Oncology
and Radiotherapy©
20(10) 2026 : 001-007 • RESEARCH ARTICLE

Personalized Radiotherapy Strategies and Prognostic Factors in Patients with Soft Tissue Sarcomas: A Retrospective Cohort Study

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ABSTRACT

Background: Soft tissue sarcomas (STS) are rare and biologically heterogeneous malignant mesenchymal tumors characterized by diverse histological subtypes, a high propensity for local recurrence, and the potential for distant metastasis. The present study aimed to evaluate the clinical and morphological characteristics of STS and to identify factors associated with tumor recurrence, metastatic progression, and treatment outcomes.

Methods: A retrospective cohort study included 101 consecutive patients with histologically confirmed STS treated at the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology (Tashkent, Uzbekistan) between 2018 and 2023. Clinical and pathological variables included age, sex, tumor location, grade of differentiation, metastatic status, treatment characteristics, radiotherapy technique, and treatment-related toxicity. According to the predominant radiotherapy technique, patients were classified into three groups: three-dimensional conformal radiotherapy (3D-CRT; n = 41), intensity-modulated radiotherapy (IMRT; n = 32), and volumetric modulated arc therapy (VMAT; n = 28). Descriptive statistics, Pearson's chi-square test, and multivariable logistic regression analysis were performed.

Results: Lower-extremity tumors represented the most common anatomical location (49.5%), and high-grade disease predominated (G3, 44.6%). Metastatic progression occurred in 20 patients (19.8%), whereas 63 patients (62.4%) remained alive without evidence of disease progression at the time of analysis. Tumor location significantly influenced radiotherapy selection ($\chi^2 = 22.48$; $p < 0.05$). Early radiation-related skin toxicity occurred more frequently after 3D-CRT, whereas IMRT and VMAT demonstrated lower rates of treatment-related adverse events. Multivariable logistic regression analysis identified increasing age (OR = 1.03, 95% CI: 1.00–1.07, p = 0.032) and the presence of metastatic disease (OR = 20.19, 95% CI: 2.46–165.70, p = 0.005) as independent factors associated with tumor recurrence.

Conclusions: Personalized radiotherapy strategies based on tumor location, biological characteristics, and treatment context were associated with favorable oncological outcomes in patients with STS. Highly conformal techniques, including IMRT and VMAT, demonstrated lower treatment-related toxicity and may represent valuable approaches for anatomically complex and biologically aggressive tumors. Increasing age and metastatic disease were independently associated with tumor recurrence.

Keywords: Soft tissue sarcoma; Radiotherapy; IMRT; VMAT; 3D-CRT; Recurrence; Metastasis; Toxicity

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Word count: 2,839 **Figures:** 02 **Table:** 06 **References:** 12

Received: 01 Oct; 2026; Manuscript No. OAR-26-194965;
Editor assigned: 03 Oct; 2026; PreQC No. OAR-26-194965 (PQ);
Reviewed: 20 Oct; 2026; QC No. OAR-26-194965;
Revised: 26 Oct ; 2026; Manuscript No. OAR-26-194965 (R);
Published: 31 Oct; 2026

INTRODUCTION

Soft tissue sarcomas (STS) comprise a rare and biologically heterogeneous group of malignant mesenchymal neoplasms that account for approximately 1% of all adult malignancies and less than 1% of cancer-related deaths worldwide [1,2]. More than 70 histological subtypes have been identified, each characterized by distinct molecular features, biological behavior, and therapeutic responses [1,3]. Despite their relatively low incidence, STS remain a significant oncological challenge because of their aggressive clinical course, substantial risk of local recurrence, and propensity for distant metastatic spread [3,4].

The prognosis of STS is highly variable and depends on numerous clinicopathological factors, including tumor size, anatomical location, histological subtype, grade of differentiation, and metastatic status [4,5]. High-grade and large tumors are associated with an increased risk of recurrence and reduced long-term survival, whereas the presence of metastatic disease remains the most important adverse prognostic factor [5,6]. The lungs represent the most frequent site of distant metastasis and account for the majority of sarcoma-related deaths [4,6].

