risk is important to guide treatment planning and prevent overtreatment.

A prospective treatment protocol for trunk wall and extremity STS was set up by the Sarcoma Group of Helsinki University Hospital (HUH), a tertiary referral centre, in 1987. Local treatment has remained the same since then. In contrast to most contemporary guidelines, patients with an adequate surgical margin were recommended to undergo surgery alone, without RT, irrespective of tumour depth or malignancy grade. The margin was defined as adequate if it included an intact anatomical barrier or a microscopically clear margin of 2.5 cm in muscle, soft tissue or fat[11]. A previous report of patients treated according to this protocol indicated that local control was high (86 per cent at 3 years) in 32 patients treated with surgery with marginal margins and RT, and even higher (95 per cent at 3 years) among 60 patients treated with surgery with a wide margin alone (only one patient received RT)[12].

The current study is an analysis of local control in a large patient cohort treated according to the same protocol and with longer follow-up. The main focus of this report is to investigate whether surgical treatment of STS is safe even without RT provided the margin is adequate according to the definition of the Sarcoma Group of HUH.

Methods

From a prospective institutional STS database, adult patients referred to the HUH Soft Tissue Sarcoma Group between August 1987 and December 2016 with a final diagnosis of STS were identified. Patients with dermatofibrosarcoma protuberans, haemangiopericytoma, desmoid fibromatosis and Kaposi sarcoma were excluded.

Each patient was evaluated at a weekly multidisciplinary meeting. Preoperative staging was done with MRI and/or CT and ultrasound. During the first years, plain chest X-ray was performed for patients with a low-grade tumour and CT for patients with high-grade tumours, whereas during the last 5 years, chest CT was performed for all patients. Core-needle biopsies and fine-needle aspirations were taken under ultrasound guidance and were planned to enable the biopsy track to be excised at the time of the surgery.

Surgical resection with wide margins (defined below) was the primary treatment in all cases where the tumour was operable without major sacrifice of function or vital anatomical structures. Reoperation, if feasible, was recommended after marginal or intralesional surgery. If preoperative assessments indicated that wide surgical margins were not achievable, resection combined with preoperative or postoperative RT was pursued. Amputation was recommended in cases where marginal resection was unachievable or where even marginal resection would lead to considerable loss of function due to extensive infiltration of a major nerve. Amputation was also considered if RT was not an option, that is in cases of local recurrence after RT and where wide resection would lead to considerable loss of function or tumour progression during preoperative RT. In some cases, limb-sparing surgery was performed at the cost of compromised local control at the patient's request.

After samples for molecular analysis were taken from fresh tumour tissue, the specimens were fixed in formalin. After fixation the surfaces were painted, the specimens dissected, and the narrowest margins measured from the tumour sections. Tumour size (cm) was defined as the largest diameter of the tumour in the surgical specimen reported by the original pathologist. The histological grade of the tumour was assigned according to the French system[13]. The final margins were evaluated on histological slides. The smallest margins as well as their locations were reported. In cases where the tumour was operated on without preoperative RT, surgical margins were defined according to a modified Enneking classification[14] where, in addition to findings at surgery, histological examination of the surgical specimen and margin width were taken into account. The surgical resection was defined as compartmental if an intracompartmental tumour and the whole muscle compartment were excised *en bloc* including the natural barriers of the compartment. Patients operated on with compartmental and wide margins were combined in the analyses.

The margin was defined as wide if the tumour was excised with a smallest microscopic margin of at least 2.5 cm. A smaller margin was accepted, however, if it consisted of an uninvolved anatomical barrier (for example a fascia). If the requirements for a wide margin were not fulfilled, the margin was classified as marginal (negative margin less than wide) or intralesional (microscopic tumour left). This margin was chosen according to contemporary guidelines of the Scandinavian Sarcoma Group[11]. This margin definition as the basis for the indication for RT has been kept unchanged for the 30 years since this protocol was written, as several analyses[12,15] have shown high local control. Recently, quality-of-life (QoL) analyses have shown a favourable functional outcome in lower extremity sarcoma patients treated according to this treatment protocol[16]. Preoperative RT was considered for patients where wide resections were not achievable without major sacrifice of function at the pretreatment multidisciplinary meeting. Since preoperative therapy may change the extent of the disease[17,18], surgical margins after preoperative therapy were classified into two groups irrespective of metric margin: cases with surgical margins free from tumour cells were classified as R0 and cases with positive margins as intralesional.

