Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–8, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.11.023

CLINICAL INVESTIGATION

RADIOTHERAPY TO IMPROVE LOCAL CONTROL REGARDLESS OF SURGICAL MARGIN AND MALIGNANCY GRADE IN EXTREMITY AND TRUNK WALL SOFT TISSUE SARCOMA: A SCANDINAVIAN SARCOMA GROUP STUDY

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Purpose: Adjuvant radiotherapy has during the past decades become increasingly used in the treatment of localized soft tissue sarcoma. We evaluated the effect of radiotherapy (RT) on local recurrence rates (LRRs) in Scandinavia between 1986 and 2005.

Methods and Materials: A total of 1,093 adult patients with extremity or trunk wall soft tissue sarcoma treated at four Scandinavian sarcoma centers were stratified according to the treatment period (1986–1991, 1992–1997, and 1998–2005). The use of adjuvant RT, quality of the surgical margin, interval between surgery and RT, and LRR were analyzed. The median follow-up was 5 years.

Results: The use of RT (77% treated postoperatively) increased from 28% to 53%, and the 5-year LRR decreased from 27% to 15%. The rate of wide surgical margins did not increase. The risk factors for local recurrence were histologic high-grade malignancy (hazard ratio [HR], 5), an intralesional (HR, 6) or marginal (HR, 3) surgical margin, and no RT (HR, 3). The effect of RT on the LRR was also significant after a wide margin resection and in low-grade malignant tumors. The LRR was the same after preoperative and postoperative RT. The median interval from surgery to the start of RT was 7 weeks, and 98% started RT within 4 months. The LRR was the same in patients who started treatment before and after 7 weeks.

Conclusion: The results of our study have shown that adjuvant RT effectively prevents local recurrence in soft tissue sarcoma, irrespective of the tumor depth, malignancy grade, and surgical margin status. The effect was most pronounced in deep-seated, high-grade tumors, even when removed with a wide surgical margin. © 2008 Elsevier Inc.

Soft tissue sarcoma, Adjuvant radiotherapy, Surgical margin, Local recurrence.

INTRODUCTION

A high malignancy grade and the quality of the surgical margin are the two most important risk factors for local recurrence (LR) of soft tissue sarcomas (STSs) (1–7). STSs were formerly regarded as relatively radioresistant tumors. In the past two decades, however, mounting evidence has shown an effect of radiotherapy (RT) on STS. Two randomized studies and several retrospective reports have indicated improved local control when surgical removal of high-grade STS was combined with RT (2, 8–14). The effect of RT has mainly been demonstrated after intralesional or marginal surgery, but improvements in local control after adding RT to wide margin surgery has also been reported (15–17). The effect of RT on low-grade malignant sarcomas is still controversial (9, 17, 18).

When the Scandinavian Sarcoma Group (SSG) was started in 1979, surgery with a wide margin was considered sufficient

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Supported in part by the Swedish Children Cancer Society, Swedish Cancer Society, and Nordic Cancer Union.

N. L. Jebsen received funding from the National Competence Center for Sarcoma and from Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway.

Conflict of interest: none.

Acknowledgments—We are grateful to Tore Wenzel-Larsen, statistician, Center for Clinical Research, Haukeland University Hospital, Bergen, Norway; Anne-Lise Salbu, coordinator, Center for Bone and Soft Tissue Tumors, Haukeland University Hospital, Bergen, Norway; and Eva-Marie Olofsson, SSG-secretariat, Department of Cancer Epidemiology, Lund University Hospital, Lund, Sweden.

Received Oct 6, 2007, and in revised form Nov 16, 2007. Accepted for publication Nov 16, 2007.

treatment of STS, and RT was used only for those with an intralesional or marginal margin. Because of the positive international experience of adjuvant RT, its use also increased in Scandinavia. In 1998, adjuvant RT was formally recommended by the SSG for intralesional and marginal margins, regardless of tumor depth, and for deep-seated, high-grade sarcoma, regardless of margin status (Clinical Protocol SSG XIII) (19). RT was recommended to begin as soon as the wound had healed. The only study on the importance of an early start of RT for STS found a better local recurrence-free survival rate (88%) in patients starting RT <4 months after surgery than in patients who started >4 months after surgery (62%) (20).

