Original Article

Extrameningeal Solitary Fibrous Tumors—Surgery Alone or Surgery Plus Perioperative Radiotherapy: A Retrospective Study From the Global Solitary Fibrous Tumor Initiative in Collaboration With the Sarcoma Patients EuroNet

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BACKGROUND: Solitary fibrous tumor (SFT) is a rare mesenchymal malignancy. Although surgery is potentially curative, the local relapse risk is high after marginal resections. Given the lack of prospective clinical trial data, the objective of the current study was to better define the role of perioperative radiotherapy (RT) in various SFT presentations by location. **METHODS:** This was retrospective study performed across 7 sarcoma centers. Clinical information was retrieved from all adult patients with extrameningeal, primary, localized SFT who were treated between 1990 and 2018 with surgery alone (S) compared with those who also received perioperative RT (S+RT). Differences in treatment characteristics between subgroups were tested using analysis of variance statistics and propensity score matching. Local control and overall survival rates were calculated from the start of treatment until progression or death from any cause. **RESULTS:** Of all 549 patients, 428 (78%) underwent S, and 121 (22%) underwent S+RT. The median follow-up was 52 months. After correction for mitotic count and surgical margins, S+RT was significantly associated with a lower risk of local progression (hazard ratio, 0.19: $P = .029$), an observation further confirmed by propensity score matching ($P = .012$); however, this association did not translate into an overall survival benefit. **CONCLUSIONS:** The results from this retrospective study investigating perioperative RT in patients with primary extrameningeal SFT suggest that combining RT with surgery in the management of this patient population is significantly associated with a reduced risk of local failures, especially in patients who have less favorable resection margins and in those who have tumors with a high mitotic count. ***Cancer* 2020;126:3002-3012**.

KEYWORDS: hemangiopericytoma, patient advocacy group, radiotherapy, solitary fibrous tumor, surgery.

INTRODUCTION

Solitary fibrous tumor (SFT), formerly known as *hemangiopericytoma*, is a rare mesenchymal tumor with an incidence of approximately 0.2 per 100,000 population per year.[1] SFTs can arise anywhere in the body, including the central nervous system/meninges, head and neck, thorax/pleura, and soft tissues. Histologically, SFT can be subdivided into typical (or classical), malignant, and dedifferentiated variants, depending on some or all of the following features: mitotic index, infiltrative margins, hypercellularity, at least focal pleomorphism, and necrosis. In particular, malignant

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SFTs are marked by >4 mitoses per 10 high-power fields (HPF).[2] SFTs are seen in patients of all ages but predominantly among those in the fifth and sixth decades of life, presenting as slowly growing masses that cause symptoms because of local compression by the primary tumor and/or because of metastatic sites.[1,3-5] Imaging features of these tumors are nonspecific, leaving a broad differential diagnosis.[6-10] Demicco et al,[5,11] Pasquali et al,[12] and Salas et al[13] have designed scores that enable a reliable prediction of both local recurrence-free and metastasis-free survival. Specifically, Salas and coworkers reported that, after multivariable analyses, older age, visceral localization of the primary tumor, and receipt of radiotherapy (RT) remained statically significant factors predicting an increased local control (LC) probability (hazard ratio [HR], 0.30; 95% CI, 0.11-0.83; $P = .021$).

For other sarcomas, the standard treatment of primary localized SFT is a wide surgical resection. However, the anatomic site of the primary tumor often may preclude wide surgical margins because of the proximity to critical and irresectable structures. This is particularly true for SFTs arising from the meninges or from the pleura.[14] For these patients, the risk of local relapse is known to be increased. The potential added value of (neo-)adjuvant RT in combination with surgery, both in the setting of a gross total resection or after less radical surgery for LC and survival, remains unclear.[1,5,15-23] The outcome for patients after definitive RT, without surgery, has recently been described by our group.[24]

The objective of this international, collaborative, retrospective study was to better define the role of perioperative RT compared with surgery alone in the management of extrameningeal SFT.

