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Review Article

Histologic Response Following Pre-Operative Radiotherapy for Soft Tissue Sarcoma (STS) in a French Reference Center and Review

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ABSTRACT

Background and Purpose: Limb sparing surgery and radiotherapy is the main treatment of patients harboring soft tissue sarcoma of the extremity. There is limited data regarding the prognostic impact of histologic response after pre-operative radiotherapy.

Patients and Methods: Between 2010 and 2018, 123 patients were treated with a pre-operative radiotherapy for soft tissue sarcoma at Leon Berard Centre (Lyon, France) and were retrospectively reviewed. All patients received a dose of 50 Gy in 25 fractions. The histologic response has been analysed by considering the following factors: necrosis $\geq 90\%$, percentage of viable tumor cells $\leq 10\%$ and fibrosis $\geq 10\%$. Overall survival (OS), local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS) and event-free survival (EFS) were evaluated.

Results: Median follow up was 33.2 months (range 2.3-128.1 months). Local recurrence occurred in 9 patients (7.5%) and 40 patients (33%) presented a distant recurrence. The 2 and 5-year OS was 84% and 63%. Histologic response factors (necrosis $\geq 90\%$, viable tumor cells $\leq 10\%$ and fibrosis $\geq 10\%$) were not predictive in DRFS and EFS. In multivariate analysis, grade was the only significant prognostic factor for EFS $P=0.0087$. Among the 14 patients with $\leq 10\%$ viable cells after irradiation 13 presented a metastatic evolution within 6 months.

Conclusion: This study showed that current histological response evaluation based on necrosis, fibrosis and viable cells could not predict clinical outcomes after radiotherapy for extremity soft tissue sarcoma. A significant proportion of patients with a good response after pre-operative radiotherapy present a metastatic recurrence.

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Introduction

Soft tissue sarcomas (STS) are rare tumors and their management is still controversial because of more than 100 histological subtypes. The combination of conservative surgery and radiotherapy (RT) has widely replaced amputations [1]. At the localized stage, surgery with negative margins associated with radiotherapy has shown a very good local

control rate of 85% for patients with intermediate or high-grade STS [2]. RT can be delivered pre-operatively or postoperatively [3]. Local control seems to be equivalent, but doses volumes and complications rates are different [4-6]. Neoadjuvant treatment has substantial effects on the histological evaluation, the histological response, particularly for necrosis, has been established as a prognostic factor in osteosarcoma and Ewing sarcoma but not for soft tissue sarcomas (STS) [7, 8]. Identifying

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predictors of outcome following neoadjuvant treatment could be useful to identify patients' subgroups for treatment intensification and/or to look for arguments to better adapt the timing of the RT.

The objective of this study is to evaluate the impact of histologic response to RT in terms of overall survival (OS), local recurrence-free survival (LRFS), distant recurrence-free survival (DRFS) and event-free survival (EFS) in a series of patients treated in a sarcoma expert French Center.

Materials and Methods

I Study Population

One hundred twenty-three patients with localized STS of the extremity, trunk and retroperitoneal area treated with a pre-operative RT at Leon Berard Centre (Lyon, France) between January 2010 and December 2018 were included in this retrospective study. We excluded patients who received nanoparticles in Nanobiotix, and those who received concomitant trabectedin in TRASTS, patients with Ewing sarcoma or patients with progressive disease after RT leading to surgery contraindication [9, 10]. Patients were extracted from the radiotherapy database cross with CIM10 code C499: malignant neoplasm of connective tissue and other soft tissue, unspecified.

Diagnostic core needle biopsies of the tumors were obtained in all patients before radiotherapy. Clinical, histopathological, radiological, and treatment characteristics as well as outcomes, were collected retrospectively from our computerized database. All the histology has been reviewed by expert pathologist from our center. RT techniques: RT delivered a dose of 50 Gy in 25 fractions to all patients. The technique was IMRT or 3D technique. Patients were treated with Tomotherapy (proximal extremity of limbs and trunk) whereas, 3D technique was preferred for distal limbs due to the difficulty in saving uneradicated strip of normal tissue with IMRT. GTV was defined as tumor volume defined on pre radiotherapy MRI, a longitudinal margin of 3 cm and a radial margin of 1.5 cm, was added to obtain the CTV except in case of natural barriers such as fascia, bone, or skin surface and additional 5mm for the PTV.

