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Clinical Investigation: Sarcoma

Patterns of Local Recurrence and Dose Fractionation of Adjuvant Radiation Therapy in 462 Patients With Soft Tissue Sarcoma of Extremity and Trunk Wall

Nina L. Jebsen, MD,[*,†] Jacob Engellau, MD, PhD,[‡] Katarina Engström, MD, PhD,[§] Henrik C. Bauer, MD, PhD,[‖] Odd R. Monge, MD,[†] Ludvig P. Muren, PhD,[¶,#] Geir E. Eide, MSc, PhD,[,††] Clement S. Trovik, MD, PhD,[*,†] and Øyvind S. Bruland, MD, PhD[§§,‖‖]**

Department of Clinical Medicine, Faculty of Medicine and Dentistry, University of Bergen, and †Department of Oncology, Haukeland University Hospital, Bergen, Norway; ‡Department of Oncology, Skåne University Hospital, Lund, Sweden; §Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden; ‖Department of Molecular Medicine and Surgery, Section for Orthopaedics and Sports Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden; ¶Department of Physics and Technology, University of Bergen, Bergen, Norway; #Department of Medical Physics, Aarhus University and Aarhus University Hospital, Aarhus, Denmark; **Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; ††Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway; §§Department of Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; and ‖‖Institute of Clinical Medicine, University of Oslo, Oslo, Norway

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Summary

There is limited evidence on dose fractionation issues in adjuvant radiation therapy (RT) of soft tissue sarcoma. In this study of 426 patients from The Scandinavian Sarcoma Group Register, no dose–response effect of RT was demonstrated. After wide margin surgery, 50 Gy in 25 fractions seemed adequate. Accelerated RT

Purpose: To study the impact of dose fractionation of adjuvant radiation therapy (RT) on local recurrence (LR) and the relation of LR to radiation fields.

Methods and Materials: LR rates were analyzed in 462 adult patients with soft tissue sarcoma who underwent surgical excision and adjuvant RT at five Scandinavian sarcoma centers from 1998 to 2009. Medical records were reviewed for dose fractionation parameters and to determine the location of the LR relative to the radiation portals.

Results: Fifty-five of 462 patients developed a LR (11.9%). Negative prognostic factors included intralesional surgical margin (hazard ratio [HR]: 7.83, 95% confidence interval [CI]: 3.08-20.0), high malignancy grade (HR: 5.82, 95% CI: 1.31-25.8), age at diagnosis (HR per 10 years: 1.27, 95% CI: 1.03-1.56), and malignant peripheral nerve sheath tumor histological subtype (HR: 6.66, 95% CI: 2.56-17.3). RT dose was tailored to margin status. No correlation between RT dose and LR rate was found in multiple Cox regression analysis. The majority (65%) of LRs occurred within the primary RT volume.

Conclusions: No significant dose–response effect of adjuvant RT was demonstrated. Interestingly, patients given 45-Gy accelerated RT (1.8 Gy twice daily/2.5 weeks) had the best local outcome.

Reprint requests to: Nina Louise Jebsen, MD, Department of Clinical Medicine, Faculty of Medicine and Dentistry, University of Bergen, Jonas Liesv. 65, N-5021 Bergen, Norway. Tel: (47) 55-97-28-22; E-mail: nina.louise.jebsen@helse-bergen.no

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(1.8 Gy twice daily) to 36 or 45 Gy, interposed with chemotherapy, was feasible and effective. In addition to malignancy grade and surgical margin, histopathologic subtype was associated with local recurrence.

A total dose of 50 Gy in 25 fractions seemed adequate following wide margin surgery. The risk of LR was associated with histopathologic subtype, which should be included in the treatment algorithm of adjuvant RT in soft tissue sarcoma.

