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RESEARCH ARTICLE

Histopathologic Patterns and Long-Term Survival of Sarcoma in Northern Iran: A 24-Year Retrospective Single-Center Study

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Abstract

Introduction: Sarcomas are rare, heterogeneous malignancies with variable survival outcomes, and long-term regional data from Iran remain limited. This study evaluated histopathologic patterns and long-term survival of sarcoma patients treated at a major referral center in northern Iran over 24 years. **Materials and Methods:** In this retrospective cohort study, all patients diagnosed with primary sarcoma at Shahid Rajaei Radiotherapy Center (Babolsar) between 2001 and 2024 were reviewed. Demographic and histopathological data were extracted, and overall survival (OS) was assessed at 1-, 2-, and 5-year intervals using Kaplan–Meier analysis and Log-rank tests. Cox proportional hazards regression was applied to examine associations between demographic and histopathologic variables and overall mortality. **Results:** A total of 278 eligible patients were included (51.1% male; mean age: 48.2±18.1 years). Soft tissue sarcomas (STS) predominated (91.7%), while Bone tissue sarcomas (BTS) accounted for 8.3% of cases and occurred at significantly younger ages ($p<0.001$). Liposarcoma (14.7%), leiomyosarcoma (12.6%), synovial sarcoma (11.9%), and malignant fibrous histiocytoma (MFH) (11.9%) were the most common STS subtypes. The overall survival was 49.3%, with 1-, 2-, and 5-year survival of 82.7%, 71.2%, and 56.5%, respectively. Median OS was longer in STS than BTS (62 vs. 43 months), although not statistically significant (Log-rank $p=0.273$). Subgroup analysis revealed significant survival differences among STS subtypes compared with BTS ($p=0.016$). In Cox analysis, age was consistently associated with increased mortality across all intervals (overall HR=1.042 per year; $p<0.001$). Leiomyosarcoma (HR=2.991; $p=0.018$) and the "Other STS" group (HR=2.741; $p=0.028$) showed higher overall mortality risk in unadjusted Cox analysis, whereas liposarcoma, synovial sarcoma, and MFH demonstrated protective effects in selected time intervals. **Conclusion:** This study highlights the predominance and histopathological heterogeneity of soft tissue sarcomas and describes survival patterns across age groups and histologic subtypes in a long-term, single-center cohort. However, the lack of data on tumor grade, stage, surgical margins, and treatment limits independent prognostic interpretation. Multicenter studies incorporating treatment details and molecular profiling are essential to improve descriptive risk characterization and future stratification frameworks.

Keywords: Soft-Tissue Sarcoma- Bone Sarcoma- Survival Outcomes- Histologic Pattern

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Introduction

Sarcomas are a rare and heterogeneous group of malignant tumors arising from mesenchymal tissues [1]. Mesenchymal cells possess the capacity to differentiate into various tissue types. These malignancies are generally classified into two major categories based on their tissue of origin: bone tissue sarcomas (BTS) and soft tissue sarcomas (STS) [2, 3]. STS and BTS account for approximately 80% and 20% of all sarcomas, respectively [2, 4-7].

According to the 2020 World Health Organization

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classification, there are more than 50 distinct subtypes of STSs, making precise categorization challenging [8, 9]. Common subtypes include fibrous histiocytomas, liposarcomas, rhabdomyosarcomas, and synovial sarcomas [3, 8]. Liposarcomas are the most frequent soft tissue malignancies, whereas fibrous histiocytomas and muscle-derived sarcomas are more common in men. Conversely, synovial sarcomas occur more frequently in women [8, 10]. STSs predominantly affect individuals older than 60 years and are responsible for more than 50% of sarcoma-related deaths, reflecting their high mortality rate [11].

Among primary BTSs, osteosarcoma is the most common and occurs predominantly in adolescents and young adults during periods of rapid growth [12]. Although this tumor may arise in any bone, it most frequently involves long bones of the extremities, such as the femur, tibia, and humerus [13, 14]. Other clinically significant bone malignancies include Ewing sarcoma and chondrosarcoma [14]. Chondrosarcoma occurs mainly in middle-aged and older adults [15]. Ewing sarcoma is an aggressive tumor that primarily affects children and adolescents and commonly arises in the pelvis, femur, humerus, ribs, and spine [16, 17].

Overall, sarcomas constitute approximately 1% of newly diagnosed malignancies worldwide [18, 19]. Despite their rarity and complexity, our understanding of their epidemiological patterns has gradually expanded [20]. Globally, soft tissue sarcomas represent roughly one in every two sarcoma cases, accounting for 0.6% of all cancers and 0.7% of cancer-related deaths [1]. The incidence of bone tumors varies substantially across populations and geographic regions [21]. According to SEER data, the overall incidence of primary malignant bone tumors in the United States is approximately 0.9 per 100,000 persons per year [22]. In contrast, the incidence of osteosarcoma is reported to be higher in certain Asian countries compared with Western nations [23, 24].

In Iran, several epidemiological investigations have addressed the incidence patterns of sarcomas. In the most recent report published in 2024, based on the Iranian National Cancer Registry (2009–2014), the annual crude incidence of sarcoma was higher in men (0.8 per 100,000) than in women (0.55 per 100,000). Moreover, the incidence of bone sarcomas was lower than that of soft tissue sarcomas, and the lower extremities represented the most common site of involvement (16.8%) [25]. Nonetheless, the incidence of soft tissue sarcoma in Iran remains lower than the global average. These disparities in gender distribution, regional patterns, and incidence rates highlight the epidemiological complexity of soft tissue sarcomas [1].