MATERIALS AND METHODS

A retrospective study was performed across 7 tertiary referral sarcoma centers by collecting data on adult patients with primary, localized, extrameningeal, SFT who underwent surgery either alone or in combination with preoperative or postoperative RT between 1990 and 2018. Meningeal SFTs were excluded from this analysis because of the specific clinical course of tumors at this location.[21] Pathologic diagnoses were locally reviewed by reference sarcoma pathologists and confirmed in all cases. Clinical information on demographics, treatment, and follow-up was retrieved from all consecutive patients who underwent surgery alone and compared with information from those who also received perioperative RT. The study population was divided into 3 subgroups based on location (pleural vs retroperitoneal vs *others* [extremity, trunk, head and neck]) and the inherent different management at the participating centers. In all participating centers, approval for this retrospective database analysis was obtained from the local Medical Ethics Committees (central approval METC15.1609). All patient data were anonymized. The study was performed in close collaboration with the Sarcoma Patients EuroNet to report the results from the perspective of patients affected with this rare disease. Toxicity was graded according to Common Terminology Criteria for Adverse Events, version 4.0 (National Cancer Institute, National Institutes of Health). Risk assessment was performed using the original model published by Demicco et al[5] because the percentage necrosis was not registered when this database was acquired.[11]

Statistical Analyses

Characteristics are presented as percentages, means ± SD, or medians (with interquartile range [IQR]) in case of skewed distribution. Differences in baseline characteristics were tested using Student *t* tests (for continuous variables), chi-square tests (for categorical variables) or analyses of variance with post-hoc Bonferroni correction (for >2 groups). The follow-up duration was calculated as the time between the start of treatment and the date of death, or loss to follow-up, or last follow-up. Cumulative incidence, 6-month, 1-year, 2-year, and 5-year mortality rates were investigated and Kaplan-Meier survival curves were plotted for overall survival (OS) and LC. Differences in survival across RT treatment subgroups and modalities were tested using log-rank tests. Cox proportional hazards analyses using multiple imputation methods and a parametric regression method (with 10 replacements for variables that had missing values) were performed to investigate the independent association between treatment and outcomes. First, we constructed a univariate model. Then, we adjusted for possible contributing variables. The assessed characteristics have been associated with outcomes and/or are closely related to treatment choice. Ultimately, variables with *P* values <.10 were combined into a multivariable model.

To further test independent associations between treatment and outcomes, we conducted a sensitivity analysis using propensity score matching. This matching procedure can help observational studies by reducing selection bias. Treatment and surgery (S) versus S+RT were

TABLE 1. Baseline Characteristics of the Entire Study Population Stratified for Surgery or Surgery Plus Radiotherapy

Characteristic	Total	S	S+RT	*P*[a]
Total no. of patients	549	428	121	
Age: Mean ± SD, y	54 ± 15.6	54.1 ± 15.7	53.8 ± 15.4	.837
Men: Mean ± SD, %	254 ± 46.3	190 ± 44.4	64 ± 52.9±	.100
Tumor size: Mean ± SD, cm	9 ± 6.5[a]	8.8 ± 6.6	10.1 ± 5.8	.084
Median follow-up, mo	52	47	65	.001
Primary site				<.001
Pleural	109	100	9	
Retroperitoneal	131	104	27	
Others (total)	309	224	85	
Extremity	178	123	55	
Trunk	97	78	19	
H&N nonmeningeal	34	23	11	
Mitotic count, mitoses per 10 HPF[b]				.657
0	132	111	21	
≤4	193	158	35	
≥5	123	98	25	
Margin status[c]				<.001
R0	323	273	50	
R1	99	71	28	
R2	17	7	10	
Acute toxicity: Yes, %	103	32	71	<.001
Late toxicity: Yes, %	40	11	29	<.001
Secondary cancer: Yes, %[d]	33	30	3	.014

Abbreviations: H&N, head and neck; HPF, high-power fields; R0, negative resection margins; R1, margins with microscopic tumor infiltration; R2, margins with macroscopic tumor infiltration; S, surgery; S+RT, surgery plus perioperative radiotherapy.
[a]*P* values ≤.05 were considered statistically significant.
[b]Number with missing values (measured if N > 10) = 44.
[c]Number with missing values = 101.
[d]Number with missing values = 110.

matched on a 1:1 ratio based on propensity scores using a nearest-neighbor approach (see Supporting Table 1). The propensity score for treatment was estimated using a Cox proportional hazard model that included influencing factors resulting from our association model, which were also the variables designating the Demicco risk-assessment score.[5,11] Data are presented as HRs with 95% CIs, which can be interpreted as relative risks. *P* values <.05 were considered statistically significant. Propensity score matching was performed in R version 3.5.1 (R Foundation for Statistical Computing) using the package MatchIt. Further analyses were performed with SPSS 25.0 (IBM Corporation).

RESULTS

In total, 549 patients (mean age, 54 years; men, 46.3%) were included who had primary tumors located in extremities (32.4%), retroperitoneum (23.9%), pleura (19.9%), trunk (17.7%), or the head and neck region (6.2%). The majority of patients had relative benign SFT histology (mitotic count: zero in 29.5%; 1-4 mitoses per 10 high-power fields [HPF] in 43.1%) and underwent resection with wide margins (negative resection margins [R0], 73.6%; microscopic tumor infiltration [R1], 22.6%).