Introduction

Optimal dose fractionation schedule in adjuvant radiation therapy (RT) in soft tissue sarcoma (STS) of the extremities and trunk wall is unknown, although a dose–response effect of RT has been reported in some studies (1-4). It is common to recommend at least 60 Gy postoperatively (daily fractions of 2 Gy) to patients with high-grade STS, with an additional dose of 6 Gy upto 16 Gy after positive margin surgery (1, 5-9). In preoperative RT, a total dose of 45 to 50 Gy is typically prescribed. In contrast, the Scandinavian Sarcoma Group (SSG) recommendation for postoperative RT is 50 Gy in 2-Gy daily fractions, plus a boost of 10 to 20 Gy following a positive surgical margin. Accelerated RT with 1.8 Gy twice daily to 36 or 45 Gy, interposed with adjuvant chemotherapy (CT), has been applied in patients with high-risk STS (10, 11). Despite differences in postoperative RT doses, local control rates in series from our institutions compare well with results from other sarcoma centers (3, 4, 12-17). Although RT has been increasingly used as adjuvant treatment of STS, we lack data to guide the choice of RT dose and schedule. Local recurrences (LRs) still occur, and the majority of these are in field (15, 18, 19).

This study evaluated SSG RT guidelines and examined the impact of RT dose fractionation on local control. Tumor-related factors of prognostic importance were also included in the analyses. Lastly, we performed a retrospective assessment of the localization of an LR in relation to the RT treatment volume.

Methods and Materials

Ethics

The study was conducted according to the Declaration of Helsinki and approved by the Regional Committee for Medical Research Ethics.

Patients and eligibility

From the SSG prospective register, 572 patients from 5 sarcoma centers (aged ≥16 years) diagnosed from 1998 to 2009 with extremity or trunk wall STS who underwent adjuvant RT were identified. Patients with dermatofibrosarcoma protuberans, Kaposi sarcoma, extraosseous osteo- and chondrosarcoma, and Ewing family tumors were not eligible, nor were patients with synchronous metastases. Only the 462 patients who underwent both primary surgery and RT at a sarcoma center, with complete recordings of parameters of prognostic importance and follow-up data, were included in the study (20). Histopathologic tumor classification and malignancy grading were performed at the sarcoma centers according to SSG guidelines, Protocol SSG VII:4 (11). Of the 110 patients excluded, 97 had missing data, primarily because RT was given at a local hospital; 13 patients were excluded because RT was administered following an LR or with palliative intent.

Radiation therapy

Details of RT were recorded retrospectively from the individual radiation charts. Patients were treated primarily with 3-dimensional conformal RT.

According to institutional guidelines, postoperative clinical target volume (CTV) should encompass the tumor bed including the affected compartment in the transverse directions and 5 cm beyond the surgical scar in the longitudinal direction. A 2-cm margin from the tumor bed in all directions was recommended for the boost volume. The planning target volume (PTV) typically encompassed the CTV + 1 cm setup margin in all directions. In preoperative RT, the gross tumor volume (GTV) was delineated as visualized on computer tomography preferably coregistered with diagnostic magnetic resonance imaging (MRI), using a 2-cm margin from the GTV to the CTV. The field border was defined by the 50% isodose curve with a margin of 5 to 8 mm to the PTV (95% isodose curve). Because PTV delineations were inaccessible in most cases, we relied on RT simulation images, diagnostic radiographs, and treating oncologist's or surgeon's evaluation regarding the location of the LR relative to the RT portals. An LR occurring within the RT portals was classified as in field. If the LR extended on both sides of the field border, a marginal recurrence was recorded. If the LR did not involve the RT portal volume, it was defined as out of field.

Chemotherapy and accelerated RT

The SSG SIN system comprising size (≥8 cm), vascular invasion, and necrosis categorizing high-grade STS patients into high- or low-risk groups, was established in 1998 (11). Grade, surgical margin, and tumor depth were determinants for RT. High-risk patients were offered 6 postoperative courses (3-week intervals) of doxorubicin plus ifosfamide with accelerated RT (1.8 Gy twice daily at 6-hour intervals to 36 Gy over 2 weeks) interpolated between the second and third CT course and, if indicated, a split-course boost (9 Gy/2.5 days, total dose 45 Gy, overall treatment time 31 days) given between the third and fourth CT course (10). The biological tumor effect of the increased dose density of the accelerated regimen and the tight relation to CT were computed by modifying the fraction dose by a factor of 1.10 and 1.15, respectively, assuming an α/β ratio for tumor and acute toxicity of

10, and of 3 for late effects. The ongoing SSG XX clinical study of patients with high-risk STS also include infiltrative tumor margin as a risk-stratifying factor (11).

Follow-up and outcome

Follow-up was scheduled at 3-month intervals for the first 2 years after the completion of treatment, at 6 months during the third and fourth year, then yearly up to 10 years. Physical examination and chest radiography were mandatory, with additional MRI when deemed necessary (tumor area inaccessible for clinical examination or suspicious findings). The date of (cytologically or histologically verified) distant or locally recurrent disease and cause of death were reported to the register.

