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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Pathologic necrosis following neoadjuvant radiotherapy or chemoradiotherapy is prognostic of poor survival in soft tissue sarcoma

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Abstract

Purpose Neoadjuvant radiotherapy ± chemotherapy and wide local excision is an accepted management of localized soft tissue sarcomas (STS). Necrosis is prognostic for survival in osteosarcomas, but the significance for STS is undetermined. This study aimed to determine if percent true necrosis, opposed to a combination of necrosis and fibrosis, leads to improved survival in extremity and trunk STS.

Methods From 2000 to 2015, 162 patients with STS were treated with neoadjuvant therapy and resection. Patient and tumor variables were reviewed, and resected specimens underwent pathological assessment. Necrosis was ratiometrically determined. Overall (OS), distant metastasis-free (DMFS), and progression-free survival (PFS) were calculated using Kaplan–Meier estimator. Survival was determined using the Fisher's exact test for univariate analysis (UVA) and logistic regression for multivariate analysis (MVA).

Results Median follow-up was 4.5 years and median necrosis was 24.97%. Necrosis predicted worse OS, DMFS, and PFS on UVA, and DMFS and PFS on MVA. Necrosis was positively correlated with size and grade. To mitigate the role of size, a sub-analysis of ≥ 10 cm tumors was performed revealing necrosis predicted decreased DMFS and PFS on UVA and MVA. In high-grade tumors, necrosis correlated with decreased DMFS and PFS on UVA. Necrosis did not predict OS in ≥ 10 cm or high-grade tumors.

Conclusions Our data suggests necrosis may be an additional independent, prognostic variable with increased necrosis predicting a worse prognosis. Necrosis may not be a measure of treatment response and instead suggests more aggressive tumor biology as high-grade, large STS were associated with increased necrosis.

Keywords Recurrence · Metastasis · Outcome · Preoperative · Radiation

Abbreviations

DMFS	Distant metastasis-free survival
Gy	Gray
MRI	Magnetic resonance imaging
MVA	Multivariate analysis
OS	Overall survival
PFS	Progression-free survival
ROC	Receiver operating characteristic
RT	Radiotherapy
STS	Soft tissue sarcoma
UVA	Univariate analysis

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Introduction

Soft tissue sarcomas (STS) are infrequently occurring, solid tumors of mesenchymal origin with unpredictable clinical and pathological behavior. STS represent 1% of adult and 12% of pediatric malignant neoplasms, with a predicted incidence in the United States of approximately 12,000 cases/year, and an approximated mortality rate of 40% (Siegel et al. 2016). The high mortality rate is largely attributed to distant metastasis. Wide local excision in combination with neoadjuvant radiotherapy (RT) with

or without chemotherapy has become widely accepted as an appropriate standard-of-care, (Mundt et al. 1995; Suit et al. 1985; Yang et al. 1998) leading to excellent local control, favorable postoperative functionality, and improved survival outcomes (Sarcoma Meta-analysis Collaboration 1997; Bedi et al. 2013a, b; DeLaney et al. 2003; Rosenberg et al. 1982; Schuetze et al. 2005; Suit and Spiro 1994).

Although several prognostic factors for STS outcomes have been identified including tumor grade and size, histologic type, invasion depth, age, and positive resection margin status, sparse data has been reported on the effect of pathological variables on survival (Gannon et al. 2018; Pisters et al. 1996; Singer et al. 1994; Stefanovski et al. 2002; Stojadinovic et al. 2002a, b; Zagars et al. 2003). Treatment-induced necrosis is strongly prognostic in osteosarcoma with > 90% necrosis predicting improved survival (Lindner et al. 1998; Picci et al. 1997; Wunder et al. 1998). However, the histological response to neoadjuvant therapy in STS and its impact on prognosis remains unclear. Studies have suggested necrosis may hold prognostic significance for local recurrence and overall survival for STS (Eilber et al. 2001; MacDermed et al. 2010). Specifically, greater percentages of necrosis (> 90%) are associated with improved 5-year local recurrence and overall survival (OS), (Eilber et al. 2001) and freedom-from-distant metastasis survival (MacDermed et al. 2010). Conversely, ≥ 70% necrosis predicted worsened 3-year disease-free survival and OS, also correlated with an increase in MR-based tumor volume following neoadjuvant therapy (Bedi et al. 2013b). Lower percentages of necrosis (20%) after neoadjuvant RT have predicted poor 5-year recurrence-free survival and OS (Schaefer et al. 2017). Despite this, conflicting evidence on the prognostic implications and prognostic percentages of pathological necrosis are reported, possibly due to differences in the techniques and methods to distinguish acellular material as true necrosis from fibrosis.