Evaluation: All patients had 2 pre-treatment imaging (before RT and before surgery) of their primary tumors with magnetic resonance imaging (MRI). Surgery was planned 4-9 weeks after the end of RT. Surgery was performed and the pathological analysis carried out by the sarcoma specialist pathologists of the Leon Berard Centre. The size of the tumor was evaluated from the largest diameter, then we compared the evolution of this larger diameter before and after RT.

The histological response was assessed based on standardized histological reports. The pathologists evaluated the percentage of necrosis, fibrosis and viable cells for each resection specimen. One block per centimeter of the tumor and one full transverse slice of the resected tumor were mapped and sampled for histologic processing. The percentage of necrosis, fibrosis and viable cells assessment was based on the histological examination of the entire tumor area sampled. Factors related to a better prognostic have been evaluated, such as histologic response factors (necrosis $\geq 90\%$, % viable tumor cells $\leq 10\%$ and fibrosis $\geq 10\%$). In this study, good responders are defined as patients who had viable tumor cells $\leq 10\%$ regardless of the rate of fibrosis and necrosis, which is analysed independently.

II Statistical Analysis

Continuous variables were described as median with range and categorical variables as numbers with percentages. Median follow-up was determined using the reverse Kaplan Meier method. Survival curves and survival rates were obtained using the Kaplan Meier method. Curves were compared using the log-rank tests.

Univariate Cox model regressions were used to find factors associated with disease recurrence-free survival. Hazard ratios were given with their 95% confidence interval (95% CI). All variables with a p-value of less than 0.15 in univariate analyses were entered in the multivariate model. Variable with more than 20% of missing data were not considered for the multivariate model. The full multivariate model is presented. Tests were two-sided and p-values lower than 0.05 were considered significant. All analyses were performed using SAS 9.4.

Table 1: Patients characteristics.

Sex	Women	60(49%)
	Men	63(51%)
Age	Median	63 years (15-86y)
Localisation	Extremity	81(66%)
	Tronc	16(13%)
	Head & Neck	1(1%)
	Pelvis	25(20%)
Histologic type	UPS	46 (37%)
	Myxofibrosarcoma	16 (13%)
	Liposarcoma dedif / Pleo	14(11,5%)
	Liposarcoma Well diff	10(8%)
	Leiomyosarcoma	9(7,5%)
	Synovialosarcoma	8(6,5%)
	Liposarcoma myxoide	8(6,5%)
	MPNST	2(2%)

	Others	10(8%)
Grade	1	13(12%)
	2	50(47%)
	3	43(41%)
Size> 10 cm	yes	70(60%)
	no	47(40%)
Mitosis count >19	yes	78(73,5%)
	no	28(26,5%)
KI67>50%	yes	54(78%)
	no	15(22%)
Chemotherapy	yes	88(71,5%)
	no	35(28,5%)
Medical staff	yes	6(5%)
	no	117(95%)
Necrosis 95%	yes	84(88%)
	no	11(12%)
	Missing data	28()
Complication	yes	82(69,5%)
	no	36(30,5%)
Reconstruction	yes	79(66%)
	no	41(34%)
Complications	infectious	3
	pain	1
	necrosis	9
	haemorrhage	3
	fistula	2
	Healing problems	12
	Renal failure	1
	NR	5

Results

I Patients' Characteristics

The cohort included 123 patients. Patient, tumor and treatment characteristics are summarized in (Table 1). The median age was 63 years (range, 15-86 years). The main localization was the extremity in 88 patients (66%). The largest diameter was > 5cm for 76% of patients and > 10 cm for 40% of patients. The most common histologic groups were UPS (37%) and 88% of sarcoma were grade 2-3. Multidisciplinary consultation meetings for pre-operative RT was performed in 95% of patients. Neoadjuvant chemotherapy was performed in 28% of patients. The T1 Gadolinium median size change before and after radiotherapy was + 3 mm (range, -77 mm, +95 mm). The margins status was R0 by 76%. Thirty-four percent of the patients needed a flap reconstruction and 30% of the patients have had post-operative complications.