RT was recommended after marginal or intralesional surgery if re-operation with wide margins was not technically possible or would lead to major sacrifice of function. The outer lamina of bone structures was included in the specimen if feasible to achieve an adequate margin, and in recent years vascular reconstruction has been used to enable wide resection also when the tumour was close to major vessels. In tumours close to major nerves, marginal surgery with RT was preferred. CT-based treatment planning and individual fixation methods were used. The target volume was defined as the involved muscle compartment in the transverse direction, with a margin of at least 5 cm longitudinally. For microscopically or macroscopically positive surgical margins, a boost was delivered to a smaller target volume (10–20 Gy in 1–2 weeks). Starting from 1998, adjuvant doxorubin-ifosfamide chemotherapy was recommended for patients with a high-grade tumour fulfilling at least two of the following criteria: size greater than 8 cm (or 5 cm in synovial sarcomas), necrosis, or vascular invasion. After treatment, patients had regular follow-up with local imaging and chest X-rays for 5 years for high-grade STS and 10 years for low-grade STS.

In accordance with the treatment protocol, adequate local treatment was defined in this study as wide or compartmental surgery alone or marginal surgery combined with postoperative RT or R0 resection after preoperative RT. The study was approved by the Joint Ethics Committee of HUH (HUS/2449/2017) and by the Ministry of Health and Social Affairs (THL/1621/5.05.00/2018).

Statistical methods

The local recurrence-free rates were calculated using Kaplan–Meier analysis. Differences in local control of different subgroups were analysed using univariable and multivariable Cox regression analysis. If the univariable test of a variable showed a significant association with local recurrence, this variable was included in a stepwise multivariable analysis Cox's proportional hazards model. Patients were not censored after developing metastatic disease. The level of significance was set at $P < 0.050$. Statistical analysis was performed with the statistical software package SPSS®, version 26.0 (IBM, Armonk, New York, USA).

Results

A total of 1708 patients with a final diagnosis of STS were identified from the database. Excluding patients with a grade 1 liposarcoma/atypical lipomatous tumour (134), a tumour located outside the extremities and trunk wall (472), palliative treatment (234), angiosarcoma (76), rhabdomyosarcoma (26), Ewing/primitive neuroectodermal tumor (PNET) (43), osteosarcoma (13), and chondrosarcoma (15) left 812 patients with treatment with curative intention for analysis. One or more exclusion criteria may apply to some patients. A flow chart of patient inclusion and exclusion numbers and criteria is shown in *Fig. 1*.

Median follow-up time for surviving patients was 5.8 (range 0.5–19.5) years. Three hundred and sixty-eight patients (45.3 per cent) were operated on with wide margins and five of them received postoperative RT. A total of 314 patients (38.7 per cent) were operated on with marginal margins and 282 of them received postoperative RT. Fifty-one patients (6.3 per cent) were operated on with free margins after preoperative RT, and 79 patients (9.7 per cent) had an intralesional (only microscopic tumour left) operation (all received RT). Five-year local control was 88.2 per cent for the whole cohort; 93.2, 90.1, and 63.4 per cent for patients treated with a wide, marginal and intralesional margin respectively. Five- and 10-year local control rates were 90.2 and 89.3 per cent respectively for patients with adequate local treatment according to the protocol, and 69.2 and 66.2 per cent respectively for inadequately treated patients (99).

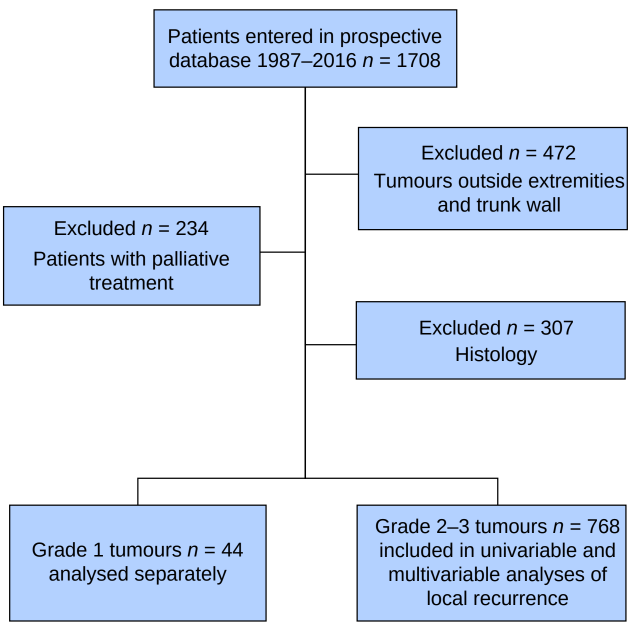


Fig. 1 Flow chart of patient selection

Grade 1 soft tissue sarcomas

Forty-four patients with a grade 1 tumour (42 patients with cutaneous leiomyosarcoma and two patients with subcutaneous myxofibrosarcoma) had a median follow-up of 5.3 (range 1.4–15.7) years. Surgical margins were marginal in 14 patients (two combined with RT) and wide in 28 patients (none received RT). None of these patients experienced local or systemic relapse. Therefore, these patients were excluded from further analyses of prognostic factors for recurrence.