In this study, a cohort of STS patients treated with neoadjuvant RT and wide local excision with or without chemotherapy was retrospectively analyzed. The purposes of this investigation were: (1) to delineate true necrosis from fibrosis and its impact on OS, distant metastasis-free survival (DMFS), and progression-free survival (PFS); and (2) to evaluate the relationship between tumor grade and size with percent necrosis and various measures of survival.

Materials and methods

This research was approved by the Medical College of Wisconsin Institutional Review Board and all investigators completed training in both human research and patient privacy.

Patient population

298 patients with primary, stage I–III STS of the lower extremity and upper extremity or chest wall treated with external beam radiation with or without neoadjuvant chemotherapy followed by wide local excision between November 2000 and August 2015 were reviewed from a single-center prospectively collected retrospective STS database. Database exclusion criteria included metastatic disease on initial presentation, age < 18 years old, follow-up of less than 6 months, STS of locations other than the extremity or chest wall, recurrent sarcomas, amputation history, and histopathologic types demonstrating rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor, Ewing's sarcoma, osteosarcoma, Kaposi's sarcoma, angiosarcoma, aggressive fibromatosis, or dermatofibrosarcoma protuberans. Of our identified 298 patients, 52 were treated with postoperative radiation, 24 were non-oncologic excisions, and 60 did not have complete records for the variables assessed in this study. As such, 162 patients were eligible for analysis. All patients received an MRI prior to biopsy and definitive therapy. Patients were staged according to the 2009 American Joint Committee on Cancer (AJCC) system, seventh edition.

Radiotherapy and chemotherapy

All STS patients were reviewed and discussed at a multidisciplinary tumor board consisting of surgical and musculoskeletal oncologists, medical and radiation oncologists, musculoskeletal radiologists, pathologists with specialty training in bone and soft tissue pathology, and other specialists pertinent to presented cases. Treatment recommendations were presented and discussed with each patient.

RT was recommended to patients with deep, intermediate- to high-grade tumors, patients who had tumors near neurovascular bundles, and in patients with anticipated close margins. Patients received a median preoperative RT dose of 50 Gy using 3D-conformal radiation or intensity-modulated RT. Clinical target volume was created by adding a 3 cm margin superiorly and inferiorly and a 1–1.5 cm margin radially to the gross tumor volume. The planning target volume was created by adding a 5 mm margin to the clinical target volume. Tumor volumes were based on CT simulations and, in applicable cases, MRI was used to acquire treatment position.

Chemotherapy was recommended to patients aged approximately < 70 years, with large (> 5 cm), deep, and high-grade lesions. Chemotherapy was delivered prior to radiation therapy, using combination doxorubicin–ifosfamide for 1–3 cycles. Depending on treatment response and side effects, adjuvant chemotherapy was considered.

Surgery

Limb-salvage wide local excision was performed 4–6 weeks following RT by 1 of 3 fellowship-trained orthopaedic oncologists. Surgery was grossly approached through non-affected tissue planes. Tumor-violated arteries and veins were sacrificed, and whenever possible, neurovascular structures preserved. Negative margins (R0) were a primary surgical objective. Vascular and reconstructive plastic surgeons were involved in cases with difficult wound closures, complex vascular reconstruction, or free or rotational tissue transfer.

