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Scientific Article

Association of Histologic Subtype With Radiation Response and Survival Outcomes in Synovial Sarcoma

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Purpose: Synovial sarcoma (SS) is a rare, aggressive soft tissue malignancy that is divided into biphasic and monophasic histologic subtypes. In addition to surgical resection, radiation therapy (RT) improves local control in patients at higher risk of recurrence. This study aimed to investigate the impact of histologic subtype on radiation response and survival outcomes in patients treated with RT as part of definitive management.

Methods and Materials: We retrospectively identified patients with SS treated with RT and surgical resection from 1997 to 2020 at Stanford Medical Center. We assessed the association between histologic subtypes (biphasic vs monophasic) and response to preoperative RT based on imaging and pathology. Volumetric response was calculated using the pre-RT and post-RT/preoperative postcontrast T1-weighted magnetic resonance imaging images. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Univariable and multivariable analyses were conducted using Cox regression models. Variables for univariable and multivariable analyses included age, histologic subtypes, tumor location, tumor size, margin status, chemotherapy, and performance status.

Results: In our study, 50 patients met the inclusion criteria. The median age was 34.8 years at diagnosis, and 36% (n = 18) received concurrent chemotherapy. Biphasic (n = 18, 36%) and monophasic (n = 32, 64%) tumors exhibited significant differences in negative margin status (94% vs 66%, P = .036). Of the 22 patients who underwent preoperative RT, 15 patients had pre-RT and post-RT imaging to assess volumetric changes. Biphasic tumors demonstrated less necrosis at the time of surgical resection but a significantly greater volumetric decrease with preoperative RT (42% vs 5%, P = .004). PFS and OS were superior in biphasic tumors (P = .003 and P = .009, respectively). Multivariable analyses identified histologic subtypes (monophasic vs biphasic) as a significant factor impacting PFS (HR, 5.65; 95% CI, 1.78-17.91; P = .003).

Conclusions: Biphasic tumors exhibit an improved volumetric response to preoperative RT and improved outcomes. These findings underscore the importance of considering histology when tailoring treatment for patients with SS.

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Introduction

Synovial sarcoma (SS) accounts for 5% to 10% of soft tissue sarcomas and is considered an aggressive, high-grade sarcoma with a 5-year mortality rate of 25%.[1,2] SS occurs primarily in the adolescent and young adult patient population and frequently arises in the knee and lower thigh.[3] The chromosome abnormality *t*(X; 18) (p11.2; q11.2) is a unique feature of these tumors that results in the formation of the SS18::SSX fusion oncogenes.[4,5] Histologically, there are 2 predominant subtypes; monophasic tumors, which are composed of sheets of spindle cells, and biphasic tumors that harbor both epithelial and spindle cell components.[6,7] Previous studies have suggested that biphasic SS have a better overall survival (OS) than monophasic SS.[8,9] However, other studies did not find statistically significant survival differences between the subtypes.[2,10,11]

Similar to other soft tissue sarcomas, the optimal care for localized SS includes complete surgical resection with radiation therapy (RT) added to improve local control in patients at high risk.[12] Chemotherapy has been associated with improved survival in patients with SS, and metastatic SS are typically chemosensitive.[13,14] SS has been described as being radioresistant.[15,16] However, a Surveillance, Epidemiology, and End Results database study found patients with SS treated with RT had statistically significant improvement in disease-specific survival (HR, 0.62; $P = .003$) and OS (HR, 0.65; $P < .001$).[17] To date, there are no reports comparing biphasic and monophasic SS RT response. In this study, we sought to compare volumetric changes and survival outcomes between the SS subtypes.