The median follow-up for the entire cohort was 52 months (IQR, 19-106 months). With respect to management (Table 1), the cohort could be subdivided into 2 subgroups; S (n = 428; 78%) and S+RT (n = 121; 22.0%). The median follow-up was 47 months (IQR, 17-102 months) in the S group and 65 months (IQR, 25-131 months) in the S+RT group. With regard to primary site (Table 2), the cohort was subdivided into pleural SFT versus retroperitoneal SFT versus *others* (extremity, trunk, head and neck).

Treatment Details for the Perioperative RT (S+RT) Subgroup

Among 121 patients in the S+RT group, 63 (52%) received preoperative RT at doses from 50.0 to 50.4 grays (Gy) in 25 to 28 fractions of 1.8 to 2.0 Gy, with a median follow-up of 63 months (IQR, 21-113 months). Postoperative RT in 58 patients (48%) was prescribed at a dose from 54.0 to 60.0 Gy in 27 to 30 fractions of 2.0 Gy, with a median follow-up of 94 months (IQR, 34-170 months). In the S+RT subgroup, significantly more patients underwent R1 resection (35.9% vs

TABLE 2. Baseline Characteristics by Primary Solitary Fibrous Tumor Site

Characteristic	Pleural SFT				Retroperitoneal SFT				Other SFTs			
	Total	S	S+RT	*P*	Total	S	S+RT	*P*	Total	S	S+RT	*P*
Total no. of patients	109	100	9		131	104	27		309	224	85	
Age: Mean ± SD, y	60.0 ± 12.7	61.0 ± 12.3	53.0 ± 15.0	.055	54.0 ± 15.0	55.0 ± 15.5	52.2 ± 13.0	.431	52.0 ± 16.2	51.0 ± 16.1	54.0 ± 16.2	.071
Men: Mean ± SD, %	48.0 ± 44.0	42 ± 42.0	6 ± 66.7	.178	66 ± 50.0	52 ± 50.0	14 ± 52.0	.864	140.0 ± 45.0	96.0 ± 43.0	44.0 ± 52.0	.160
Tumor size: Mean ± SD, cm	9.1 ± 7.8	8.7 ± 7.9	13.5 ± 5.5	.097	13.3 ± 6.8	13.5 ± 7.0	12.5 ± 6.1	.538	7.3 ± 4.8	6.8 ± 4.5	8.9 ± 5.4	.001
Mitotic count, mitoses per 10 HPF				.058				.101				.188
0	31	31	0		21	19	2		80	61	19	
≤4	26	25	1		47	36	11		120	97	23	
≥5	28	24	4		38	35	3		57	39	18	
Margin status				.000				.006				.003
R0	76	74	2		44	41	3		203	158	45	
R1	15	11	4		31	26	5		53	34	19	
R2	2	1	1		8	4	4		7	2	5	
Demicco score[a]				.013				.633				<.001
Low	60	59	1		63	48	15		238	191	47	
Moderate	31	25	6		54	45	9		64	30	34	
High	18	16	2		14	11	3		7	3	4	
Outcome												
No. of LF events	9	8	1	.410	20	17	3	.487	9	6	3	.666
No. of OS events	13	9	4	.001	33	28	5	.889	47	24	23	.022

Abbreviations: HPF, high-power fields; LF, local failure; OS, overall survival; R1, negative resection margins; R2, margins with microscopic tumor infiltration; R3, margins with macroscopic tumor infiltration; RT, radiotherapy; S, surgery; S+RT, surgery plus perioperative radiotherapy; SFT, solitary fibrous tumor.

[a]The Demicco score concerns all patients within the respective subgroups by site; if death occurred within 1 month after diagnosis or insufficient data were available, some patients were not taken into account for calculating the Kaplan-Meier curves provided in Supporting Figures 1, 2, and 3 (note differences in the number of patients at risk with respect to this table).