Grade 2–3 soft tissue sarcomas

A total of 768 patients had grade 2–3 tumours. Patient characteristics according to surgical margins and RT are shown in *Table 1*. Three hundred and thirty-three (43.4 per cent) patients were treated with wide or compartmental surgery alone, 45.2 per cent during the first half of the interval, and 42.3 per cent during the last 15 years. A wide or compartmental margin was more often achieved in superficial tumours than in deep tumours (*Table 1*). Furthermore, patients with wide or compartmental resections had smaller tumours. One hundred and twenty patients (15.6 per cent) received adjuvant chemotherapy.

Pattern of recurrence

A total of 266 (34.6 per cent) patients with grade 2–3 tumour had recurrence. Isolated local recurrence was detected in 55 patients. Isolated systemic relapse was seen first in 178 patients and 33 patients developed simultaneous local and systemic recurrence.

Kaplan–Meier curves for local recurrence-free survival according to local treatment are shown in *Fig. 2*. The median follow-up for surviving patients was 5.8 (range 0.5–19.5) years. For clarity, patients with an intralesional margin and RT either before surgery or after surgery were grouped together as were patients with compartmental resection and with wide margins because of similar local control rates. Kaplan–Meier curves for every treatment category separately (combination of margin and RT) and 5-, 8-, and 10-year local recurrence-free survival rates in these groups are shown in *Fig. S1* and *Table S1* respectively. Radiation doses are shown in *Table S2*.

Five-, 8-, and 10-year local control rates for all patients with grade 2–3 sarcomas were 87.2, 87.1, and 86.3 per cent respectively. Local control after adequate treatment at 5 years was high (90.1 per cent) and similar in patients treated with wide surgical margins alone, patients treated with wide margins and postoperative RT, and in the combined group of patients treated with marginal margins and postoperative RT or preoperative RT and R0 resection (92.2, 100.0, and 88.3 per cent respectively) (*Fig. 2*). Local control was considerably worse after intralesional surgery and RT (63.3 per cent). The 5-year local

Table 1 Description of patient, tumour and treatment characteristics of the 768 patients with grade 2–3 soft tissue sarcoma by treatment category

