



Overall Survival and Prognostic Factors in Sarcomas of the Forearm: A Multicenter Retrospective Cohort Study

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OBJECTIVE

To characterize overall survival (OS) and prognostic factors in sarcomas of the forearm and hand after exclusion of carcinoma and other non-sarcoma diagnoses and to explore OS according to index surgical strategy.

METHODS

This multicenter retrospective cohort included 59 unique patients with histologically defined forearm and hand sarcoma treated at four tertiary referral centers between November 2008 and March 2025. Overall survival was analyzed using Kaplan-Meier and log-rank methods. Univariable Cox models evaluated baseline prognostic factors. A parsimonious age-adjusted Cox model assessed baseline regional nodal and/or distant metastatic disease, with Firth-penalized Cox regression performed as a sparse-event sensitivity analysis.

RESULTS

Median age was 48 years; 53 patients had soft-tissue sarcoma and 6 had bone sarcoma. Eleven deaths occurred. Estimated OS was 92.7% at 1 year and 74.8% at both 3 and 5 years. Baseline regional nodal and/or distant metastatic disease was present in 6 of 53 classifiable patients (3 regional nodal only and 3 distant pulmonary metastases) and was associated with poorer OS (5-year OS, 44.4% vs 84.1%; log-rank $p=0.024$). In the conventional age-adjusted Cox model, the association persisted (HR, 6.85; 95% CI, 1.31-35.79; $p=0.023$), with a similar Firth-penalized estimate (HR, 7.36; 95% profile-likelihood CI, 1.41-34.58; $p=0.020$). OS did not differ by limb-sparing surgery versus amputation ($p=0.904$).

CONCLUSION

Baseline regional nodal and/or distant metastatic disease was associated with substantially poorer OS. Limb-sparing surgery was the predominant definitive strategy. Because outcome events were sparse and treatment selection was retrospective, adjusted and surgical comparisons should be interpreted cautiously.

Keywords: Limb Salvage; metastasis; prognosis; sarcoma; survival analysis; upper extremity.

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INTRODUCTION

Sarcomas of the forearm are rare and present distinctive oncologic and reconstructive challenges. Soft-tissue sarcomas constitute less than 1% of all malignancies, and the dense concentration of tendons, nerves, vessels, and small functional compartments in the forearm can make oncologically adequate resection technically demanding.[1–3] Even relatively limited resections may have substantial functional consequences.

Historically, amputation was frequently used to obtain local control in extremity sarcoma. Improvements in imaging, multidisciplinary treatment, oncologic surgery, radiotherapy (RT), systemic therapy, and reconstruction have enabled limb-sparing surgery to become the preferred approach when adequate margins can be obtained without compromising oncologic principles.[4–9] Nevertheless, amputation remains necessary in selected patients with extensive neurovascular involvement, uncontrolled local disease, or limited reconstructive options.

Prognosis in extremity sarcoma is influenced by tumor biology, metastatic disease, tumor burden, histologic subtype, and treatment selection.[10–13] The roles of chemotherapy and RT vary according to histology, stage, and clinical context. Published forearm-specific series remain small, and their case mix is heterogeneous.[3,7,9,14] Analyses that combine carcinoma with sarcoma may introduce diagnostic heterogeneity that obscures sarcoma-specific prognostic relationships.

The present study therefore evaluated a histologically restricted, patient-level cohort of forearm sarcomas. The primary objectives were to estimate OS, evaluate baseline prognostic factors using time-to-event methods, and explore OS according to index surgical strategy while explicitly addressing sparse events and treatment-selection bias.

MATERIALS AND METHODS

Study Design and Cohort

This retrospective multicenter cohort study was conducted in accordance with the ethical criteria of the 1964 Declaration of Helsinki and was approved by the Ankara Etlik City Hospital Ethics Committee with the Approval No: AEŞH-BADEK1-2025-661 and Approval Date: 24.12.2025.

This retrospective multicenter cohort included patients treated for a primary sarcoma of the forearm between November 2008 and March 2025 at four tertiary

oncology referral centers (Ankara Etlik City Hospital, Ankara University Faculty of Medicine, Gazi University Faculty of Medicine, Abdurrahman Yurtaslan Oncology Training and Research Hospital). The source database contained 76 tumor records. For the sarcoma-specific analysis, patients with histologically confirmed carcinoma were excluded: 10 squamous cell carcinoma records, 2 adenocarcinoma records, and 1 clear cell carcinoma record (13 records in total). To maintain a histologically coherent sarcoma cohort, one malignant melanoma and two records coded only as peripheral nerve sheath tumor without a malignant/sarcoma specification were also excluded. Sixty eligible sarcoma records remained. One patient contributed two eligible sarcoma episodes; for patient-level analysis, the earliest index sarcoma was retained and the later record was removed, yielding 59 patients (Fig. 1).