Analyses

The relation between RT and LR was analyzed with dose as a categorical variable, grouped by fractionation schedule and total dose. RT dose, as a continuous variable, was analyzed using equivalent RT dose to dose in 2 Gy fractions (EQD2) (21). An α/β ratio of 10 was assumed for tumor effect.

Statistical methods

Descriptive data are given as counts (%), medians, means, and ranges. Gosset's independent-sample *t* test was chosen to compare distribution of prognostic factors for the dichotomous factor "pre- or postoperative RT." Time to LR was computed from the date of the last operation of the primary tumor. The Kaplan-Meier method was used to estimate survival curves and the log−rank (Mantel-Cox) test for comparing groups. Univariate analysis by Cox regression included factors reported in previous studies to have a prognostic impact on LR. Cox multiple regression with the likelihood ratio test was used to examine simultaneous effects of potential prognostic factors for LR and to plot survival curves. Backward stepwise selection (ie, including all factors in the model and eliminating the insignificant one by one) was used for obtaining the final adjusted model. Post hoc analyses for interactions between covariates were performed in the final model. Competing risk hazard ratios (HRs) for LR were calculated treating death without LR as a competing event. The most common category for the categorical covariates and mean values for continuous covariates were generally chosen in the plots. A P value $\leq .05$ was considered statistically significant. Statistical analysis and data preparation were carried out using the PASW Statistics 18.0 (SPSS, Chicago, IL) software package and STATA 12 (Statistical package, StataCorp, College Station, TX).

Results

Characteristics of the 462 patients are displayed in Table 1. Rare histopathologic subtypes and undifferentiated STS were grouped as "other types." Four-fifths of the patients had not been subjected to any invasive diagnostics before referral to a sarcoma center, and only 25 patients (6%) required an incision biopsy for diagnosis at the center.

Table 1 Patient, tumor, and treatment characteristics in 462 STS patients

Characteristic	Value	
Age at diagnosis (y) median (range)	61	(16-94)
Tumor size (cm), median (range)	9.0	(1-40)
EQD2 (Gy), median (range)	50	(20-70)
Sex, n (%)		
Male	257	(55.6)
Female	205	(44.4)
Tumor site, n (%)		
Lower extremity (incl. gluteal)	297	(64.4)
Upper extremity (incl. shoulder)	88	(18.9)
Trunk wall (incl. axillae and groin)	77	(16.7)
Location, n (%)		
Subcutaneous	78	(16.9)
Deep	384	(83.1)
Malignancy grade, n (%)		
Low grade (grade 1 and 2)	55	(11.9)
High grade (grade 3 and 4)	407	(88.1)
Histopathologic subtype, n (%)		
UPS	181	(39.2)
Liposarcoma	90	(19.5)
Synovial sarcoma	49	(10.6)
Leiomyosarcoma	45	(9.7)
MPNST	26	(5.6)
Other types	71	(15.4)
Number of operations, n (%)		
1	439	(95.0)
≥2	23	(5.0)
Surgical margin, n (%)*		
Intralesional	72	(15.6)
Marginal	270	(58.4)
Wide	120	(26.0)
Chemotherapy, n (%)		
Adjuvant	142	(30.7)
No chemotherapy	320	(69.3)

Abbreviations: EQD2 = biologically effective radiation therapy dose equivalent to 2 Gy fractions; incl. = including; MPNST = Malignant peripheral nerve sheath tumor; STS = soft tissue sarcoma; UPS = Undifferentiated pleomorphic sarcoma.

* Intralesional = micro- or macroscopically positive; marginal = <10 mm cuff of uninvolved tissue; wide = uninvolved fascia or ≥10 mm cuff of healthy tissue on formalin-fixed specimen.

