

Prognostic factors in adult soft tissue sarcoma treated with surgery combined with radiotherapy: a retrospective single-center study on 164 patients

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Abstract

The aim of the present study is to assess the disease profile, outcome and prognostic factors in patients treated with surgery combined with radiotherapy (RT), with or without chemotherapy (CXT), for soft-tissue sarcoma (STS) in a multidisciplinary setting. One hundred and sixty-four patients with STS treated between 1980 and 2010 at the *Centre Hospitalier Universitaire Vaudois* were enrolled in this retrospective study. Seventy-six percent of patients underwent postoperative RT with (24%), or without (52%) CXT, 15% preoperative RT with (5%), or without (10%) CXT, surgery alone (7%), or RT alone (2%) with or without CXT. The median follow-up was 60 months (range 6-292). Local failure was observed in 18%, and distant failure in 21% of the patients. Overall survival (OS), disease-free survival (DFS), local control (LC) and distant metastases-free survival (DMFS) were 88%, 68%, 83%, and 79% at 5 years, and 80%, 56%, 76%, and 69% at 10 years, respectively. In univariate analyses, favorable prognostic factors for OS, DFS, and DMFS were tumor size 6 cm or less, World Health Organization (WHO)/Zubrod score 0, and stage 2 or less. Age and superficial tumors were favorable only for OS and DMFS respectively. STS involving the extremities had a better outcome regarding DFS and LC. Histological grade 2 or less was favorable for DFS, DMFS, and LC. Radical surgery was associated with better LC and DMFS. RT dose more than 60 Gy was favorable for OS, DFS, and LC. In multivariate analyses, independent factors were age for OS; tumor size for OS, DFS and DMFS; WHO/Zubrod score for OS, DFS and LC; hemoglobin level for DFS; site for

DFS and LC; tumor depth for DMFS; histological grade for DFS and LC; surgical procedure for LC and DMFS; and RT dose for OS.

This study confirms that in a multidisciplinary setting, STS have a fairly good prognosis. A number of prognostic and predictive factors, including the role of surgery combined with RT, were identified. Regarding RT, a dose of more than 60 Gy was associated with a better outcome, at the price of a higher toxicity. We could not demonstrate a superiority of preoperative RT over postoperative RT.

Introduction

Soft-tissue sarcomas (STS) are uncommon solid tumors of the adult, accounting for only 1% of all cancers. STS present with wide variations in anatomic sites, subtypes, and prognosis.¹ Management with adequate surgery and radiotherapy (RT) yield excellent control rates and good function.² Distant metastases, if they occur, are usually a later event.

The histological grade of STS is the most important prognostic factor for the outcome regarding distant metastasis and OS.^{3,4} Several grading systems based on cellularity, cellular pleomorphism, mitotic count, and necrosis correlate with prognosis. The French *Fédération Nationale des Centres de Lutte Contre Le Cancer* (FNCLCC) grading system is divided into a three-grade scale, and is rated on the total score of the following parameters: tumor differentiation, mitotic rate, and degree of necrosis.⁴

Conservative surgery with wide excision whenever possible, followed or preceded by RT is considered to be the current standard treatment.⁵⁻¹³

Chemotherapy (CXT) has been primarily applied in metastatic disease. In high-risk localized STS (size >5 cm, grade II/III), surgical resection followed by RT alone is followed by a mediocre OS, due to the high incidence of distant metastases. Thus, CXT is often integrated into the multidisciplinary approach.¹⁴ A nomogram was established to predict the 12-year sarcoma-specific survival rate using age, histological subtype, grade, tumor size, depth, and anatomical site.^{15,16} Other clinical factors like performance status, blood count, surgical margins, and treatment modality influencing patients' survival remain a matter of controversy. Thus, the purpose of the present study was to collect data on all patients with STS treated with combined therapy in our institution, to assess the disease profile, and analyze all the potential prognostic or therapeutic factors.