The current management of localized STS is based on a multidisciplinary approach integrating surgery, radiotherapy, and systemic treatment [7]. Complete surgical resection with negative margins remains the cornerstone of treatment, whereas radiotherapy has become an essential component of organ-preserving strategies aimed at improving local control and maintaining functional outcomes [7,8]. According to contemporary international recommendations, radiotherapy is particularly beneficial in patients with high-grade tumors, large lesions, and anatomically complex disease sites [8,9]. Recent advances in radiation oncology have facilitated the implementation of individualized treatment planning using modern techniques, including intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), which improve target coverage and reduce radiation exposure to surrounding normal tissues [8-10].

Despite considerable progress in surgical and radiation techniques, reliable prognostic stratification of patients with STS remains challenging. Patients with apparently similar clinicopathological characteristics frequently demonstrate markedly different clinical outcomes, suggesting that currently available prognostic models remain incomplete [5,11]. Moreover, most prognostic studies have

been performed in highly selected populations from specialized sarcoma centers and may not fully reflect outcomes observed in routine clinical practice [11,12]. Therefore, analyses of real-world cohorts remain important for identifying factors associated with recurrence and metastatic progression and for optimizing individualized therapeutic strategies in patients with STS.

Aim. To evaluate the clinical and morphological characteristics of soft tissue sarcomas and to identify factors associated with tumor recurrence, metastatic progression, and treatment outcomes in patients treated between 2018 and 2023.

MATERIALS AND METHODS

Study Design and Patients

A retrospective cohort study was conducted at the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology (Tashkent, Uzbekistan). The study included 101 consecutive patients with histologically confirmed soft tissue sarcomas (STS) who underwent treatment between January 2018 and December 2023.

The study population comprised 54 (53.5%) male and 47 (46.5%) female patients. The mean age of the patients was 41.7 ± 15.3 years (median, 44 years; interquartile range [IQR], 26–55 years; range, 17–68 years).

Clinical and pathological data were retrospectively retrieved from medical records and institutional databases. The analyzed variables included patient age, sex, anatomical tumor location, tumor size, histological subtype, grade of differentiation, presence of metastatic disease, surgical treatment characteristics, systemic therapy, radiotherapy technique, treatment-related toxicity, and disease recurrence.

Treatment Characteristics

All patients underwent individualized multimodal treatment strategies based on multidisciplinary decision-making and tumor characteristics. Therapeutic approaches included combinations of surgery, radiotherapy, and systemic treatment. According to the predominant radiotherapy technique, patients were classified into three clinical groups: Group I (n = 43), predominantly treated with surgery followed by three-dimensional conformal radiotherapy (3D-CRT); Group II (n = 30), treated using intensity-modulated radiotherapy (IMRT); and Group III (n = 28), treated using volumetric modulated arc therapy (VMAT).

Study Outcomes

The primary study endpoint was tumor recurrence. Secondary endpoints included metastatic progression and treatment-related toxicity. Tumor recurrence was defined as radiologically and/or histologically confirmed local disease progression after completion of primary treatment. Metastatic progression was defined as the occurrence of distant metastatic lesions detected during follow-up.

Statistical Analysis

Descriptive statistics were used to summarize baseline demographic, clinical, and pathological characteristics. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were presented as frequencies and percentages.

Group comparisons were performed using Pearson's chi-square (χ^2) test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables when appropriate. Multivariable logistic regression analysis was performed to identify factors independently associated with tumor recurrence. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. Adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Ethics Statement

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. Owing to the retrospective design of the study and the use of anonymized data, the requirement for informed consent was waived.

RESULTS

A total of 101 patients with histologically confirmed soft tissue sarcomas (STS) were included in the study. The cohort comprised 54 (53.5%) male and 47 (46.5%) female patients, with a mean age of 41.7 ± 15.3 years (median, 44 years; interquartile range [IQR], 26–55 years; range, 17–68 years). Lower-extremity tumors represented the most frequent anatomical location (49.5%), followed by tumors of the trunk (18.8%), upper extremities (16.8%), pelvis (8.9%), head and neck (4.0%), and abdominal cavity (2.0%). Histological grading demonstrated predominance of high-grade disease, with G3 tumors observed in 45 patients (44.6%), followed by G2 tumors in 30 patients (29.7%), G1 tumors in 25 patients (24.8%), and G4 tumors in one patient (1.0%). Metastatic disease was absent in 81 patients (80.2%), whereas 20 patients (19.8%) developed distant metastatic progression [Table 1].

