original article

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Soft tissue sarcomas of the trunk wall (STS-TW): a study of 343 patients from the French Sarcoma Group (FSG) database

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Background: Soft tissue sarcomas of the trunk wall (STS-TW) are usually studied together with soft tissue sarcomas of other locations. We report a study on STS-TW forming part of the French Sarcoma Group database.
Patients and methods: Three hundred and forty-three adults were included. We carried out univariate and multivariate analysis for overall survival (OS), metastasis-free survival (MFS) and local recurrence-free survival (LRFS).
Results: Tumor locations were as follows: thoracic wall, 82.5%; abdominal wall, 12.3% and pelvic wall, 5.2%. Median tumor size was 6.0 cm. The most frequent tumor types were unclassified sarcoma (27.7%) and myogenic sarcoma (19.2%). A total of 44.6% of cases were grade 3. In all, 21.9% of patients had a previous medical history of radiotherapy (PHR). Median follow-up was 7.6 years. The 5-year OS, MFS and LRFS rates were 60.4%, 68.9% and 58.4%, respectively. Multivariate analysis retained PHR and grade for predicting LRFS and PHR, size and grade as prognostic factors of MFS. Factors influencing OS were age, size, PHR, depth, grade and surgical margins. The predictive factors of incomplete response were PHR, size and T3.
Conclusions: Our results suggest similar classical prognostic factors as compared with sarcomas of other locations. However, a separate analysis of STS-TW revealed a significant poor prognosis subgroup of patients with PHR.
Key words: predictive factors, prognostic factors, soft tissue sarcoma, trunk wall

introduction

Soft tissue sarcomas (STS) are uncommon, biologically and histologically heterogenous neoplasms arising from mesenchymal tissues throughout the body [1]. Soft tissue sarcomas of the trunk wall (STS-TW) include tumors of the chest wall and flank, spinal and paraspinal regions and tumors of the pelvic wall. Although less common than sarcomas arising in the extremities, sarcomas in these locations represent ~20% of all STS [2]. STS-TW are usually studied together with primary extremity tumors or with retroperitoneal or internal trunk tumors, but it is not clear whether tumors in such different localizations exhibit the same clinical behavior. Higher median survival (34 months) has been reported for extremity sarcomas as compared with truncal (trunk wall and internal trunk) (20 months) or retroperitoneal (21 months) lesions [3]. Singer et al. [4] demonstrated that the location (extremity, trunk wall and internal trunk or retroperitoneal) was important for overall survival (OS) with significantly different survival distributions. Moreover, tumor site has also been correlated with the advent of local recurrences [2]. Few studies have addressed the prognosis for patients with primary STS of the chest wall [5–7]. Published studies reported limited patient populations (n = 49–149) and excluded abdominal wall tumors. This study was undertaken on a large series of trunk wall sarcoma from the French Sarcoma Group (GSF) database as part of the Conticanet (Connective Tissue Cancer Network) database (http://www.conticabase.org) to examine their clinical behavior.

patients and methods

patient selection

From 1 January 1980 to 31 December 2007, 3429 consecutive adult patients with an STS were treated for their first tumoral event in 22 participating

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cancer centers and were entered in the GSF database. Among these patients, 372 (10.8%) had a histologically proven STS arising in the trunk wall. Twenty-nine of 372 patients who had evidence of metastatic spread at the time of diagnosis were excluded from this study. We restricted our analysis to patients with local disease to obtain a more homogenous patient population. Metastasis at diagnosis is clearly an adverse prognostic factor. The following definitions were used to distinguish the varying sites of primary trunk wall tumor. Chest wall tumors were extrapleural neoplasms in the region bordered superiorly by the clavicles, inferiorly by the rib margin and medially by the medial border of the scapula. Tumors of the scapular girdle were classified with extremity tumors. Paraspinal tumors arose on the back from the level of the C7 vertebral body superiorly to the base of the spine, inferiorly and medially to a line parallel with the medial scapular border. Abdominal wall tumors were extraperitoneal neoplasms below the inferior rib margin and above the pubis. Tumors in the intra-abdominal area and pelvis were considered as internal trunk tumors and were excluded from the analysis. The diagnosis of STS was based on the conclusive clinical and imaging findings, which were then confirmed by histological analysis.

pathology review

Histological slides of all patients entered were reviewed by the pathology subcommittee of the GSF. This subcommittee included 20 pathologists and a monthly slide review session was carried out. For each tumor, one to eight slides were collegially reviewed. Immunohistochemistry was used to confirm the diagnosis of sarcoma or for tumor typing. Histological typing was based on the World Health Organization histological typing of soft tissue tumors [8]. Tumor grade was evaluated according to the previously established Fédération Nationale des Centres de Lutte Contre le Cancer system based on tumor differentiation, mitotic count and necrosis [9, 10].

data collection

Data concerning patients, clinical tumor characteristics, treatment modalities and their results and outcome were obtained from a retrospective review of medical records. These and histological data were entered into a centralized computerized database (http://www.conticabase.org). The following nine variables were analyzed for their potential prognostic and predictive value: age at presentation, sex, previous medical history of radiotherapy (PHR), tumor size, tumor site (thoracic wall, abdominal wall, pelvic wall), T of the American Joint Committee on Cancer/ International Union Against Cancer (UICC) tumor–node–metastasis (TNM) classification (TNM Classification of Malignant Tumors, 6th edition. New York: Wiley, 2002) (T1: tumor size < 5 cm; T2: tumor size > 5 cm without extension to bone or to neurovascular structures; T3: tumoral extension to bone and/or to neurovascular structures), tumor depth (superficial or deep tumors), histological type, tumor grade and result of surgery (complete versus incomplete).