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Materials and Methods

Patients

We collected data on 164 eligible patients treated between 1980 and 2010 at the CHUV. Our inclusion criteria included age over 16 years, confirmed pathological diagnosis of soft tissue sarcoma, no evidence of distant metastases, and a minimum of 6 months follow-up after treatment. All the medical records were reviewed for age, gender, tumor size, involved sites, WHO/Zubrod performance status, hemoglobin (Hb), stage, treatment modality, time and site of relapse, treatment-related complications, time and cause of death, and date of last follow-up visit. Patients' data collection was approved by our Institutional Review Board.

Data collected on each patient included medical history, physical examination, complete blood count, operative records, and pathological reports. The pathological examinations were performed (Pr L.G.) according to the WHO classification,¹⁷ and FNCLCC grading system.⁴ Stage was established with the AJCC TNM staging system.¹⁸ WHO performance status was established according to medical records.

Patients were treated with multimodality

therapy as decided during our multidisciplinary sarcoma tumor boards. Treatments included surgical resection, RT, CXT, or a combination of these.

Early and late toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) V 3.0.

Statistical methods

OS was calculated from the date of diagnosis to the date of last follow-up or death from any cause. DFS was calculated from the date of diagnosis to the date of death or recurrence. LC was calculated from the date of diagnosis to the date of local recurrence. DMFS was calculated from the date of diagnosis to the date of distant metastases. Survival curves were computed according to Kaplan-Meier, and compared, using the Log-rank and the Wilcoxon test. Differences were considered significant if the P value was 0.05 or less (two-tailed). Multivariate analysis with Cox regression was used to determine prognostic factors. All prognostic factors identified in the univariate analyses with a P value 0.20 or less were included in the multivariate analyses.

Results

Patients' characteristics are presented in Tables 1 and 2. Median age was 50 years (range 15-89), and there were 75 (46%) women and 89 (54%) men. The most commonly involved sites were the lower extremity (52%), trunk (21%), upper extremity (15%), head and neck (7%), and retroperitoneum (5%). Median tumor size was 6 cm (range 1.5-36). Using the WHO classification, we identified liposarcoma in 23% of patients, malignant fibrous histiocytoma (MFH) in 21%, leiomyosarcoma in 12%, fibrosarcoma in 9%, synovial sarcoma in 9%, rhabdomyosarcoma in 5%, malignant peripheral nerve sheath tumor in 4%, angiosarcoma in 4%, and other or undefined types of sarcoma in 13% of patients.

Sixty-two percent of MFH occurred in the older age group (age >50 years), whereas 80% of synovial sarcoma occurred in the younger age group (age ≤50 years) (P=0.012). According to the FNCLCC grading system, grade I was identified in 24%, grade 2 in 35%, and grade 3 in 41% of patients. According to the AJCC TNM system, 25% of patients presented with stage I, 54% with stage II, and 21% with stage III. Most patients (62%) had a good WHO performance status.

The majority of patients (76%) received postoperative RT, of which 24% with combined CXT, and 52% with no CXT. Preoperative RT was administered in 15% of patients with (5%) or without (10%) CXT. Only 9% of patients underwent surgery (7%) or RT (2%) alone with or without CXT. Regarding patients treated with preoperative RT, 76% of patients had larger tumors (≥6 cm) than those receiving postoperative RT (P=0.021). Median total RT dose was 60 Gy (range 14.4-76). Altogether, 55 patients (34%) patients, all with grade 3 tumors, received a combination CXT. Of these, 4 patients had a concomitant RT-CXT schedule, and the remainder a sequential RT-CT schedule. Nine patients were given pre-operative CXT. The rest received post-operative CXT, following RT in 42 cases and concomitant with RT in 4 cases. Most patients (84%) received a combination or ifosfamid and adriamycin, with a median of 4 cycles (range: 1-9). The remainder were given various combinations of other drugs, including vincristine, dactinomycine, irinotecan and epirubicine. Chemotherapy was given in the following sites: head and neck (5 patients), trunk (23), the retroperitoneum (3), the upper extremity (9) and the lower extremity (15).