Pathologic assessment

Original pathology reports and pathology slides of each case were centrally re-reviewed per a specific protocol consistent with previous reports in the literature (Eilber et al. 2001; MacDermed et al. 2010; Roberge et al. 2010; Schaefer et al. 2017; Vaynrub et al. 2015; Wunder et al. 1998) by a board-certified pathologist fellowship trained in both cytopathology and surgical pathology, with specialization in musculoskeletal neoplasms, blind to clinical and survival outcomes. Additionally, we utilized a second pathologist to determine inter-rater variability with necrosis percentages, as measured by the concordance coefficient (measures agreement between two variables to evaluate reproducibility and inter-rater reproducibility, with the closer the value to 1, the higher agreement between two individuals). Percentage of viable tumor, necrosis, and fibrosis/hyalinization was scored per slide and the overall necrosis percentage was calculated for the entire specimen, so that the sum of the three components totaled 100%. Viable cells were quantified as stainable, atypical tumor cells with hyperchromatic nuclei, smudged and clumped chromatin, cellular and nuclear pleomorphism, large nucleoli, atypical and bizarre mitoses, loss of tissue polarity, and increased cellular size. Necrosis was quantified as a confluent area composed of necrotic tumor cells (preserved cellular outline "ghost" cells with loss of nuclear stain) amongst other degenerate cells, karyorrhectic nuclear debris, and polymorphonuclear neutrophil infiltrate. Fibrosis/hyalinization was quantified as hypocellular areas with deposition of dense, amorphous, uniform eosinophilic material, with/without dense collagenous matrix with fibroblasts embedded within (Schaefer et al. 2017). Histologic subtype, tumor grade, and tumor size were determined following initial diagnostic biopsy and confirmed with surgically resected specimens.

Statistical analyses

Percent necrosis and size cut-offs were determined from receiver operating characteristic (ROC) curves. OS, DMFS, PFS rates were estimated using the Kaplan–Meier estimate of survival function. The log-rank test was used to compare two survival curves. The Fisher exact test was used for UVA. A logistic regression analysis was used for MVA on any variable with a p value of 0.25 or less on UVA. For all analyses, type I error was maintained at 0.05 and all tests were two-sided. All statistical analyses were performed using MedCalc (Version 15.6, MedCalc Software bvba, Ostend, Belgium).

Results

Patient characteristics

The median age at diagnosis was 57.69 years, ranging between 18 and 92 years. 101 (62.3%) males were included, and 137 (84.6%) patients had a Karnofsky performance status greater than 80. The median and mean follow-up were 53.9 and 45.9 months, respectively.

Tumor characteristics and histopathology

The median tumor size prior to treatment initiation was 10.03 cm. All patients received neoadjuvant RT and 56 (34.6%) patients received neoadjuvant chemotherapy prior to definitive therapy. Local control was 99%. For those patients who developed metastatic disease, time to distant metastasis was 33.75 months.

122 (75.3%) patients had tumors localized to the lower extremity; while 40 patients (24.7%) had tumors located in the upper extremity/chest wall. 73 (45.1%) patients had tumors $\geq$ 10 cm. Central histopathological review determined undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (25.9%) as the most frequent tumor subtype. Other common histologies included liposarcoma (19.1%), myxofibrosarcoma (15.4%), and spindle cell sarcoma (16.0%). 123 (75.9%) patients had tumors classified as high-grade. 30 (18.5%) patients had tumors classified as stage I, 26 (16.1%) as stage II, and 106 (65.4%) as stage III. Clinical and pathological patient information is summarized in Table 1.

Clinical outcomes

The median percent necrosis in our cohort was 24.97%. Utilizing 2 reviewing pathologists, the concordance correlation coefficient demonstrated a value of 0.9487. A percent necrosis cut-off of 10% was determined from ROC curve analysis. Patients with greater than or equal to 10% necrosis on pathological examination had worse OS on UVA ($p = 0.0168$) (Fig. 1a; Table 2). DMFS was negatively influenced by necrosis on UVA and MVA ($p = 0.0001$ and $p = 0.005$, respectively) (Fig. 1b). Percent necrosis was also