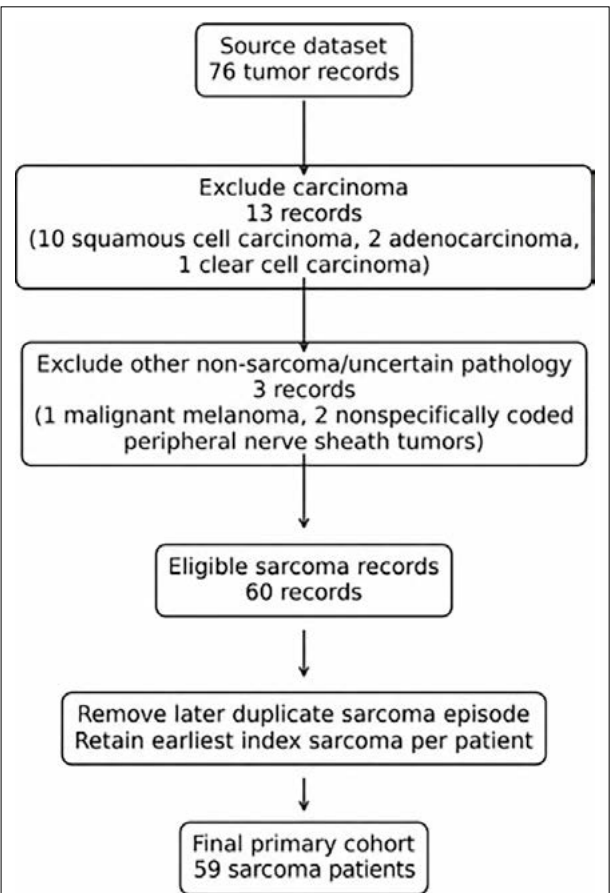


Fig. 1. Study cohort derivation. Carcinoma and other non-sarcoma and uncertain diagnoses were excluded, and one later duplicate eligible sarcoma episode was removed to obtain a unique-patient primary cohort.

Patients referred only for treatment of a metastatic lesion to the forearm or hand, patients previously treated at another institution before referral, and records with benign final pathology were also ineligible. No imputation was performed. Analyses used complete cases for each variable, and denominators are reported when data were missing or non-classifiable.

Variables, Data Definitions, and Outcomes

Demographic variables included age, sex, laterality, and anatomic site. Tumor variables included proximal/middle/distal location, depth, volar/dorsal compartment, histopathologic diagnosis, and maximum tumor dimension. The source field labelled “GRADE” contained stage-like entries rather than reproducible histologic grade; therefore, histologic grade could not be analyzed. Source-recorded stage was not included in primary inferential analyses because a uniform staging system and edition could not be verified retrospectively across the study period.

Baseline regional nodal and/or distant metastatic disease was defined solely from the metastatic-status field recorded at the index treatment assessment, before survival follow-up. “Present” included either documented regional nodal involvement or distant metastasis; the two components were also tabulated separately in the Results. “Absent” required an explicit record of no metastasis. Blank or indeterminate entries were treated as missing. This baseline definition was used for all Kaplan-Meier and Cox analyses and did not incorporate metastases that developed during follow-up.

Index definitive surgery was categorized as limb-sparing resection or amputation when classifiable (Fig. 2). The source database coded surgical margins as negative (“-”), close (<1 cm), or positive (“+”); these neutral categories were retained, and close/positive status was combined only for exploratory prognostic modeling. Because chemotherapy and RT could be delivered in neoadjuvant or adjuvant settings and treatment timing was heterogeneous, these variables were summarized as treatment exposures and were not modeled as baseline causal survival exposures.

Local recurrence was defined as documented recurrence at the primary operative site and was reported descriptively because recurrence timing was incomplete and death represents a competing event. OS time zero was the index operation. Survival time was measured to death from any cause or last documented follow-up using the recorded follow-up interval in months. Follow-up duration was summarized using the reverse Kaplan-Meier method.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR), and categorical variables as number and percentage. Baseline characteristics according to index surgical strategy were explored using the Mann-Whitney U test for continuous variables and Fisher’s exact test for categorical variables because subgroup sizes were small and uneven. No imputation was performed; analyses used complete cases for each variable and denominators are reported when data were missing or non-classifiable.