statistical analysis

OS was computed from the date of initial diagnosis to the date of death (whatever the cause) or last follow-up. Metastasis-free survival (MFS) was calculated from the date of initial diagnosis to the date of first metastasis or last follow-up, and local recurrence-free survival (LRFS) was defined from the date of initial diagnosis to the date of first local recurrence or the date of last follow-up only for patients with a complete response (disappearance of all signs of cancer in response to treatment). Follow-up times were described as medians by use of the inverse Kaplan–Meier estimator [11]. Continuous variables were expressed as median (range) and categorical variables were expressed as percentage. Survival curves were obtained by the Kaplan–Meier method and compared with the log-rank test. The Cox proportional hazards model was used to calculate adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). The link between the variables and the achievement of a response was determined by chi-square tests. Analysis was carried out to assess the relative influence of predictive factors for incomplete remission, using a logistic regression model in a forward stepwise procedure (Cox 1970). All statistical tests were two sided and the threshold for statistical significance was $P = 0.05$. Variables with a P value inferior to 0.05 were tested in the multivariate analysis. Analyses were carried out with SPSS software (version 13.0, SPSS, Inc., Chicago, IL).

results

patient and disease characteristics

Patient characteristics are presented in Table 1. The median age was 55.5 years (range 16.1–89.2). One hundred and forty-seven of the 343 patients (42.9%) were male and 196 (57.1%) patients were female. Tumor locations were as follows: thoracic wall, 283 (82.5%); abdominal wall, 42 (12.3%) and pelvic wall, 18 (5.2%). Tumor size was known in 329 cases (95.9%) and with a median of 6.0 cm. The most frequent tumor types were unclassified (undifferentiated) sarcoma (27.7%) and myogenic sarcoma (rhabdomyosarcoma and leiomyosarcoma) (19.2%). Dermatofibrosarcoma protuberans and angiosarcoma represented 11.1% and 7.9% of the tumors, respectively. Sixty-five cases (19%) were grade 1, 118 (34.4%) were grade 2 and 153 (44.6%) were grade 3. Two hundred and forty-seven tumors (72%) were deeply located (infiltrating or located beneath the superficial aponeurosis). Invasion of neurovascular structures or bone was present in 57 patients (16.6%). Regional node involvement was present in four patients (1.2%). Seventy-five patients (21.9%) had a PHR in the area of the primary site.

treatment characteristics

The treatment of patients with local wall trunk sarcoma is presented in Table 2.

local treatment. Surgical procedures were simple local excision for 95 (27.7%), wide resection for 227 (66.2%) and unknown for 21 (6%). Limits of surgical resection were known in 314 (91.5%) cases. Two hundred and seventy-two (79.3%) patients had a surgical resection as macroscopically complete. We carried out an analysis through chi-square test to demonstrate that surgical procedures and surgical resection as macroscopically complete rate were the same for tumors of abdominal wall, thoracic wall and pelvis. No difference was reported for these sublocations for surgical procedure. However, patients with thoracic wall sarcomas had less often a surgical resection as macroscopically complete (data not shown). A histological evaluation of surgical margins was available in only 125 (36.4%) cases. Radiotherapy generally included photons or electrons with a median dose of 50 Gy. Surgery was followed by radiotherapy for 148 (43.1%) patients and seven (2%) patients received preoperative radiotherapy to reduce tumor bulk.

chemotherapy. All patients who received chemotherapy were treated with an anthracyclin-containing regimen using a median of three drugs, which were administered for a median of six cycles. Chemotherapy was given to 123 patients (35.8%), as adjuvant and/or neoadjuvant treatment in 102 (29.7%) patients or as palliative treatment in 21 (6%) patients.

Table 1. Patients' and disease characteristics at baseline

	Overall patients ($N = 343$)
Age at diagnosis, years	
Median (range)	55.5 (16.1–89.2)
Sex, *n* (%)	
Male	147 (42.9)
Female	196 (57.1)
Tumor localization, *n* (%)	
Thoracic wall	
Axillary	39 (11.4)
Anterior and lateral chest wall	123 (35.9)
Posterior chest wall	107 (31.2)
Subclavicular	9 (2.6)
Supraspinous fossa	5 (1.5)
Abdominal wall	
Umbilical region	1 (0.3)
Abdominal trunk	41 (12)
Pelvis	
Perineal region	16 (4.7)
Sacrococcygeal region	2 (0.6)
Tumor size (cm)	
≤5	145 (42.3)
≥6 and ≤10	128 (37.3)
>10	56 (16.3)
Unknown	14 (4.1)
Histological diagnosis and subtype, *n* (%)	
Liposarcoma	23 (6.7)
Rhabdomyosarcoma and leiomyosarcoma	66 (19.2)
Myxofibrosarcoma	21 (6.1)
MPNST	21 (6.1)
Synovial sarcoma	20 (5.8)
Dermatofibrosarcoma protuberans	38 (11.1)
Angiosarcoma	27 (7.9)
Unclassified sarcoma	95 (27.7)
Others	32 (9.3)
Tumor grade (FNCLCC), *n* (%)	
Grade 1	65 (19)
Grade 2	118 (34.4)
Grade 3	153 (44.6)
Unknown	7 (2)
Depth, *n* (%)	
Superficial	96 (28)
Deep	247 (72)
TNM staging, *n* (%)	
T1	132 (38.5)
T2	146 (42.6)
T3	57 (16.6)
Unknown	8 (2.3)
Regional node involvement, *n* (%)	
Yes	4 (1.2)
No	339 (98.8)
PHR, *n* (%)	
No	268 (78.1)
Yes	75 (21.9)

MPNST, malignant peripheral nerve sheath tumor; PHR, previous medical history of radiotherapy.