TABLE 3. Univariate Associations With Overall Survival and Local Progression Using Pairwise Deletion

Variable	OS (95% CI)	*P*	LC (95% CI)	*P*
S+RT [Ref: S]	1.74 (1.12-2.69)	.013[a]	0.63 (0.27-1.45)	.278
Age	1.042 (1.03-1.06)	<.001[a]	0.99 (0.97-1.02)	.580
Sex [Ref: Men]	1.00 (0.66-1.50)	.996	0.64 (0.33-1.26)	.184
Primary site [Ref: Pleural]				
Retroperitoneal	1.61 (0.84-3.07)	.152	1.49 (0.67-3.13)	.333[a]
Other	1.21 (0.65-2.23)	.554	0.35 (0.13-0.90)	.030[a]
Mitotic count [Ref: ≤4 Mitoses per 10 HPF]	3.29 (2.09-5.18)	<.001[a]	3.45 (1.66-7.16)	.001[a]
Margin status [Ref: R0]				
R1	1.15 (0.69-1.91)	.605	3.59 (1.58-8.14)	.002[a]
R2	1.35 (0.58-3.16)	.486	6.40 (2.22-18.46)	.001[a]
Tumor size, cm	1.05 (1.03-1.08)	<.001	1.07 (1.03-1.11)	.001[a]

Abbreviations: HPF, high-power field; LC, local control; OS, overall survival; R1, negative resection margins; R2, margins with microscopic tumor infiltration; R3, margins with macroscopic tumor infiltration; Ref, reference category; S, surgery; S+RT, surgery plus radiotherapy.
[a]These *P* values indicate a significant difference.

TABLE 4. Univariate Associations With Overall Survival and Local Progression Using Multiple Imputation Methods

Variable	OS (95% CI)	*P*	LC (95% CI)	*P*
S+RT [Ref: S]	1.74 (1.12-2.69)	.013[a]	0.63 (0.27-1.45)	.278
Age	1.042 (1.03-1.06)	<.001[a]	0.99 (0.97-1.02)	.580
Sex [Ref: Men]	1.00 (0.66-1.50)	.996	0.64 (0.33-1.24)	.184
Primary site [Ref: Pleural]				
Retroperitoneal	1.61 (0.84-3.07)	.152	1.45 (0.65-3.20)	.363[a]
Other	1.21 (0.65-2.23)	.554	0.33 (0.13-0.84)	.019[a]
Mitotic count [Ref: ≤4 Mitoses per 10 HPF]	2.96 (1.79-4.89)	<.001[a]	3.45 (1.66-7.16)	.001[a]
Margin status [Ref: R0]				
R1	1.17 (0.70-1.89)	.550	3.52 (1.53-8.10)	.003[a]
R2	1.24 (0.52-2.98)	.627	5.50 (1.90-16.10)	.002[a]
Tumor size, cm	1.05 (1.03-1.08)	<.001[a]	1.06 (1.03-1.12)	.001[a]

Abbreviations: HPF, high-power field; LC, local control; OS, overall survival; R1, negative resection margins; R2, margins with microscopic tumor infiltration; R3, margins with macroscopic tumor infiltration; Ref, reference category; S, surgery; S+RT, surgery plus radiotherapy.
[a]These *P* values indicate a significant difference.

20.6% in the S subgroup; $P = .004$). A comparison between preoperative RT versus postoperative RT did not reveal a significant difference in either the LC rate or the OS rate.

Analyses by Treatment Allocation

Comparison of surgery versus S+RT

Among the patients who underwent surgery, there were significantly less extremity primaries and significantly more pleural primaries (69.1% vs 91.7%, respectively; $P < .001$) as well as a higher probability of tumors resected with R0 margins (84.5% vs 15.5%, respectively; $P < .0001$). The median tumor size in the S+RT subgroup was 10.1 cm versus 8.8 cm in the S subgroup ($P = .084$). For details, see Table 1.

LC and local progression-free survival

Overall, no significant differences in the time to local failure or local progression-free survival (LPFS) were observed between the S and S+RT groups. On univariable analysis, the factors significantly associated with local progression were retroperitoneal versus pleural SFT site (HR, 1.49; 95% CI, 0.67-3.13), a mitotic count >4 mitoses per 10 HPF (HR, 3.45; 95% CI, 1.66-7.16; $P = .001$), R1 margin status (HR, 3.59; 95% CI, 1.58-8.14; $P = .002$) or macroscopic tumor infiltration (R2 margin status) (HR, 6.40; 95% CI, 2.22-18.46; $P = .001$) versus R0 margin status, and larger tumor size (HR, 1.07; 95% CI, 1.03-1.11; $P = .001$), as detailed in Tables 3 and 4.

Overall, the type of treatment (S vs S+RT) was not significantly associated with local progression (HR, 0.63; 95% CI, 0.27-1.45; $P = .278$). In patients who underwent surgery alone, 31 (7.2%) local relapses occurred comparable to 7 (6.1%) local relapses in the S+RT group. However, after correction for mitotic count and surgical margins, S+RT was significantly associated with a lower chance of local progression (HR, 0.19; 95% CI, 0.04-0.84; $P = .029$) (Tables 5 and 6).