In 1986, the SSG established a register of soft tissue and bone sarcomas, including registration of detailed patient, tumor, treatment, and follow-up data. This register and the gradually increased use of RT gave us an opportunity to assess the effect of RT in relation to the surgical margins and histologic malignancy grade in STS patients treated at Scandinavian sarcoma centers between 1986 and 2005.

METHODS AND MATERIALS

Patients and referral

The study was conducted in accordance with the Helsinki Declaration of 1975 (revised in 2000) and was approved by the Regional Committee for Medical Research Ethics and the Ombudsman for Privacy in Research, Norwegian Social Science Data Service.

The SSG Register currently contains information on >5,000 patients. It includes data on about 90% of all sarcomas treated in Sweden and Norway and is considered representative of the population. The remaining 10% of STSs not reported are mainly small subcutaneous lesions or STSs diagnosed in patients with severe other disease or with a sarcoma diagnosis established after death (21). The participating institutions follow the SSG guidelines regarding the choice of treatment modalities, classification of surgical margins, histopathologic classification, and malignancy grading (22).

A total of 1,888 adult patients (>16 years old) with STS of the extremity or trunk wall were reported from the four largest sarcoma centers contributing to the SSG Register between 1986 and 2005. For this study, patients with dermatofibrosarcoma protuberans, Kaposi's sarcoma, mesothelioma, myxoid chondrosarcoma, Ewing's sarcoma/peripheral primitive neuroectodermal tumor, or Grade 1 liposarcoma/atypical lipomatous tumor (not considered for adjuvant RT in Scandinavia) were excluded, as were patients with overt metastases at diagnosis of the primary tumor ($n = 86$) and patients first referred after local recurrence ($n = 93$). Also, 474 patients referred after surgery and 142 patients referred after open biopsy were excluded. When patients with STS undergo surgery outside of a sarcoma center, most tumors are shelled out or removed piecemeal because the sarcoma diagnosis is often not recognized before surgery (23–25). The amount of tumor tissue remaining after such unplanned surgery often cannot be accurately established, and reliable assessment of the surgical margin after reoperation is difficult. Likewise, an open surgical biopsy performed by a surgeon with no experience with sarcoma might contaminate the wound with tumor tissue, making margin assessment after definitive surgery unreliable.

The remaining 1,093 adult patients with primary, nonmetastatic STS of the extremity or trunk wall, who had been referred before any surgery, constituted the study group (Table 1). They were treated at one of the four sarcoma centers with surgery alone ($n = 598$), with surgery and adjuvant RT ($n = 381$), surgery and chemotherapy ($n = 33$), or surgery and both chemotherapy and RT ($n = 81$).

Of the 1,093 patients, 51% were male. The median age was 65 years (range, 16–95 years). Two-thirds of the tumors were located in the lower extremity, including the gluteal region, and one-fifth were located in the upper extremity. Three-quarters of the tumors were deep seated. The median tumor size was 8 cm (range, 1–47 cm). Two-thirds of the patients had undergone no invasive procedure before referral to the sarcoma center. In the remaining patients, either a fine-needle or core biopsy had been performed before referral (Table 2).

The histopathologic classification and malignancy grade were determined at the different centers using the SSG guidelines (22). The

Table 1. Patient and tumor characteristics

Characteristic	Value
Gender	
Male	553 (51)
Female	540 (49)
Age at diagnosis (y)	
Median	65
Range	16–95
Tumor site	
Lower extremity	
Gluteal	73 (7)
Thigh	469 (43)
Knee	39 (4)
Lower leg	127 (12)
Foot	28 (2)
Upper extremity	
Shoulder	57 (5)
Upper arm	78 (7)
Elbow	17 (1)
Lower arm	47 (4)
Hand	7 (1)
Trunk	
Upper trunk	76 (7)
Lower trunk	35 (3)
Groin	40 (4)
Location	
Subcutaneous	274 (25)
Deep seated	817 (75)
Tumor size (cm)	
Median	8
Range	1–47
Malignancy grade	
1	26 (2)
2	145 (14)
3	332 (31)
4	585 (53)
Histopathologic type	
MFH	473 (43)
Liposarcoma	171 (16)
Leiomyosarcoma	91 (8)
Synovial sarcoma	86 (8)
MPNST	66 (6)
Fibrosarcoma	47 (4)
Myxofibrosarcoma	36 (3)
Other	37 (3)
Unclassified	86 (8)

Abbreviations: MFH = malignant fibrous histiocytoma, MPNST = malignant peripheral nerve sheath tumor.