The etiology of most sarcomas remains unknown. Ionizing radiation particularly radiotherapy administered for prior malignancies is a recognized external risk factor in a minority of cases [26]. Other risk factors include occupational exposure to chemicals such as phenoxyacetic acids and chlorophenol-containing compounds [27]. Several hereditary syndromes are also associated with an increased risk of sarcoma, most notably neurofibromatosis type 1, hereditary retinoblastoma, and Li-Fraumeni syndrome [27, 28].

Despite their rarity and biological heterogeneity, long-term regional data on sarcoma histopathologic distribution and survival outcomes from Iran remain limited. This study aims to characterize sarcoma patterns and long-term survival in patients treated at a major referral center in northern Iran over a 24-year period.

Materials and Methods

1. Study Design and Setting

This retrospective cohort study included all patients who presented to the Shahid Rajaei Radiotherapy Center in Babolsar (Mazandaran Province, Northern Iran) over a 24-year period, from January 2001 to December 2024. This center is one of the major oncology and radiotherapy hubs in Northern Iran and receives referrals not only from Mazandaran Province but also from neighboring provinces, including Golestan, Gilan, and Semnan.

A census sampling method was applied, and all eligible patients during the study period were included.

Inclusion criteria:

• Definitive diagnosis of Sarcoma malignancy confirmed by histopathologic examination

• Availability of a registered medical record at Shahid Rajaei Radiotherapy Center

• Presence of minimum required data for survival analysis

Exclusion criteria:

• Medical records with incomplete or insufficient information (missing vital status, and missing histology)

• Pathological diagnoses unrelated to the Sarcoma

• Cases involving secondary malignancies or metastatic tumors

The primary outcome of the study was overall survival, defined as the status of alive or deceased during the entire follow-up period and specifically at 1-, 2-, and 5-year intervals. Associations between demographic, pathological, and clinical characteristics and patient survival were assessed.

This research project was approved by the Ethics Committee of Babol University of Medical Sciences (Approval Code: IR.MUBABOL.HRI.REC.1403.301). All ethical principles were strictly observed, and patient data were collected and analyzed confidentially without any identifying information.

2. Data Collection

Data were extracted from the electronic medical records of all patients diagnosed with primary sarcoma at the center. Extracted variables included demographic information (age, sex, marital status [single/married], and place of residence [urban/rural]) and pathological/clinical characteristics (histopathologic subtype, categorized as Soft-Tissue Sarcoma or Bone-Tissue Sarcoma and their subgroups), as well as vital status and mortality data (vital status and date of death when applicable).

Overall survival was calculated based on the time from the initial pathological diagnosis to death or the last

follow-up. Survival was assessed at 1-year, 2-year, and 5-year intervals.

To complete vital status and confirm causes or dates of death, family members of patients were contacted when necessary. In cases requiring precise verification of death dates, official authorization was obtained to access the Mazandaran Provincial Civil Registration Organization database.

3. Statistical Analysis

Descriptive statistics were reported using appropriate measures: mean (standard deviation), median (interquartile range), minimum, and maximum for continuous variables; and frequency (percentage) for categorical variables. The Kolmogorov–Smirnov test was applied to assess the normality of continuous variables.

Associations between categorical variables were analyzed using the Chi-square test, and Fisher's exact test was applied when expected cell counts were insufficient. The Cochran–Armitage trend test was used to evaluate associations involving ordinal categorical variables.

Overall survival analysis was conducted using the Kaplan–Meier method, with comparisons performed using the Log-Rank test. Cox proportional hazards regression was used to assess potential predictors of mortality. The proportional hazards assumption was assessed using a combination of graphical diagnostics and time-dependent inspection of hazard patterns. Given the long study period and heterogeneous histologic subtypes, potential departures from strict proportionality were considered in the interpretation of time-specific hazard ratios.

Data management was performed using Microsoft Excel 2019, and all statistical analyses were conducted using SPSS software (version 27). A p-value of <0.05 was considered statistically significant.

Results

Between January 2001 and December 2024, an initial search of all archived medical records at the Shahid Rajaei Radiotherapy Center in Babolsar identified 356 registered cases. After applying the inclusion and exclusion criteria, 78 cases were excluded due to incomplete or insufficient data and misclassification of non-sarcoma diagnoses. Ultimately, 278 eligible cases were included in the final analysis (Figure 1).

During the 24-year study period, the highest number of sarcoma cases was recorded in 2023 (27 cases), while the lowest occurred in 2006 (4 cases). Overall, males represented a slightly higher proportion of cases than females, although the dominant sex varied by year. In recent years, the number of female patients presenting to our center increased, with females comprising the majority of cases in 2022 (n=16), 2023 (n=15), and 2024 (n=9). The lower number of cases recorded in 2024 is likely attributable to the mismatch between the Gregorian and Persian calendar systems, as patient files are registered based on the Persian calendar (Figure 2).

A total of 278 patients met the eligibility criteria and were included in the analysis. Of these, 142 (51.1%) were male and 136 (48.9%) were female, yielding an approximately equal male-to-female ratio (1:1). The mean age at diagnosis was 48.19±18.08 years (range: 2–89 years). The mean age in men (49.85±19.19) was not significantly different from women (46.46±16.73) (p=0.117).

Regarding marital status, 42 patients (15.1%) were single and 236 (84.9%) were married. Additionally, 106 patients (38.1%) resided in rural areas, while 172 (61.9%) lived in urban regions.