OS was estimated using the Kaplan-Meier method with 95% confidence intervals (CIs), and survival distributions were compared using the log-rank test. Univariable Cox proportional-hazards models evaluated age, maximum tumor dimension, sex, anatomic site, depth, tumor size >5 cm, baseline regional nodal and/or distant metastatic disease, close/positive margin status, and index surgical strategy. To limit overfitting, the adjusted analysis was restricted to a prespecified Cox model containing age and baseline regional nodal and/or distant metastatic disease. Because only 8 deaths occurred among the 53 complete cases entering the adjusted model, a Firth-penalized Cox regression using the Jeffreys invariant-prior penalty was performed as a sparse-event sensitivity analysis; 95% CIs and p values for the penalized model were obtained from the penalized profile likelihood. Schoenfeld-residual rank-correlation checks were used to assess the proportional-hazards assumption for the conventional Cox model. Sensitivity analyses were performed in the forearm-only subgroup and the soft-tissue-sarcoma-only subgroup. Two-sided p values <0.05 were considered statistically significant. Analyses were performed using the free and open-source software R (version 4.4.1, <https://cran.r-project.org>), SPSS for Windows Version 23.0 statistical package (Chicago, IL).

RESULTS

Fifty-three patients (89.8%) had soft-tissue sarcoma and 6 (10.2%) had bone sarcoma. The most frequent source-recorded diagnoses were pleomorphic sarcoma (n=10), myxofibrosarcoma (n=7), liposarcoma (n=6), synovial sarcoma (n=6, including 1 biphasic), rhabdomyosarcoma (n=4, including 2 alveolar), and leiomyosarcoma (n=3, including 1 pleomorphic); the complete histologic distribution is provided in Table 1. Median age was 48 years (IQR, 38–61 years), 37 patients (62.7%) were male, and 54 tumors (91.5%) were