Table 2. Referral pattern, surgery, and margin status stratified by study period for 1,093 patients

	1986–1991		1992–1997		1998–2005		Total	
Variable	*n*	%	*n*	%	*n*	%	*n*	%
Referral pattern								
Virgin	141	62	227	67	403	77	771	71
Fine-needle aspiration	78	34	83	24	36	7	197	18
Core biopsy	9	4	30	9	84	16	123	11
Surgical procedure								
Amputation	18	7	23	7	37	7	78	7
Local excision	210	93	317	93	487	93	1014	93
Surgical margin								
Intralesional	21	9	20	6	44	8	85	8
Marginal	77	34	112	33	210	40	399	37
Wide*	130	57	208	61	271	52	609	56

* Included myectomy and compartmental margins.

most frequent histologic type was malignant fibrous histiocytoma (MFH) (43%). Since 2003, these tumors have more often been called high-grade pleomorphic sarcoma or classified as myxofibrosarcoma, leiomyosarcoma, or liposarcoma. A total of 964 tumors (83%) were high grade (Grade 3 or 4) in the four-grade system used. The morphology of 1,000 STSs from the SSG Register were re-examined by a peer-review committee of Scandinavian pathologists in connection with other studies (26). Of our subset of patients, 39% had been included in that re-examination. The distribution of tumor features (histologic type, malignancy grade, size, and depth) was similar in the different centers (data not shown). The preoperative diagnosis at the sarcoma centers was by fine-needle biopsy (72%), core-needle biopsy (19%), or open biopsy (6%); 3% of the tumors were resected without a preceding biopsy. In Scandinavian sarcoma centers, a needle biopsy is the recommended diagnostic procedure (21).

Surgery

The type of surgical margin obtained was primarily classified according to Enneking *et al.* (27) in cooperation between the surgeon and pathologist. An intralesional margin was recorded when the plane of the excision, in any part of the tumor, passed through the tumor, leaving microscopic or macroscopic tumor tissue behind. A marginal margin was recorded when the plane of excision passed outside the tumor, but in any part too close to the tumor to merit a wide margin. A wide margin was recorded when the excised tumor all around was surrounded by a cuff of healthy tissue or uninvolved fascia. A compartmental margin was recorded when the entire compartment containing the tumor was removed. The margin obtained by myectomy was regarded as a subtype of the wide margin and was applied to strictly intramuscular lesions (not subjected to open biopsy) when the involved muscle, from origin to insertion, was completely removed (28). The terms ''negative/positive microscopic margins'' or ''contaminated wide margins'' were not used. Myectomy and compartmental margins were grouped as wide margins. Using this definition, a wide margin was achieved in 589 (56%) of the 1093 patients. Amputation was performed in 7% of the extremity tumors.

To examine whether classification of the surgical margin adhered to the SSG guidelines, a random sample comprising one-quarter of the tumors were evaluated by a panel of sarcoma surgeons, who scrutinized the surgical and pathology reports. It was found that one center had systematically used measurements of physical tissue distances on formalin-fixed specimens to differentiate between marginal and wide margins. This center reported 15% fewer cases of wide margins than the others, which could be explained by the tissue shrinkage/deformation caused by the formalin fixation ''converting'' a wide margin to a marginal margin.

Radiotherapy

Radiotherapy was administered to 462 (42%) of 1,093 patients to a dose of 50 Gy in 25 fractions within 5 weeks. If the surgical margin was intralesional, an additional dose of 10–20 Gy was usually given. RT was given postoperatively to 356 patients and preoperatively to 106 patients.

Follow-up and outcome

The patients are routinely followed for 10 years. Physical examination of the primary tumor area and a chest X-ray are mandatory, with additional magnetic resonance imaging of the primary tumor site when necessary. The median follow-up time for survivors was 5 years (range, 0.1–20 years) for the whole group and 3 years (range, 0.1–9 years) for the patients diagnosed between 1998 and 2005. A LR was diagnosed in 153 patients (14%), 340 (31%) developed metastases, 309 (28%) died of their disease, and 217 (20%) died of unrelated causes.