Among all patients, 255 cases (91.7%) were diagnosed with Soft-Tissue Sarcoma (STS), and only 23 cases (8.3%) were classified as Bone-Tissue Sarcoma (BTS). Within STSs, 20 distinct histological subtypes were identified. The most common subtype was Liposarcoma (41 cases, 14.7%), followed by Leiomyosarcoma (35 cases, 12.6%), Synovial Sarcoma (33 cases, 11.9%), and Malignant Fibrous Histiocytoma (MFH) (33 cases, 11.9%) (Figure 3). However, diagnoses recorded as MFH reflect historical pathology reports and were not reclassified according to the 2020 WHO terminology (undifferentiated pleomorphic sarcoma). Also, subtypes with fewer than 10 cases were grouped as "Other Soft-Tissue Sarcomas," comprising 12 histologies and a total of 44 cases (15.8%).

Within BTSs, the most common diagnoses were Osteosarcoma and Ewing Sarcoma, each accounting for 8 cases (34.8%), followed by Chondrosarcoma with 7 cases (30.4%). The mean age at diagnosis was significantly

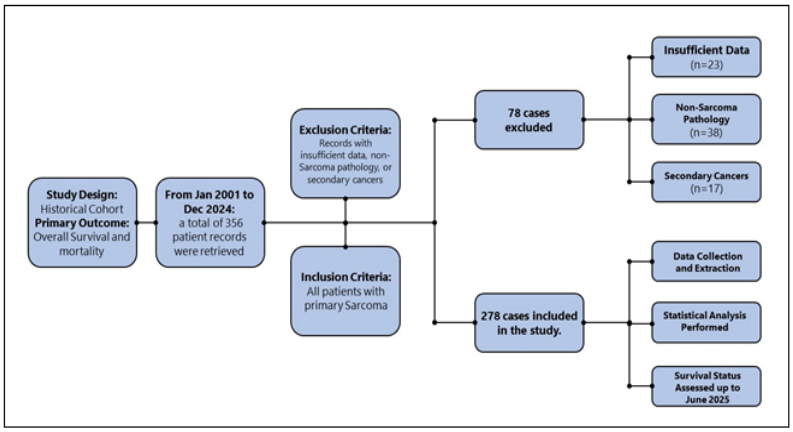


Figure 1. Flowchart of the Study Design Illustrating the Selection Process of Sarcoma Patients, Inclusion and Exclusion Criteria, and the Final Number of Cases Analyzed (n=278).

Table 1. Demographic and Histopathologic Characteristics of Patients with Sarcoma, Including age (mean ± SD), Marital Status (single vs. married), Residential Status (urban vs. rural), Histologic Types, and Vital Status (alive vs. deceased), Stratified by Sex

Variables		Total	Male (n=142, 51.1%)	Female (n=136, 48.9%)	p-value
Age (year) (mean±SD)		48.2±18.1	49.9±19.2	46.5±16.7	0.117
Marital Status N (%)	Single	n=42	26 (18.3)	16 (11.8)	0.128
	Married	n=236	116 (81.7)	120 (88.2)	
Type of Residence N (%)	Rural	n=106	49 (34.5)	57 (41.9)	0.204
	Urban	n=172	93 (65.5)	79 (58.1)	
Histologic Subtypes N (%)	Pleomorphic Sarcoma	n=19	14 (9.9)	5 (3.7)	<0.001
	Fibro Sarcoma	n=20	6 (4.2)	14 (10.3)	
	Rhabdomyo Sarcoma	n=13	11 (7.7)	2 (1.5)	
	Lipo Sarcoma	n=41	25 (17.6)	16 (11.8)	
	Synovial Sarcoma	n=33	15 (10.6)	18 (13.2)	
	Leiomyo Sarcoma	n=35	9 (6.3)	26 (19.1)	
	Spindle Cell Sarcoma	n=17	7 (4.9)	10 (7.4)	
	MFH	n=33	22 (15.5)	11 (8.1)	
	Other Soft-Tissue Sarcoma	n=44	22 (15.5)	22 (16.2)	
	Bone-Tissue Sarcoma	n=23	11 (7.7)	12 (8.8)	
Overall Mortality N (%)	Alive	n=137	64 (45.1)	73 (53.7)	0.151
	Death	n=141	78 (54.9)	63 (46.3)	

higher in the STS group (49.45±17.58 years) compared with the BTS group (34.26±18.10 years) (p<0.001). This marked difference indicates that BTSs tend to present at substantially younger ages than STSs.

Based on Table 1, the mean age of male and female patients did not differ significantly (49.9±19.2 vs. 46.5±16.7 years; p=0.117). Married women represented the largest subgroup of affected individuals (120 cases, 88.2%), although no statistically significant association was observed between sex and marital status (p=0.128). Similarly, residential status showed no significant relationship with sex (p=0.204). Overall, the prevalence of STSs was higher than BTSs in both sexes 92.3% in men (131 cases) vs. 91.2% in women (124 cases) while BTSs were slightly more frequent among women (12 cases, 8.8%) than men (11 cases, 7.7%); however, these differences were not statistically significant (p=0.745).

As shown in Table 1, the distribution of STS histologic subtypes demonstrated a highly significant association with sex (p<0.001). Pleomorphic sarcoma, rhabdomyosarcoma, liposarcoma, and MFH were significantly more common in men, whereas fibrosarcoma and leiomyosarcoma showed significantly higher frequencies in women.

Although overall mortality was not significantly associated with sex (p=0.151), male patients exhibited a higher cumulative mortality compared to females (54.9% vs. 46.3%). Correspondingly, overall survival was higher among women than men (53.7% vs. 45.1%).