Table 1 Clinical and pathological characteristics

Parameter	Entire cohort				24-month follow-up			
	No subset	≥ 10 cm	HG	HG + ≥ 10 cm	No subset	≥ 10 cm	HG	HG + ≥ 10 cm
N	162	73	123	54	116	51	90	40
Gender								
M	101	53	74	31	73	38	54	28
F	61	20	49	23	43	14	36	12
Age, years								
≤ 70	124	55	88	39	89	38	65	30
> 70	38	18	35	15	27	13	25	10
Median (range)	57.69 (18–92)	57.9 (19–91)	58.82 (18–92)	59.25 (19–91)	55.59 (18–92)	54.8 (18–87)	56.83 (18–92)	54.23 (18–87)
Karnofsky performance status								
81–100	137	55	102	45	103	42	78	31
≤ 80	25	18	21	9	13	9	12	9
Cardiovascular disease								
No	139	62	105	47	106	46	81	35
Yes	23	11	18	7	10	5	9	5
Diabetes								
No	141	73	106	50	107	44	84	36
Yes	21	10	17	4	9	7	6	4
Smoking history								
No	106	49	79	37	78	37	59	29
Yes	56	24	44	17	38	14	31	11
Grade								
Low/intermediate	39	19	0	0	36	11	0	0
High	123	54	123	54	90	40	90	40
Size, cm								
Median	10.03	14.5	99	0	9.68	13.86	9.51	0
≥ 10	73	73	54	54	51	51	40	40
Location								
Upper extremity	40	15	31	10	24	8	20	7
Lower extremity	122	58	92	44	92	43	70	33
Histology								
Undifferentiated/MFH	42	20	41	18	30	12	28	11
Liposarcoma	31	17	16	11	27	14	14	8
Synovial cell	26	11	18	10	19	9	16	8
Myxofibrosarcoma	25	9	20	6	20	8	16	6
Leiomyosarcoma	15	6	13	5	7	3	6	3
MPNST	7	3	6	1	3	1	3	1
Extraskeletal myxoid chondrosarcoma	4	2	1	1	3	1	1	1
Other	12	5	8	2	7	3	6	2
Wound complication								
No	114	48	86	35	96	36	66	27

Table 1 (continued)

Parameter	Entire cohort				24-month follow-up			
	No subset	≥ 10 cm	HG	HG + ≥ 10 cm	No subset	≥ 10 cm	HG	HG + ≥ 10 cm
Yes	48	25	37	19	30	15	24	13
Flap reconstruction								
No	93	40	69	33	67	30	51	22
Yes	69	33	54	21	49	21	39	18
Chemotherapy								
No	106	46	67	27	66	30	41	17
Yes	56	27	56	27	50	21	49	23
Follow-up, months								
Median (range)	55.9 (5.5–179.6)	45.61 (5.5–153.5)	53.91 (5.7–179.6)	46.69 (5.7–153.5)	73.27 (17.0–179.6)	59.92 (24.9–148.1)	69.74 (17.0–179.6)	55.34 (24.9–148.1)
Necrosis, %								
Median	24.97	32.86	28.72	37.59	23.85	28.25	26.68	35.7
≥ 15	80	43	69	35	23.85	26	42	24
≥ 10	87	47	75	36	23.85	28	45	25

HG high-grade, *MFH* malignant fibrous histiocytoma, *MPNST* malignant peripheral nerve sheath tumor

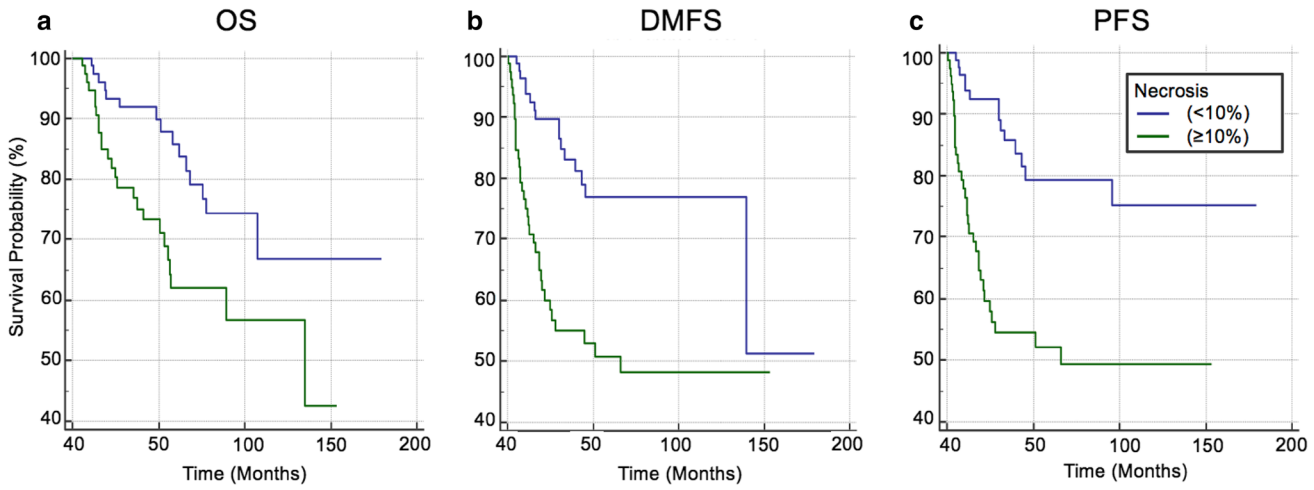

Fig. 1 Relationship between percent pathological necrosis and survival in the entire cohort. **a** Overall survival (OS), **b** distant metastasis-free survival (DMFS), and **c** progression-free survival (PFS)

predictive of poorer PFS on UVA and MVA ($p < 0.0001$ and $p = 0.0005$, respectively) (Fig. 1c).