Statistical analysis

Patients were stratified into three groups according to the year of diagnosis: 1986–1991 ($n = 228$), 1992–1997 ($n = 340$), and 1998–2005 ($n = 525$). Changes over time of the estimated local recurrence rates (LRRs), surgical margin type, and use of RT were analyzed. Also, the use of RT relative to the surgical margin type and average interval between surgery and RT were analyzed.

Descriptive data were compared using chi-square exact tests when feasible. For survival analysis, we used a Kaplan-Meier survival analysis with a log–rank (Mantel-Cox) test of equality of survival distributions. Univariate analysis of potential prognostic factors was done using the Cox regression method. Factors reported in previous studies to have prognostic effect on LR were included in the survival analyses. Cox multiple regression analysis was used to examine simultaneous effects of potential prognostic factors for LR and to estimate LRRs for different patterns of risk factors for LR. The multivariate Cox model was preferred to illustrate LRR in relation to RT, because this model adjusts for other variables related to

local control. The most common category for the nonsignificant categorical covariates and mean values for continuous covariates were chosen in the plots. The interval to local and distant relapse was calculated from the date of the last operation for the primary tumor. A p value of <0.05 was considered statistically significant. The software used for statistical analysis and data preparation was Statistical Package for Social Sciences, version 14.0 (SPSS, Chicago, IL).

RESULTS

The annual number of patients referred (before any surgery) increased with time. The fraction of wide surgical margin (including myectomy and compartmental margins) was similar, and the amputation rate did not change over time (Table 2).

Local recurrence

The estimated 5-year LRR was 27% in the 1986–1991 group and 15% in the 1998–2005 group (p <0.001; Table 3 and Fig. 1). The LRR was the same among the four centers, with similar LRR rates after preoperative and postoperative RT (data not shown).

The surgical margin type and malignancy grade had a significant prognostic value on both univariate and multivariate analyses (Table 4). Tumor size was analyzed as a continuous variable, with the hazard ratio (HR) calculated per 10 cm, and was of minor importance, although statistically significant. On multivariate analysis, malignancy grade (HR, 5), an intralesional margin (HR, 6), a marginal margin (HR, 3), and no RT (HR, 3) were the strongest prognostic factors for LR.

Radiotherapy

The use of adjuvant RT increased from 28% to 53% (p <0.001) between the first and last period (Table 3). In the case of an intralesional or a marginal surgical margin, the use of RT increased from 62% to 82% and 56% to 76%, respectively (Table 5). A marked increase was also noted, from 5% to 30%, in the use of RT in patients with wide margins. The increased use of RT after marginal/intralesional margins was mainly seen in the intermediate period, 1992–1997. Since 1998, the increase in the use of RT has been most pronounced after wide margin surgery. The use of RT increased at a similar rate among the four centers. On univariate analysis, patients receiving RT did not have a significantly lower LR risk. However, on multivariate analysis, with correction for the confounding prognostic factors related to patient selection for RT, RT was of highly significant importance

Table 3. Estimated local recurrence rates, wide surgical margin and use of radiotherapy stratified by study period

Variable	1986–1991	1992–1997	1998–2005	p
5-year local recurrence rate (%)	27	16	15	<0.001
Wide* margin (%)	57	61	52	0.02
Adjuvant radiotherapy (%)	28	36	53	<0.001

* Included myectomy and compartmental margins.

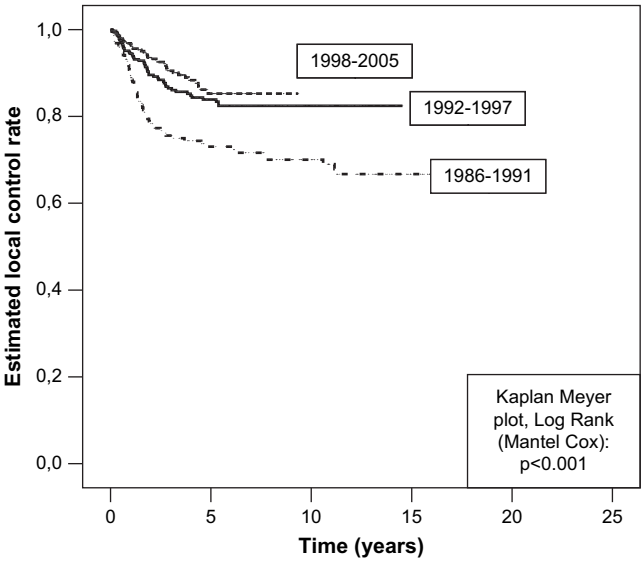


Fig. 1. Local control rate for three different periods.