As noted earlier, vital status was assessed through June 2025. Vital status was determined through telephone follow-up and verification with the Civil Registration Office of Mazandaran Province (Sari City). Overall, 141 patients (50.7%) had died and 137 patients (49.3%) were alive at last follow-up. The one-year cumulative mortality was 17.3% (48 patients). By two years, 80 patients (28.8%) had died, and by five years, 121 patients (43.5%) were deceased. Among all deaths, only 20 patients survived longer than five years.

The mean age of deceased patients was significantly higher than that of survivors (54.60±17.77 vs. 41.60±15.96; p<0.001). A similar pattern was observed in the one-year follow-up, where the mean age was 55.21 ± 20.16 among deceased patients compared with 46.73 ± 17.31 among survivors (p=0.003). In the two-year follow-up, patients who died were also older (55.48±18.80 vs. 45.25±16.96; p<0.001). At five years, the mean age remained significantly higher in the deceased group compared with survivors (55.75±17.76 vs. 42.36±16.11; p<0.001).

Table 2 summarizes the associations between demographic variables (sex, marital status, residence type) and histopathologic category (STS vs. BTS) with overall, one-year, two-year, and five-year mortality. Only sex showed a significant association with five-year mortality (p=0.047), whereas all other variables demonstrated no significant relationship across any mortality interval (p>0.05). However, when STS cases were subdivided into their more common histologic subtypes, significant associations emerged with short-term mortality at one year (p=0.001) and two years (p=0.021), while no significant associations were observed for five-year or overall mortality (Table 3).

In the overall study population (278 patients), the

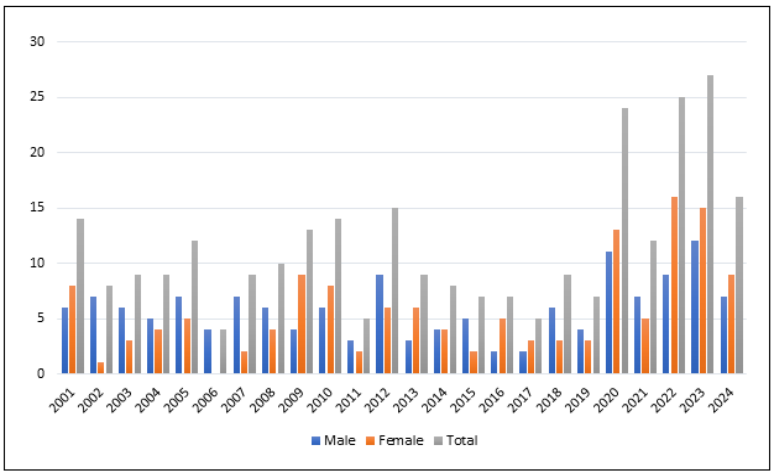


Figure 2. Annual Distribution of Sarcoma Cases by Sex among Patients Treated at Shahid Rajaei Radiotherapy Center from 2001 to 2024.

estimated overall survival was 49.3%. The one-, two-, and five-year survival were 82.7%, 71.2%, and 56.5%, respectively. Based on the Kaplan–Meier analysis, the median overall survival for patients with STS and BTS was estimated at 62 months and 43 months, respectively, with no statistically significant difference (Log-Rank p=0.273). However, in a separate analysis comparing individual STS subtypes with the BTS group, the association reached statistical significance (Log-Rank p=0.016). Rhabdomyosarcoma and Liposarcoma demonstrated notably high median overall survival times of 121 months and 111 months, respectively, whereas Leiomyosarcoma, Spindle Cell Sarcoma, and MFH showed median survival times of 24 months, 12 months, and 48 months. Among the rarer subtypes categorized as Other Soft-Tissue Sarcomas, the median overall survival was 60 months. For several common subtypes, including Pleomorphic Sarcoma, Fibrosarcoma, and Synovial Sarcoma, the median survival could not be calculated by the software.

In the analysis of one-year survival, although the median survival could not be estimated for the overall histologic categories (STS vs. BTS) or for the individual STS subtypes, the results mirrored those of overall survival. The median survival did not differ significantly between STS and BTS (Log-Rank p=0.226); however, a statistically significant difference was observed when comparing STS subtypes with the BTS group (Log-Rank p<0.001). Similar patterns were noted in both the two-year and five-year survival analyses (Figure 4).

In the Cox proportional hazards analysis evaluating factors associated with patient mortality, age, sex, and sarcoma histologic subtypes were entered into the model, with BTS considered as the reference category (Table 4). The results demonstrated that age was a significant risk-enhancing factor across all time intervals, including overall, 1-year, 2-year, and 5-year mortality. Specifically, the risk of overall mortality increased by 4.2% per year of age (HR=1.042; p<0.001; 95% CI:

Table 2. Results of the Chi-square Analysis Evaluating the Association between Demographic and Histopathologic Variables (sex, marital status, residence type, and histologic category [STS vs. BTS]) and Overall, One-year, Two-year, and Five-year Mortality in Patients with Sarcoma