Radiation therapy

RT was administered postoperatively to 84% (Table 2). The median time interval between surgery and RT was 64 days in the postoperative setting and 28 days preoperatively. A higher dose than 50 Gy was prescribed in only 16% of the cases. Twenty-two percent of the patients were treated according to one of the SSG high-risk protocols (10, 11) with postoperative CT and accelerated RT to 36 Gy (n=78) or 45 Gy split-course following intralesional surgery (n=17) (10). Accelerated 45 Gy was administered as a continuous (mainly preoperative) course in 9 patients. A minor proportion of the patients received nonstandard regimens with hyperfractionation (1.5/1.6 Gy twice daily, n=5) or moderate hypofractionation with daily doses of 3 Gy (n=7). Mean and median RT doses for the whole study group were 48 and 50 Gy,

Table 2 Distribution of potential prognostic factors among radiation therapy groups in 462 STS patients

Radiation therapy group	All (n=462)	< 50 Gy (n=38)	36 Gy acc (n=78)	45 acc split (n=17)	45 Gy acc (n=9)	50 Gy/25 (n=245)	>50-60 Gy (n=56)	>60 Gy (n=19)
Age, y (mean)	59.4	57.5	52.2	47.1	53.0	63.5	57.1	60.3
Size, cm (mean)	9.9	10.7	10.9	10.9	12.3	9.5	9.8	8.4
Deep location (%)	83.1	89.5	92.3	88.2	88.9	80.8	78.6	68.4
Trunk location (%)	16.2	23.7	9.0	17.6	11.1	16.7	21.4	10.5
High-grade malignancy (%)	88.1	57.9	100.0	100.0	100.0	89.4	83.9	78.9
Histotype MPNST (%)	5.6	5.3	6.4	17.6	11.1	4.9	5.4	0.0
≥2 operations (%)	5.0	2.6	3.8	11.8	0.0	6.5	1.8	0.0
Margins								
Wide (%)	26.0	31.6	32.1	11.8	55.6	27.8	10.7	10.5
Marginal (%)	58.4	50.0	64.1	35.3	22.2	61.2	60.7	47.4
Intralesional (%)	15.6	18.4	3.8	52.9	22.2	11.0	28.6	42.1
CT given (%)	30.7	21.1	100.0	100.0	66.7	11.4	7.1	5.3
Preoperative RT (%)	16.0	52.6	3.8	0.0	88.9	15.5	8.9	0.0

Abbreviations: acc = accelerated; CT = chemotherapy; MPNST: malignant peripheral nerve sheath tumor; split = split-course; STS = soft tissue sarcoma.

respectively. These values were similar when the RT dose was calculated in EQD2.

Three-dimensional planning (including intensity modulated radiation therapy in some cases) was used in 89% of the patients and opposing portals in 11%. In 179 cases for which RT volumes were available, the mean PTV was 1440 cm^3. There were no differences in PTV ($P=.857$) or tumor size ($P=.473$) between the group given preoperative RT (n=27, mean PTV 1476 cm^3, mean tumor size 10.3 cm) and the group undergoing postoperative treatment (n=152, mean PTV 1434 cm^3, mean tumor size 9.8 cm).

Local recurrence

Median follow-up time was 4.1 years (range 0.1-13.0). Fifty-five of 462 (11.9%) patients experienced a LR, 9 of whom had >1 LR. In 49 of 55 (89%) patients, the location of the recurrence in relation to the irradiated volume could be determined: most LRs (32/49, 65%) were located within the RT field portals, 10 (20%) involved the field margin, and 7 (14%) were out of field. The latter were excluded from the further analyses of RT groups and prognostic factors for LR. No imbalance was found concerning prognostic factors and the location of LR. All LRs following the accelerated 45 Gy split-course regimen (n=5) or total doses >60 Gy (n=2) were in field, in contrast to 4 of 5 (80 %) after accelerated 36 Gy, 15 of 23 (65.2 %) after 50 Gy, and 5 of 8 (62.5%) after a total dose of >50 to 60 Gy. Subsequent to standard fractionated doses <50 Gy, 4 of 6 (66.7%) LRs were out of field.

Estimated 5- and 10-year local recurrence rate (LRR) were 13% and 15%, with similar LRRs after preoperative and postoperative RT. LRRs did not differ between the five SSG centers. There were significant differences in distribution of risk factors for LR between the groups given disparate RT schedules (Table 2).

No dose−response relationship was found between local control and RT dose as a continuous variable computed as EQD2. By grouping RT according to fractionation schedules and total doses in Gy with 50 Gy/25 fractions as reference dose, the 45-Gy split-course regimen had a significantly lower local control rate in the univariate analyses (Table 3). Dose higher than 50 Gy did not improve local control. When adjusting for additional prognostic factors, no significant differences were detected between the RT groups (Table 3).