Table 2. Treatment characteristics and outcome

	Overall patients ($N = 343$)
Surgical procedures, *n* (%)	
Simple local excision	95 (27.7)
Wide resection	227 (66.2)
Unknown	21 (6.1)
Surgical resections as macroscopically complete, *n* (%)	
Yes	272 (79.3)
No	42 (12.2)
Unknown	29 (8.5)
Surgical margins, *n* (%)	
Microscopically complete tumor resection (R0)	96 (28)
Microscopically incomplete tumor resection (R1)	26 (7.6)
Macroscopically incomplete resection (R2)	3 (0.9)
Unknown	218 (63.5)
Radiotherapy, *n* (%)	
No radiotherapy	185 (53.9)
Preoperative radiotherapy	7 (2)
Postoperative radiotherapy	148 (43.1)
Unknown	3 (0.9)
Chemotherapy, *n* (%)	
No chemotherapy	219 (63.8)
Preoperative chemotherapy	23 (6.7)
Postoperative chemotherapy	62 (18)
Preoperative and postoperative chemotherapy	17 (5)
Palliative chemotherapy	21 (6.1)
Unknown	1 (0.2)
Follow-up	
Follow-up, years, median, 95% CI	7.6 (6.3–9)
Overall survival, months, median	155.5
Metastasis-free survival, months, median	NR
Complete response	290 (84.5)
Incomplete response	53 (15.5)
Local recurrence-free survival, months, median	NR
Metastatic recurrence, *n* (%)	90 (26.2)
Local recurrence, *n* (%)	83 (24.2)
Death	145 (42.3)

CI, confidence interval; NR, not reached.

outcome

Median follow-up was 7.6 years (95% CI 6.3–9).

recurrence. At the end of the follow-up, metastatic recurrence was observed in 90 (26.2%) patients and local recurrence in 83 (24.2%) patients.

survival analysis. OS, MFS and LRFS of the 343 patients with trunk wall STS is depicted in Figure 1A–C. The OS rates at 5 and 10 years were 60.4% and 53.7%, respectively. The LRFS rates at 5 and 10 years were 58.4% and 55.5%, respectively. The MFS rates at 5 and 10 years were 68.9% and 66.4%, respectively. One hundred forty-five patients (42.3%) were deceased at the time of analysis, with a median OS of 155.5 months. The rate of tumor mortality was 30.6%. Other causes of death were treatment complications in 4 (1.2%), extraneous in 25 (7.2%) and unspecified in 11 (3.2%) cases. Median MFS and median LRFS had not been reached.

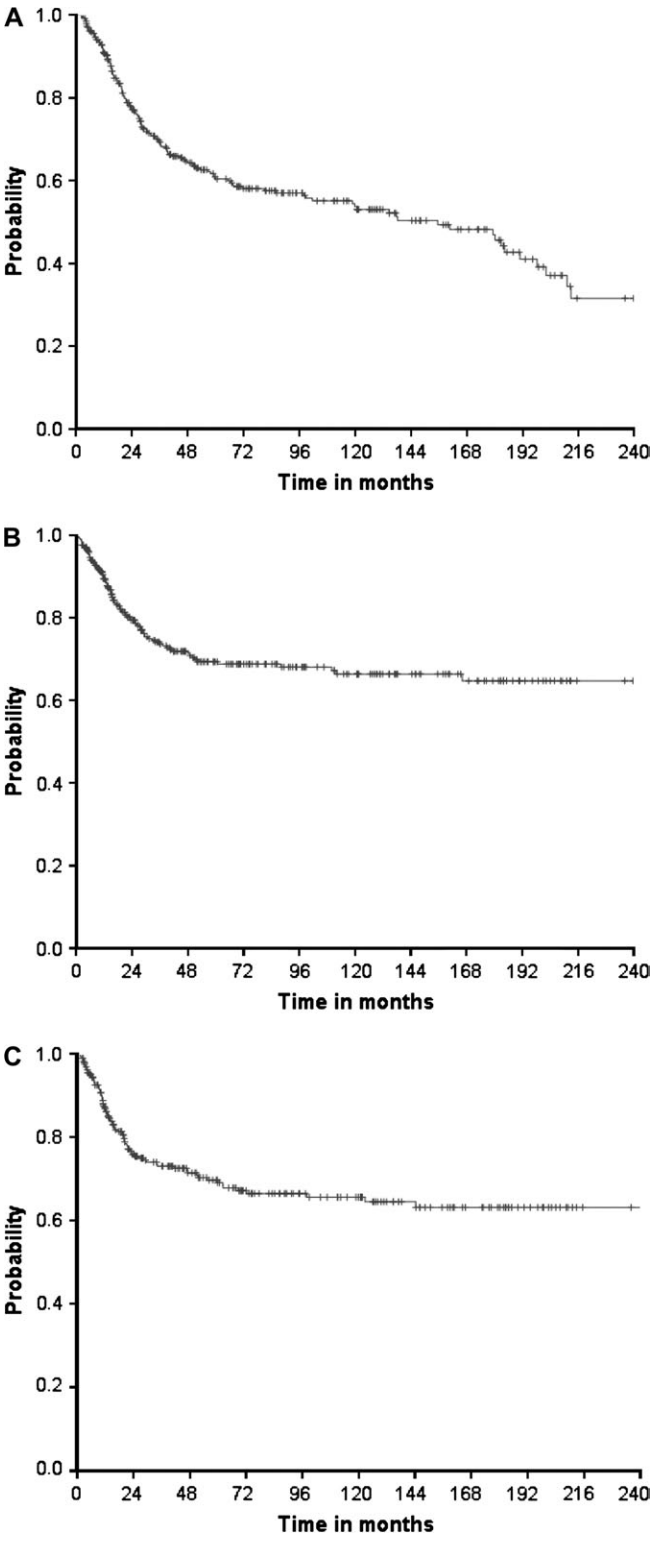

Figure 1. (**A**) Probability of overall survival of the 343 patients. (**B**) Probability of metastasis-free survival of the 343 patients. (**C**) Probability of local recurrence-free survival of the 343 patients.