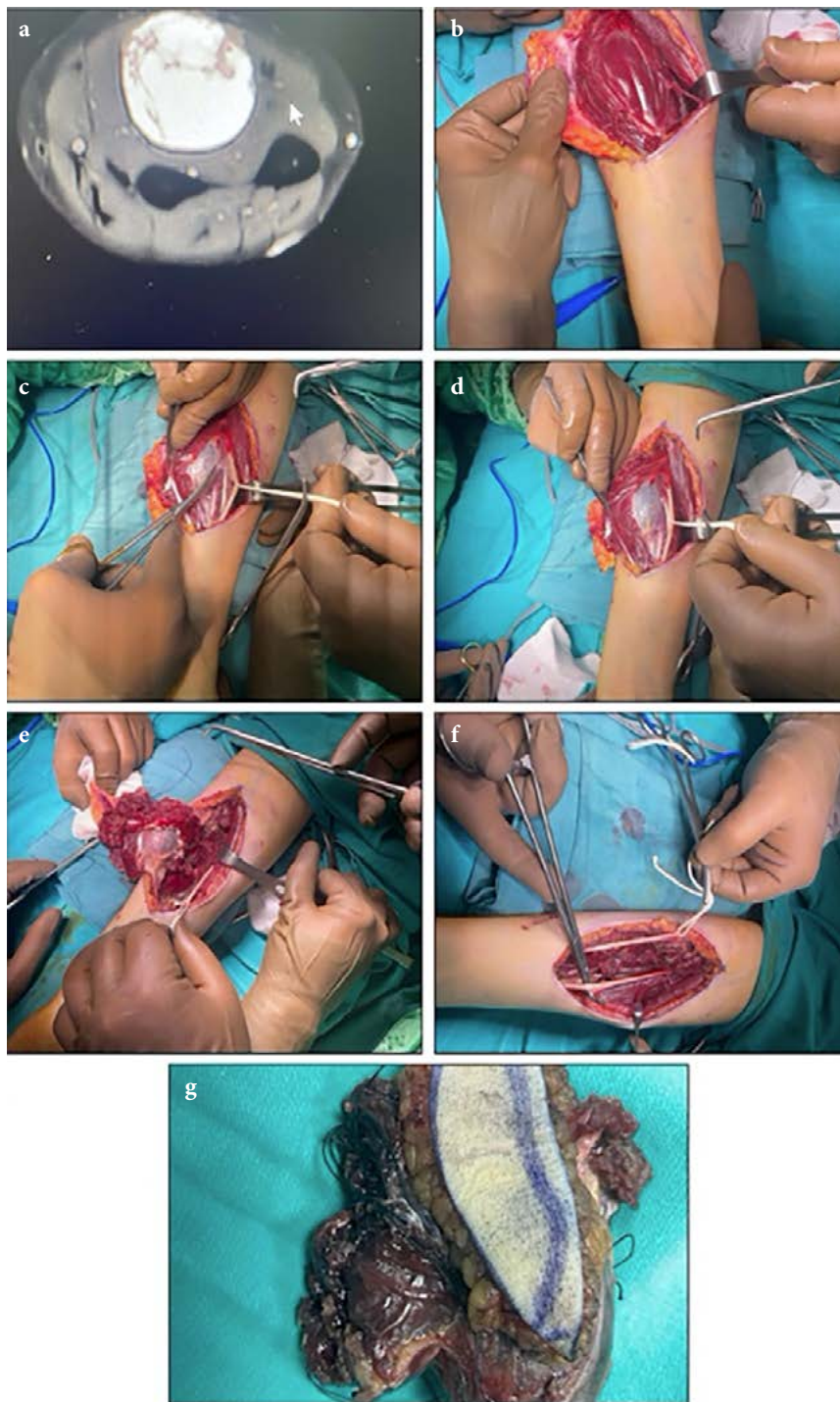


Fig. 2. Representative preoperative imaging and intraoperative sequence of limb-sparing resection of a forearm sarcoma. (a) Preoperative axial magnetic resonance image demonstrating the forearm lesion and its relationship to the surrounding osseous and soft-tissue structures. (b) Initial surgical exposure of the involved compartment. (c) Progressive circumferential dissection with identification and protection of adjacent neurovascular structures. (d) Mobilization of the tumor while preserving uninvolved critical structures. (e) En bloc tumor resection during limb-sparing surgery. (f) Final operative field after tumor removal, demonstrating preservation of the major neurovascular structures and the resulting resection bed. (g) Gross appearance of the resected specimen.

Table 1. Baseline clinical, tumor, treatment, and histopathologic characteristics

Characteristic	Value	
	n	%
Age (years)	48.0 (38.0–61.0)	
Male sex	37	62.7
Deep tumor	40	67.8
Maximum tumor dimension (cm)	12.0 (7.0–17.8)	
Tumor >5 cm	49/58	84.5
Soft-tissue sarcoma	53	89.8
Bone sarcoma	6	10.2
Baseline regional nodal and/or distant metastatic disease	6/53	11.3
Limb-sparing definitive surgery	45/53	84.9
Amputation	8/53	15.1
Chemotherapy exposure	28	47.5
Radiotherapy exposure	26	44.1
Local recurrence	11	18.6
Deaths	11	18.6
Median follow-up (months)	36 (reverse Kaplan–Meier)	
Histopathologic subtype		
Pleomorphic/undifferentiated pleomorphic sarcoma	10	18.6
Myxofibrosarcoma	7	11.9
Liposarcoma	6	10.2
Synovial sarcoma	6	10.2
Malignant peripheral nerve sheath tumor	3	5.1
Clear cell sarcoma	3	5.1
Angiosarcoma	3	5.1
Ewing sarcoma	3	5.1
Osteosarcoma	3	5.1
Leiomyosarcoma	3	5.1
Epithelioid sarcoma	2	3.4
Alveolar rhabdomyosarcoma	2	3.4
Dermatofibrosarcoma protuberans	2	3.4
Rhabdomyosarcoma, other/not otherwise specified	2	3.4
Fibrosarcoma	2	3.4
Malignant mesenchymal tumor, not otherwise specified	1	1.7

Values are n (%) or median (interquartile range), unless otherwise indicated. Denominators vary because complete-case analysis was used for missing or non-classifiable data. Histopathologic labels were standardized from the source pathology terminology for presentation.

located in the forearm. Forty tumors (67.8%) were deep. Median maximum tumor dimension was 12.0 cm (IQR, 7.0–17.8 cm), and 49 of 58 tumors with available measurements (84.5%) exceeded 5 cm.

Baseline regional nodal and/or distant metastatic status was classifiable in 53 patients. Three patients had regional nodal disease only and 3 had distant metastases (all pulmonary); no patient had both regional nodal and distant metastatic disease at baseline. Thus, 6 of 53 classifiable patients (11.3%) met the composite baseline

advanced-disease definition. Definitive surgical strategy was classifiable in 53 patients: 45 (84.9%) underwent limb-sparing surgery and 8 (15.1%) underwent amputation. Chemotherapy was recorded in 28 patients (47.5%) and RT in 26 (44.1%). Local recurrence was documented in 11 patients (18.6%). Eleven deaths (18.6%) occurred during follow-up. Median follow-up by reverse Kaplan–Meier analysis was 36 months (Table 1).