Variables	Type	Total	Overall Mortality N (%)		1-Year Mortality N (%)		2-Year Mortality N (%)		5-Year Mortality N (%)	
			Alive (n=137)	Death (n=141)	Alive (n=230)	Death (n=48)	Alive (n=198)	Death (n=80)	Alive (n=157)	Death (n=121)
Sex	Male	n=142	64 (46.7)	78 (55.3)	112 (48.7)	30 (62.5)	99 (50.0)	43 (53.8)	72 (45.9)	70 (57.9)
	Female	n=136	73 (53.3)	63 (44.7)	118 (51.3)	18 (37.5)	99 (50.0)	37 (46.3)	85 (54.1)	51 (42.1)
	P-Value		0.151		0.082		0.571		0.047	
Marital Status	Single	n=42	26 (19.0)	16 (11.3)	36 (15.7)	6 (12.5)	31 (15.7)	11 (13.8)	27 (17.2)	15 (12.4)
	Married	n=236	111 (81.0)	125 (88.7)	194 (84.3)	42 (87.5)	167 (84.3)	69 (86.2)	130 (82.8)	106 (87.6)
	P-Value		0.076		0.579		0.688		0.268	
Type of Residence	Rural	n=106	51 (37.2)	55 (39.0)	92 (40.0)	14 (29.2)	78 (39.4)	28 (35.0)	59 (37.6)	47 (38.8)
	Urban	n=172	86 (62.8)	86 (61.0)	138 (60.0)	34 (70.8)	120 (60.6)	52 (65.0)	98 (62.4)	74 (61.2)
	P-Value		0.76		0.16		0.495		0.83	
Overall Histologic Subtypes	Soft-Tissue	n=255	128 (93.4)	127 (90.1)	213 (92.6)	42 (87.5)	184 (92.9)	71 (88.8)	145 (92.4)	110 (90.9)
	Bone-Tissue	n=23	9 (6.6)	14 (9.9)	17 (7.4)	6 (12.5)	14 (7.1)	9 (11.3)	12 (7.6)	11 (9.1)
	P-Value		0.309		0.243		0.252		0.664	

Table 3. Results of the Chi-square Analysis Assessing the Association between STS Histologic Subtypes and the BTS Group with Overall, One-year, Two-year, and Five-year Mortality in Patients with Sarcoma

Variables	Type	Total	Overall Mortality N (%)		1-Year Mortality N (%)		2-Year Mortality N (%)		5-Year Mortality N (%)	
			Alive (n=137)	Death (n=141)	Alive (n=230)	Death (n=48)	Alive (n=198)	Death (n=80)	Alive (n=157)	Death (n=121)
Histologic Subtypes	Pleomorphic Sarcoma	n=19	11 (8.0)	8 (5.7)	15 (6.5)	4 (8.3)	13 (6.6)	6 (7.5)	11 (7.0)	8 (6.6)
	Fibro Sarcoma	n=20	13 (9.5)	7 (5.0)	20 (8.7)	0 (0.0)	17 (8.6)	3 (3.8)	15 (9.6)	5 (4.1)
	Rhabdomyo Sarcoma	n=13	7 (5.1)	6 (4.3)	10 (4.3)	3 (6.3)	10 (5.1)	3 (3.8)	9 (5.70)	4 (3.3)
	Lipo Sarcoma	n=41	22 (16.1)	19 (13.5)	37 (16.1)	4 (8.3)	33 (16.7)	8 (10.0)	26 (16.6)	15 (12.4)
	Synovial Sarcoma	n=33	21 (15.3)	12 (8.5)	31 (13.5)	2 (4.2)	26 (13.1)	7 (8.8)	23 (14.6)	10 (8.3)
	Leiomyo Sarcoma	n=35	15 (10.9)	20 (14.2)	27 (11.7)	8 (16.7)	19 (9.6)	16 (20.0)	16 (10.2)	19 (15.7)
	Spindle Cell Sarcoma	n=17	5 (3.6)	12 (8.5)	8 (3.50)	9 (18.8)	7 (3.5)	10 (12.5)	5 (3.20)	12 (9.9)
	MFH	n=33	13 (9.5)	20 (14.2)	29 (12.6)	4 (8.3)	26 (13.1)	7 (8.8)	15 (9.6)	18 (14.9)
	Other Soft-Tissue Sarcoma	n=44	21 (15.3)	23 (16.3)	36 (15.7)	8 (16.7)	33 (16.7)	11 (13.8)	25 (15.9)	19 (15.7)
	Bone-Tissue Sarcoma	n=23	9 (6.6)	14 (9.9)	17 (7.4)	6 (12.5)	14 (7.1)	9 (11.3)	12 (7.6)	11 (9.1)
	P-Value		0.26		0.001		0.021		0.082	

1.030–1.053). Age similarly elevated the risk of 1-year (HR=1.029; p=0.002), 2-year (HR=1.034; p<0.001), and 5-year mortality (HR=1.038; p<0.001).

Regarding histologic subtypes, leiomyosarcoma was associated with a significantly higher risk of overall mortality compared with BTS, with patients exhibiting nearly a three-fold increased risk (HR=2.991; p=0.018). Likewise, the Other STS group showed a significant increase in overall mortality, corresponding to an approximately 2.7-fold higher risk (HR=2.741; p=0.028).

Conversely, several histologies demonstrated protective effects relative to BTS. In 1-year mortality, liposarcoma reduced the risk of death by 82% (HR=0.176; p=0.048), while synovial sarcoma was associated with an 84% reduction (HR=0.163; p=0.032). In 2-year mortality, synovial sarcoma remained protective, decreasing the risk by 65% (HR=0.354; p=0.042).

In 5-year mortality, multiple histologies continued to show protective behavior. Synovial sarcoma remained associated with a 60% risk reduction (HR=0.406; p=0.042), and MFH also acted as a protective factor, reducing 5-year mortality by 56% (HR=0.444; p=0.041). Notably, the Other STS group, despite its adverse effect on overall mortality, exhibited a protective association in 5-year mortality, lowering the risk by 59% (HR=0.410; p=0.025). Visual inspection of survival patterns suggested that the proportional hazards assumption may not hold uniformly across all histologic subtypes, particularly in early follow-up intervals, indicating potential time-dependent effects.

Discussion

1. Overall Interpretation

This cohort reflects a sarcoma case mix dominated by soft tissue sarcomas, consistent with reports from population-based registries worldwide. While the overall distribution aligns with international data, the long observation period and regional referral context provide insight into temporal and demographic patterns that merit further discussion [7, 8, 12, 29].