Methods and Materials

Study design

Stanford's Institutional Review Board approved this retrospective study. Patients with SS histology were queried from the Radiation Oncology Data Warehouse, which aggregates data from electronic medical records. Patients who were diagnosed with localized biopsy-confirmed SS treated at our institution between 1997 and 2020 who underwent surgical resection and received either preoperative or postoperative RT within 3 months of surgery were included. Demographic information, pathologic data, treatment details, follow-up, patterns of recurrence, and survival status were collected. Primary outcomes included volumetric response to radiation, progression-free survival (PFS), and OS. We included the following variables in the univariable and multivariable analyses for PFS and OS: patient age at diagnosis, monophasic or biphasic histology, tumor size, surgical margin status (negative vs positive), concurrent chemotherapy (no vs yes), and Eastern Cooperative Oncology Group (ECOG) performance status at time of RT. Tumors were designated as biphasic or monophasic based on histologic findings found in the pathology reports.

Measuring volumetric response

A subset of patients treated with preoperative RT with pretreatment and post-RT/presurgery magnetic resonance imaging available were analyzed for volumetric response to RT. Thin-cut, 1 to 1.5 mm slice thickness, postcontrast T1-weighted images were imported into MIM software Inc., version 7.3.3, for contouring pretreatment and post-RT tumor volumes. The volumetric decrease was calculated as:

$$\frac{PreRT\ volume - PostRT\ volume}{PreRT\ volume}$$

We also used the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) to determine if there was a complete response, partial response, stable disease, or disease progression.[18] Pathologic response was based on percent tumor necrosis at the time of surgical resection after neoadjuvant RT.[19]

Statistical analysis

Analyses were conducted using R version 4.3.0 (R Core Team), SAS version 9.4 (Statistical Analysis Systems), and Prism version 10.2.2 (GraphPad). Fisher exact tests were used to compare categorical variables and Wilcoxon rank sum tests were used for continuous variables. Correlation between variables was assessed using the Spearman correlation coefficient. Survival curves were created using the Kaplan-Meier method. Univariable and multivariable analyses used Cox proportional hazards regression to identify variables associated with mortality. In our analysis, we included age as a continuous variable, histology (biphasic vs monophasic), tumor size as a continuous variable, surgical margin status (negative vs positive), concurrent systemic therapy (yes vs no), and ECOG performance status. On OS multivariable analysis, ECOG and age were not used as stratified variables because of nonproportional hazards.

Results

Patient characteristics

A total of 50 patients with SS were identified (Table 1). The median age at the time of diagnosis was 34.8 years

Table 1 Baseline patient and treatment characteristics

Attribute	Total (%)	Biphasic (%)	Monophasic (%)	*P* value
n	50	18 (36)	32 (64)	
Median age at diagnosis (range)	34.8 (13.2-70.3)	37.0 (13.2-70.3)	34.6 (15.2-68.5)	.762
Gender				.083
Female	22 (44)	11 (61)	11 (34)	
Male	28 (56)	7 (39)	21 (66)	
ECOG performance status				.126
0	29 (58)	13 (72)	16 (50)	
≥1	21 (42)	5 (28)	16 (50)	
Tumor size (cm) (range)	7.1 (2.7-18.0)	7.5 (2.8-17.0)	6.8 (2.7-18.0)	.642
Tumor location				.248
Extremity	31 (62)	13 (72)	18 (56)	
Head and neck	6 (12)	0 (0)	6 (19)	
Trunk/abdomen	10 (20)	4 (22)	6 (19)	
Visceral	3 (6)	1 (6)	2 (6)	
Margin status				**.036**[a]
Negative	38 (76)	17 (94)	21 (66)	
Positive	12 (24)	1 (6)	11 (34)	
Radiation				.068
Postoperative	28 (56)	7 (39)	21 (66)	
Preoperative	22 (44)	11 (61)	11 (34)	
Dose (range)	55 (45-66)	50 (44−63)	57 (45-66)	.650
Fractions (range)	26 (22-35)	25 (22-35)	29 (25-35)	.935
Concurrent chemotherapy				1.000
No	32 (64)	12 (67)	20 (63)	
Yes	18 (36)	6 (33)	12 (37)	

[a]P-value statistically siginificant (< 0.05).