II Histologic Response

Necrosis has been evaluated in 95 patients. The Median rate of necrosis was 10% (range, 0-100%). Necrosis \geq 90% has been highlighted in 11 patients (12%). The percentage of viable cells is available for 100 patients. Viable tumor cells \leq 10% have been highlighted in 34 patients (34%). The median percentage of viable cells after radiotherapy was 27.5% (range 0-100%). Thirteen patients had \leq 1% of viable tumor cells and 5 patients had no viable residual tumor (pathologic complete response). All patients with \leq 10% of viable tumor cells after radiotherapy also had a high rate of necrosis. (\geq 90%). Fibrosis has been evaluated in 70 patients. The median rate of fibrosis was 20% (range 0-100%) and for 54 patients (77%), fibrosis \geq 10% was described.

Table 2: Median, LRFS, DRFS, EFS and OS.

	Median	At 2years	At 5 years
LRFS	Not reached	94%	80%
DRFS	Not reached	69%	54%
OS	Not reached	84%	63%
EFS	44,5 months (min:27-max:not reached)	63%	41%

III Survival

Median follow up was 33.2 months (range 2.3-128.1 months). Nine patients (7,5%) presented a local recurrence and 40 patients (33%) presented a distant recurrence. At the end of the study, 22 patients died (20%) of cancer progression. The 2 and 5-years OS was 84% and 63%. The 2 and 5-year EFS was 63 and 41%. LRFS and DRFS were 94% and 69% at 2 years and 80% and 54% at 5 years. These results are summarized in (Table 2).

IV Prognostics Factors

i Univariate Analysis

In univariate analysis, none of the histologic response factors (necrosis $\geq 90\%$, viable tumor cells $\leq 10\%$ and fibrosis $\geq 10\%$) were predictive with the statistically significant differences in DRFS and EFS. R1 margins does not have a significant impact on DRFS and EFS. On the other hand, the factors related to the tumor are predictive of the patient's outcome. Grade, mitosis count ≥ 19 (calculated from the number of mitosis for 10 High power fields corresponding to 1.734 mm²), Ki 67 $\geq 50\%$ have an impact on EFS, as well as size > 10 cm. Grade and mitosis count ≥ 19 and Ki 67 $\geq 50\%$ influence the DRFS. Those results are summarized in (Table 3). Regarding histological classification, no statistically significant difference in terms of histologic response factors was found.

Table 3: Univariate analysis for DRFS and EFS.

DRFS					EFS					
	nb	HR	95%CI		p	nb	HR	95%CI		p
Sex	120				0,4135	123				0,2942
Women		Ref					Ref			
Men		1.297	0,695	2,419			1,346	0,773	2,343	
Grade	103				0.0058	106				0.0131
1		Ref					Ref			
2		2.398	0.54	10.649			2.435	0.718	8.256	
3		8.83	1.367	24.863			4.588	1.380	15.249	
Large diameter	114				0.1658	117				0.0327
<10		Ref					Ref			
≥10		1.572	0.829	2.982			1.861	1.052	3.29	
Mitoses	103				0.0064	105				0.0132
<19		Ref					Ref			
≥19		2.5	1.294	4.833			2.12	1.171	3.841	
Ki 67	67				0.0271	69				0.0198
<50		Ref					Ref			
≥50		2.486	1.1068	5.575			2.467	1.154	5.272	
Fibrosis	68				0.317	70				0.2947
<10		Ref					Ref			
≥10		0.653	0.284	1.504			0.668	0.314	1.42	
Chemotherapy	120				0.2538	123				0.2091
Yes		Ref					ref			
No		1.462	0.762	2.806			1.447	0.813	2.574	
Margin	115				0.7614	118				0.1106
R0		Ref	ref				Ref			
R1		1.268	0.598	2.688			1.548	0.797	3.007	
R2		1.42	0.338	5.971			2.685	0.945	7.633	
Necroses	94				0.0393	95				0.2751
<90%		Ref					ref			
≥90%		2.032	0.887	4.658			1.569	0.699	3.524	
Viable cells	98					100				0.6905
>10%		Ref	ref				ref			
<10%		1.36	0.697	2.563	0.3669		1.14	0.599	2.169	

ii Multivariate Analysis

In multivariate analysis, the only grade was a significant prognostic factor for EFS $P=0.0087$. For multivariate analyses, Ki67 and fibrosis

were not included because of a higher rate of missing data. These results are summarized in (Table 4).