High age at the time of diagnosis, high malignancy grade, and intralesional surgical margin were negative prognostic factors for local control in the fully adjusted Cox regression model and the final backward stepwise model (Table 3, Fig. 1). Furthermore, significant differences in LRRs among histopathologic subtypes were found, with malignant peripheral nerve sheath tumor (MPNST) displaying the highest risk using the most common category undifferentiated pleomorphic sarcoma (UPS) as reference (Table 3, Fig. 2). When applying the competing risk Cox regression model, the results were similar. The final competing risk model included the following factors: age (HR: 1.22, $P=.039$), malignancy grade (HR: 5.1, $P=.014$), histotype (liposarcoma, HR: 2.26, $P=.043$; MPNST, HR: 5.72, $P=.001$), and surgical margin (intralesional vs wide, HR: 6.21, $P<.001$).

Almost one-third of the patients received CT in accordance with SSG clinical studies for adjuvant treatment of high-risk STS. Local control rate was not influenced by CT (Table 3).

Discussion

Because of the heterogeneous patient material and risk-tailored RT administered within a restricted range of doses, in addition to promising results with accelerated RT to low total doses, we could not demonstrate a RT dose−response effect in STS. Another limitation of our study is that comparisons were performed within nonrandomized data, illustrated by the fact that the different RT groups are unbalanced concerning risk factors (Table 2). Furthermore, our analyses on polynomial subgroups entail reduction of the statistical strength. Hence, subanalyses must be interpreted with the greatest care. The reliability of the reported surgical margins in our institutions is, however, high (20). The fraction of patients operated with intralesional surgical margins predominantly represents microscopic positive margins because macroscopic intralesional margins are uncommon following careful treatment planning at a sarcoma center. The present material comprises tumors with overall poor prognosis: 81% were >5 cm, 88% high grade, 83% deep seated, with 71% corresponding to American Joint Committee

Table 3 Potential prognostic factors for local recurrence by simple and multiple Cox regression analysis of 462 STS patients

	Unadjusted models (n=462)			Fully adjusted model (n=462)			Final backward stepwise model (n=462)		
Factor	HR	95% CI	P*	HR	95% CI	P	HR	95% CI	P
Age at diagnosis per 10 y	1.14	(0.96-1.36)	.136	1.32	(1.03-1.69)	.031	1.27	(1.03-1.56)	.025
Sex			.784			.638			
Male vs female	1.08	(0.61-1.92)		1.56	(0.63-2.12)				
Tumor size per 10 cm	1.51	(0.98-2.34)	.061	1.23	(0.68-2.23)	.501			
Tumor depth			.217			.382			
Deep vs subcutaneous	1.79	(0.71-4.52)		1.54	(0.58-4.06)				
Location			.852			.459			
Trunk vs extremity	0.85	(0.36-2.01)		0.70	(0.28-1.79)				
Malignancy grade			.063			.025			.021
High vs low	3.83	(0.93-15.8)		6.02	(1.26-28.8)		5.82	(1.31-25.8)	
Subgroups histotype			.014			.002			.002
UPS	1	reference		1	reference		1	reference	
Liposarcoma	1.08	(0.47-2.50)		1.54	(0.62-3.86)		2.04	(0.85-4.90)	
Leiomyosarcoma	0.82	(0.24-2.86)		0.67	(0.18-2.51)		0.67	(0.19-2.33)	
Synovial sarcoma	1.37	(0.53-3.56)		2.97	(0.92-9.59)		2.15	(0.72-6.40)	
MPNST	4.59	(1.92-11.0)		7.91	(2.72-23.0)		6.66	(2.56-17.3)	
Other types	1.57	(0.66-3.75)		3.33	(1.23-9.04)		3.15	(1.25-7.97)	
Number of operations			.333			.444			
2 vs 1	0.38	(0.05-2.72)		0.45	(0.06-3.44)				
Surgical margin			<.001			<.001			<.001
Wide	1	reference		1	reference		1	reference	
Marginal	1.52	(0.65-3.56)		1.62	(0.62-4.20)		1.63	(0.67-3.97)	
Intralesional	5.86	(2.46-14.0)		7.54	(2.61-21.8)		7.83	(3.08-20.0)	
Chemotherapy			.528			.494			
Yes vs no	1.21	(0.67, 2.21)		1.58	(0.43, 5.84)				
Timing of RT			.962			.325			
Preoperative vs postoperative	0.98	(0.46-2.10)		1.59	(0.63-4.04)				
RT groups			.046			.357			
50 Gy	1	reference		1	reference				
< 50 Gy	0.93	(0.28-3.12)		1.13	(0.30-4.25)				
36 Gy acc	0.99	(0.40-2.45)		1.93	(0.43-8.70)				
45 Gy acc split	4.52	(1.82-11.2)		3.58	(0.75-17.0)				
45 Gy acc	1.29	(0.17-9.57)		0.32	(0.03-4.19)				
> 50-60 Gy	1.95	(0.89-4.26)		1.80	(0.79-4.08)				
> 60 Gy	1.36	(0.32-5.79)		0.78	(0.15-3.91)				
EQD2	1.00	(0.96-1.04)	.951	-	-				