A direct relationship was seen between percent necrosis and tumor size ($p < 0.0001$), and grade ($p < 0.0001$). Due to this, subset analyses were performed on patients with tumors ≥ 10 cm and those with high-grade disease. 73 (45%) patients had tumors ≥ 10 cm, and 123 (76%) patients had high-grade disease. In those with ≥ 10 cm tumors, percent necrosis was associated with decreased DMFS on UVA and MVA ($p = 0.0055$ and $p = 0.0363$, respectively) (Fig. 2b). Similar findings were seen for PFS on both UVA and MVA ($p = 0.0052$ and $p = 0.0240$, respectively) (Fig. 2c). Necrosis was not an independent risk factor for OS in patients with ≥ 10 cm tumors (Fig. 2a). High-grade disease DMFS was worsened by necrosis on UVA ($p = 0.0039$) (Fig. 3b). Percent necrosis also predicted for worsened PFS in patients with high-grade tumors on UVA ($p = 0.0014$) (Fig. 3c), while not influencing OS (although trending significance) ($p = 0.0539$) (Fig. 3a). In a subset analysis of patients with both high-grade disease and tumors ≥ 10 cm, necrosis predicted for worsened PFS on UVA and MVA ($p = 0.0096$ and $p = 0.0166$, respectively). Necrosis did not predict OS or DMFS in this group.

The median percent necrosis in a subset analysis selecting for patients with a minimum 24-month follow-up was 23.85%. DMFS was negatively influenced by necrosis on

Table 2 Necrosis outcome data

	Entire cohort		24-month follow-up	
	UVA (*p*)	MVA (*p*)	UVA (*p*)	MVA (*p*)
No subset				
OS	0.0168	0.2101	0.0925	–
DMFS	0.0001	0.005	0.006	0.0243
PFS	< 0.0001	0.0005	0.0089	0.0877
≥ 10 cm				
OS	0.0827	–	0.1415	–
DMFS	0.0055	0.0363	0.0475	0.1239
PFS	0.0052	0.024	0.015	0.087
Intermediate/low-grade				
OS	0.1006	0.1304	0.423	–
DMFS	0.0101	0.028	0.281	–
PFS	0.0101	0.028	0.281	–
High-grade				
OS	0.0539	–	0.1511	–
DMFS	0.0039	0.2192	0.0207	0.0538
PFS	0.0014	0.0677	0.0619	–
High-grade + ≥ 10 cm				
OS	0.4507	–	0.3514	–
DMFS	0.0559	–	0.1286	–
PFS	0.0096	0.0166	0.1090	–

DMFS distant metastasis-free survival, *MVA* multivariate analysis, *OS* overall survival, *PFS* progression-free survival, *UVA* univariate analysis

UVA and MVA ($p = 0.0060$ and $p = 0.0243$, respectively). Percent necrosis also predicted poorer PFS on UVA ($p = 0.0089$), however, OS was not predicted by necrosis in this group. 51 (44%) patients had tumors ≥ 10 cm, and 90 (76%) patients had high-grade disease. In tumors ≥ 10 cm, percent necrosis predicted worse DMFS on UVA ($p = 0.0475$). Necrosis also predicted worsened PFS on UVA (0.0150) for these patients. OS was not predicted by necrosis in patients with tumors ≥ 10 cm. High-grade disease DMFS was impacted by necrosis on UVA ($p = 0.0207$). OS and PFS were not predicted by necrosis on UVA in this group. In patients with both high-grade disease and tumors ≥ 10 cm, necrosis was not predictive of OS, DMFS, or PFS.

Lastly, in intermediate- or low-grade tumors the median percent necrosis within this group was 13.43%. Necrosis predicted worse DMFS ($p = 0.0101$, $p = 0.028$) and PFS ($p = 0.0101$, $p = 0.028$) on UVA and MVA, however, did predict OS within this group. When those patients with a minimum follow-up of 24 months were analyzed, necrosis did not predict any measure of survival.