Table 4: Multivariate analysis for DRFS and EFS.

DRFS		Number of patients	HR	95 %CI		p
Grade	1	81	ref			0,0641
	2		1,993	0,437	9,093	
	3		4,113	0,923	18,326	
Nécrose	<90%	81	ref			0,1392
	≥90%		1,953	0,804	4,745	
EFS		nb	HR	95%	CI	p
Grade	1	94 ref				0,0087
	2		1,541	0,332	7,143	
	3		4,239	0,977	18,388	
Size	<10cm					0,142
	≥10cm		1,678	0,841	3,348	
Margins	R0		ref			
	R1		1,442	0,661	3,145	
	R2		1,925	0,443	8,37	

“Good responders versus bad responders” (patients who had viable tumor cells ≤ 10). No statistical differences ($p=0,5$) were observed in OS between good and bad responders (Figure 1). It should be noted that among patients with distant recurrence (40 patients), 14 patients were good responders and 22 patients were bad responders. The majority of

“good responders” were women (10/14), UPS (10/14), extremity (11/14), RO surgery (12/14), 10/11 had not received CT and 6/14 had complications. Among the 14 good responders who had metastatic recurrences, 13 presented this evolution within 6 months.

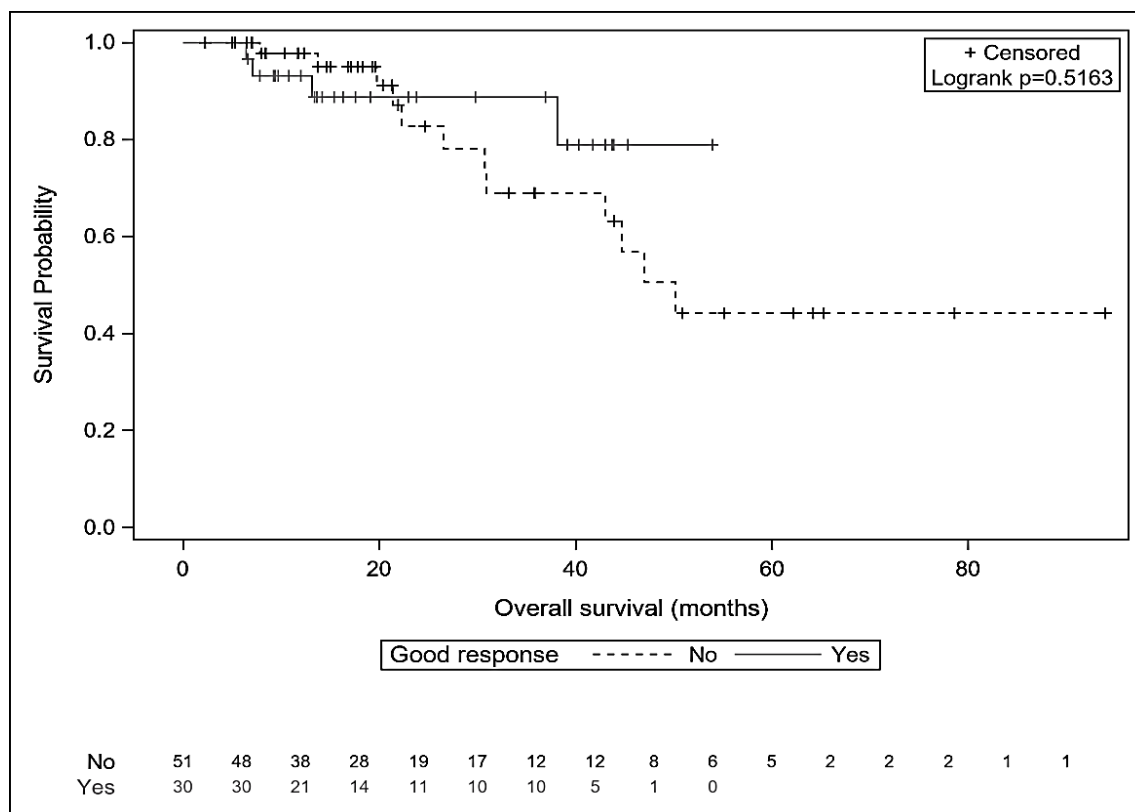


Figure 1: OS ‘good responders’ versus ‘bad responders’.