Characteristics	Total	Wide margin	Marginal margin and RT	Preoperative RT and R0 resection	Microscopically positive margin and RT	Wide margin and RT	Marginal margin
Total	768	333 (43.4)	280 (36.5)	51 (6.6)	79 (10.3)	5 (0.7)	20 (2.6)
Sex							
Male	406 (52.9)	183 (55.0)	144 (51.4)	29 (56.9)	38 (48.1)	0 (0)	12 (60.0)
Female	362 (47.1)	150 (45.0)	136 (48.6)	22 (43.1)	41 (51.9)	5 (100)	8 (40.0)
Mean(s.d.) age at diagnosis (years)	59(58)	61(58)	59(58)	48(51)	63(61)	51(44)	53(53)
Site							
Lower extremity	468 (60.9)	203 (61.0)	164 (58.6)	39 (76.5)	49 (62.0)	3 (60.0)	10 (50.0)
Upper extremity	150 (19.5)	78 (23.4)	67 (23.9)	9 (17.6)	13 (16.5)	1 (20.0)	6 (30.0)
Trunk	150 (19.5)	52 (15.6)	49 (17.5)	3 (5.9)	17 (21.5)	1 (20.0)	4 (20.0)
Histology							
UPS/NOS	340 (44.3)	149 (44.7)	125 (44.6)	24 (47.1)	32 (40.5)	2 (40.0)	8 (40.0)
Liposarcoma	130 (16.9)	49 (14.7)	49 (17.5)	9 (17.6)	18 (22.8)	1 (20.0)	4 (20.0)
Leiomyosarcoma	101 (13.2)	52 (15.6)	30 (10.7)	5 (9.8)	9 (11.4)	0 (0)	5 (25.0)
Synovial sarcoma	71 (9.2)	26 (7.8)	30 (10.7)	8 (15.7)	7 (8.9)	0 (0)	0 (0)
Myxofibrosarcoma	56 (7.3)	25 (7.5)	21 (7.5)	2 (3.9)	7 (8.9)	0 (0)	1 (5.0)
Other specified	70 (9.1)	32 (9.6)	25 (8.9)	3 (5.9)	6 (7.6)	2 (40.0)	2 (10.0)
Grade							
Intermediate	174 (22.7)	82 (24.6)	58 (20.7)	7 (13.7)	15 (19.0)	0 (0)	12 (60.0)
High	594 (77.3)	251 (75.4)	222 (79.3)	44 (86.3)	64 (81.0)	5 (100)	8 (40.0)
Depth							
Superficial*	243 (31.6)	160 (48.0)	56 (20.0)	5 (9.8)	10 (12.7)	3 (60.0)	9 (45.0)
Deep	525 (68.4)	173 (52.0)	224 (80.0)	46 (90.2)	69 (87.3)	2 (40.0)	11 (55.0)
Mean(s.d.) tumour size (cm)†	6(7.3)	5(5.8)	7(7.9)	8(9.7)	10(11.3)	3(4.3)	4(4.5)
Postirradiation sarcoma							
Yes	24 (3.1)	12 (3.6)	5 (1.8)	0 (0)	2 (2.5)	0 (0)	5 (25.0)
No	744 (96.9)	321 (96.4)	275 (98.2)	51 (100)	77 (97.5)	5 (100)	15 (75.0)
Primary *versus* local recurrence							
Primary	720 (93.8)	313 (94.0)	263 (93.9)	48 (94.1)	72 (91.1)	5 (100)	19 (95.0)
Local recurrence	48 (6.2)	20 (6.0)	17 (6.1)	3 (5.9)	7 (8.9)	0 (0)	1 (5.0)
Referral reason							
Primary tumour, non-treated	451 (58.7)	162 (48.6)	175 (62.5)	46 (90.2)	60 (75.9)	0 (0)	8 (40.0)
Inadequate surgery	269 (35.0)	151 (45.3)	88 (31.4)	2 (3.9)	12 (15.2)	5 (100)	11 (55.0)
Local recurrence	48 (6.3)	20 (6.0)	17 (6.1)	3 (5.9)	7 (8.9)	0 (0)	1 (5.0)
Number of operations							
1	477 (62.1)	160 (48.0)	190 (67.9)	48 (94.1)	70 (88.6)	1 (20.0)	8 (40.0)
>1	291 (37.8)	173 (52.0)	90 (32.1)	3 (5.8)	9 (11.4)	4 (80.0)	12 (60.0)
Amputation‡							
Yes	50 (8.1)	30 (11.8)	11 (4.8)	6 (12.5)	0 (0)	1 (25.0)	2 (14.3)
No	568 (91.9)	225 (88.2)	220 (95.2)	42 (87.5)	66 (100)	3 (75.0)	12 (85.7)
Chemotherapy							
Yes	120 (15.6)	21 (6.3)	48 (17.1)	22 (43.1)	21 (26.6)	1 (20.0)	0 (0)
No	648 (84.4)	312 (93.7)	232 (82.9)	29 (56.9)	58 (73.4)	4 (80.0)	20 (100)

Values are *n* (%) unless otherwise indicated. *Subcutaneous tumours with or without cutaneous extension but without involvement of the deep fascia. †Tumour size was determined in 721 cases. ‡Of 618 patients with an extremity or a limb girdle tumour. UPS/NOS, undifferentiated pleomorphic sarcoma/not otherwise specified; RT, radiation therapy.

control rate was the same (90.1 per cent) during the first (1987–2001) and the latter (2002–2016) inclusion intervals.