(HR, 3; p <0.001; Table 4). In an explorative *post hoc* analysis, no significant covariance was found between RT and malignancy grade or depth or between malignancy grade and tumor size or depth. The effect of RT increased with an increasing number of risk factors (high malignancy grade and intralesional or marginal margin; Fig. 2). For patients with deep-seated, high-grade tumors (673 of 1,093, 62%), the risk of LR without RT was more than three times greater than that with RT.

Radiotherapy improved local control regardless of the surgical margin type. The 5-year local control rate was 28% without RT and 62% after RT for an intralesional margin, 74% vs. 81% for a marginal margin, and 87% vs. 93% after a wide margin (including myectomy and compartmental margins). The improvement in the estimated (using the multivariate Cox model) local control rates after RT differed for different combinations of tumor characteristics (depth and malignancy grade) and surgical margin type (Table 6). The

Table 4. Univariate and multivariate Cox regression analysis results of potential prognostic factors for local recurrence

	Univariate		Multivariate	
Prognostic factors for local recurrence	HR	95% CI	HR	95% CI
Age at diagnosis (per 10 y)	1.1	1.0–1.3	1.1	1.0–1.2
Gender (male vs. female)	1.1	0.8–1.5	1.1	0.8–1.5
Location (deep vs. subcutaneous)	1.4	1.0–2.2	1.4	0.9–2.2
Site (trunk vs. extremity)	1.9	1.3–2.7	1.4	0.9–2.2
Size (per 10 cm)	1.5	1.2–1.9	1.3	1.0–1.7
Malignancy grade (high vs. low)	3.5	1.8–6. 8	4.8	2.4–9.6
Surgical margin				
Intralesional vs. wide*	3.9	2.5–6.1	6.3	3.6–10.9
Marginal vs. wide*	1.6	1.1–2.3	2.6	1.7–4.0
Radiotherapy (no vs. yes)	1.0	0.8–1.4	2.8	1.9–4.3
Chemotherapy (no vs. yes)	1.1	0.7–2.0	1.3	0.7–2.3

Abbreviations: HR = hazard ratio; CI = confidence interval.
* Included myectomy and compartmental margins.

Table 5. Percentage of patients given radiotherapy related to surgical margin stratified by study period

Surgical margin	1986–1991 (%)	1992–1997 (%)	1998–2005 (%)
Intralesional	62	85	82
Marginal	56	73	76
Wide*	5	11	30

* Included myectomy and compartmental margins.

multivariate analysis on the prognostic factors for LR demonstrated that the effect of RT was also significant for low-grade STSs. The number of LRs in low-grade tumors was low, with only nine LRs occurring in 171 patients, of whom 38 (22%) had received RT. All the LRs developed among the 133 patients treated with surgery alone.