Discussion

Determining STS prognosis poses a significant clinical challenge due to histologic heterogeneity and tumor behavior, and varied treatment regimens among institutions. Studies have demonstrated that large, high grade tumors have a higher risk of developing metastatic disease. Inherent tumor biology and response to therapy are likely significant prognostic indicators; however, the significance of pathologic variables including tumor necrosis remains limited. Pathologic necrosis has been an accepted standard to assess efficacy of neoadjuvant RT and higher rates of necrosis (≥ 90%) are regarded as complete treatment response (Stacchiotti et al. 2009; Uhl et al. 2006). The prognostic value of true pathological necrosis for STS remains unclear, and an evidence-based true necrosis percentage, separate from fibrosis, has not been defined to be predictive of survival

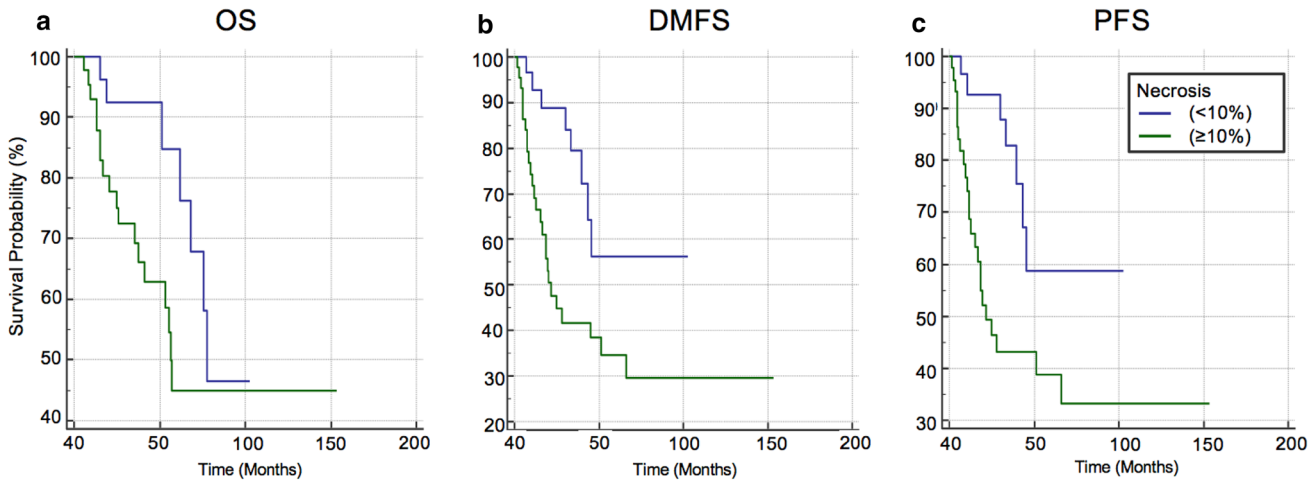

Fig. 2 Relationship between percent pathological necrosis in ≥ 10 cm tumors and survival in the entire cohort. **a** Overall survival (OS), **b** distant metastasis-free survival (DMFS), and **c** progression-free survival (PFS)