prognostic factors

prognostic factors of LRFS. In univariate analysis (Table 3), PHR ($P = 2.74 \times 10^{-13}$) (Figure 2), grade ($P = 0.009$) (Figure 3) and histological type ($P = 0.012$) had a significant impact on LRFS. In multivariate analysis, PHR (HR 4.208, 95% CI 2.632–6.728, $P = 1.95 \times 10^{-9}$) and grade (grade 2: HR 2.231, 95% CI 0.978–5.086; grade 3: HR 2.885, 95% CI 1.290–6.45; $P = 0.015$) remained statistically significant (Table 4).

prognostic factors of MFS. Univariate analysis (Table 3) showed that seven variables were statistically correlated with MFS: PHR ($P = 0.006$) (Figure 4), size ($P = 0.001$), depth ($P = 0.002$), tumoral extension to bone and/or to neurovascular structures ($P = 0.004$), grade ($P = 8 \times 10^{-6}$) (Figure 5), histological type ($P = 0.013$) and results of surgery ($P = 0.002$). Multivariate analysis retained PHR (HR 2.246, 95% CI 1.339–3.767, $P = 0.002$), size (size between 6 and 10 cm: HR 1.412, 95% CI 0.841–2.372; >10 cm: HR 2.635, 95% CI 1.416–4.907; $P = 0.023$) and grade (grade 2: HR 2.03, 95% CI 0.757–5.44; grade 3: HR 5.027, 95% CI 1.99–12.701; $P = 2.88 \times 10^{-5}$) as prognostic factors of MFS (Table 5). Because dermatofibrosarcoma protuberans are tumor of intermediate malignancy (Enzinger's classification 2008) and consequently do not metastasize, we carried out the same analysis excluding this histological subtype ($n = 38$). In multivariate analysis, similar prognostic factors were reported. Only crude HRs were slightly different (data not shown).

prognostic factors of OS. The factors influencing OS in univariate analysis were age ($P = 0.00025$), PHR ($P = 6.4 \times 10^{-8}$) (Figure 6), size ($P = 5.9 \times 10^{-7}$), depth ($P = 2.4 \times 10^{-5}$), tumoral extension to bone and/or to neurovascular structures ($P = 5.6 \times 10^{-5}$), grade ($P = 2.5 \times 10^{-7}$) (Figure 7), histological type ($P = 7.8 \times 10^{-5}$) with a better outcome for the dermatofibrosarcoma protuberans subtype and a significantly poorer outcome for angiosarcoma and surgical resection as macroscopically complete ($P = 7.8 \times 10^{-11}$) (Table 3). In the multivariate analysis, age (HR 1.663, 95% CI 1.123–2.463, $P = 0.011$), PHR (HR 2.180, 95% CI 1.361–3.492, $P = 0.001$), size (size between 6 and 10 cm: HR 1.412, 95% CI 1.157–6.753; >10 cm: HR 2.098, 95% CI 1.232–3.575; $P = 0.023$), depth (HR 1.728, 95% CI 1.01–2.957, $P = 0.046$), grade (grade 2: HR 2.796, 95% CI 1.157–6.753; grade 3: HR 4.533, 95% CI 1.903–10.8; $P = 0.001$) and surgical resection as macroscopically complete remained statistically significant (HR 2.794, 95% CI 1.773–4.403, $P = 9.44 \times 10^{-6}$) (Table 6).

predictive factors of complete response

Univariate analysis showed that five of the nine parameters tested were correlated with the achievement of a complete response of the tumor with a $P < 0.05$ and could be selected for multivariate analysis (Table 7). Correlation was observed for tumor location ($P = 0.04$) (thoracic and pelvic wall versus abdominal wall). In multivariate analysis, the predictive factors of incomplete response were PHR ($P = 0.001$), size ($P = 0.003$) and tumoral extension to bone and/or to neurovascular structures ($P = 0.021$).

comparison of patients with previous history of radiotherapy with those with no previous history of radiotherapy

The mean age differed significantly between the two groups: 63.7 ± 13.9 versus 49.2 ± 18 ($P = 4.2 \times 10^{-6}$) (Table 8).