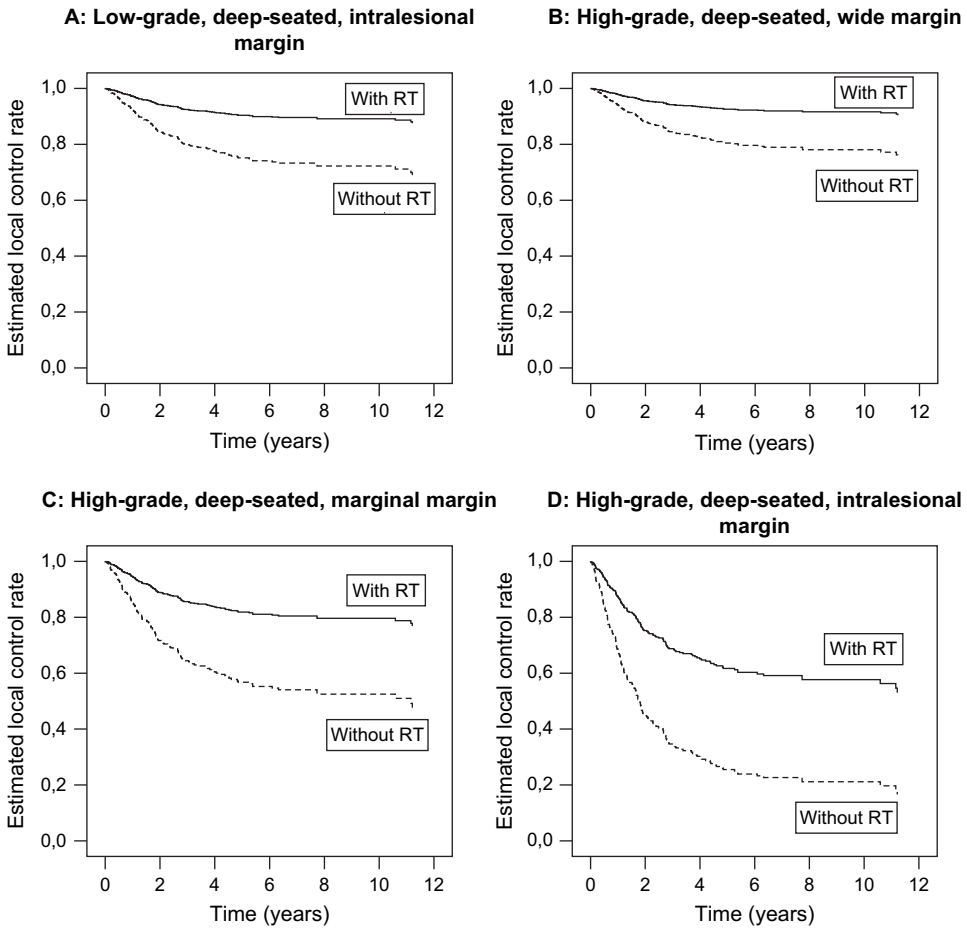
The median time from surgery of the primary tumor to the start of postoperative RT was 7 weeks (range, 2–50 weeks) and was similar in the three periods. Of the 356 patients receiving RT, 326 (98%) started RT within 4 months after surgery, and 93% had started RT within 3 months. We could not demonstrate a change in the LRR with an increasing interval between surgery and RT, neither when the interval was analyzed as a continuous variable nor when dichotomized at 7 weeks.

Chemotherapy

Adjuvant chemotherapy (CHT) was administered to selected patients according to the SSG protocols (19, 29). Since 1998, the SSG has recommended adjuvant CHT for patients <70 years with high-risk STS, defined as high-grade STS with at least two of the following three risk factors: size >8 cm, vascular invasion, and necrosis (19). In the present study, 124 patients (11%) received CHT; 88 of these patients also received adjuvant RT. Comparing the 1986–1991 group with the 1998–2005 group, the percentage of patients undergoing CHT increased from 2% to 19%. We did not find any improvement in LR related to the use of CHT on either univariate or multivariate analysis. However, the group that received CHT was small.

DISCUSSION

This study was of a large, prospective series of STSs treated at four sarcoma centers according to common



* The calculations are based on the multivariate Cox model (Table 4). For the other covariates in the model, the diagram is based on mean values for continuous and the most common category for categorical covariates.

Fig. 2. (A–D). Local control rates* with and without radiotherapy (RT) for different combinations of grade, tumor depth, and surgical margin type. *Calculations based on multivariate Cox model (Table 4); for other covariates in model, diagram based on mean values for continuous, and most common category for categorical, covariates.

Table 6. Predicted 5-year local control rates* stratified by radiotherapy use and tumor and treatment features

Variable	5-y Local control rate (%)	
	No RT (n = 622)	RT (n = 453)
Subcutaneous, low grade		
Wide† margin	0.97	0.99
Marginal margin	0.97	0.99
Intralesional margin	0.82	0.93
Subcutaneous, high grade		
Wide† margin	0.86	0.95
Marginal margin	0.67	0.87
Intralesional margin	0.38	0.71
Deep, low grade		
Wide† margin	0.96	0.98
Marginal margin	0.89	0.96
Intralesional margin	0.75	0.90
Deep, high grade		
Wide† margin	0.80	0.93
Marginal margin	0.57	0.82
Intralesional margin	0.26	0.62

* Calculations determined from multivariate Cox model (Table 4); for other covariates in model, data based on mean values for continuous and most common category for categorical covariates.