After propensity score matching to test for an independent association between allocated management and outcomes, the association between treatment and local recurrence remained statistically significant, with a beneficial effect on LC observed for additional perioperative RT ($P = .012$) (Fig. 1). Nonetheless, no significant difference in OS was observed ($P = .325$) (Fig. 2). Baseline characteristics of matched cases for this analysis are shown in Supporting Table 1.

Overall survival

The S subgroup had a significantly longer median OS compared with the S+RT group (227 vs 195 months; $P = .012$). On univariable analyses, S+RT (HR, 1.74; 95% CI, 1.12-2.69; $P = .013$), older age (HR, 1.042; 95% CI, 1.03-1.06; $P \leq .001$), a mitotic count >4 mitoses per HPF (HR, 3.29; 95% CI, 2.09-5.18; $P \leq .001$), and greater tumor size (HR, 1.05; 95% CI, 1.03-1.08; $P \leq .001$) were all significantly associated with worse OS (Tables 3 and 4). After correction for age, mitotic count,

TABLE 5. Multivariate Cox Regression Analyses of Overall Survival and Local Control Using Pairwise Deletion

Model	OS (95% CI)	*P*	LC (95% CI)	*P*
1. Model 1, S+RT [Ref: S]	1.74 (1.12-2.69)	.013[a]	0.63 (0.27-1.45)	.278
2. Model 1 + age	1.65 (1.06-2.58)	.026[a]	0.63 (0.27-1.45)	.279
3. Model 1 + sex	1.75 (1.13-2.71)	.012[a]	0.59 (0.25-1.36)	.213
4. Model 1 + primary site	1.88 (1.19-2.96)	.007[a]	0.83 (0.36-1.94)	.66
5. Model 1 + mitotic count	1.30 (0.77-2.17)	.323	0.33 (0.10-1.12)	.076
6. Model 1 + margin status	1.48 (0.91-2.41)	.113	0.34 (0.12-0.97)	.045[a]
7. Model 1 + tumor size	1.82 (1.15-2.90)	.010[a]	0.64 (0.24-1.70)	.372
8. Model 1 + age, mitotic count, and tumor size	1.11 (0.64-1.95)	.704		
9. Model 1 + margin status and mitotic count			0.19 (0.04-0.84)	.029[a]

Abbreviations: LC, local control; OS, overall survival; Ref, reference category; S, surgery; S+RT, surgery plus radiotherapy.
[a]These *P* values indicate a significant difference.

TABLE 6. Multivariate Cox Regression Analyses for Overall Survival and Local Control Using Multiple Imputation Methods

Model	OS (95% CI)	*P*	LC (95% CI)	*P*
1. Model 1, S+RT [Ref: S]	1.74 (1.12-2.69)	.013[a]	0.63 (0.27-1.45)	.278
2. Model 1 + age	1.65 (1.06-2.58)	.026[a]	0.63 (0.27-1.45)	.279
3. Model 1 + sex	1.75 (1.13-2.71)	.012[a]	0.59 (0.25-1.36)	.213
4. Model 1 + primary site	1.88 (1.19-2.96)	.007[a]	0.83 (0.36-1.94)	.663
5. Model 1 + mitotic count	1.30 (0.77-2.17)	.323	0.43 (0.17-1.10)	.077
6. Model 1 + margin status	1.50 (0.94-2.40)	.100	0.35 (0.13-0.93)	.036[a]
7. Model 1 + tumor size	1.73 (1.11-2.72)	.016[a]	0.67 (0.27-1.64)	.378
8. Model 1 + age, mitotic count, and tumor size	1.21 (0.71-2.06)	.492		
9. Model 1 + margin status and mitotic count			0.29 (0.11-0.82)	.019[a]

Abbreviations: LC, local control; OS, overall survival; Ref, reference category; S, surgery; S+RT, surgery plus radiotherapy.
[a]These *P* values indicate a significant difference.