2. Epidemiological Patterns and Therapeutic Advances

According to Figure 2, the number of patients presenting to this center has increased in recent years. Additionally, the incidence among women in this region has risen considerably, although overall, men still represented the majority of cases in the entire study. The marked increase in case numbers in recent years may reflect evolving referral patterns, expanded catchment areas, improved diagnostic capabilities, and earlier case detection, while greater diagnostic accuracy may also contribute to an apparent improvement in short-term survival outcomes. The study by Asef-Kabiri et al. (2021), based on Iran's national cancer registry (2009–2014), similarly reported the predominance of STS over BTS (83.53% vs. 16.47%), with men comprising a larger proportion of diagnoses [30]. Likewise, Dehghan et al. (2025) confirmed the higher incidence of STS among Iranian men and reported that the incidence of sarcoma in Iran remains below the global average [1, 31-34].

It should be noted, however, that because the present study is retrospective and single-center, its generalizability to the entire Iranian population is limited. Therefore, multi-center investigations incorporating clinicopathological variables across diverse geographic regions of Iran are needed to establish a more comprehensive perspective on histopathological distribution, risk factors, and survival across sarcoma subtypes.

Our cohort spanned the period from 2001 to 2024, during which sarcoma management underwent substantial evolution, including the introduction of multimodal treatment strategies and targeted therapies. However, incomplete documentation of treatment modalities in this retrospective dataset precluded evaluation of how such therapeutic advances may have influenced

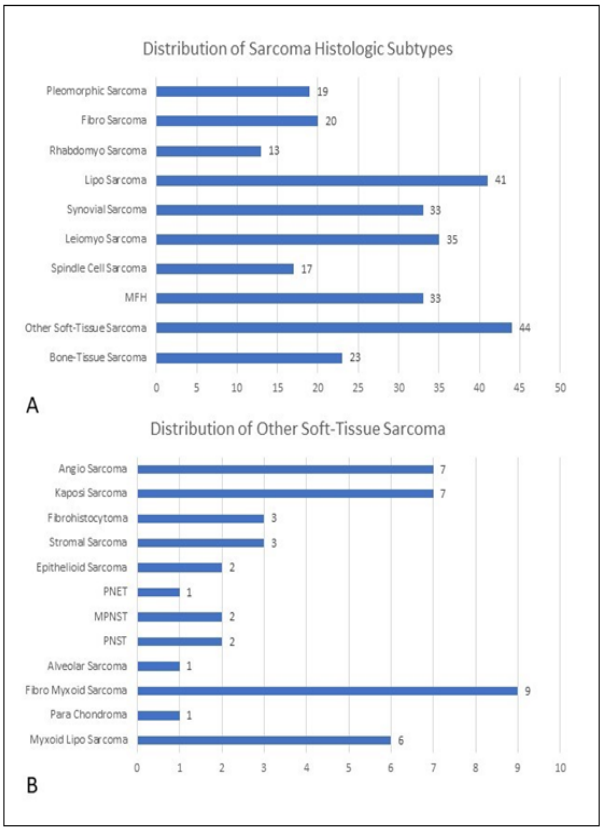


Figure 3. Histopathological Distribution of Sarcoma Subtypes among Patients Treated at Shahid Rajaei Radiotherapy Center from 2001 to 2024. A: Distribution of Sarcoma Histologic Subtypes; B: Distribution of Other Soft-Tissue Sarcomas.

observed survival trends, particularly in more recent years [35, 36]. Several targeted and novel agents such as pazopanib, trabectedin, and eribulin have entered treatment algorithms; in certain cases, molecular/TKI-based therapies or TRK inhibitors have demonstrated remarkable outcomes. Emerging combinations such as VEGFR-TKIs plus immune checkpoint inhibitors (ICIs) have shown promise in alveolar soft part sarcoma (ASPS) and select sensitive subtypes [37, 38]. In bone sarcomas, standard treatments remain (e.g., surgery plus combination chemotherapy for osteosarcoma; multimodal systemic chemotherapy with surgery/radiotherapy for Ewing sarcoma), although efforts continue to address chemoresistance and evaluate immunomodulators or agents such as mifamurtide [39, 40].

3. Interpretation of Histopathological Findings

As noted, soft tissue sarcomas were markedly more prevalent than bone sarcomas in our cohort. Furthermore, BTS occurred at younger ages than STS. The study by Hosseini et al. (2025) similarly reported that Ewing sarcoma and osteosarcoma were the most common bone malignancies consistent with our findings [17].

Within STS cases, liposarcoma was the most common subtype (14.7%), which aligns with many clinical studies identifying liposarcoma as one of the most prevalent STS subtypes [41, 42]. Leiomyosarcoma and synovial sarcoma were also frequent in our cohort. Zhu et al. (2024) reported that age, male sex, lack of surgery, soft-tissue primary tumor site, and chemotherapy correlated with poorer prognosis in pediatric synovial sarcoma [43]. MFH also accounted for a substantial proportion, and previous studies note that MFH represents approximately 15% of STS cases with a five-year survival near 60% [44].

Overall, the histological distribution observed in our study is broadly similar to international reports. However, the percentages may vary due to single-center sampling, referral patterns, and access to advanced molecular diagnostics.