Table 3. Univariate analysis for prognostic factors in OS, MFS and LRFS

Factors	No. of patients	5-year OS rate	10-year OS rate	Log rank	5-year MFS rate	10-year MFS rate	Log rank	5-year LRFS rate	10-year LRFS rate	Log rank
Age (year)										
≤55	172	0.674	0.626	**0.00025**	0.713	0.700	0.466	0.728	0.694	0.114
>55	171	0.530	0.439		0.668	0.614		0.654	0.617	
Sex										
Male	147	0.612	0.541	0.645	0.680	0.632	0.367	0.741	0.699	0.118
Female	196	0.598	0.536		0.704	0.691		0.652	0.622	
PHR										
No	268	0.676	0.608	**6.4×10^{-8}**	0.733	0.707	**0.006**	0.773	0.732	**2.74×10^{-13}**
Yes	75	0.328	0.251		0.501	0.429		0.292	0.292	
Tumor size (cm)										
≤5	145	0.727	0.670	**5.9×10^{-7}**	0.772	0.737	**0.001**	0.735	0.688	0.819
6–10	128	0.602	0.508		0.679	0.643		0.670	0.654	
>10	56	0.335	0.293		0.463	0.463		0.671	0.671	
Tumor depth										
Superficial	96	0.785	0.715	**2.4×10^{-5}**	0.809	0.800	**0.002**	0.762	0.732	0.168
Deep	247	0.539	0.474		0.650	0.607		0.662	0.625	
TNM classification										
T1, T2	278	0.700	0.605	**5.6×10^{-5}**	0.715	0.690	**0.004**	0.723	0.688	0.071
T3	57	0.401	0.401		0.579	0.526		0.532	0.532	
FNCLCC grade										
1	65	0.910	0.834	**2.5×10^{-7}**	0.931	0.840	**8×10^{-6}**	0.868	0.827	**0.009**
2	118	0.609	0.544		0.708	0.708		0.650	0.632	
3	153	0.481	0.416		0.578	0.550		0.637	0.592	
Histological type										
Liposarcoma	23	0.771	0.675	**7.8×10^{-5}**	0.777	0.777	**0.013**	0.756	0.756	**0.012**
Rhabdomyosarcoma and leiomyosarcoma	66	0.490	0.404		0.620	0.564		0.750	0.750	
Myxofibrosarcoma	21	0.761	0.609		0.699	0.699		0.603	0.603	
MPNST	21	0.508	0.444		0.749	0.655		0.686	0.686	
Synovial sarcoma	20	0.671	0.537		0.615	0.615		0.654	0.561	
Dermatofibrosarcoma protuberans	38	1	0.938		0.92	0.85		0.919	0.848	
Angiosarcoma	27	0.221	–		0.474	–		0.295	0.295	
Unclassified sarcoma	95	0.557	0.511		0.676	0.676		0.620	0.620	
Others	32	0.647	0.607		0.578	0.413		0.747	0.593	
Localization										
Thoracic wall	283	0.573	0.517	0.07	0.680	0.642	0.298	0.673	0.648	0.573
Abdominal wall	42	0.796	0.674		0.792	0.792		0.758	0.718	
Pelvic wall	18	0.660	0.566		0.690	0.690		0.808	0.673	
Surgical resections as macroscopically complete										
Yes	272	0.694	0.622	**7.8×10^{-11}**	0.727	0.700	**0.002**	0.700	0.661	0.119
No	42	0.305	0.222		0.547	0.469		0.558	0.558	

Bold values represent $P < 0.05$.

OS, overall survival; MFS, metastasis-free survival; MPNST, malignant peripheral nerve sheath tumor; LRFS, local recurrence-free survival; PHR, previous medical history of radiotherapy.

Female gender and angiosarcoma histological subtype were significantly more represented in the group of patients with PHR ($P = 1.9 \times 10^{-13}$ and $P = 10^{-7}$, respectively). STS occurred more frequently in the thoracic wall and superficial tissue in patients with PHR ($P = 0.006$ and $P = 0.003$, respectively). Tumoral extension to bone and/or to neurovascular structures was greater in the group of patients with PHR ($P = 0.002$). Finally, patients with PHR were less often in complete response after a first line of treatment ($P = 3.7 \times 10^{-5}$). Grade and size were not associated with previous history of radiotherapy.

discussion

STS can be classified according to their location as extremities, head and neck, trunk wall and internal trunk (retroperitoneal space, intra-abdominal area, pelvis and intrathoracic) [2]. This study concerned a large series of adult patients treated for their

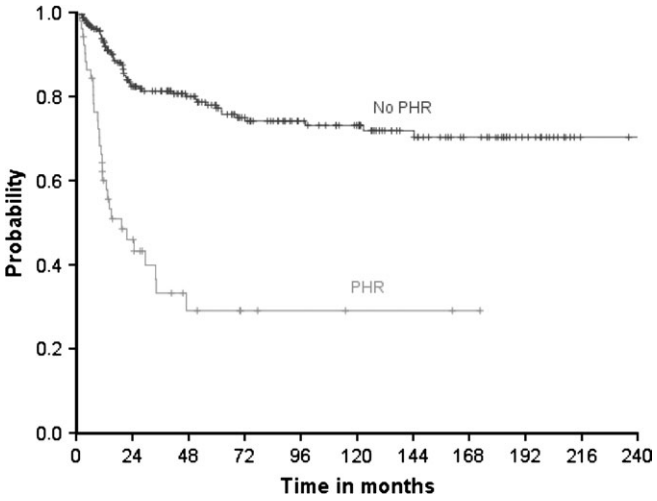

Figure 2. Effect of previous medical history of radiotherapy (PHR) on local recurrence-free survival. Patients with PHR had a significantly poorer outcome compared with those without PHR ($P = 2.74 \times 10^{-13}$).

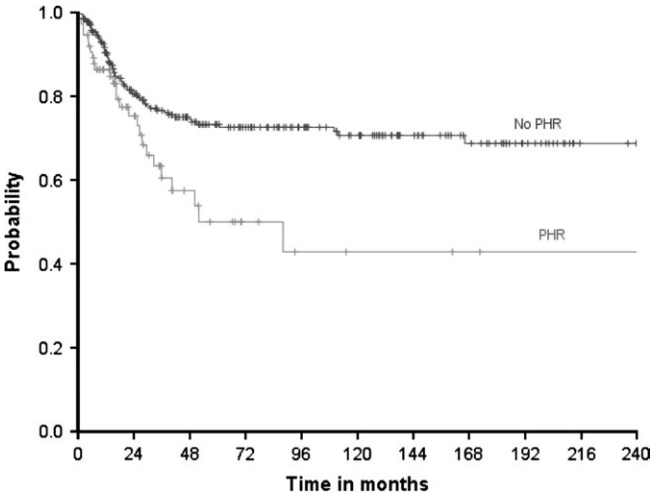

Figure 4. Effect of previous medical history of radiotherapy (PHR) on metastasis-free survival. Patients with PHR had a significantly poorer outcome compared with those without PHR ($P = 0.006$).