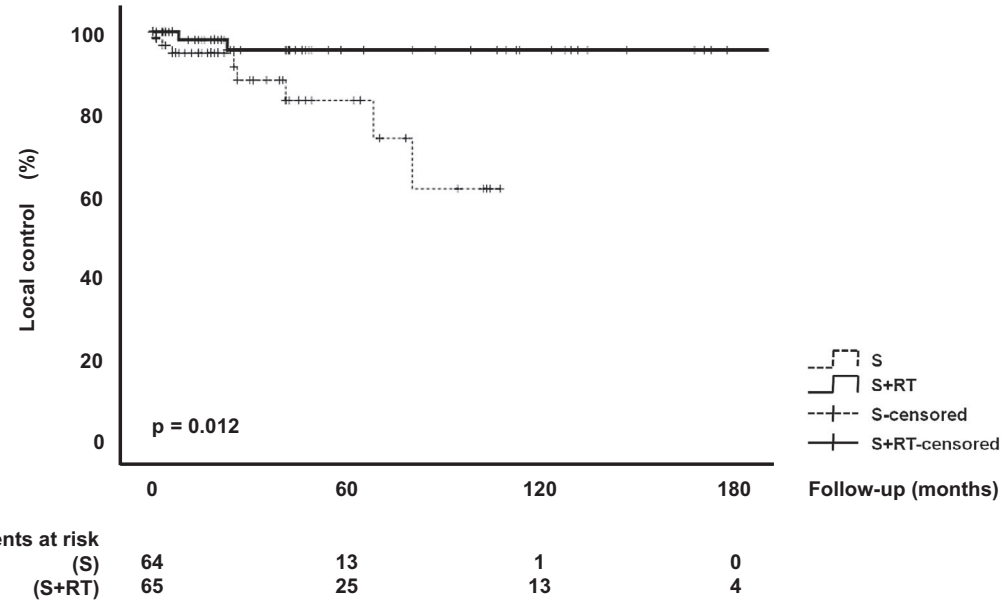

FIGURE 1. Local control is illustrated after propensity score matching, comparing surgery (S) versus surgery plus perioperative radiotherapy (S+RT).

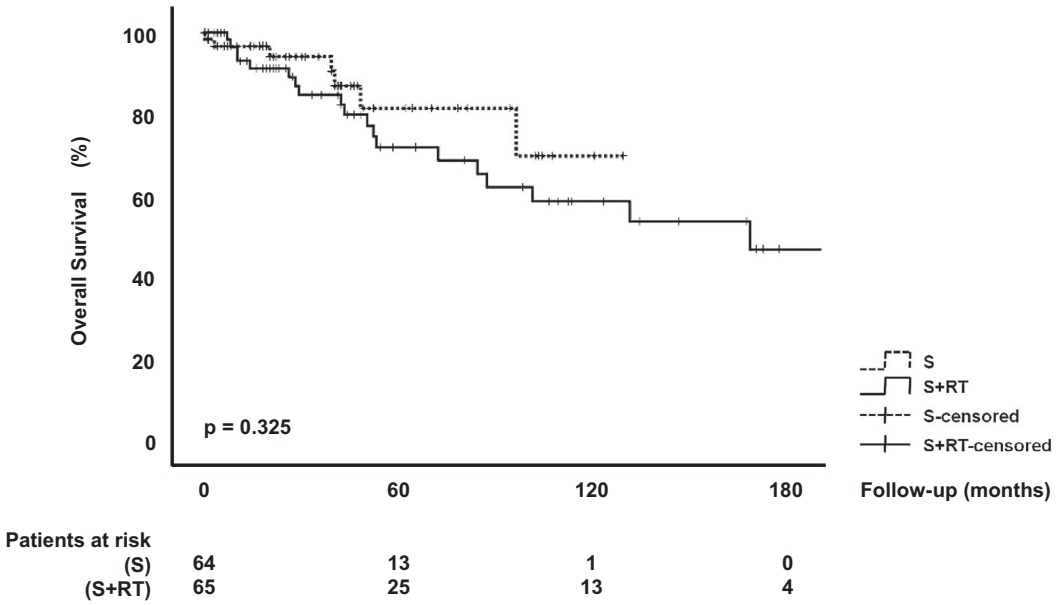

FIGURE 2. Overall survival is illustrated after propensity score matching, comparing surgery (S) versus surgery plus perioperative radiotherapy (S+RT).

and tumor size, the association between S+RT and OS disappeared and did not remain significant (HR, 1.11; 95% CI, 0.64-1.95; $P = .704$) (Tables 5 and 6). Note that these 3 criteria, derived from our univariable analysis, are the same criteria used to determine the Demicco score.[5]

Toxicity

More acute and late toxicities of any grade were observed in the S+RT subgroup compared with the S subgroup (7.5% vs 58.7%; $P < .001$ [predominantly grade 1 skin erythema]; and 2.6% vs 24.0%; $P < .001$, respectively). In the perioperative phase, more wound-healing problems occurred (n = 14) along with more hemorrhagic events (n = 7). The most serious late complications were an amputation because of persistent wound infection (n = 1) and femoral neuropathy (n = 1).