† Included myectomy and compartmental margins.

guidelines and with complete follow-up. The LRRs decreased as the use of adjuvant RT increased. Our findings are in concordance with previous publications on the effect of RT for localized STS (2, 8–14). When we examined other treatment-related factors (surgical margin type, interval from surgery to the start of RT, use of adjuvant chemotherapy), we could not demonstrate any relation to the improved local control rate. The 5-year LRR in the group given adjuvant RT was 19% compared with 17% for those without RT (which explains the insignificant HR for RT on univariate analysis). However, the patients who underwent RT were more likely to have had deep, high-grade tumors excised with an intralesional or marginal margin. The presence of several risk factors for LR seemed to be, in part, compensated for when RT was used before or after surgery.

Several factors of prognostic significance for LR have been reported (1–5, 30), and these were included in our analyses. Most studies have agreed that high malignancy grade and an intralesional or a marginal surgical margin have the strongest negative prognostic value for LR; this was confirmed in our study. Specific histologic types have been associated with high risk of LR, especially MFH (4). We also found that MFH had the greatest LRR, although this was not statistically significant on univariate analysis compared with the other histologic types. When dichotomizing histologic type into MFH or other histologic type on multivariate analysis, we found a significantly greater risk of LR in the MFH group (data not shown). However, because of the long recruitment time for the study patients, during which the histologic classification systems have changed, we chose to exclude the morphologic diagnosis from the multivariate analysis. This did not change the significance of the other prognostic factors. Recently, a peripheral tumor growth pattern, defined as pushing or infiltrative, was shown to correlate strongly with LR risk (and distant metastasis risk) (31). The tumor growth pattern was not systematically classified in our patient series and therefore could not be correlated with LR.

Our multivariate analysis also demonstrated a significant effect of RT for low-grade tumors. Choong *et al*. (32) found the same, reporting a correlation among LR, large tumor size, and the absence of RT in a study of 132 low-grade STS. Yang *et al*. (9) reported that RT decreased the risk of LR on the basis of six LRs after surgery alone for 19 low-grade tumors compared with one LR in 22 that received adjuvant RT. Mollabashy *et al*. (18) concluded that RT had no effect on LR among 108 low-grade STSs. Pisters *et al*. (8, 17) found no effect of RT (brachytherapy) among 45 patients with low-grade tumors. In our series, the LRR for low-grade STSs resected with a wide margin was low (≤5% after 5 years). Therefore, we suggest that for low-grade STSs, RT should be reserved for tumors resected with an intralesional or a marginal margin.

We also found a clear effect of RT when combined with surgery with a wide margin, confirming the long-term results reported from a randomized brachytherapy study (17). In our study, the effect was especially pronounced for high-grade, deep-seated tumors. This indicates that for high-grade, deep-seated tumors, which constitute about 60% of extremity sarcomas, the use of RT does not allow for compromising the surgical margin. A previous report from the SSG Register demonstrated LRRs after an intralesional or a marginal margin with RT (24%) similar to the LRRs after surgery alone with a wide margin (25%) (15). The relatively high LRR was at that time (1986–1993) comparable to those of other series of deep-seated sarcomas (9, 10). Stotter *et al*. (16) reported similar findings in 175 STSs, of which 152 were deep seated. Wide or radical surgery without RT, and marginal or intralesional surgery with RT, had equal local control rates (16). However, a superior local control rate was obtained when RT was added to a wide surgical margin (16). Adjuvant RT has been reported to result in local control rates of about 90% in other studies in which most tumors were high grade and deep seated and had been resected with a negative margin (17, 33). Our criteria for recording a wide margin were strict, which might explain the relatively low rate of wide margins reported. This could also explain the low LRR after wide margin surgery without RT (around 10%) for all tumors, except for deep-seated, high-grade tumors (20%).