(range, 13.2-70.3 years) and 36% received concurrent chemotherapy. There were 22 female (44%) and 28 male (56%) patients. Most had an ECOG of 0 (n = 29, 58%). The median tumor size was 7.1 cm (range, 2.7-18.0 cm). The most common sites were extremity (n = 31, 62%), head and neck (n = 6, 12%), and trunk/abdomen (n = 3, 6%). Thirty-eight patients (76%) had negative surgical margins and 12 patients (24%) had positive surgical margins. Fifty-six percent (n = 28) of patients received postoperative RT and 44% (n = 22) received preoperative RT. Patients were treated to a median dose of 55 Gy (range, 45-66 Gy). Most patients did not receive concurrent chemotherapy (n = 32, 64%).

There were 18 (36%) and 32 (64%) tumors with biphasic and monophasic histology, respectively. Although there were more head and neck tumors in the monophasic group, there was not a significant difference in tumor locations between the 2 groups. Biphasic tumors had significantly higher rates of negative margins than monophasic tumors (94% vs 66%, P = .036). Of the 10 patients with monophasic tumors with positive margins, 4 patients received preoperative RT and 6 patients received postoperative RT.

Volumetric response

Of the 22 patients treated with preoperative RT, 15 patients had both pre-RT and post-RT imaging to assess volumetric changes. Eight patients (53%) had biphasic tumors and 7 patients (47%) had monophasic tumors. The volumetric decrease for biphasic tumors was significantly greater than for monophasic tumors (Fig. 1, median 41% vs 5%, P = .004). By RECIST 1.1, 25% (n = 2) of patients with biphasic tumors achieved a partial response and 75% (n = 6) had stable disease. Most patients with monophasic tumors (n = 6, 86%) had stable disease, whereas 1 patient experienced progressive disease

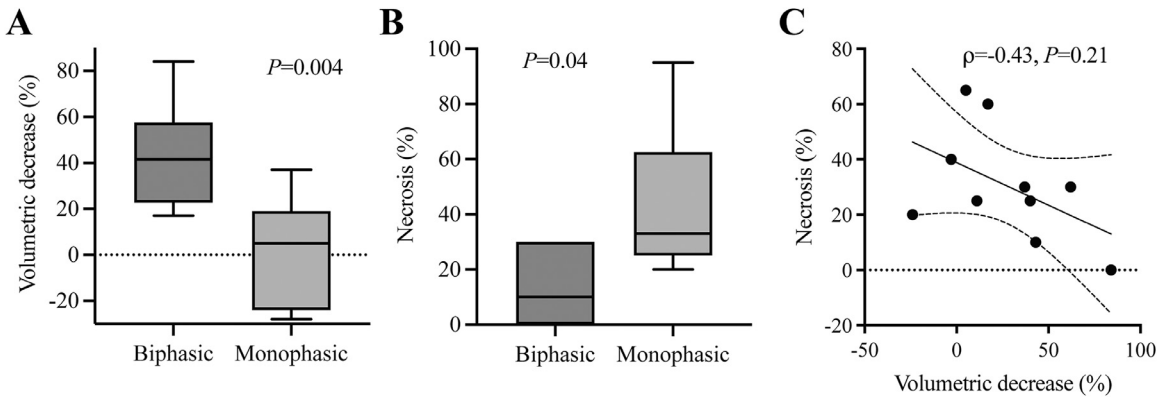

Figure 1 Response to preoperative radiation therapy (RT) by histologic subtype. Box and whisker plots of (A) volumetric decrease measured by imaging and (B) percent necrosis at the time of surgical resection in biphasic and monophasic synovial sarcomas treated with preoperative RT. Boxes show the interquartile range and whiskers extend to the maximum and minimum values. (C) Correlation of percent necrosis and volumetric decrease in synovial sarcomas treated with preoperative RT. Line of best fit and 95% CI are displayed on the graph.