Univariable and multivariable analyses of local control

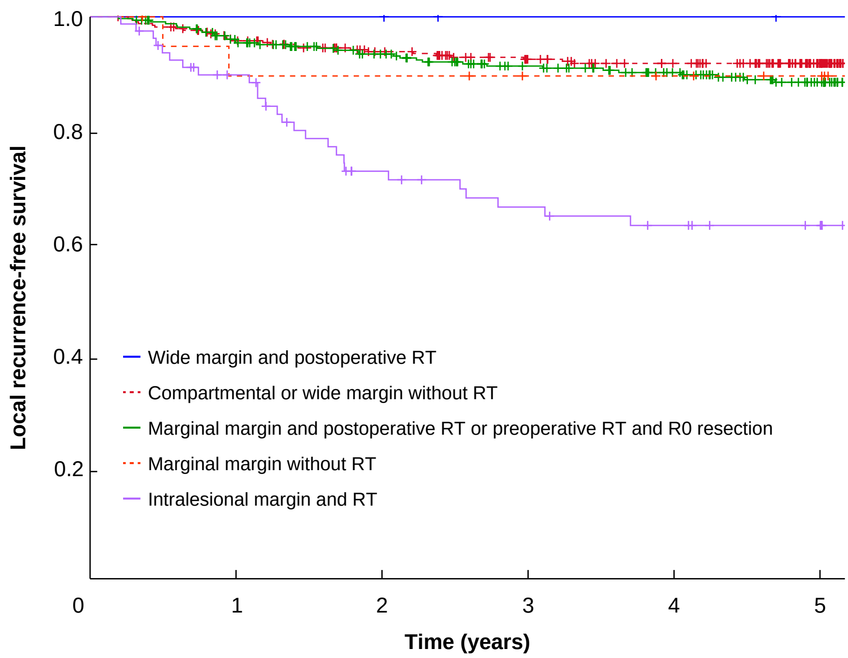
In univariable analyses for all 768 patients, eight factors were significantly related to local control (*Table 2*). Four factors had the strongest impact on local control: resection margin, tumour depth, tumour size, and administration of RT. Paradoxically, local control was higher in patients referred after inadequate surgical margins than in patients referred with an intact tumour. However, the proportion of patients with a deep tumour was higher (82.3 *versus* 47.2 per cent), and tumour size was larger (median 7.9 *versus* 3.8 cm) in the latter group. Of the 113 patients without residual tumour in the re-resection specimen and a wide margin in the final operation, 102 received no further local treatment and had 5-year local control of 95.1 per cent. In a stepwise multivariable analysis, five factors (resection margin, tumour depth, tumour size, tumour site, and age at diagnosis) retained their significance.

Univariable and multivariable analyses of local control in patients treated with wide surgical margins alone

When analysing only patients treated with a wide or compartmental margin alone (333), tumour depth, tumour size, and sex were significant in univariable analysis, whereas only depth of tumour retained its significance in a stepwise multivariable analysis with hazards ratio (HR) 3.154 (95% c.i. 1.265 to 7.860) (*Table 3*).

Preoperative radiation therapy and/or combined preoperative chemotherapy

Thirty-four of the 68 patients treated with preoperative RT also received preoperative chemotherapy. Combination therapy was carried out with hyperfractionated RT sandwiched between chemotherapy courses in 32 patients as described in Nevala *et al.* in 2019[19]. In 62 of these 68 patients the tumour was located in the extremities. Six amputations were performed. In nine patients, preoperative treatment enabled limb-sparing surgery with a negative margin in contrast to preoperative imaging,



No. at risk	0	1	2	3	4	5
Wide margin and postoperative RT	5	5	5	3	3	2
Compartmental or wide margin without RT	333	308	281	259	242	193
Marginal margin and postoperative RT or preoperative RT and R0 resection	331	302	272	243	221	185
Marginal margin without RT	20	17	17	15	14	12
Intralesional margin and RT	79	65	47	41	37	33

Fig. 2 Local control in grade 2–3 sarcomas by treatment category

RT, radiation therapy.

which indicated that free margins were not achievable with surgery alone. Local control at 5 years was 79.2 per cent in these 68 patients (*Fig. S1*).

Deviations from protocol

Ninety-five per cent (777) of all patients were treated according to protocol guidelines. Excluding low-grade tumour patients, 25 (3.1 per cent) had protocol violations.

Five patients had a final wide margin but also received postoperative RT. Reasons for adjuvant RT were histology associated with risk of lymphatic vessel invasion (alveolar soft part sarcoma, clear cell sarcoma) (2), multiple operations causing uncertainty in margin assessment (2), and concurrent invasive carcinoma and sarcoma of the breast (1). Local control was 100.0 per cent in this group.

Twenty patients with grade 2–3 tumours were treated with marginal surgery without postoperative RT. None of these patients received postoperative combination chemotherapy. The most common reason for not giving postoperative RT was an expected low risk for local recurrence due to intermediate malignancy grade (13). Other reasons for marginal surgery without RT were radiation-associated sarcoma (three), wound complication (two), patient refusal (one), and treatment of a local recurrence where RT had been used for a primary tumour (one). For patients with marginal surgery without adjuvant RT, 5-year local recurrence-free survival rates were 100 and 75 per cent for intermediate-grade (12) and high-grade (eight) tumours respectively.

Discussion

This study evaluates the results of a prospective treatment protocol that was set up more than 30 years ago in a large tertiary referral centre. In patients treated per-protocol, the local control rate was high (90.1 per cent). The local control rate was best among patients managed with wide surgery alone (91 per cent). This local control rate compares favourably with other recent large series reporting local control rates varying from 65 to 100 per cent[6,7,9,20–37] (*Table S3*).