Local failure was observed in 18% of the patients, after a median time of 31 months (range 6-139). Of these, 62% of patients failed within the RT volume, 21% failed at the margin of the RT volume, and 17% of patients failed outside the RT volume.

Distant failures were observed in 34 (21%) patients (lung in 17, lung and other sites in 4, lung and liver in 5, liver only in one, other sites

Table 1. Patients' clinical and treatment characteristics.

Clinical characteristics	N	%
Median age		
≤50	76	46
>50	88	54
Gender		
Female	75	46
Male	89	54
Involved sites		
Lower extremity	85	52
Trunk	35	21
Upper extremity	24	15
Head and neck	11	7
Retroperitoneum	9	5
Median tumor size (longest axis)		
<6cm	70	43
≥6 cm	94	57
Histological subtype		
Liposarcoma	37	23
Malignant fibrous histiocytoma	34	21
Leiomyosarcoma	21	12
Fibrosarcoma	15	9
Synoviosarcoma	15	9
Rhabdomyosarcoma	8	5
MPNST	6	4
Angiosarcoma	6	4
Others	22	13
Histological grade		
Grade 1	40	24
Grade 2	57	35
Grade 3	67	41
TNM stage		
Stage 1	41	25
Stage 2	88	54
Stage 3	35	21
WHO/Zubrod performance status		
0	101	62
1	52	32
2	9	5
3	2	1
Treatment modality		
Preoperative radiotherapy ± CXT	25	15
Postoperative radiotherapy ±CXT	124	76
Surgery ± CXT	12	7
RT ± CXT	3	2
RT dose*		
>60 Gy	88	54
≤60 Gy	76	46

RT, radiotherapy; CXT, chemotherapy; MPNST, malignant peripheral nerve sheath tumor. *Median dose 60Gy: preoperative RT 50 Gy, postoperative RT 64Gy.

Table 2. Sites involved and pathological subtypes.

Pathological subtype	Head & neck	Trunk	Retroperitoneum	Upper extremity	Lower extremity	Total
Liposarcoma	1	3	5	0	28	37
MFH	1	10	1	2	20	34
Leiomyosarcoma	1	3	1	4	12	21
Fibrosarcoma	0	1	1	5	8	15
Synovial sarcoma	1	3	1	4	7	16
Rhabdomyosarcoma	1	4	0	2	1	8
MPNST	0	2	0	1	3	6
Angiosarcoma	3	2	0	0	1	6
Others	3	7	0	6	5	21
Total	11	35	9	24	85	164

in 8 patients), after a median time of 24 months (range 5-109). With a median follow-up of 60 months (range 6-292), 61% of the patients were alive without evidence of disease, 24% were alive with disease, 12% were dead from the disease, and 3% had died from other causes (3 from a second malignant tumor, 2 from unrelated causes). OS, DFS, LC, and DMFS were 88%, 68%, 83%, and 79% at 5 years, and 80%, 56%, 76%, and 69% at 10 years, respectively (Supplementary Table 1) (Figure 1). On univariate analyses (Supplementary Table 1), statistically significant factors favorably influencing OS were younger age (50 years or less), small tumor size (less than 6 cm), WHO performance 0, stage II or less, and RT dose more than 60 Gy. For DFS, the favorable factors were tumor at an extremity, tumor size less than 6 cm, WHO performance score 0, Hb level 100 g/mL or more, stage II or less, histological grade 2 or less, and RT dose more than 60 Gy. For LC, tumor at an extremity, WHO performance score 0, histological grade 2 or less, radical surgery, and RT dose more than 60 Gy were favorable factors. For DMFS, tumor size less than 6 cm, WHO performance score 0, superficial tumors, stage II or less, histological grade 2 or less, and radical surgery were favorable factors (Supplementary Table 1).