(14%) according to the RECIST criteria. In contrast to the volumetric response, percent necrosis at the time of surgical resection after preoperative RT was significantly higher in monophasic tumors than in biphasic tumors (median 33% vs 10%, $P = .04$). However, only one monophasic tumor (14%) achieved ≥95% necrosis. Across all patients treated with preoperative RT, there was a nonsignificant negative correlation between volumetric decrease and pathologic necrosis ($\rho = -0.43$, $P = .21$). For example, 1 monophasic tumor increased in volume by 24% (Fig. 2A, B) and had 40% necrosis by pathology, and 1 biphasic tumor decreased in volume by 84% but no necrosis was noted in the pathology report (Fig. 2C-F).

Survival analysis

Of the 50 patients, 8% (n = 4) of patients experienced local recurrence and 54% (n = 27) experienced distant recurrences. The 4 patients who experienced local recurrence had tumors with monophasic histology, and 3 patients (75%) received postoperative RT. Patients with biphasic tumors had significantly better PFS ($P = .003$, Fig. 3) and OS ($P = .009$, Fig. 4). The median PFS for monophasic SS was 2.29 years (CI, 1.13-3.47 years) and <50% of patients with biphasic SS experienced progression. The median OS of the monophasic cohort was 7.87 years (CI, 4.77-NA years) and not reached for biphasic SS. The upper limits for OS could not be calculated because of a lack of events.

On multivariable analysis, age as a continuous variable (HR, 1.04; 95% CI, 1.00-1.08; $P = .031$) and monophasic histology (HR, 5.65; 95% CI, 1.78-17.91; $P = .003$) were associated with worse PFS (Table 2). On multivariable analysis, larger tumor size (HR, 1.17; 95% CI, 1.02-1.34; $P = .026$) was significantly associated with decreased OS (Table 3). There was a trend toward monophasic histology having worse OS (HR, 5.28; 95% CI, 0.94-29.70; $P = .059$).

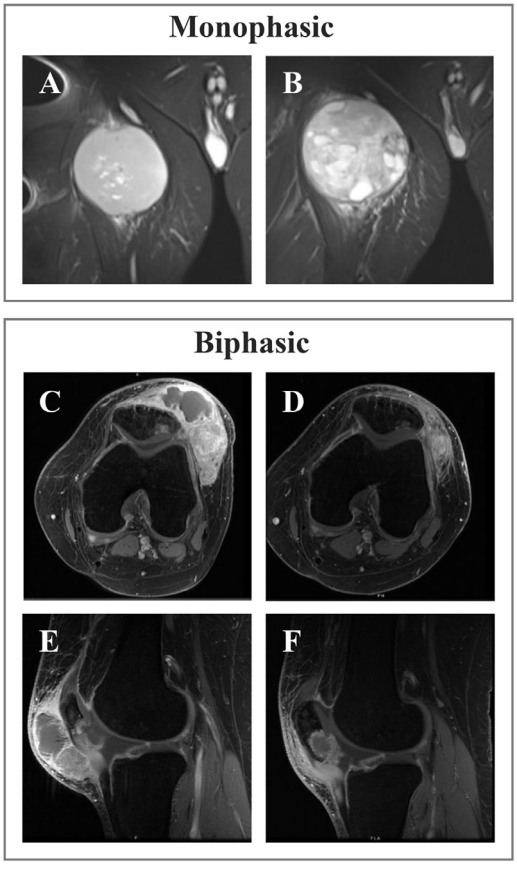

Figure 2 Tumor response after preoperative radiation therapy (RT). Representative monophasic tumor before RT (A) and after RT (B). Representative biphasic tumor before RT in the axial (C) and sagittal (E) views and after RT in the axial (D) and sagittal (F) views.