Abbreviations: acc = accelerated; acc split = accelerated split-course, ie, with treatment gap; CI = confidence interval; EQD2 = RT dose equivalent to dose in 2 Gy fractions; HR = hazard ratio; MPNST = malignant peripheral nerve sheath tumor; RT = radiation therapy; STS = soft tissue sarcoma; UPS = undifferentiated pleomorphic sarcoma.

* From Likelihood ratio test.

on Cancer stage III, which is a high percentage compared with a recent reported series (16).

On the basis of SSG experience that 50 Gy is effective in completely resected STS (14), a limited number of patients had received 60 Gy and only a few >60 Gy. This variability was too small to disclose a dose–response effect. In contrast to our findings, a cutoff value of 60 to 64 Gy has been reported in previous studies demonstrating superior local control with higher dose levels (1-4). The escalated total doses have usually been motivated by unfavorable prognostic factors. Although SSG recommend 50 Gy in 25 fractions following marginal or wide surgical margins in deep-seated high-grade tumors, compared with 60 Gy outside Scandinavia, LRRs in our institutions are comparable to most reported findings, suggesting that 50 Gy may be sufficient following wide margin surgery (Fig. 1A) (2-4, 13, 15,17). After inadequate surgery, there is a rationale for increasing the dose (Fig. 1B) (1-4). The largest study on RT dose showed improved local control with RT ≥64 Gy, in particular, after positive and uncertain surgical margins (2).

It is interesting that the 45-Gy accelerated group (no split) displayed the best local outcome in the fully adjusted regression model, although not statistically significant (Fig. 1). Promising tumor control with accelerated RT (10) concurs with results from studies in head and neck cancer (22). Not surprisingly, split-course RT tends to result in inferior local control compared with continuous RT regimens (Fig. 1) (22). RT toxicity was not recorded in the register but has been reviewed and found to be moderate for the patients undergoing accelerated RT (10).

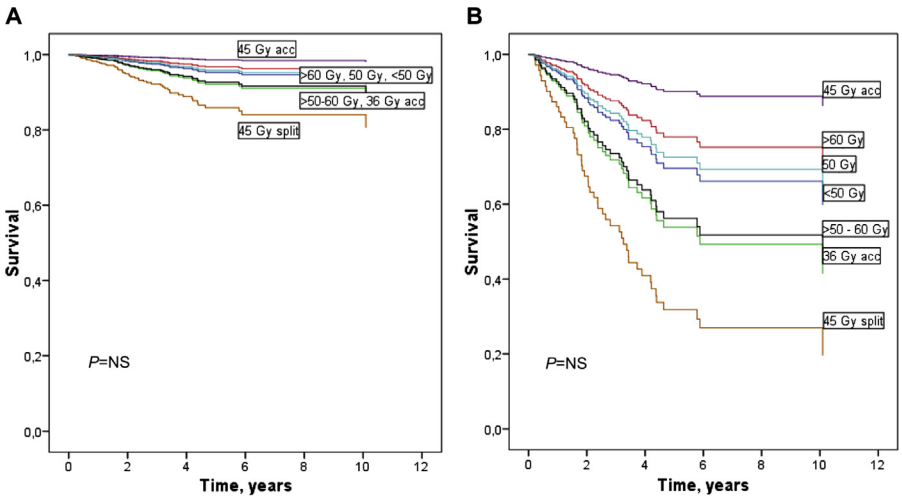

Fig. 1. Local recurrence-free survival by radiation therapy dose/fractionation and surgical margin, n = 462. (A) Wide surgical margin (n = 120). (B) Intralesional surgical margin (n = 72). Fully adjusted Cox regression model, mean value for continuous variables (age and tumor size), and the most common value for the categorical variables (undifferentiated pleomorphic sarcoma histotype, high malignancy grade, male, deep location, extremity site, one operation, no chemotherapy, postoperative radiation therapy). NS = not significant.