On multivariate analyses (Supplementary Table 2), independent prognostic factors for OS were age 50 years or younger, tumor size, WHO performance status, and RT dose more than 60 Gy. For DFS, tumor size, WHO performance status, histological grade, Hb level, and tumor site were independent prognostic factors. For LC, tumor site, WHO performance status, histological grade, and radical surgery were significant. For DMFS, tumor size, tumor depth, histological grade, and radical surgery were significant (Supplementary Table 3).

Toxicity

Grade 1 toxicity was observed in 9% of patients: grade 1 erythema in 8% and grade 1 dysphagia in 1%. Grade 2 toxicity was observed in 20% of patients: grade 2 edema, telangiectasis or fibrosis in 16%; grade 2 joint dysfunction in 1% and grade 2 pain or dysphagia in 3%. Toxicity higher than grade 3 was observed in 6% of patients: muscular atrophy and joint dysfunction in 4%, grade 4 liponecrosis and osteonecrosis in 2%. The incidence of grade 2 or more toxicity was found to be more frequent after a high dose of RT (>60 Gy) (P=0.03). There was no statistical difference regarding grade 2 toxicity or more between preoperative RT and postoperative RT (P=0.16) (Supplementary Table 3).

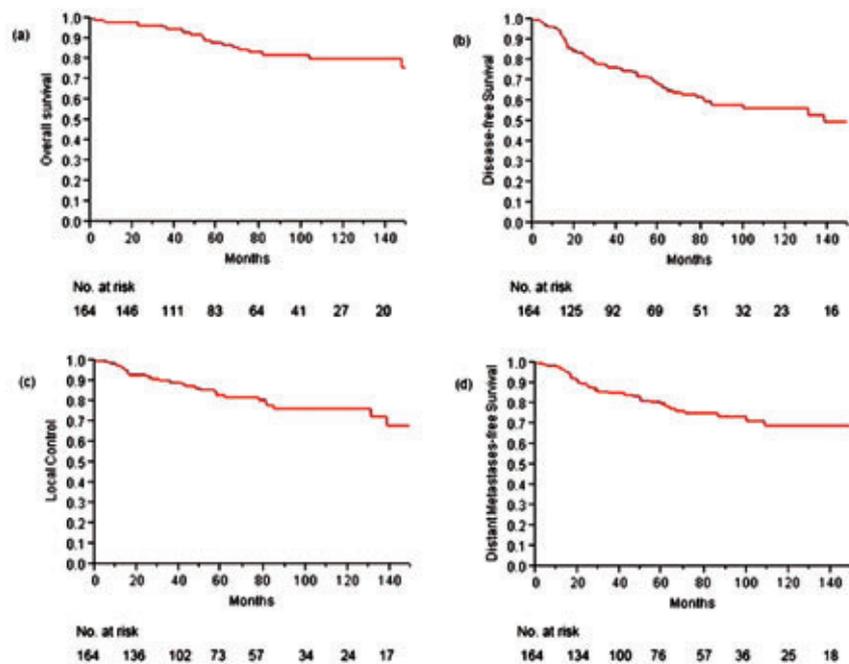


Figure 1. Overall survival (a), disease-free survival (b), local control (c), and distant metastases-free probability (d) in 164 patients with soft-tissue sarcoma.