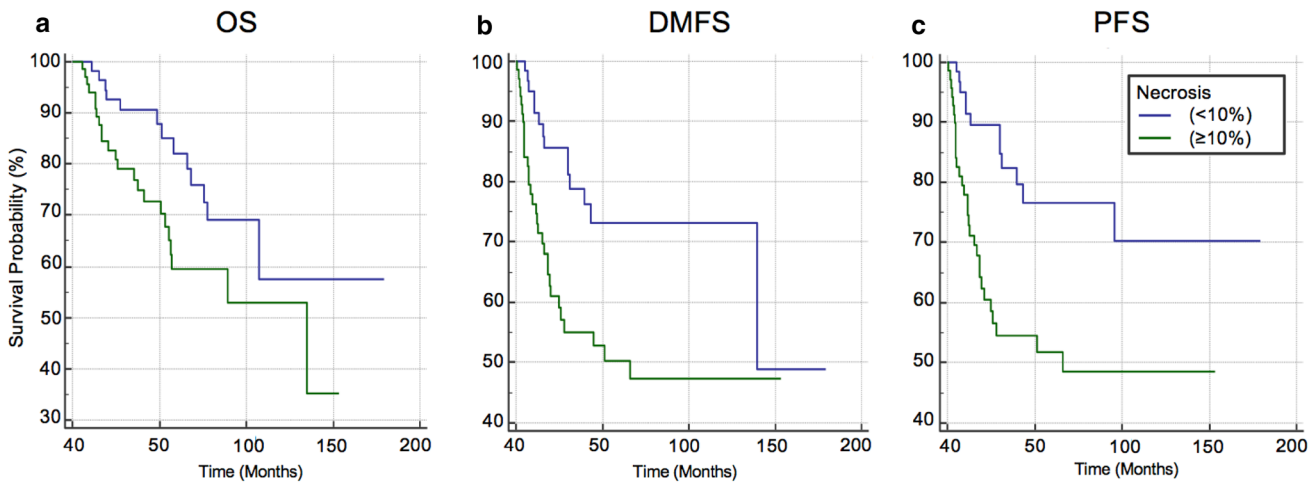

Fig. 3 Relationship between percent pathological necrosis in high-grade disease and survival in the entire cohort. **a** Overall survival (OS), **b** distant metastasis-free survival (DMFS), and **c** progression-free survival (PFS)

outcomes. We aimed to differentiate true necrosis, separate from fibrosis, on pathological re-review.

In this study, necrosis correlated with poorer OS, DMFS, and PFS on UVA, and DMFS and PFS on MVA in the entire cohort. When 24-month follow-up patients were assessed, necrosis predicted poorer DMFS and PFS on UVA and MVA. The median percent necrosis in this cohort following neoadjuvant therapy was 24.97%, significantly lower than previous investigations. High percentages of post-treatment necrosis (≥ 90%) have been shown to improve survival (Eilber et al. 2001; MacDermed et al. 2010; Mack et al. 2005). Eilber et al., demonstrated patients with < 95% necrosis were 2.51 times more likely to develop local recurrence and 1.86 times more likely to have a disease-specific death, when compared to those with ≥ 95% necrosis, (Eilber et al. 2001) suggesting more necrosis yields improved clinical outcomes. Conversely, no significant relationship between percent necrosis and various measures of survival has been documented (Bedi et al. 2013a, b; DeLaney et al. 2003; Mullen et al. 2014; Ryan et al. 2008).

Differences in the former studies and the present may be in part due to necrosis quantification as total acellular material on pathologic review, without the separation and distinction of true necrosis from fibrosis as done here. The previous studies did not detail methods of pathologic review to specify the cellular characteristics interpreted and reported as necrosis. These investigations report high percentages or near-complete necrosis, perhaps a result of the inexact nature of determining necrosis from fibrosis or grouping true coagulative necrosis with fibrosis/hyalinization on pathological review, reporting a single "necrosis" percentage or "greater than" threshold value. Inconsistencies may also be due to different institutional conventions utilized by pathologists to report STS necrosis. The European Organization for Research and Treatment of Cancer—Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) proposed a standardized method to examine STS pathological response to neoadjuvant radiotherapy, including a 5 grade score dependent on the proportion of stainable (non-necrotic) tumor cells (Wardelmann et al. 2016). Evaluation of the prognostic value of this score found no association with recurrence-free survival or OS (Schaefer et al. 2017). Despite this, no international consensus or standardized method exists for pathologists to evaluate and record/grade percent necrosis in STS.

High-grade tumor biology has repeatedly been shown to have a profound influence on STS survival (Pisters et al. 1996; Singer et al. 1994; Stefanovski et al. 2002; Stojadinovic et al. 2002a; Zagars et al. 2003). Large and high-grade STS are noted to have significantly higher percent necrosis at initial diagnosis, contrasted from other forms of malignant human neoplasms (Bedi et al. 2013a, b). A compounding relationship between high tumor grade and size, and percent necrosis may exist, as it is well known that tumor vascular density tends to decrease as size increases, predisposing tumor to ischemia and consequent necrosis as tumors outgrow their vascular supply (Pettersson et al. 2000). Necrosis may be a product of inherent aggressive tumor biology related to large size and high-grade disease, as opposed to treatment response. Here we demonstrate that necrosis predicts DMFS and PFS in tumors ≥ 10 cm, as well as, in tumors that are high-grade. However, in subset analyses that included only patients with tumors that were both high-grade and ≥ 10 cm, necrosis fell out of significance for survival. Such findings suggest grade and size may represent stronger prognostic factors than necrosis, especially in more aggressive STS (as demonstrated by size and grade).