In univariable Cox models, baseline regional nodal and/or distant metastatic disease was associated with

Table 2. Univariable Cox proportional-hazards analyses for overall survival

Variable	n	Deaths	HR	95% CI	p
Age, per year	59	11	1.02	0.98–1.06	0.268
Maximum tumor dimension, per cm	58	11	1.00	0.91–1.10	0.983
Male sex	59	11	1.16	0.34–3.97	0.813
Baseline regional nodal and/or distant metastatic disease	53	8	4.54	1.08–19.06	0.039
Amputation vs limb-sparing surgery	53	11	1.10	0.24–5.09	0.904

HR: Hazard ratio; CI: Confidence interval. Hazard ratios for continuous variables are expressed per one-unit increase. These analyses account for follow-up duration and censoring and replace cross-sectional alive/deceased comparisons.

Table 3. Selected baseline and treatment characteristics according to index surgical strategy

Characteristic	Limb-sparing surgery (n=45)		Amputation (n=8)		p
	n	%	n	%	
Age (years)	51.0 (42.0–63.0)		47.0 (37.0–56.0)		0.510
Maximum tumor dimension (cm)	11.0 (7.0–15.0)		18.0 (14.0–21.8)		0.052
Deep tumor	29/45	64.4	8/8	100	0.088
Baseline regional nodal and/or distant metastatic disease	6/40	15.0	0/7	0	0.571
Close/positive margin	13/44	29.5	0/8	0	0.177
Chemotherapy exposure	17/45	37.8	7/8	87.5	0.017
Radiotherapy exposure	18/45	40.0	4/8	50.0	0.705

Values are median (interquartile range) or n/N (%). Continuous variables were compared using the Mann-Whitney U test and categorical variables using Fisher's exact test. Missing denominators reflect non-classifiable data. The imbalances support substantial confounding by indication in the surgical survival comparison.

poorer OS (HR, 4.54; 95% CI, 1.08–19.06; $p=0.039$). Age, maximum tumor dimension, sex, tumor depth, tumor size >5 cm, close/positive margin status, and amputation versus limb-sparing surgery were not significantly associated with OS (Table 2).

No deaths occurred among the 6 patients with bone sarcoma, so a stable Cox HR comparing bone with soft-tissue sarcoma was not estimable. Histologic grade was not analyzed because it was not reliably recorded, and source-recorded stage was excluded from primary inference because a uniform staging system and edition could not be verified across the retrospective study period.

Among 53 patients with classifiable definitive surgery, 45 underwent limb-sparing resection and 8 underwent amputation. Tumors in the amputation group were larger (median 18.0 vs 11.0 cm; $p=0.052$) and all were deep (100% vs 64.4%; $p=0.088$). Chemotherapy exposure was substantially more frequent after selection for amputation (87.5% vs 37.8%; $p=0.017$), whereas RT exposure was similar (50.0% vs 40.0%; $p=0.705$). These imbalances demonstrate clinically important confounding by indication and preclude causal interpretation of the surgical survival comparison (Table 3).

For the entire cohort, estimated OS was 92.7% (95% CI, 81.7–97.2%) at 1 year and 74.8% (95% CI, 58.2–85.6%) at both 3 and 5 years. Median OS was not reached (Fig. 3a; Table 4).

Baseline regional nodal and/or distant metastatic disease was associated with poorer OS. Among 47 patients with explicitly absent baseline regional nodal or distant metastatic disease, 5 deaths occurred and estimated 5-year OS was 84.1% (95% CI, 65.2–93.2%); median OS was not reached. Among 6 patients with baseline regional nodal and/or distant metastatic disease, 3 deaths occurred, estimated 5-year OS was 44.4% (95% CI, 6.6–78.5%), and median OS was 26 months ($p=0.024$) (Fig. 3b; Table 4).