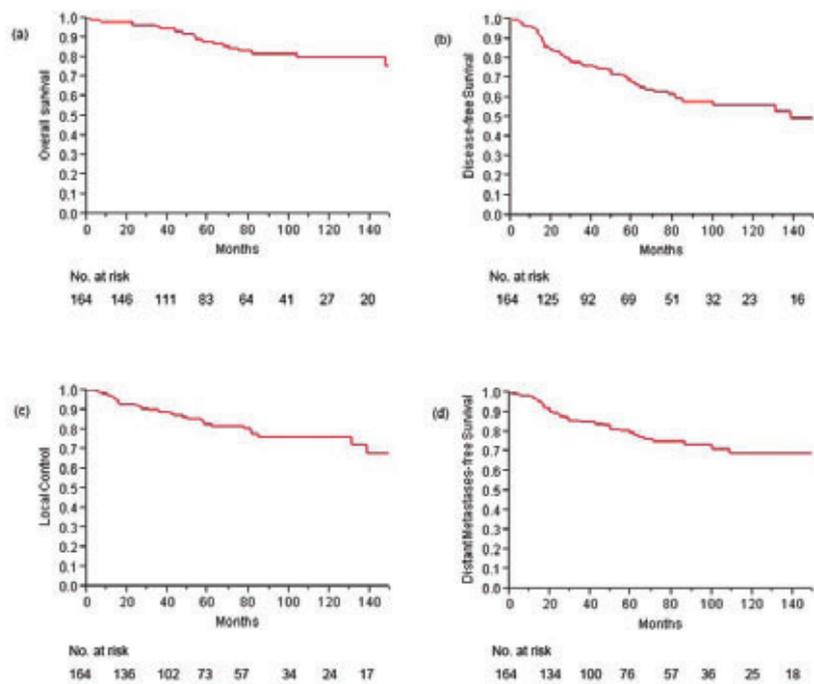


Figure 2. Overall survival (a), disease-free survival (b), local control (c), and distant metastases-free probability (d) for patients with (red) or without (green) chemotherapy.

Discussion

Patient characteristics

This retrospective study represents our experience in treating patients with STS in a multidisciplinary setting. It has yielded relatively similar patients' characteristics to those in the literature. Tumors most commonly occurred in patients aged around 50. The most frequent sites were the extremities, and especially the lower limbs. The predominant histological subtypes were liposarcoma (23%) and MFH (21%) as in previous reports. Intermediate to high histological grade (2 or more) dominated our data and a majority of patients had a good performance status.

Outcome

LC for the entire population was altogether good (5- and 10-year LC rate of 83% and 76%) and comparable with other studies.^{5-10,19-27} Distant failures were documented in 21% of the patients. The overall outcome (5- and 10-year OS of 88% and 80%, DFS of 68% and 56%, DMFS of 79% and 69%) was in the higher range compared to other studies.^{7,10,11,15}

Prognostic factors

Younger age has been found to be a favorable factor for DFS and OS in other reports on STS.^{15,16} Both univariate and multivariate analyses revealed that a better outcome could be predicted for patients under 50 years of age.

Tumor size is well known to be a predictive factor for OS, DFS, or DMFS in STS. The majority of papers take 5 cm as a cut-off value, which is the size limit in the current TNM staging system.^{18,19} The median tumor size in our study was 6 cm. We took both 5 and 6 cm as cut-off values for our univariate analysis, and found that both sizes could be used.

Tumor depth, as used in the TNM staging system, is related to prognosis. Our data confirm that superficial tumors had a better DMFS than deeper tumors. Besides this, we also showed that the DFS and LC of extremity STS were better than that of other sites. Unlike other studies, we could not find a significant difference between upper and lower extremity STS as far as survival was concerned although there was a non-significant trend in favor of upper limb STS.

The prognostic impact of the histological subtype *per se* is a matter of controversy.^{11,15,20} However, significant differences between histological subtypes may not be found when grade is taken into account.¹¹ Thus, the rate of progression and hematogenous dissemination are mainly determined by grade.²¹ In our study, patients with lower and intermediate grade STS (grade 2 or less) had a better outcome, confirming other published series.^{15,16,20}

Surgery

A positive margin results in a much higher risk of local recurrence.^{22,23} In our univariate analysis, although LC was inferior when the margins were positive, we could not demonstrate a statistically significant difference, probably because the number of patients with positive margins was quite small. In a further analysis of patients with positive margins, we found that there was a non-significant better OS, DFS, LC, or DMFS in the group of patients receiving a higher dose of irradiation. Some authors have reported reasonably good LC in the case of positive margins, provided patients were treated with higher RT doses.²⁴