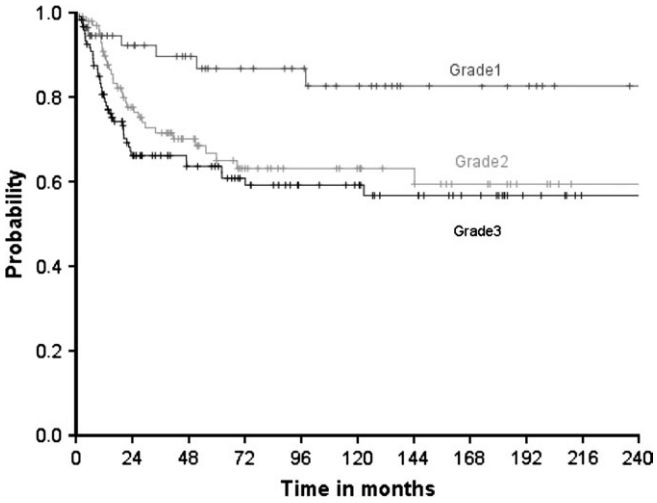

Figure 3. The effect of tumor grade (FNCLCC system) on local recurrence-free survival: grade 1 versus grade 2 versus grade 3 ($P = 0.009$).

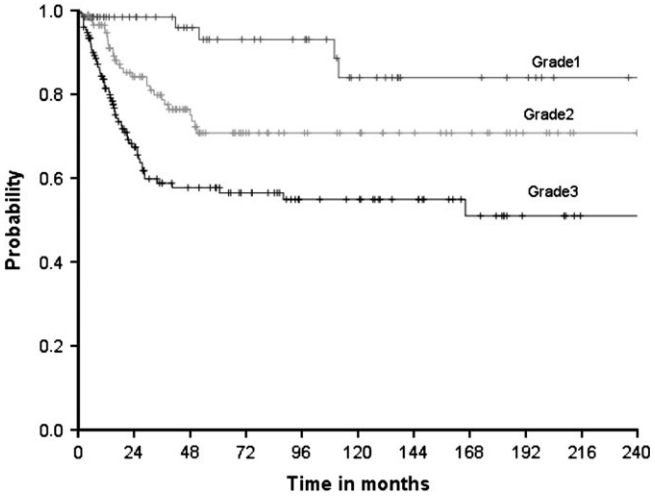

Figure 5. Effect of tumor grade (FNCLCC system) on metastasis-free survival: grade 1 versus grade 2 versus grade 3 ($P = 8 \times 10^{-6}$).

Table 4. Multivariate local recurrence-free survival analysis

	Crude hazard ratio	95% confidence interval	*P* value
PHR	4.208	2.632–6.728	1.95×10^{-9}
FNCLCC grade			
1			0.015
2	2.231	0.978–5.086	0.056
3	2.885	1.290–6.45	0.01

PHR, previous medical history of radiotherapy.

first diagnosis of local STS arising in the thoracic, abdominal and pelvic walls. STS-TW were usually analyzed together with STS of other primary sites [10, 12]. Some authors included visceral and retroperitoneal tumors [13], while others studied only STS of the chest wall [5–7] without demonstrating that this location is a determinant of prognosis. In our study, thoracic wall was the most frequent tumor site (82.5%) while location was not a significant predictor of poor survival. It is likely that surgical procedures and therapeutic strategies in most teams remain similar, regardless of the location of STS-TW. The main aims of this study were to identify significant prognostic variables in a large group of localized adult STS-TW and to determine predictive factors for the achievement of a complete response. Some earlier studies reported STS-TW as being rare (18.7%–20.9% of locally controlled STS) [2, 12]. In our patient cohort, 10% of the 3429 adult patients in the whole GSF database had STS-TW with no evidence of metastatic spread at the time of diagnosis. Twenty-nine patients (8.4%) had metastatic disease at the time of presentation while metastasis rate at diagnosis was 9.7% in the whole STS population [2]. In this study, dermatofibrosarcoma protuberans and angiosarcoma were overrepresentated as histological subtype in STS-TW (11.1% and 7.9%, respectively).

Table 5. Multivariate metastasis-free survival analysis

	Crude hazard ratio	95% confidence interval	*P* value
PHR	2.246	1.339–3.767	0.002
Tumor size (cm)			
≤5			0.023
6–10	1.412	0.841–2.372	0.192
>10	2.635	1.416–4.907	0.002
FNCLCC grade			
1			2.88×10^{-5}
2	2.03	0.757–5.444	0.159
3	5.027	1.99–12.701	0.001

PHR, previous medical history of radiotherapy.