Radiotherapy techniques were distributed as follows: three-dimensional conformal radiotherapy (3D-CRT) was administered to 41 patients (40.6%), intensity-modulated radiotherapy (IMRT) to 32 patients (31.7%), and volumetric modulated arc therapy (VMAT) to 28 patients (27.7%). The choice of irradiation technique was closely related to the clinical group and reflected the gradual implementation of increasingly conformal radiotherapy approaches according to tumor characteristics and treatment complexity [Figure 1].

Lower-extremity sarcomas were predominantly treated with 3D-CRT, whereas IMRT and VMAT were more frequently used for anatomically complex regions, including the trunk, pelvis, head and neck, and abdominal cavity. The association between tumor location and radiotherapy technique was statistically significant ($\chi^2 = 22.48$; $p < 0.05$) [Table 2].

Analysis of biological characteristics demonstrated variability in proliferative, angiogenic, and anti-apoptotic activity among

Table 1: Baseline Clinical and Pathological Characteristics of Patients with Soft Tissue Sarcomas (n = 101).

Variable	n (%) or Value
Age, mean ± SD	41.7 ± 15.3 years
Male sex	54 (53.5%)
Female sex	47 (46.5%)
Lower extremities	50 (49.5%)
Upper extremities	17 (16.8%)
Trunk	19 (18.8%)
Head and neck	4 (4.0%)
Abdominal cavity	2 (2.0%)
Pelvis	9 (8.9%)
G1	25 (24.8%)
G2	30 (29.7%)
G3	45 (44.6%)
G4	1 (1.0%)
Metastases absent	81 (80.2%)
Metastases present	20 (19.8%)

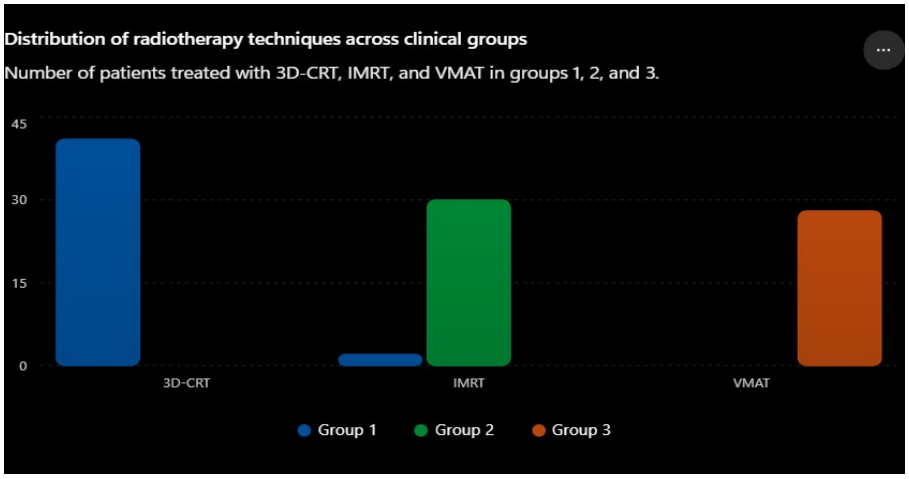


Figure 1: Distribution of Radiotherapy Techniques Across Clinical Groups Primary tumor location significantly influenced radiotherapy planning.

Table 2: Primary Tumor Location According to Radiotherapy Technique.

Location	Total	3D-CRT	IMRT	VMAT
Lower extremities	50 (49.5%)	25 (61.0%)	12 (37.5%)	13 (46.4%)
Upper extremities	17 (16.8%)	7 (17.1%)	6 (18.8%)	4 (14.3%)
Trunk	19 (18.8%)	5 (12.2%)	6 (18.8%)	8 (28.6%)
Head and neck	4 (4.0%)	3 (7.3%)	0 (0.0%)	1 (3.6%)
Abdominal cavity	2 (2.0%)	0 (0.0%)	1 (3.1%)	1 (3.6%)
Pelvis	9 (8.9%)	1 (2.4%)	7 (21.9%)	1 (3.6%)
Total	101 (100%)	41 (100%)	32 (100%)	28 (100%)

treatment groups. Higher Ki-67 and VEGF expression levels were observed more frequently in patients treated with IMRT, whereas elevated Bcl-2 expression was more common among patients receiving VMAT. Because of the retrospective and non-randomized design of the study, these findings should be interpreted as descriptive associations rather than causal relationships [Table 3].