Biases by date of diagnosis

To rule out time biases, 3 equally large subsets of 183 patients (1990-2007 vs 2007-2013 vs 2013-2018) were compared. Over time, the addition of RT was highest in the 1990 to 2007 cohort (28.2% vs 16.5% vs 19.3%, respectively; $P = .018$). However, in addition to this observation, no further clinically relevant differences in baseline or treatment characteristics could be observed. Specifically, the rates of R0, R1, and R2 resections remained stable over the years ($P = .357$); and, for the entire cohort, no statistically significant differences could be observed in OS ($P = .346$) or LC ($P = .226$) comparing patients who were diagnosed in any of the 3 time cohorts.

Analyses by Primary SFT Site

Pleural SFT patient subgroup

Patients who had pleural SFTs (n = 109) were predominantly managed by surgery alone (n = 100; 92%). In this group, as shown in Table 2 and compared with the entire patient population studied, there were no significant imbalances with respect to age, sex, tumor size, or mitotic count. However, there were significantly more R0 resections (86% vs 29%) and less R1 resections in the S+RT-group (13% vs 57%) as well as a relatively low-risk Demicco scores (59% of low-risk patients in the S-group vs 67% of moderate-risk patients in the S+RT-group; $P = .013$). As expected by the low number of irradiated patients (n = 9) and the low number of local relapses (n = 9), there were no significant differences in LC, LPFS, or OS. Furthermore, for patients who had pleural SFTs, the Demicco score was unable to predict OS ($P = .320$) (see Supporting Fig. 1).

Retroperitoneal SFT patient subgroup

Patients who had a primary retroperitoneal SFT (n = 131) also were managed predominantly with surgery alone (n = 104; 79%); however, a significantly higher percentage received RT compared with those who had pleural SFT (21% vs 8%; $P = .008$). In this group, there were

TABLE 7. Literature Overview of Solitary Fibrous Tumor Series Reporting on Perioperative Radiotherapy

Reference	Total No.	No. in Perioperative RT	Median Dose and Range, if Available, Gy	Sites	Malignant: Mitotic Index >4 Mitoses per 10 HPF, %	Final Margin Status, %	LC at 5 Years, %	LC at 10 Years, %	OS, %	Median FU, mo	Remarks
Preoperative RT series											
Current study	549	63	25 × 2	All	13.0	R0, 79.0; R1, 17.0	95.8		78.7 (5 y)	63.0	
Wushou 2015[15]	804	20	NA	All	48.0	NA		~44.0 at 100 mo		85.6	LC read from Fig. 1G
Bishop 2018[26]	31	17	50	All	67.0	R1, 42.0	100.0		95.0 (5 y)	59.0	
Postoperative RT series											
Current study	549	58	27-30 × 2	All	59.0	R0, 30.0; R1, 50.0	95.9		66.6 (5 y)	94.0	
Wushou 2015[15]	804	212	NA	All	48.0	NA		~56.0 at 100 mo		85.6	LC read from Fig. 1G
van Houdt 2013[17]	81	19	NA	All	40.0	R1, 25.0					MA
Bishop 2018[26]	31	14	58 (50-65)	All	26.0	R1, 42.0	100.0		95.0 (5 y)	59.0	
Gao 2016[27]	1	1	60	Pelvis	1.0	NA					LC ≥6.5 y, n = 1

Abbreviations: FU, follow-up; Gy, grays; HPF, high-power fields; LC, local control; NA, data not available; OS, overall survival; R1, negative resection margins; R2, margins with microscopic tumor infiltration; R3, margins with macroscopic tumor infiltration; RT, radiotherapy.

no significant imbalances with respect to age, sex, tumor size, mitotic count, or in Demicco score. Despite a significantly lower R0/R1 resection rate in the S+RT-group compared with in the S group (67% vs 94%; $P = .003$), this did not translate into more local failures (12% vs 16%, respectively; $P = .489$). There also was no significant difference in OS after the addition of RT. However, within this subgroup of patients with retroperitoneal SFT, the Demicco score could reliably predict OS ($P = .031$) (see Supporting Fig. 2).