Discussion

We presented a cohort of 123 patients treated with pre-operative RT for limb and trunk sarcoma. In our study, tumors are lesions larger than 5 cm in 76% of cases and 88% are grade 2-3 which is in accordance with ESMO recommendations for pre-operative RT [11].

The results in terms of LRFS, OS and DRFS are comparable to those of the important series of the literature. With a median FU of 33 months, 2 years LRFS, OS and DRFS are respectively 94% (9 local recurrences) 69% and 84%. Wang *et al.*, reported a 2-year LRFS at 94%, a 2-year

DRFS at 65%, and 2-year OS at 80% very similar to results of the present series [5]. As it has already been published in pre-operative RT series, the majority of tumors tend to increase in size at the end of radiotherapy [12]. The median volume variation intended for this study is +3 mm (range, -77 mm +95 mm). R0 margins were obtained in only 76% of patients, and R1 in 30 cases. The impact of margins on local control does not seem to have the same impact in the case of pre-operative versus post-operative RT [13]. Radiotherapy allows closer surgical margins to preserve critical structures and function [14].

Table 5: Response according histology.

	<10 % viable cell	≥90%Necrosis	≥10% Fibrosis
Leiomyosarcoma 9pts	2pts 2NS	0 pts 2 NS	3pts 5 NS
Myxoid liposarcoma 8pts	0 pts 3NS	0 pts 2 NS	5pts 3NS
Liposarcoma 24 pts	2pts 9NS	0 pts 2 NS	9 pts 12NS
UPS 46 pts	20 pts 5NS	8 pts 9 NS	22 pts 14NS
Myxofibrosarcoma 16 pts	5 pts 4 NS	1 pts 6 NS	5pts 10NS
Synovialosarcoma 8pts	3pts 0NS	1 pts 1 NS	5pts 2NS
Others 12 pts	1pts 3NS	1 pts 5 NS	4 pts 7NS

NS: Not specified.

One of the main issues is the surgical complication rate. In our study, we showed that the surgical complication rate (30%) was comparable to 35% of wound complications described by O'Sullivan in a randomized study between pre-operative RT versus postoperative RT [15]. Regarding prognostic factors, it should be noted that the factors concerning the initial disease are prognostic factors in this study (grade, tumor size ≥ 10 cm). It seems that the sarcomas with the best response rate to radiotherapy in this series are UPS. Table 5 on the other hand, the histological response criteria have no prognostic value. Necrosis ≥ 90%, a percentage of viable tumor cells ≤ 10, fibrosis ≥ 10% have no impact on DRFS and EFS. There are a couple of possible explanations: first, there is no impact of histologic response on survival data and then there is a lack of power.

Schaefer *et al.* found that hyalinization/fibrosis was an independent favorable predictor for RFS and OS [16]. However, few authors have focused on fibrosis as a prognostic factor. Roberge *et al.*, also described

hyalinization/fibrosis as a category of treatment response, but the authors did not correlate histologic findings with outcomes [17]. For necrosis, results available in the literature are discordant. Indeed, the definition of necrosis itself may be variable and it's currently difficult to distinguish post-treatment necrosis and preexisting tumor necrosis. Several studies have used the percentage of necrosis as a marker of evaluation of therapeutic response, often with a cut-off of 95% beyond/above for which complete pathological response is defined. Some studies found a positive impact prognosis on survival and some others did not even suggesting negative impact of necrosis [12, 16, 18-23]. These studies are summarized in (Table 6). A recent meta-analysis of 21 studies and 1663 patients found that patients with necrosis ≤ 90% had a higher risk of recurrence and death. Extremity tumors were most common (93%), 77% were grade 2-3, 25% had received CT alone, 5% RT alone and 56% CT and RT [24].