Formerly, the use of RT in Scandinavia was determined only by the quality of the surgical margin obtained (34). A single-institution study found that strictly intramuscular tumors, not subjected to a preceding open biopsy, and with no tumor invasion of the muscle fascia, had a low LRR after a wide resection and without RT (two LRs in 30 tumors, 25 of which were high grade) (35). We could not verify this in our multicenter study. Another Swedish study of 129 subcutaneous sarcomas found that none of the low-grade tumors and 7% of the high-grade tumors developed LR after wide local

excision without RT (36). Other investigators have presented favorable local control rates after surgery alone for low-risk STSs (37–40). Alektiar *et al*. (37) did not find improved local control after RT in 204 patients with Stage IIB (high grade, size ≤5 cm) STSs of the extremity who had negative surgical margins. Geer *et al*. (39) demonstrated that RT did not affect local control in a group of 174 patients with small (<5 cm) STSs of the extremities.

Recent reviews have recommended adjuvant RT for most patients with extremity STS (7, 41, 42). However, our findings and the cited studies (36–39) imply that low-grade, subcutaneous, and deep-seated STSs can be safely treated by wide excision alone, irrespective of size. Whether the estimated 5-year local control rate of 86% (Table 6) for patients with high-grade, subcutaneous tumors resected with a wide margin requires RT depends on the expected morbidity caused by surgical removal of LR.

Few reports exist about the importance of the interval from surgery to the start of RT. One would expect that a protracted time until the start of RT would decrease the probability of eradicating residual tumor cells that have had a chance to repopulate. Schwartz *et al*. (20) studied the effect of delayed postoperative RT on local control of 58 STSs of the extremities and trunk wall and found that a delay of >4 months was associated with inferior local control. An increased LRR after delayed onset of RT has been reported for carcinomas of the breast and upper aerodigestive tract (43, 44). The SSG has recommended that postoperative RT be started as soon as the wound has healed. However, the median interval from surgery to the start of postoperative RT was 7 weeks in our series. Information on the reasons for this delay was not reported to the Register; however, we believe that postoperative complications (wound healing problems, infections, late general recovery) were the most frequent explanations. Furthermore, the surgical procedure sometimes requires reconstruction with skin transplantation or musculocutaneous flaps, which prolongs the wound healing time. The availability of RT might sometimes have been a problem. The postoperative chemotherapy given to 10% of the patients before RT could also have contributed to the delay. However, we found that the interval from surgery to the start of RT did not influence the LR risk. Our results indicate that a delay of ≤4 months to the onset of RT does not compromise local control.

The decreased LRR did not translate into a decreased rate of metastasis. The 5-year metastasis-free survival rate was similar (67%, 67%, and 63%) for the three periods studied. On multivariate analysis, including tumor characteristics and treatment, we found no association between the surgical margin type, the use of RT, and the risk of metastasis (data not shown). This was not surprising, because it has repeatedly been shown that the type of treatment for the primary tumor, which relates to the different risks of LR, does not influence the metastatic rate of STSs in the extremity or trunk wall (4, 10, 12, 17, 45). Hence, it seems that metastases from these sarcomas have been, in most cases, seeded before the primary tumor has been removed.

CONCLUSION

Adjuvant RT decreased the LRR of STSs, irrespective of surgical margin type, tumor depth, and malignancy grade. Tumor resection with an intralesional or a marginal margin necessitates RT. The effect of RT was small on low-grade tumors, irrespective of depth, after resection with a wide margin. The effect was moderate in high-grade, subcutaneous tumors resected with a wide margin. Whether this risk requires RT depends on the expected morbidity caused by surgical treatment of LR. RT had a pronounced effect in high-grade, deep-seated tumors, including after resection with a wide margin. In these tumors, the RT regimen used (50 Gy in 25 fractions within 5 weeks) could not compensate for less-extensive surgery. Thus, a marginal resection combined with RT was followed by a substantially greater LRR than a wide resection combined with RT. Whether intensifying the RT would allow for less-extensive surgery is not clear. It is a delicate balance to weigh the advantage of function-preserving surgery against the increased morbidity risk with escalating the radiation dose. The choice might be facilitated by new approaches in enhancing RT effects and optimizing the radiation dose distribution in adjuvant treatment of STS.

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