Patients with primary SFTs in the extremities, trunk, and head and neck region (nonmeningeal)

Once again, surgery was the predominant mode of management (n = 224; 72%) for patients who had extremity, trunk, or head and neck primary SFTs (n = 309). RT was also received by these patients in a significantly greater percentage compared with those who had pleural primary SFTs (28% vs 8%; $P \leq .0001$). In this group, there also were no significant imbalances with respect to age, sex, or mitotic count. Also, after R0 resection, 81% of these patients did not receive RT, whereas 28% of those who had R1 resection status did receive perioperative RT ($P = .003$). For patients in this largest subgroup, OS was highly significantly predicted by the Demicco score ($P \leq .0001$) (see Supporting Fig. 3).

DISCUSSION

This retrospective, observational study of 549 patients who had SFTs compared treatment with surgery alone (S) with management that included perioperative RT (S+RT). The data presented suggest that, after propensity score matching for an independent association between patient characteristics, treatments, and outcomes, a highly significant beneficial effect of the addition of perioperative RT on LC could be observed in terms of LPFS ($P = .012$), but this did not translate into a survival benefit. In multivariable analyses, after correcting for margin status and mitotic count, the HR for LC was 0.19 ($P = .029$) with the addition of RT.

Although the S subgroup had a significantly longer median OS compared with the S+RT group (227 vs 195 months; $P = .012$), after correction for age, mitotic count, and tumor size, the association between treatment type and OS disappeared and did not remain significant (HR, 1.11; 95% CI, 0.64-1.95). Remarkable was the observation that, when the results from our study were compared with those from our prior analysis,[24] the LC and OS rates were comparable in patients who received RT for macroscopic tumors after undergoing debulking surgery (ergo, R2 resection) and those who did not undergo any surgery at all, as in our previous report.[24] Although this outcome should be formally tested prospectively, it may suggest that surgeons need not embark on morbid and function-depriving procedures if more conservative, function-sparing procedures can be combined with perioperative RT, in which doses of RT to approximately 60 Gy appear to compensate for less radical surgery.

Furthermore, our current data are in line with 2 available risk scores in the setting of SFT. First, the Demicco score,[5] designed to predict OS, is validated in this cohort (except in our pleural SFT subgroup). The 3 criteria derived from our univariable analyses (age, mitotic count, and tumor size) overlap with the criteria designated by Demicco and coworkers.[5] Second, Salas et al[13] proposed that a visceral localization, no RT, and increasing age were related to local failure. Indeed, the highest rate of local failures in our cohort also was observed in the retroperitoneal SFT subgroup, but age correlated only to OS, and not to LC.

The role of surgery, especially in the nonmetastatic setting, is undisputed.[12,25] The frequently cited claim in the literature of the alleged inefficacy of RT prompted our task group to embark on a global database collection to gain further insight into the role of RT, with all the inherent caveats of retrospective studies. Furthermore, in our analyses of treatment allocation, all primary sites were lumped together, acknowledging the observation that, of all sites, a retroperitoneal SFT site has the highest risk of local failure. Here, although additional RT may be valid, the question cannot be answered because of the rarity of these tumors.

Publications on perioperative RT in SFT are summarized in Table 7,[15,17,26,27] excluding meningeal SFT. In brief, most series have reported on postoperative RT and have included a total 246 patients; and, when patients from the current study are included, the total is 304 patients. Our LC and OS rates are consistent with these data. Preoperative RT has been reported in only 100 patients in total, including those in the current study, with LC and OS probabilities at least as good as those after postoperative RT.

This was a retrospective study, with all the limitations thereof. However, to our knowledge, this is one of the largest series of surgically treated patients with or without RT reported in the literature to date. Furthermore, detailed conclusions on subgroups (eg, by site) may lack statistical power. Because SFT is a rare disease with an estimated 230 cases per year in the United States, it is unlikely that prospective, randomized, clinical trials will ever be conducted.[28]

For now, if an R1 resection (or worse) is anticipated or has already been performed in a patient who has an SFT with a high mitotic count, perioperative RT could

help to improve LC of the disease. This should be discussed among sarcoma specialists in tertiary referral centers as part of a shared decision-making process with our patients.

The Perspective of Patients With Sarcoma

From the patient's perspective, this retrospective study provides insightful data regarding the treatment of a very complex and heterogeneous group of rare tumors for which the indications for RT have been unclear. We conveyed our intention to compare perioperative RT versus surgery alone in a previous report.[24] The data presented here suggest that, in patients who have unfavorable resection margins and a high mitotic count, the addition of perioperative RT should be considered for this very rare disease by multidisciplinary tumor boards in tertiary referral centers. For most others, the burden of additional RT can be spared. The Sarcoma Patients EuroNet encourages the sarcoma scientific community to further explore the presented data by embarking on a prospective registry of SFT.

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AUTHOR CONTRIBUTIONS

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