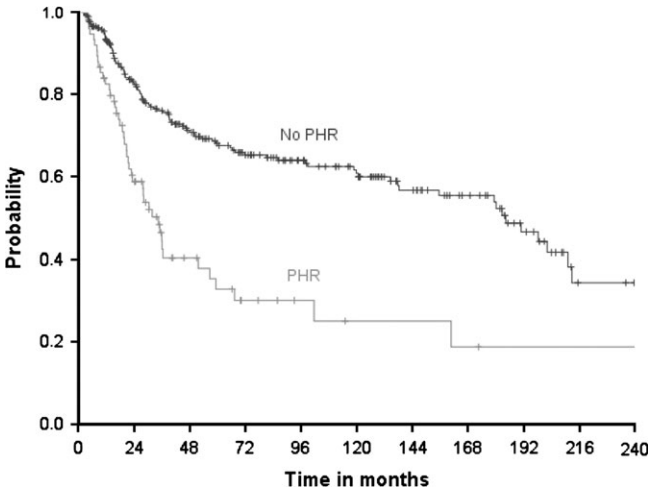

Figure 6. Effect of previous medical history of radiotherapy (PHR) on overall survival: patients with PHR had a significantly poorer outcome ($P = 6.4 \times 10^{-8}$).

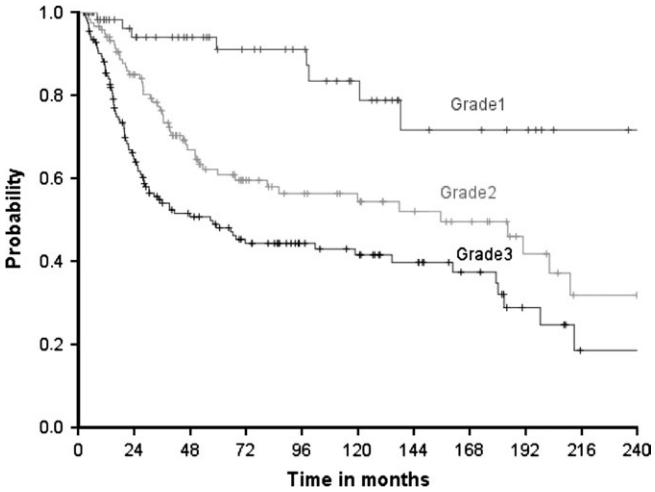

Figure 7. Effect of tumor grade (FNCLCC system) on overall survival: grade 1 versus grade 2 versus grade 3 ($P = 2.5 \times 10^{-7}$).

Table 6. Multivariate overall survival analysis

	Crude hazard ratio	95% confidence interval	*P* value
Age	1.663	1.123–2.463	0.011
PHR	2.180	1.361–3.492	0.001
Tumor size (cm)			
≤5			0.023
6–10	1.412	0.919–2.169	0.115
>10	2.098	1.232–3.575	0.006
Depth	1.728	1.01–2.957	0.046
FNCLCC grade			
1			0.001
2	2.796	1.157–6.753	0.022
3	4.533	1.903–10.8	0.001
Surgical resections as macroscopically complete	2.794	1.773–4.403	9.44×10^{-6}

PHR, previous medical history of radiotherapy.

Guillou et al. [10] reported only 2.4% of angiosarcoma in a population of 410 adult patients with STS and dermatofibrosarcoma protuberans was not a representative histological subtype in series concerning sarcoma of the extremities [14, 15]. It is likely that the institutions that treated dermatofibrosarcoma protuberans were different from those that treated other histological subtypes. The median tumor size was 6 cm and 42.3% of tumors measured <5 cm. However, series of patients with only STS of the extremities showed approximately the same rate of tumors measuring <5 cm [15, 16].

In STS of the extremities, local recurrences occurred in 235 patients (19%) and distant recurrences occurred in 322 patients (26%) [16]. The actuarial 5- and 10-year LRFS rates were 79% and 74%, respectively [16]. In the current study, local recurrence and metastases recurrence rates were approximately the same as for localized STS of the extremities. However, STS-TW LRFS rates at 5 and 10 years were lower (58.4% and 55.5%, respectively), suggesting that a microscopically complete resection and adequate local control were more difficult to obtain in the trunk wall, even if patients with STS-TW received radiotherapy to the same extent (43.1%) [16]. A significant difference was observed in LRFS between localized STS-TW and STS of the extremities (data not reported).

In this study, histological evaluation of surgical margins was unknown in 63.5%, which underlines the difficulty in evaluating surgical margins as a prognostic factor in retrospective studies. Macroscopically incomplete surgery, grade and PHR were significantly associated with the advent of local recurrences in multivariate analysis. The relationship between PHR and local recurrence has not been reported so far and appears specific to trunk wall sarcoma. The reason for this could be the higher frequency of previously irradiated trunk cancers, mainly breast carcinomas. Radiation-induced sarcomas may be more infiltrative and more biologically aggressive lesions. Therefore, patients with PHR may not receive the optimal therapeutic strategy such as a combination of surgery and radiotherapy. Finally, angiosarcoma was significantly more represented in this subgroup and was mainly multifocal. For this reason, optimal local control was not achieved.