Our results confirm surgical margin and malignancy grade as the most important prognostic factors for local control (12, 13, 23). Furthermore, the significance of histologic subtype was demonstrated as MPNST was associated with a 35% 5-year risk of a LR, whereas UPS, liposarcoma, and leiomyosarcoma each had 5-year LRR of approximately 10%. Poor local outcome after treatment of MPNST has also been reported in previous studies

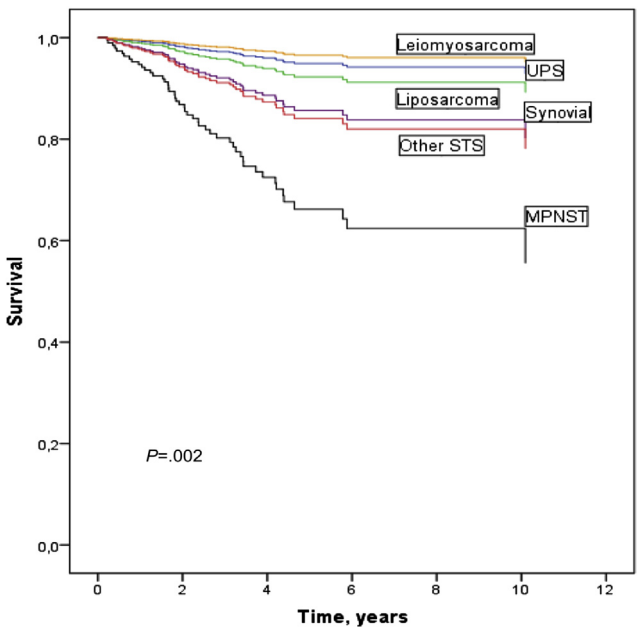

Fig. 2. Local recurrence-free survival by histopathologic subtype and wide surgical margin, n = 462. Fully adjusted cox regression model, mean value for continuous variables (age and tumor size), and the most common value for the categorical variables (high malignancy grade, male, deep location, extremity site, one operation, no chemotherapy, postoperative radiation therapy). MPNST = malignant peripheral nerve sheath tumor; STS = soft tissue sarcoma; UPS = undifferentiated pleomorphic sarcoma.

of prognostic factors (12, 23). Histologic subtypes represent a biological diversity that influence radiosensitivity and should be taken into account in the clinical setting.

The majority of LRs (65%) in our cohort were in field, as in other reports (18, 19). Princess Margaret Hospital reported on the geometric relationship between LR (n = 60) and RT volume; 82% recurred within the target volume and 15% out of field (18). In 25 cases of STS LRs from the Royal Marsden Hospital, 84% of LRs arose in target volume I or II (19). Fourteen percent (7/49) of LRs in our study were out of field. This suggests a too narrow field border, although target volume designations were similar to volume definitions presented from Princess Margaret Hospital, which the authors concluded to be appropriate. Out-of-field LRs were regarded mainly as instances of uncharacteristic disease spread or intercompartmental contamination during surgery (18). One-fifth of LRs in our study arose in the periphery of the PTV, involving the tissue at the field border receiving 50% of the prescribed dose. The tumor periphery is believed to hold a high fraction of clonogenic cancer stem cells, hence, inadequate dose delivery in the perimeter of the CTV, may explain some of the local failures.

In conclusion, a total dose of 50 Gy seems adequate following wide margin surgery, whereas intralesional margins call for a higher RT dose. Accelerated RT appears to be feasible and effective in adjuvant RT of STS. Most LRs were in field. Varying radiosensitivity for diverse histologic subtypes of STS suggests tailoring the RT dose according to histologic subtype in addition to grade, size, depth, and the critical factor surgical margin. Considering the rarity of STS, a multigroup clinical trial could conceivably shed more light on the optimization of adjuvant RT dose in STS.

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