Postoperative radiotherapy doses ranged from 30 to 66 Gy. The most frequently prescribed regimens were 50 Gy, administered to 29 patients (28.2%), and 60 Gy, administered to 25 patients (24.3%). Higher doses were generally prescribed following tumor resection, whereas lower doses were more commonly used after biopsy procedures or in less radical clinical situations [Table 4].

Regarding disease control, 63 of 101 patients (62.4%) remained alive without evidence of disease progression at the time of analysis. The proportion of progression-free patients was numerically higher following VMAT and 3D-CRT than after IMRT. However, the association between radiotherapy technique and time to recurrence did not reach statistical significance ($\chi^2 = 10.76$; $p = 0.705$) [Figure 2].

Metastatic progression was not observed during follow-up in 81 patients (80.2%), whereas 20 patients (19.8%) developed distant metastases. The lungs represented the most frequent site of metastatic spread, followed by regional lymph nodes and bone involvement. Brain metastases were rare. The distribution of metastatic progression across radiotherapy groups appeared

Table 3: Distribution of Ki-67, VEGF, and Bcl-2 Expression According to Radiotherapy Technique.

Expression	Total	3D-CRT	IMRT	VMAT
Ki-67 (proliferative activity)				
High (≥40%)	34 (33.7%)	12 (11.9%)	17 (16.8%)	5 (5.0%)
Low (<20%)	27 (26.7%)	12 (11.9%)	4 (4.0%)	11 (10.9%)
Moderate (20–39%)	40 (39.6%)	17 (16.8%)	11 (10.9%)	12 (11.9%)
VEGF (angiogenesis, % positive cells)				
High (≥50%)	32 (31.7%)	7 (6.9%)	17 (16.8%)	8 (7.9%)
Low (<20%)	22 (21.8%)	12 (11.9%)	4 (4.0%)	6 (5.9%)
Moderate (20–49%)	47 (46.5%)	22 (21.8%)	11 (10.9%)	14 (13.9%)
Bcl-2 (anti-apoptotic activity, % positive cells)				
High (≥50%)	26 (25.7%)	10 (9.9%)	2 (2.0%)	14 (13.9%)
Low (<20%)	29 (28.7%)	10 (9.9%)	16 (15.8%)	3 (3.0%)
Moderate (20–49%)	46 (45.5%)	21 (20.8%)	14 (13.9%)	11 (10.9%)
Total	101 (100%)	41 (40.6%)	32 (31.7%)	28 (27.7%)

Table 4: Postoperative Radiation Dose According to Surgical Procedure.

RT dose (Gy)	Limb amputation	Open biopsy	Tumor resection	Excisional biopsy	Total
30	0 (0.0%)	1 (1.0%)	6 (5.8%)	0 (0.0%)	7 (6.8%)
40	0 (0.0%)	0 (0.0%)	5 (4.9%)	0 (0.0%)	5 (4.9%)
45	0 (0.0%)	1 (1.0%)	5 (4.9%)	2 (1.9%)	8 (7.8%)
48	0 (0.0%)	0 (0.0%)	4 (3.9%)	0 (0.0%)	4 (3.9%)
50	0 (0.0%)	6 (5.8%)	23 (22.3%)	0 (0.0%)	29 (28.2%)
54	0 (0.0%)	4 (3.9%)	3 (2.9%)	0 (0.0%)	7 (6.8%)
56	0 (0.0%)	3 (2.9%)	7 (6.8%)	0 (0.0%)	10 (9.7%)
60	1 (1.0%)	2 (1.9%)	22 (21.4%)	0 (0.0%)	25 (24.3%)
66	1 (1.0%)	0 (0.0%)	7 (6.8%)	0 (0.0%)	8 (7.8%)
Total	2 (1.9%)	17 (16.5%)	82 (79.6%)	2 (1.9%)	101 (100%)