4. Mortality and Survival

The overall survival in this study was 49.3%, and the one-, two-, and five-year survival were 82.7%, 71.2%, and 56.5%, respectively. However, Administrative censoring was present for recently enrolled patients, which may limit short-term survival estimates. Kaplan-Meier and Log-Rank analyses showed a longer median survival in STS compared with BTS (62 vs. 43 months), though this difference was not statistically significant. The shorter median survival observed among bone sarcoma patients may reflect a higher proportion of advanced or metastatic disease at presentation, as well as treatment-era effects, given that a substantial portion of the cohort predates contemporary multimodal chemotherapy protocols. For bone sarcomas, Hosseini et al. (2025) reported significantly variable survival based on tumor type, with 50–60% survival for osteosarcoma and approximately 70% for Ewing sarcoma [17]. According to the American Cancer Society and SEER reports, the five-year relative survival for soft tissue sarcoma between 2010 and 2016 was 81% (localized), 56% (regional), and 15% (distant metastasis) [45]. The observed 5-year overall survival of 56.5% in our cohort approximates survival reported for regionally advanced disease in SEER registries, suggesting a predominance of non-localized presentations or referral bias toward more advanced cases.

Importantly, when STS subgroups were analyzed alongside BTS individually, the differences became statistically significant ($p=0.016$). This highlights that the broad classification of STS vs. BTS may obscure substantial within-group heterogeneity a trend recognized in other studies, where distinct subtypes (e.g., rhabdomyosarcoma, liposarcoma, synovial sarcoma) demonstrate highly variable survival profiles [42, 43]. Thus, subgroup analyses are crucial.

In our results, rhabdomyosarcoma and liposarcoma demonstrated longer median survivals (121 and 111 months, respectively). Previous studies report >90% survival in very low-risk rhabdomyosarcoma, 50–70% in intermediate-risk disease, and approximately 20–30% in high-risk cases [46- 48]. Conversely, leiomyosarcoma and spindle cell sarcoma exhibited shorter survival durations, which partially aligns with existing literature, though large variability remains due to factors such as subtype, location, staging, surgical outcomes, and systemic therapy availability. For instance, myxoid liposarcoma generally has a better prognosis compared to dedifferentiated liposarcoma [42]. Zhao et al. (2025) similarly showed that

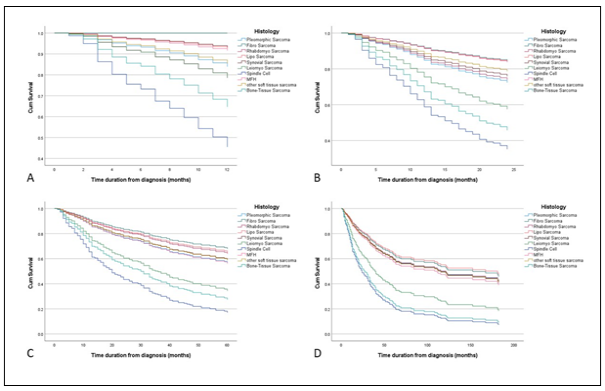


Figure 4. Four Kaplan-Meier Survival Curves Stratified by Histologic Subtype, Showing Cumulative Survival at 1-, 2-, 5-year, and Overall Time Horizons. Log-Rank tests compared each subtype with bone-tissue sarcoma (reference).

well-differentiated liposarcoma had the most favorable prognosis, with five- and ten-year survival rates of 82% and 68%, respectively [49].

5. Age as the Strongest Predictor of Survival

Age consistently emerged as a strong, linear predictor of increased mortality risk across all time intervals. This relationship is logical and has been widely reported in large sarcoma cohorts, where advanced age correlates with poorer survival outcomes [50, 51].

6. Histological Effects in the Cox Model

In our Cox model, leiomyosarcoma increased the overall risk of mortality by nearly threefold (HR=2.991; p=0.018). This may reflect the inherently aggressive nature of leiomyosarcoma, delayed diagnosis, or the predominance of challenging anatomical locations (e.g., intra-abdominal or uterine). Several studies have reported poorer prognosis for leiomyosarcoma in specific sites (e.g., uterine, retroperitoneal) [52].

The "Other STS" category, which included the rarer subtypes in our study, showed an approximately 2.7-fold higher overall mortality risk (p=0.028). This likely reflects the aggregation of several biologically aggressive or high-risk subtypes within this group; however, this association may also be influenced by statistical instability due to small sample sizes and sparse events, confounding by unmeasured clinicopathological variables, and the markedly divergent natural histories of the heterogeneous subtypes encompassed within this category.

Associations observed for liposarcoma, synovial sarcoma, and MFH should be interpreted with caution. In selected time intervals, these subtypes showed lower hazard estimates relative to BTS (HR<1 with statistical significance at 1-, 2-, or 5-year follow-up), which may reflect contextual and methodological factors rather than true protective biological effects. Potential explanations include the overrepresentation of lower-grade entities (e.g., well-differentiated liposarcoma), a higher proportion

Table 4. Cox Proportional Hazards Regression Results Evaluating the Effects of Demographic and Histopathologic Variables on Overall, 1-year, 2-year, and 5-year Mortality in Patients with Sarcoma. Hazard ratios (HRs), 95% confidence intervals (95% CI), and p-values are reported for each variable.

