Size-Stratified Chemotherapy Effects in Rare Soft Tissue Sarcomas: A Propensity Matched Cohort Analysis

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INTRODUCTION: Soft tissue sarcomas (STS) represent a diverse group of rare cancers, with over 50 histologic subtypes with differing responses to chemotherapy. Although tumor size is an established prognostic factor, its influence on the benefit of chemotherapy within specific histologies remains poorly understood. This study aimed to evaluate chemotherapy effectiveness across five rare STS subtypes stratified by tumor size using propensity score matching to isolate treatment effects.

METHODS: We conducted a retrospective analysis of 4,936 patients with five rare STS subtypes (undifferentiated pleomorphic sarcoma [UPS], dedifferentiated liposarcoma [DDLPS], fibromyxosarcoma, epithelioid sarcoma, and synovial sarcoma) using Surveillance, Epidemiology, and End Results data from 2000-2021. This study was deemed exempt from IRB review as it utilized publicly available, de-identified data. The cohort included both males and females across all age groups. Patients with non-metastatic disease were included in analysis with treatment modalities limited to first-line therapy regimens. Patients were stratified by tumor size (<5 cm, 5-10 cm, >10 cm), and propensity score matching was applied within each subtype-size cohort using age group, sex, tumor grade, and surgical status to control for confounders. Cox regression assessed the impact of chemotherapy on overall survival, with results presented as hazard ratios (HR) and 95% confidence intervals (95% CI).

RESULTS SECTION: Analysis included 1,928 UPS (39.1%), 1,171 DDLPS (23.7%), 1,329 fibromyxosarcoma (26.9%), 223 epithelioid sarcoma (4.5%), and 285 synovial sarcoma (5.8%) patients. Sex distribution varied by subtype: UPS (40.3% female), DDLPS (32.0% female), fibromyxosarcoma (47.4% female), epithelioid sarcoma (45.7% female), and synovial sarcoma (45.6% female). Across 15 matched cohorts with common support ranging from 30-730 patients, chemotherapy effects varied substantially by subtype and tumor size. Synovial sarcoma was the only subtype demonstrating significant survival benefit, specifically in 5-10 cm tumors (HR=0.48, 95% CI: 0.24-0.96, p=0.039). Conversely, chemotherapy was associated with worse survival in multiple cohorts: 5-10 cm fibromyxosarcomas (HR=3.50, 95% CI: 2.21-5.54, p<0.001), DDLPS >10 cm (HR=1.71, 95% CI: 1.33-2.18, p<0.001), small and medium UPS tumors (HR=2.45 and 1.42 respectively, both p<0.05), and 5-10 cm epithelioid sarcomas (HR=1.92, 95% CI: 1.05-3.52, p=0.035). UPS showed a non-significant trend toward benefit only in tumors >10 cm (HR=0.80, 95% CI: 0.60-1.05, p=0.107). No other subtype-size combinations demonstrated chemotherapy benefit (Table 1).

DISCUSSION: This study represents the first comprehensive evaluation of chemotherapy effectiveness using subtype- and size-stratified propensity matching across 15 distinct rare sarcoma cohorts. The differential responses observed reflect underlying molecular mechanisms: synovial sarcoma's chemosensitivity stems from preserved p53-mediated apoptotic pathways and unique SS18-SSX fusion biology, while resistant subtypes harbor distinct mechanisms including MDM2 amplification in DDLPS, TP53 mutations in UPS, SMARCB1 loss in epithelioid sarcoma, and low proliferative rates in fibromyxosarcoma [1]. The size-dependent benefit in synovial sarcoma (5-10 cm optimal range) suggests a therapeutic window where tumor burden justifies systemic therapy without compromising effectiveness. Similarly, the trend toward benefit in large UPS tumors may reflect increased growth activity or clonal selection favoring chemosensitive phenotypes. These findings extend previous registry analyses and align with clinical trial data showing higher response rates in synovial sarcoma compared to other subtypes. Study limitations include retrospective design, absence of performance status and treatment details in SEER data, and focus solely on overall survival without quality-of-life metrics. The stratified design successfully uncovered subtype- and size-specific patterns of therapeutic benefit, neutrality, or harm that remain hidden in combined sarcoma analyses.

SIGNIFICANCE/CLINICAL RELEVANCE: This work provides the first evidence-based framework for size-stratified, histology-specific chemotherapy decision-making in rare sarcomas, demonstrating that treatment effectiveness varies dramatically by both subtype and tumor size. These findings support abandoning one-size-fits-all approaches in favor of personalized treatment strategies that consider molecular subtype and tumor burden when making chemotherapy recommendations.

REFERENCES:

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Sarcoma Subtype	Size Category	HR (95%-CI)	P Value	Matched Cohort Size
UPS	<5 cm	2.45 (1.40-4.29)	0.002	689
	5-10 cm	1.42 (1.08-1.87)	0.013	712
	>10 cm	0.80 (0.60-1.05)	0.107	471
DDLPS	<5 cm	1.14 (0.27-4.82)	0.856	130
	5-10 cm	1.68 (1.04-2.70)	0.033	292
	>10 cm	1.71 (1.33-2.18)	<0.001	730
Fibromyxosarcoma	<5 cm	2.37 (0.74-7.63)	0.148	527
	5-10 cm	3.50 (2.21-5.54)	<0.001	534
	>10 cm	1.83 (1.08-3.10)	0.024	249
Epithelioid Sarcoma	<5 cm	2.04 (0.73-5.74)	0.175	76
	5-10 cm	1.92 (1.05-3.52)	0.035	87
	>10 cm	1.92 (0.82-4.51)	0.135	30
Synovial Sarcoma	<5 cm	0.98 (0.39-2.46)	0.961	79
	5-10 cm	0.48 (0.24-0.96)	0.039	92
	>10 cm	0.85 (0.45-1.60)	0.608	55

Table 1. Hazard ratios and 95%-Confidence Intervals for individual sarcoma subtypes with respective propensity matched cohort sizes