No histopathological or imaging method exists allowing the distinction between treatment-induced and tumor-related pathologic changes, such as necrosis. A pre-existing necrotic core inherent to tumor biology may confound necrosis percentages on pathological review. The vast majority of patients treated at our center receive neoadjuvant RT as standard-of-care for STS of the extremity or trunk, which aligns with national and international consensuses (Dangoor et al. 2016; EMSO/European Sarcoma Network Working Group 2014; von Mehren et al. 2018). Due to this, it is difficult to make comparisons between tumors that underwent neoadjuvant RT versus those that did not, although such a comparison would provide meaningful information regarding baseline percent necrosis. Only post-treatment necrosis of resected specimens is analyzed, allowing no discrimination between pre- and post-treatment percentages. Pathological changes may not represent an ideal measure of treatment response. Perfusion weighed MRI has been proposed as one method to indirectly depict tumor-cell necrosis (Uhl et al. 2006). Specifically, in osteosarcoma, perfusion-weighted imaging was correlated directly with microvessel density, vascular permeability, and regional blood volume and flow, leading authors to conclude findings as indirect depictions of tumor necrosis (Uhl et al. 2006). Others have suggested volume contrast analysis through dynamic contrast-enhanced MRI can be utilized as an early predictor of histologic response (tumor cell necrosis rate) in STS following chemoradiotherapy (Xia et al. 2017).

Limitations of this study include a modest cohort size and a heterogeneous sarcoma profile collected at a tertiary referral center. In addition, the treatment profile here contains patients who did and did not receive chemotherapy. Despite this, on UVA, chemotherapy was consistently not predictive for any measure of survival in any patient group analyzed. Another limitation was the retrospective design of this study which inherently introduced biases. Experimentally, necrosis is not uniformly evaluated because of prominent variability in pathological review, the subjective determination of percent necrosis, the technical challenge to evaluate the entirety of a large STS, and the variability in pathological slide preparation. To limit interobserver variability, this study utilized two central histopathological reviewers specializing in musculoskeletal pathology who were blind to clinical outcomes. It is possible that bias may have been introduced in a small number of cases as the reviewing pathologists attended weekly tumor board meetings where a small number of patients included in this re-review were presented and discussed. At the time of re-review, the slides and reports were de-identified to the reviewing pathologist. Lastly, the results of this investigation may not be generalizable given the unique heterogenous tumor profile analyzed and the intra-institutional treatment regimen provided.

While our study suggests necrosis may to be an independent prognostic factor for patient outcomes, it should not be used alone to advise patients or guide medical/surgical therapy. Rather, this information should be included with patient-specific characteristics such as age and pre-existing medical conditions, and tumor-specific characteristics. In addition, necrosis as a prognostic factor should be evaluated in larger patient cohorts, possibly through the utilization of a central multi-center database, to remove the heterogeneity of tumor subtype and variable treatments (neoadjuvant RT ± chemotherapy, adjuvant RT) administered to patients to determine the clinical efficacy of this information. Investigations utilizing histologic subtype databases may illustrate specific histologic subtype prognostic factors; however, this is limited by the infrequent occurrence of STS. With the further advancement of personalized medicine and understanding of STS pathogenesis and treatment response, the identification of novel prognostic factors whether radionomics, molecular signals, protein/RNA expression, and/or circulating tumor DNA may represent additional, future, and specific prognostic factors. The development of a grading system, as well as, a reproducible and standardized method for determining true necrosis from fibrosis would likely improve the correlation between necrosis and prognosis in STS.

Conclusion

Assessing the prognostic significance of STS necrosis following neoadjuvant therapy is challenging, producing literature disparities, and conflicting conclusions. Much of this challenge rests with the difficulty in standardizing the determination of true necrosis, separate from fibrosis, on pathological review. The findings of this study demonstrate an association between necrosis and tumor size and grade, but also suggest that pathological necrosis appears to have selective, independent prognostic value in STS for worse survival. Pathologic necrosis may not be a measure of treatment response and instead suggests more aggressive tumor biology. This data indicates that the amount of necrosis following neoadjuvant therapies may be an additional, independent, prognostic variable, warranting further investigations into the mechanisms by which necrosis may be involved in tumor-related outcomes and as a prognostic determinant.

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Compliance with ethical standards

Conflict of interest The author(s) declares that they have no conflict of interests.

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