Timing between surgery and radiotherapy

The optimal timing of RT relative to surgery for STS has been controversial since the 1980s. Preoperative RT has the potential advantage of producing a better functional outcome than postoperative RT, due to smaller treatment volumes and lower doses. Retrospective analyses have reported a favorable LC in patients treated with preoperative RT.^{5,6,10,25-27} and even a reduced cancer-specific mortality in a recent large multi-institutional analysis.¹⁰ A unique prospective randomized trial demonstrated a better functional outcome, and a slight improvement in OS in the preoperative RT arm.^{12,13} The main concern regarding preoperative RT is a higher rate of wound complications. However, these high rates of wound complications were mainly reported in advanced stage patients treated with complicated resections. Thus, the high incidence of wound complications with preoperative RT could be partially ascribed to advanced disease.^{12,27} The analysis of our data provided no difference in outcome between preoperative and postoperative RT. These results are possibly due to a much higher proportion of large tumors in the preoperative group, namely 76% of tumors measuring more than 6 cm ($P=0.02$). During the 16 years of this observation, our RT protocols have changed. However and according to the most recent and convincing data and recommendations,^{12,13,26,28} our current policy is to deliver pre-operative RT, to a total dose of 50 Gy, with a few exceptions.

Radiotherapy

A RT dose of approximately 60 Gy is generally accepted as a standard dose in STS.^{5,6,19,20} In our study, a median preoperative dose of 50 Gy and a median postoperative dose of 64 Gy were delivered, in accordance with published papers.^{12,21} Some reports have demonstrated a dose-response relationship regarding LC, and in our series, a RT dose of more than 60 Gy was followed by a significantly better OS and DFS, but with only a marginally significant improvement of LC.

Chemotherapy

The benefit of adjuvant or adjuvant CXT in the management for STS is still controversial. A few randomized trials have failed to show any advantage of adjuvant chemotherapy.^{29,30} However, two meta-analyses have demonstrated a marginal efficacy of CXT on DFS and DMFS.^{14,31} Our series failed to suggest an advantage when CXT was added to local therapy but this is most likely due to an imbalance in the prognostic factors between the two groups of patients (Figure 2). As for radiotherapy, the policy regarding CXT has changed in our institution over the years. Currently we recommend adjuvant CXT in case of high-grade STS of the extremity, mainly in liposarcoma, leiomyosarcoma or undifferentiated pleomorphic sarcoma, using a combination of ifosfamid and Adriamycin.³¹ In some situations, we recommend now neo-adjuvant CT in addition to the neoadjuvant RT, to decrease the tumor size and facilitate the surgery.¹ In rhabdomyosarcoma we use now a protocol of neo-adjuvant CXT, resection, radiotherapy and adjuvant chemotherapy with a combination of vincristine, dactinomycin and irinotecan.³²

Toxicity

We found a non-significantly higher incidence of late complications in patients treated with postoperative RT. This might be ascribed to the fact that patients with post-operative RT received higher doses to larger volumes. Overall, a higher RT dose was significantly associated with a grade 2 or more toxicity (Supplementary Table 3).

Conclusions

In conclusion, STS have a good prognosis with fairly high rates of 5- and 10-year OS. Younger age (≤ 50 years), WHO/Zubrod score 0, tumor size < 6 cm, histological grade 2 or less, and extremity locations were favorable prognostic factors at diagnosis. We also found that DFS was better with high Hb levels, and that superficial tumors were followed by a lower rate of distant metastases. Radical surgery was related to a better local or distant control. There was no clear superiority when preoperative RT was given regarding survival, local control, or complication rates but admittedly the number of patients benefiting from preoperative RT was limited. An RT dose of more than 60 Gy was associated with a better outcome (OS, DFS, and LC) at a cost of higher rate of complications.

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