The treatment guidelines used differ from those of ESMO and NCCN in that RT after surgery with a wide margin is not recommended, whereas ESMO and NCCN guidelines consider omitting RT only for selected tumours[1,2]. In the study protocol, surgery with a wide margin without RT is the preferred treatment when feasible. The definition of margins also differs between this protocol and these guidelines. One of the problems in comparing studies is the different and often vague definition of surgical margins. The definition of ‘adequate surgical margins’ differs, and no international consensus prevails on this issue[26,38]. In addition to margin width, some classifications also take into consideration other factors like the tissue type forming the margin[39] or the anatomic location[6]. The definition of a wide margin used in this study is a microscopic free margin of at least 2.5 cm. Only some reports have, like the present one, used an exact metric definition (*Table S3*). The most widely used cut-offs for adequate margin alone were 5 mm[9,26,28] and 10 mm[7,20–22,30]. Generally, local recurrence rate decreased with wider margins[7,20,26–29], especially with larger margin cut-offs,

Table 2 Description of patient, tumour and treatment characteristics of the 768 patients with a grade 2–3 tumour, and the corresponding estimates of 5-year local control

Characteristics	Patients	Estimated 5-year local control, %	Univariable		Multivariable	
			HR (95% c.i.)	P§	HR (95% c.i.)	P¶
Sex			1.443 (0.959, 2.173)	0.079		
Male	406 (52.9)	84.9				
Female	362 (47.1)	90.1				
Age at diagnosis (years)			1.013 (1.001, 1.025)	0.035	1.014 (1.001, 1.027)	0.044
<50	255 (33.2)	91.1				
50–66.9	256 (33.3)	84.9				
>66.9	257 (33.5)	85.9				
Site			1.315 (1.042, 1.660)	0.021	1.293 (1.014-1.647)	0.038
Lower extremity	468 (60.9)	89.2				
Upper extremity	150 (19.5)	81.9				
Trunk	150 (19.5)	85.8				
Grade			1.768 (1.029, 3.099)	0.039	1.327 (0.728-2.586)	0.328
Intermediate	174 (22.7)	91.7				
High	594 (77.3)	86.2				
Depth			3.013 (1.709, 5.315)	<0.001	2.231 (1.177, 4.229)	0.014
Superficial*	243 (31.6)	93.7				
Deep	525 (68.4)	84.1				
Tumour size† (cm)			1.074 (1.052, 1.098)	<0.001	1.060 (1.032, 1.089)	<0.001
<4.7	262 (36.3)	94.7				
4.7–8.1	235 (32.6)	86.9				
8.2	224 (31.1)	79.1				
Postirradiation sarcoma			0.787 (0.288, 2.148)	0.640		
Yes	24 (3.1)	82.1				
No	744 (96.9)	87.8				
Primary *versus* local recurrence			2.184 (0.691, 6.906)	0.184		
Primary	720 (93.8)	86.9				
Local recurrence	48 (6.3)	95.1				
Referral reason			0.688 (0.493, 0.959)	0.027	0.928 (0.609-1.412)	0.726
Primary tumour, non-treated	451 (58.7)	83.1				
Primary tumour, inadequate surgery	269 (35.0)	93.2				
Local recurrence	48 (6.3)	94.9				
Margin category			0.560 (0.428, 0.732)	<0.001	0.692 (0.525, 0.913)	0.009
Intralesional (+RT)	79 (10.3)	63.0				
Marginal	300 (39.1)	88.8				
Preoperative RT and R0 resection	51 (6.6)	83.1				
Wide	338 (44.0)	91.7				
Amputation‡			1.454 (0.530, 3.986)	0.464		
Yes	50 (8.1)	90.7				
No	568 (91.9)	88.1				
Chemotherapy			1.471 (0.889, 2.434)	0.134		
Yes	120 (15.6)	81.8				
No	648 (84.4)	88.1				
Radiation therapy			2.017 (1.309, 3.107)	0.01	0.519 (0.247-1.092)	0.084
Yes	415 (54.0)	84.2				
No	353 (46.0)	91.7				

Values are *n* (%) unless otherwise indicated. *Subcutaneous tumours with or without cutaneous extension but without involvement of the deep fascia. †Tumour size was determined in 721 cases. ‡Of 618 patients with an extremity or a limb girdle tumour. §Log rank test; Cox analysis for continuous variables. ¶Cox analysis. HR, hazards ratio; RT, radiation therapy.

such as 10 mm[7,27] or 20 mm[27]. With lower cut-off values, ranging from 0 to 9.9 mm, improvement was not as clear, and in the large study by Harati *et al.* (643) no improvement in local control was seen when margins increased from less than 1 mm to more than 5 mm[29]. The need for a margin larger than a few millimetres is supported by the study of White *et al.*[40]. They found tumour cells in the tissues surrounding the tumour in 10 of 15 cases. In four cases, tumour cells were located at a distance of over 1 cm[40]. In the patient series where all or some patients had received RT, local control was better in almost all studies after wider margins. Furthermore, as in the present study, the risk of local relapse was uniformly high after intralesional surgery despite RT.