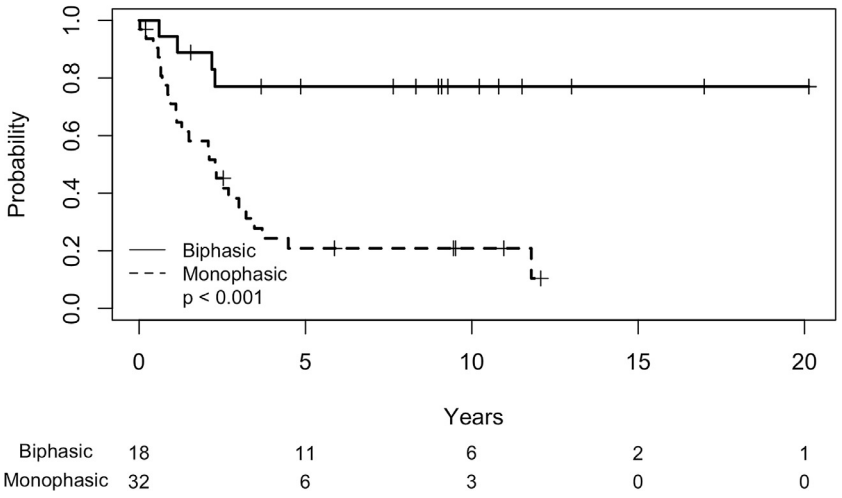

Figure 3 Progression-free survival stratified by histologic subtypes.

Discussion

Numerous studies have evaluated prognostic factors for SS, but there are no prior reports assessing tumor response to RT by histologic subtype.[20] Our study found a nonsignificant negative correlation between volumetric response and pathologic response, suggesting that pathologic necrosis may not identify all patients who respond favorably to preoperative RT. In soft tissue sarcomas, the clinical significance of pathologic necrosis after neoadjuvant RT is controversial with some studies finding no association between pathologic necrosis and outcomes[21,22] and other studies reporting a correlation between favorable pathologic response (defined as ≥95% necrosis) and improved survival.[19,23,24] Although monophasic tumors had a significantly better pathologic response, the median percent necrosis was only 33%, and a pathologic complete response was only observed in 1 tumor. In contrast, biphasic tumors had an improved volumetric response to RT, superior PFS, and a trend toward improved OS on multivariable analysis compared with monophasic tumors.

There is ongoing debate of whether RT should be delivered pre- or postoperatively; although lower rates of wound complications are reported for patients undergoing postoperative RT, preoperative RT often treats smaller target volumes with lower doses resulting in decreased long-term toxicity.[25,26] Therefore, identifying patients who may benefit from preoperative radiation is critical. In our study, biphasic tumors had a greater median volumetric decrease after preoperative RT than monophasic tumors (41% vs 5%, $P = .004$). The substantial decrease in tumor volume suggests that preoperative RT could improve the ability to resect biphasic tumors. Preoperative RT has been associated with higher rates of R0 resections,[27] and in our study, all patients with biphasic

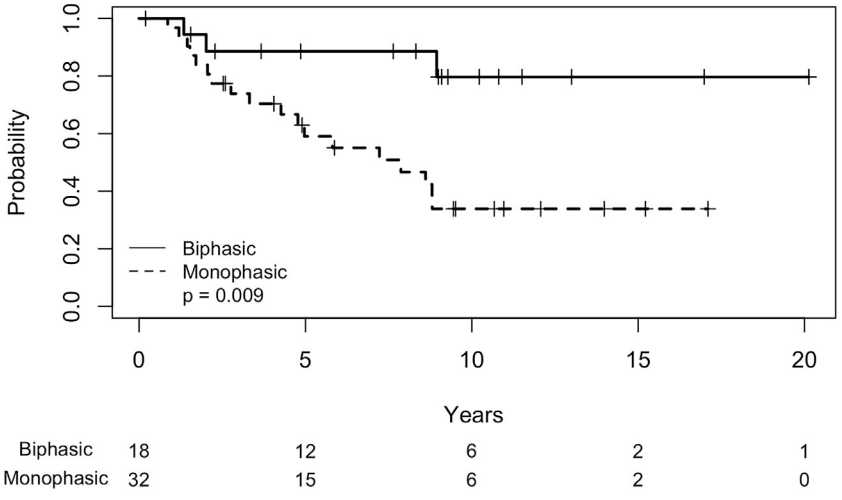

Figure 4 Overall survival stratified by histologic subtypes.