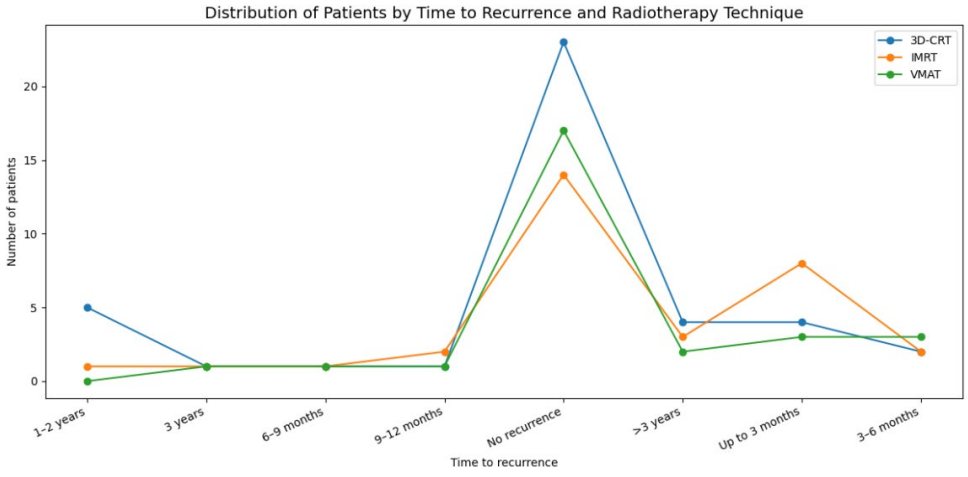


Figure 2: Time to Recurrence According to Radiotherapy Technique.

descriptive and did not indicate a clear relationship with irradiation technique.

Multivariable logistic regression analysis demonstrated that increasing age was independently associated with a higher probability of tumor recurrence (OR = 1.03, 95% CI: 1.00–1.07, p = 0.032). The presence of metastatic disease was also significantly associated with recurrence (OR = 20.19, 95% CI: 2.46–165.70, p = 0.005). Although high-grade tumors (G3–G4) demonstrated a tendency toward increased recurrence risk compared with low-grade lesions (G1–G2), this association did not reach statistical significance (OR = 1.86, 95% CI: 0.70–4.94, p = 0.214) [Table 5].

Toxicity analysis demonstrated that the most common early adverse events were radiation epitheliitis and skin erythema. These complications occurred more frequently after 3D-CRT, whereas lower frequencies were observed in patients treated with IMRT and VMAT. Among late complications, joint pain and contracture were the most frequent events, whereas late radiation ulcers were uncommon. Because individual patients could experience more than one adverse event, the number of complications exceeded the total number of patients included in the study [Table 6].

Table 5: Multivariable Logistic Regression Analysis of Factors Associated with Tumor Recurrence.

Variable	Adjusted OR	95% CI	p-value
Age (per 1-year increase)	1.03	1.00–1.07	0.032
Grade G3–G4 vs G1–G2	1.86	0.70–4.94	0.214
Metastatic disease (Yes vs No)	20.19	2.46–165.70	0.005

Table 6: Early and Late Treatment-Related Toxicity According to Radiotherapy Technique.

Complications	3D-CRT	IMRT	VMAT	Total
Early complications				
Anemia, allergic reactions	8 (2.3%)	6 (1.8%)	2 (0.6%)	16 (4.7%)
Leukopenia, agranulocytosis, pancytopenia	2 (0.6%)	1 (0.3%)	1 (0.3%)	4 (1.2%)
Alopecia	2 (0.6%)	1 (0.3%)	1 (0.3%)	4 (1.2%)
Radiation epitheliitis	44 (12.8%)	22 (6.4%)	6 (1.8%)	72 (21.1%)
Skin erythema	43 (12.6%)	21 (6.1%)	7 (2.0%)	71 (20.7%)
Late complications				
Joint pain	12 (5.5%)	11 (5.0%)	6 (2.8%)	29 (13.3%)
Contracture	8 (3.7%)	10 (4.6%)	6 (2.8%)	24 (11.0%)
Late ulcer	2 (0.9%)	2 (0.9%)	1 (0.5%)	5 (2.3%)
No complications	20 (9.2%)	16 (7.3%)	15 (6.9%)	51 (23.4%)
Total	42 (19.3%)	39 (17.9%)	28 (12.8%)	109 (50.0%)

DISCUSSION

The present findings demonstrate that personalization of radiotherapy in soft tissue sarcoma (STS) was driven primarily by tumor location, technical feasibility, and biological characteristics rather than by a uniform treatment algorithm. This observation is consistent with the ASTRO Clinical Practice Guideline, which emphasizes that radiotherapy strategies for adult STS should be individualized according to tumor site, resectability, target volume geometry, and the need to spare adjacent critical normal tissues [8]. Salerno et al. further highlighted that appropriate integration of radiotherapy with surgery contributes substantially to improved local control and functional preservation [8].