Several studies, like the present one, have demonstrated that local control can be achieved in STS with surgery with adequate margins without RT[6,7,32,34]. In a report from Princess Margaret Hospital, local control was 84 per cent among 42 of 54 patients with clear margins[32]. In 2018, a report of 390 patients from Istituti Tumori in Milan, Italy, compared patients in which RT needed to be avoided for any reason with patients receiving RT, and local control was 84 and 81 per cent respectively[34]. Rydholm *et al.* reported a local recurrence rate of only 7 per cent among 56 subcutaneous and intramuscular tumours treated with a wide margin alone[6]. Baldini *et al.* reported a 10-year actuarial local control rate of 93 per cent among 74 patients treated with function-sparing surgery without RT[7].

Table 3 Univariable and multivariable analysis of 333 patients with grade 2–3 sarcomas treated with a wide margin alone

Characteristics	Patients	Estimated 5-year local control, %	HR (95% c.i.)	P§	HR (95% c.i.)	P¶
Sex			2.682 (1.139, 6.315)	0.024	0.496 (0.206-1.195)	0.118
Male	183 (55.0)	88.6				
Female	150 (45.0)	95.2				
Age at diagnosis (years)			1.012 (0.990, 1.035)	0.277		
<51	112 (33.6)	91.8				
51–67	110 (33.0)	93.4				
>67	111 (33.3)	89.7				
Site			1.110 (0.687, 1.794)	0.671		
Lower extremity	203 (69.1)	91.7				
Upper extremity	52 (15.6)	87.3				
Trunk	78 (23.4)	94.6				
Grade			3.026 (0.913, 10.093)	0.070		
Intermediate	82 (24.6)	97.5				
High	251 (76.4)	89.7				
Depth			2.881 (1.223, 6.789)	0.016	3.154 (1.265, 7.860)	0.014
Superficial*	160 (48.0)	95.3				
Deep	173 (52.0)	88.3				
Tumour size† (cm)			1.091 (1.015, 1.174)	0.018	1.050 (0.968-1.140)	0.238
<3.6	102 (32.8)	96.0				
3.6–6.5	107 (34.4)	92.7				
>6.5	102 (32.8)	86.2				
Postirradiation sarcoma			21.798 (0.017, 66829)	0.249		
Yes	12 (3.6)	100				
No	321 (96.4)	91.4				
Primary *versus* local recurrence			22.502 (0.033, 15151)	0.351		
Primary	313 (94.0)	91.2				
Local recurrence	20 (6.0)	100				
Referral reason			0.790 (0.441, 1.441)	0.427		
Primary tumour, non-treated	162 (48.6)	87.7				
Primary tumour, inadequate surgery	151 (45.3)	94.6				
Local recurrence	20 (6.0)	100				
Amputation‡			1.312 (0.307, 5.601)	0.714		
Yes	30 (11.8)	92.3				
No	225 (88.2)	90.6				
Chemotherapy			1.265 (0.299, 5.535)	0.749		
Yes	21 (6.3)	89.9				
No	312 (93.7)	91.8				

Values are *n* (%) unless otherwise indicated. *Subcutaneous tumours with or without cutaneous extension but without involvement of the deep fascia. †Tumour size was determined in 311 cases. ‡Of 255 patients with an extremity or a limb girdle tumour. §Log rank test; Cox analysis for continuous variables. ¶Cox analysis. HR, hazards ratio.

Low tumour grade was associated with excellent local control in the current study, irrespective of treatment or surgical margins. In this population, none of the patients with low-grade tumours experienced a local recurrence. In accordance with Rydholm *et al.*[6], the current study found that local control was high in subcutaneous tumours treated with surgery alone, 95.3 per cent in high-grade and 100.0 per cent in intermediate-grade sarcomas. Thus, a margin smaller than the 2.5 cm recommended in the treatment protocol may be sufficient for superficial STS. In intermediate- and high-grade sarcomas, tumour depth was statistically significantly associated with local control in multivariable analysis but was, however, high even among deep tumours (88.3 per cent). It is important to note that factors that have been linked to local recurrence risk have also been associated with the risk of developing metastatic disease and consequently higher mortality rate. In the present study, 75 per cent of the patients with deep high-grade tumours treated with wide surgery alone developed distant metastases. Thus, the proportion of patients in which more effective local treatment might have affected long-term survival remains small. A higher risk of further local recurrence has previously been linked to the treatment of a local recurrence[35,41]. The current study did not replicate this finding. Instead, the 5-year local control rate among this population was 95.2 per cent for all the treated patients and 100.0 per cent for the 20 patients who were operated on with wide margins after the diagnosis of recurrence.