Table 6: Necrosis response by literature.

Studies	Number of patients	% of patients with necrosis	Impact on survival
Eiler <i>et al.</i> 2001	496	≥95%=14% <95%=48% No residual tumor=38%	≥ 95 % necrosis =Positive predictive on LC and OS
MacDermid <i>et al.</i> 2009	34	≥95%=50% No residual tumor=11,8%	≥ 95 % necrosis =Positive predictive on DRFS
Canter RJ <i>et al.</i> 2010	25	≥95%=8%	≥ 95 % necrosis =Non significant positive predictive on DFS

Schaefer I- <i>et al.</i> 2017	100	No residual tumor=73% 2-90%=27%	2-90% necrosis =<unfavorable predictive on OS
Vayntrub M <i>et al.</i> 2014	207	≥90%=25%	≥ 90 % necrosis =Non significant positive predictive on DFS
Shah D <i>et al.</i> 2012	30	≥90%=10%	≥ 95 % necrosis =Non significant positive predictive on 3 years DRFS
Mullen JT 2014	113	≥95% =44% ≥95% =56%	≥ 95 % necrosis =Non significant predictive on OS and LC
Gannon NP <i>et al.</i> 2018	162	≥10% =87 pts	≥10% necrosis unfavorable predictive on DRFS and PFS

LC: Local Control; OS: Overall Survival Free; DRFS: Distant Recurrence Free Survival and PFS: Progression Free Survival; DFS: Disease Free Survival.

The European Organization for research and Treatment of Cancer-Soft tissue and Bone Sarcoma Group (EORTC-STBSG) recently proposed a standardized approach, which includes guidelines for the pathological examination and histologic response score based on the percentage of stainable tumor cells ranging in 5 scores, 0 at ≥ 50% stainable tumor cells [21]. This score has been tested on 100 patients, but no association was found between response core and recurrence free-survival (RFS) and overall survival (OS) [16]. Despite strong arguments to use % viable tumor cells as the surrogate endpoint, the actual trial Act. In. Sarc pathologic complete response defined as ≤ 5% viable tumor cells as the primary endpoint.

In the present study, the percentage of residual cells did not influence the prognosis of patients either. However, it is interesting to note that among patients with metastases, those in whom metastases occurred rapidly were all good responders. In these patients, the correct response is the sign of a very necrotic tumor that has a very poor prognosis even if it initially responds to RT. In this case 14/34 good responders had distant recurrence and 13 recurred before 6 months. We also observed that only 1 patient/14 had received CT. In this series patients who have been treated with chemotherapy have no better prognosis than others, but this is probably explained by the fact that the decision of neoadjuvant RT was taken in a context of insufficient response to CT to operate. Some authors have highlighted the feasibility of CT in addition to RT in this indication. There is no evidence that adjuvant or neoadjuvant chemotherapy is beneficial in localized STS, the majority European experts recommended neoadjuvant chemotherapy for mildly resectable grade 2-3 tumors [25]. The whole issue is to identify which patient could benefit from this treatment and when.

Ultimately, prospective studies are needed to identify response factors to pre-operative treatment (CT, RT) like histologic, radiologic or molecular factors and also to identify which patients have the highest risk for relapse and tailoring therapy accordingly. The main limitations of our study were that retrospective data and CT (28%) can be a confounding factor.

Conclusion

This study failed to show prognostic impact on treatment histologic response like necrosis ≥ 90%, % viable tumor cells ≤ 10% and fibrosis ≥ 10%, probably due to lack of trial power. However, 1/3 of patients with a good responders' profile had metastatic recurrence before 6 months, suggesting that histologic response was not a strong factor correlated to a better outcome.

Ethics Approval and Consent to Participate

An information note is given to each patient treated at the Leon Berard Centre explaining the possible use of their biological sample for research purposes. Patients have a right of opposition.

Availability of Data and Material

The data from this study are available.

Competing Interests

None.

Funding

None.

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