Table 7. Predictive factors of incomplete response in univariate analysis

Factors	No. of patients	Incomplete response, *n* (%)	Complete response, *n* (%)	Log rank
Age (year)				
≤55 ans	172	26(15.1)	146(84.9)	0.863
>55 ans	171	27(15.8)	144(84.2)	
Sex				
Male	147	19(12.9)	128(87.1)	0.262
Female	196	34(17.3)	162(82.7)	
PHR				
No	268	30(11.2)	238(88.8)	**3.72×10^{-5}**
Yes	75	23(30.7)	52(69.3)	
Localization				
Thoracic and pelvic wall	301	51(16.9)	250(83.1)	**0.04**
Abdominal wall	42	2(4.8)	40(95.2)	
Tumor size (cm)				
≤5	145	11 (7.6)	134(92.4)	**2.13×10^{-4}**
6–10	128	21(16.4)	107(83.6)	
>10	56	17(30.4)	39(69.6)	
Tumor depth				
Superficial	96	6(6.2)	90(93.8)	**0.003**
Deep	247	47(19)	200(81)	
TNM classification				
T1, T2	278	32(11.5)	146(52.5)	**5.36×10^{-6}**
T3	57	20(35.1)	37(64.9)	
FNCLCC grade				
1	65	6(9.2)	59(90.8)	0.139
2	118	17(14.4)	101(85.6)	
3	153	30(19.6)	123(80.4)	
Histological type				
Liposarcoma	23	1(4.3)	22(95.7)	0.053
Rhabdomyosarcoma and leiomyosarcoma	66	11(16.7)	55(83.3)	
Myxofibrosarcoma	21	2(9.5)	19(90.5)	
MPNST	21	7(33.3)	14(66.7)	
Synovial sarcoma	20	1(5)	19(95)	
Dermatofibrosarcoma protuberans	38	2(5.3)	36(94.7)	
Angiosarcoma	27	7(25.9)	20(74.1)	
Unclassified sarcoma	95	17(17.9)	78(82.1)	
Others	32	5(15.6)	27(84.4)	

Bold values represent $P < 0.05$.
MPNST, malignant peripheral nerve sheath tumor; PHR, previous medical history of radiotherapy.

Table 8. Patients with previous medical history of radiotherapy (PHR) compared with those with no previous history of radiotherapy

	Patients with no PHR ($n = 268$)	Patients with PHR ($n = 75$)	*P*
Age (year, mean ± SD)	49.2 ± 18.7	63.7 ± 13.9	**4.2×10^{-6}**
Sex			
Male (%)	53.4	5.3	**1.9×10^{-13}**
Female (%)	46.6	94.7	
Localization			
Thoracic wall (%)	79.1	94.7	**0.006**
Abdominal wall (%)	14.9	2.7	
Pelvis (%)	16	2.7	
Histological type (%)			NS
Liposarcoma	8.6	0	
Rhabdomyosarcoma and leiomyosarcoma	20.5	14.7	
Myxofibrosarcoma	7.5	1.3	
MPNST	6	6.7	
Synovial sarcoma	7.1	1.3	
Dermatofibrosarcoma protuberans	14.2	0	
Angiosarcoma	0.4	34.7	
Unclassified	25.4	36	
Others	10.4	5.3	
Histological angiosarcoma subtype (%)			
Angiosarcoma	0.4	34.7	**10^{-7}**
FNCLCC grade (%)			
1	21.8	10.7	NS
2	34.5	37.3	
3	43.7	52	
Tumor depth (%)			
Superficial	24.3	41.3	**0.003**
Deep	75.7	58.7	
Tumor size (cm) (%)			
≤5	43.5	46.4	NS
6–10	39.2	37.7	
>10	17.3	15.9	
TNM classification (%)			
T1	39.7	38.4	**0.002**
T2	46.9	31.5	
T3	13.4	30.1	
Complete response after the first line of treatment (%)			
Yes	88.8	69.3	**3.7×10^{-5}**
No	11.2	30.7	

Bold values represent $P < 0.05$.
MPNST, malignant peripheral nerve sheath tumor; SD, standard deviation; NS, not significant.

FNCLCC histological grade is an independent predictive factor for metastasis development in most adult STS [12]. Unsurprisingly therefore, grade was again the most important independent prognostic factor for MFS in this series of STS-TW. The other independent factors were size and radiation-induced etiology.

In the study by Sastre-Garau et al. [17], multivariate analysis showed that three parameters were correlated with complete removal: T of the TNM classification (T3 versus T1 or T2), tumor site (internal trunk/retroperitoneum versus all other sites) and the presence of necrosis foci of the tumoral tissue (presence of necrosis versus no necrosis). In our study, multivariate analysis showed that T3 of the TNM classification was a predictive factor for no complete response. Tumor size >10 cm was found to be the most important predictor with a HR of 4.819. Obtaining complete removal after surgery is crucial for curing STS. Predictive factors for the achievement of complete removal have been defined whatever the location [17]. One aim of our work was to determine the clinical and

pathological parameters that can be determined before surgery and are associated with failure to obtain a complete response at the end of the primary multimodal treatment of STS-TW. Predictive parameters may be taken into account in any assessment of tumors in order to specify the indications for conservative surgery and those for radio- or chemotherapy as preoperative approaches to STS-TW. In this regard, PHR and size were specific for this particular STS location.

In contrast with series of STS of the extremities or series of sarcomas irrespective of tumor localization, a separate analysis of STS-TW revealed a significant subgroup of patients with PHR, representing 21.9% of cases in this site. Patients with PHR were female (94.7%) and older (mean age: 63.7 $\pm$ 13.9). The main initial tumor treated with radiotherapy was breast cancer and radio-induced sarcomas were mainly angiosarcomas of the thoracic wall in which complete tumor removal was difficult to achieve. Furthermore, PHR was associated with poorer OS and MFS. PHR was a predictive factor of no complete response. Therapeutic radiation for malignant and benign diseases has been associated with secondary malignancies, including sarcomas [18, 19]. Radiation-induced sarcoma has been reported but mainly in single case reports and several very small series [20] concerned the most common subtypes like angiosarcoma, osteosarcoma, fibrosarcoma and MFH [18, 19, 21–23]. The prognosis for patients with postradiation solid tumors, and sarcomas in particular, is poor [19, 24]. Tumors in areas with prior irradiation may behave more aggressively and progress more rapidly [25]. Our findings demonstrate that PHR is a major prognostic and predictive factor in STS-TW, so patients with PHR should be considered separately.

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