The use of RT in the treatment of STS has gradually increased according to several large recently published STS patient series. Gronchi *et al.* reported 1094 patients treated for their primary extremity STS at their institution during 1987–2007. The percentage of patients receiving RT increased from 32.4 to 60 per cent, whereas the 5-year local recurrence rate decreased from 15 to 6 per cent[42]. A study from the registry of the Scandinavian Sarcoma Group (5071) spanning the years 1987 to 2011 reported that the use of RT increased from 18 to 33 per cent, whereas the 3-year local recurrence rate decreased from 20 to 14 per cent[43]. In a nationwide Finnish study of STS in the extremity or trunk wall treated in 2005 to 2010 or 1998 to 2001, RT after marginal or intralesional surgery increased from 66 to 78 per cent, whereas 5-year local recurrence free survival increased from 77 to 86 per cent[44]. Altogether, these results suggest that increased use of RT is one factor responsible for improved local control in recent years. Other factors may also be important, like increased awareness of the disease, the strong development of imaging, histological methods, and surgical reconstructive techniques enabling better planning and evaluation of surgical margins. In the Italian series, the proportion of superficial STS referred to the centre increased from 8.8 to 36.7 per cent, whereas the proportion of patients with a definite intralesional margin decreased from 20.4 to 6.9 per cent in the Finnish study. Thus, drawing firm conclusions from historical controls may be treacherous. In contrast, the proportion of patients given RT in the present series remained constant during the whole study interval, as did the local recurrence rate. The benefits of RT must be weighed against its side effects. RT of soft tissue is usually well tolerated. However, in a study on lower extremity STS patients treated at the current study institution, RT was associated with impaired functional status[16], although most of the patients had a good or excellent limb function similar to or even better than patients in previously published sarcoma series. RT may cause fibrosis, joint stiffness, and oedema[45]. Moreover, the small risk of secondary malignancy should also be considered. The present study shows that RT may be avoided in a large proportion of patients with STS operated on with adequate margins. On the other hand, excessively large resections compromising important anatomical structures may also cause morbidity rate. Therefore, the choice of treatment modality to ensure not only optimal control but also minimal morbidity rate is of extreme importance, and should optimally be done by a multidisciplinary team together with the patient.

Most treatment guidelines for STS are based on a relatively low level of evidence. Recommendations concerning RT are largely based on four small, randomized trials in which numbers of patients ranged from only 43 patients to 164 patients[4,5,46,47]. In the absence of RCTs, the best evidence guiding treatment policy are results from well-defined cohort studies, such as the current study. Despite the predefined treatment protocol, patient wishes and practical circumstances can sometimes prevent strict adherence to the protocol. This may be seen as a weakness of the present study as 5 per cent of the patients had protocol deviations. This can, on the other hand, also be seen as a strength of the present study since patients like these are often not eligible for inclusion in prospective and randomized trials and therefore not reported. Further limitations should also be considered when interpreting these results. First, this is a single-institution study from a tertiary centre. Therefore, certain patient groups are over-represented. An example of this is the high number of patients (34 per cent) that had been referred from another centre after inadequate surgery. Secondly, the patients in the current study population were treated over a long interval of time between 1987 and 2016. Diagnostics as well as surgical and RT techniques have improved and can cause heterogeneity within the population. Still, the population represents a unique opportunity to study the effect of treatment guideline rules on local recurrence risk because the treatment protocol has been consistent, and decision-making centralized to the multidisciplinary treatment team.

These results indicate that local management should be primarily guided by the quality of surgical margins achieved. This analysis also revealed that a few details of the local protocol may need revision. Thus, a surgical margin of 2.5 cm may be unnecessarily large for subcutaneous and low-grade sarcomas, and, conversely, deep high-grade sarcomas may benefit from RT despite generous surgical margins. Despite the prospective strict treatment guidelines, the present study is still a retrospective analysis, with all its limitations. Thus, there is still a need for large, randomized studies comparing local control and QoL between different treatment protocols to define the optimal treatment of STS.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Data are available upon request from the corresponding author.

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