Variables	Overall Mortality			1-Year Mortality			2-Year Mortality			5-Year Mortality		
	HR	95.0%CI for HR	P-Value	HR	95.0%CI for HR	P-Value	HR	95.0%CI for HR	P-Value	HR	95.0%CI for HR	P-Value
Age	1.042	1.030-1.053	<.001	1.029	1.011-1.047	0.002	1.034	1.019-1.049	<.001	1.038	1.026-1.050	<.001
Sex	1.132	0.794-1.613	0.494	1.788	0.962-3.322	0.066	1.288	0.807-2.055	0.289	1.301	0.887-1.907	0.178
Histology: Pleomorphic Sarcoma/BTS	0.895	0.320-2.505	0.833	0.403	0.106-1.524	0.18	0.414	0.141-1.221	0.11	0.438	0.170-1.129	0.087
Histology: Fibrosarcoma/ BTS	0.994	0.342-2.884	0.991	-	-	0.963	0.217	0.058-0.810	0.023	0.299	0.103-0.866	0.026
Histology: Rhabdomyo Sarcoma/BTS	0.857	0.374-1.965	0.715	0.553	0.134-2.281	0.413	0.388	0.103-1.463	0.162	0.344	0.107-1.105	0.073
Histology: Liposarcoma/ BTS	1.017	0.412-2.509	0.971	0.176	0.048-0.652	0.009	0.224	0.084-0.601	0.003	0.329	0.148-0.733	0.007
Histology: Synovial Sarcoma/BTS	1.933	0.837-4.465	0.123	0.163	0.032-0.815	0.027	0.354	0.130-0.963	0.042	0.406	0.171-0.968	0.042
Histology: Leiomyo Sarcoma/BTS	2.991	1.205-7.423	0.018	0.555	0.180-1.711	0.305	0.709	0.300-1.678	0.434	0.824	0.382-1.778	0.621
Histology: Spindle Cell Sarcoma/BTS	1.076	0.472-2.450	0.862	1.806	0.628-5.197	0.273	1.336	0.535-3.336	0.535	1.366	0.598-3.120	0.459
Histology: MFH/BTS	1.011	0.451-2.268	0.979	0.202	0.054-0.752	0.017	0.227	0.082-0.633	0.005	0.444	0.204-0.967	0.041
Histology: Other STS Sarcoma/BTS	2.741	1.114-6.745	0.028	0.361	0.118-1.105	0.074	0.307	0.122-0.774	0.012	0.41	0.188-0.893	0.025

of localized and surgically resectable tumors referred to this center, poorer early survival among aggressive bone sarcomas (such as metastatic osteosarcoma or Ewing sarcoma), as well as sparse events and unmeasured confounders including stage and treatment modality. Moreover, the variability and occasional reversal of hazard ratios across time intervals suggest potential non-proportional hazards and highlight the instability of subtype-specific estimates during early follow-up. Collectively, these findings are more consistent with heterogeneous disease biology, time-dependent effects, and limited statistical power than with stable, independent prognostic associations. Accordingly, histologic subtype in the present Cox models should be regarded as an exploratory descriptive factor rather than a definitive prognostic determinant, particularly in the absence of adjustment for tumor grade, stage, and treatment. Given the number of comparisons performed, p-values should also be interpreted cautiously, as some statistically significant findings may reflect chance variation.

Strengths and Limitations

The main strength of this study lies in its 24-year timespan and relatively large single-center cohort, supported by clinically verified mortality data. However, its retrospective nature resulted in missing key variables including tumor stage, grade, immunohistochemical (IHC) characterization, molecular profiles, surgical margin status, anatomical location, and treatment modality documentation largely because these assessments were not routinely available, systematically recorded, or financially accessible during earlier years of the study period, preventing their inclusion in statistical analyses. In addition, limited sample sizes within rare histologic subtypes reduced statistical power, and incomplete documentation of treatment details constrained adjustment for major prognostic factors. Accordingly, the observed associations should be interpreted cautiously as descriptive rather than definitive prognostic estimates. Future studies would benefit from prospective, multicenter designs with standardized diagnostic, treatment, and molecular work-ups.

In conclusion, in this 24-year single-center cohort from northern Iran, soft tissue sarcomas constituted the majority of cases, and the distribution of major histologic subtypes including liposarcoma, leiomyosarcoma, synovial sarcoma, and MFH was broadly consistent with international reports. Survival outcomes varied across age groups and histologic categories, with increasing age showing a consistent association with mortality, reflecting expected demographic effects. Certain histologic subtypes, including leiomyosarcoma and the heterogeneous "Other STS" group, demonstrated higher mortality risks in unadjusted analyses, while others exhibited more favorable short-term survival patterns; however, these associations should be interpreted cautiously given the absence of tumor grade, stage, margin status, and treatment data. Overall, the findings primarily provide descriptive epidemiologic insight into long-term sarcoma patterns in this region. Multicenter studies with standardized documentation of stage, treatment, and molecular characteristics are required to contextualize survival patterns and improve regional epidemiologic understanding.

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Clinical trial registration

Not applicable.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest related to this study.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

This study did not use any custom code. All analyses were performed using SPSS version 27 and Microsoft Excel.

Author Contributions

Dr. Danial Fazelat-Panah contributed to the conceptualization, funding acquisition, investigation, methodology development, project administration, supervision, drafting of the original manuscript, and critical revision and editing of the final version. Mr. Seyed Reza Najafi, as the corresponding author, was responsible for data curation, investigation, drafting of the original manuscript, and critical review and editing of the paper.Dr. Hoda Shirafkan contributed to the study methodology and performed the statistical analyses. Dr. Masoumeh Karimi, Nima Noori, Shabnam Ashofteh, Ghazaleh Tahernezhad, contributed to data collection and curation.

Ethics Approval Statement

This study was approved by the Ethics Committee of Babol University of Medical Sciences (Approval Code: IR.MUBABOL.HRI.REC.1403.301). All patient data were obtained in accordance with institutional guidelines and remained confidential throughout the study.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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Declaration on generative AI and AI-assisted technologies in the writing process

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the writing, editing, data analysis, or preparation of this manuscript. All components of the work including conceptualization, methodology, data extraction, statistical analysis, interpretation of findings, and manuscript drafting were performed solely by the authors.

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