Table 2 Progression-free survival univariable and multivariable analyses

	Univariable			Multivariable		
Covariables	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (continuous variable)	1.02	0.99-1.05	.184	1.04	1.00-1.08	**.031**[a]
Histology (monophasic vs biphasic)	5.63	1.95-16.28	**.001**[a]	5.65	1.78-17.91	**.003**[a]
Tumor location (extremity vs nonextremity)	1.40	0.66-2.96	.385	1.08	0.45-2.56	.868
Tumor size (continuous variable)	1.08	0.98-1.18	.114	1.08	0.99-1.18	.092
Margin status (negative vs positive)	0.37	0.17-0.80	**.012**[a]	0.35	0.12-1.01	.052
Concurrent chemotherapy (no vs yes)	0.98	0.45-2.13	.964	1.04	0.39-2.80	.934
ECOG (1 vs 0)	0.98	0.46-2.07	.949	0.78	0.32-1.90	.590

[a]P-value statistically siginificant (< 0.05).

Table 3 Overall survival univariable and multivariable analyses

	Univariable			Multivariable		
Covariables	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (continuous variable)	1.02	0.99-1.05	.184			
Histology (monophasic vs biphasic)	4.46	1.31-15.20	**.017**[a]	5.28	0.94-29.70	.059
Tumor location (extremity vs nonextremity)	1.20	0.49-2.90	.690	1.29	0.44-3.75	.640
Tumor size (continuous variable)	1.13	1.02-1.24	**.014**[a]	1.17	1.02-1.34	**.026**[a]
Margin status (negative vs positive)	0.61	0.24-1.51	.283	0.94	0.24-3.75	.929
Concurrent chemotherapy (no vs yes)	0.91	0.38-2.19	.827	0.83	0.23-2.96	.772
ECOG (1 vs 0)	1.33	0.55-3.21	.528			

[a]P-value statistically siginificant (< 0.05).

tumors who underwent preoperative RT achieved negative surgical margins.

Several studies have evaluated the association of histologic subtypes with survival outcomes with mixed results. Hajdu et al[28] reported biphasic sarcomas had significantly better 5-year survival than monophasic sarcomas (55% vs 34%). Another study by Cagle et al[8] reported that 86% of patients with biphasic, highly glandular tumors did not experience progression at 36 months compared with 38% of patients with low glandular and/or monophasic tumors. Singer et al[11] found the biphasic subtype trended toward more favorable survival outcomes than monophasic tumors. In contrast, a study by Lewis et al[2] that included 112 patients did not find a statistically significant difference in PFS and tumor-related mortality at 5 years. In our series, we found biphasic tumors had greater PFS and a trend toward improved OS than monophasic tumors by multivariable analysis. The discrepancy between our patient cohort and the aforementioned study may be attributed to the treatment characteristics; in our study, all patients received RT compared with 46% of the patients in the report by Lewis et al.[2] If the association between histologic subtype and outcomes can be confirmed in additional cohorts, future prospective trials could investigate changes in radiation dose based on SS subtype.

Because of the rarity of SS, our study has a limited number of patients. Given the retrospective nature of our study, we were unable to assess long-term radiation complications. Although risk-stratifying by histologic subtype is a useful tool, the type of gene fusion (SS18::SSX1 vs SS18::SSX2) has been suggested to be prognostic.[4] In our study, a minority of patients were tested for the type of gene fusion, which prevented further analysis. In patients with a positive margin after neoadjuvant RT, a boost can be delivered and may be a potential confounder of outcomes. A notable strength of our study was treatment with modern radiation and surgical techniques in contrast with publications comparing biphasic and monophasic subtypes published before 1990.

Conclusion

In our patient cohort, biphasic tumors exhibited significantly improved volumetric response and improved outcomes compared with monophasic tumors. These

findings underscore the significance of histology in tailoring treatment strategies for patients.

Disclosures

Everett J. Moding has served as a paid consultant for Guidepoint and GLG. The other authors declare that they have no financial interests/personal relationships, which may be considered as potential competing interests.

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