In our cohort, lower-extremity sarcomas were predominantly managed with 3D-CRT, whereas IMRT and VMAT were more frequently selected for anatomically complex regions, including the trunk, pelvis, head and neck, and abdominal cavity. This pattern appears clinically rational and is in agreement with contemporary radiotherapy recommendations. Current guidelines emphasize that highly conformal techniques are particularly valuable when target coverage must be balanced against the protection of nearby organs at risk and preservation of normal tissue function [2,10].

The postoperative dose distribution observed in our series also corresponded to accepted standards of care. Most patients received adjuvant doses ranging from 50 to 66 Gy, with dose escalation to 60–66 Gy in higher-risk settings. Similar dose-fractionation approaches have been recommended in international guidelines and have been associated with improved local control in selected patients with high-risk disease [2,8].

An additional observation of our study was the tendency for patients with higher Ki-67 and VEGF expression to be treated with IMRT or VMAT rather than with 3D-CRT. These findings should not be interpreted as evidence that molecular profile alone determines the optimal radiotherapy technique. Rather, they likely reflect clinical decision-making in which biologically more aggressive tumors are frequently larger, less favorably located, or situated closer to critical structures, thereby necessitating the use of more conformal planning techniques. This interpretation is consistent with current guideline-based practice, where advanced radiotherapy approaches are recommended when improved normal tissue sparing is required [5].

Multivariable logistic regression analysis demonstrated that increasing age and the presence of metastatic disease were independently associated with tumor recurrence. Although high-grade tumors showed a tendency toward increased recurrence risk, the association did not reach statistical significance. These findings are generally consistent with previous studies indicating that advanced disease burden and unfavorable clinicopathological characteristics are important determinants of treatment outcomes in patients with STS [1,6].

The toxicity profile observed in our cohort deserves particular attention. Early skin reactions were more frequently observed after 3D-CRT, whereas IMRT and VMAT demonstrated lower rates of cutaneous toxicity. Similar observations have been reported previously. Di Brina et al. demonstrated that VMAT is feasible in extremity STS and is associated with acceptable toxicity profiles [3]. Furthermore, Simões et al. highlighted the importance of dose-volume relationships in the development of treatment-related morbidity, supporting the rationale for highly conformal dose delivery whenever technically feasible [4,9].

Several limitations of the present study should be acknowledged. First, the retrospective single-center design may have introduced selection bias. Second, the relatively limited sample size reduced the statistical power of subgroup analyses. Third, treatment allocation was not randomized; therefore, baseline differences between groups may have influenced survival and toxicity outcomes. Finally, immunohistochemical data were not available for all patients, potentially limiting the assessment of biological

prognostic factors. Nevertheless, the study provides real-world evidence regarding the personalization of radiotherapy strategies in patients with soft tissue sarcomas.

CONCLUSIONS

In this retrospective cohort of 101 patients with soft tissue sarcomas, personalized radiotherapy strategies based on tumor location, biological characteristics, and treatment context were associated with favorable oncological outcomes. At the time of analysis, 62.4% of patients remained alive without evidence of disease progression.

Higher Ki-67 and VEGF expression levels were more frequently observed in patients managed with highly conformal radiotherapy techniques, reflecting the tendency to use IMRT and VMAT in anatomically complex and biologically more aggressive disease. Multivariable analysis demonstrated that increasing age and the presence of metastatic disease were independently associated with tumor recurrence.

Overall, the findings support an individualized approach to radiotherapy planning in soft tissue sarcoma and suggest that highly conformal techniques may improve treatment safety while maintaining effective tumor control. Prospective multicenter studies are warranted to validate these observations.

DECLARATIONS

ETHICAL CONSIDERATIONS

The study was approved by the Ethics Committee of Tashkent State Medical University and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Due to the retrospective observational design of the study and the use of anonymized clinical and imaging data, the requirement for informed consent was waived by the Ethics Committee.

CLINICAL TRIAL NUMBER

Not applicable.

CLINICAL TRIAL NUMBER

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are not publicly available due to institutional and ethical restrictions related to patient confidentiality but are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

The authors received no specific funding for this study.

AUTHORS' CONTRIBUTIONS

OA conceived and designed the study. OA, BU, and KS collected the clinical and radiological data. GM contributed to data acquisition and interpretation. NK participated in patient management and critically revised the manuscript. EC contributed to data verification and manuscript editing. MK performed the statistical analysis, interpreted the data, drafted the manuscript, and served as the corresponding author. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

ACKNOWLEDGEMENTS

Not applicable.

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