In the conventional age-adjusted Cox model restricted to 53 patients with classifiable baseline regional nodal and/or distant metastatic status (8 deaths), the composite advanced-disease variable remained associated with mortality (HR, 6.85; 95% CI, 1.31–35.79; $p=0.023$), whereas age was not significant (HR per year, 0.979; 95% CI, 0.939–1.020; $p=0.305$). Given the sparse number of events, Firth-penalized Cox regression was performed as a sensitivity analysis and produced a similar estimate for baseline regional nodal and/or distant metastatic disease (HR, 7.36; 95% profile-likelihood

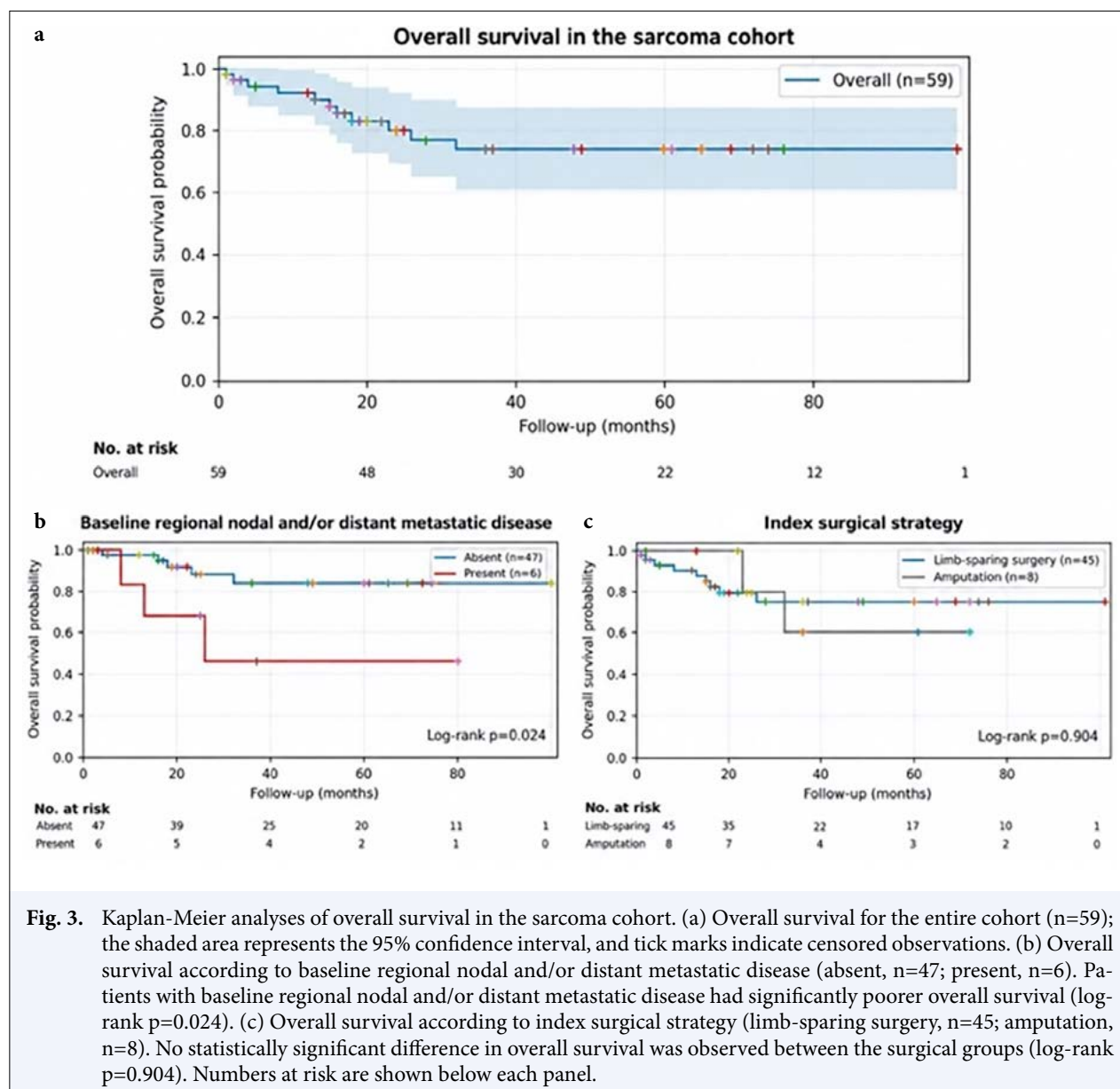


Table 4. Kaplan–Meier overall survival estimates

Group	n	Deaths	1-year OS, % (95% CI)	3-year OS, % (95% CI)	5-year OS, % (95% CI)	Median OS, months	Log-rank p
Overall cohort	59	11	92.7 (81.7–97.2)	74.8 (58.2–85.6)	74.8 (58.2–85.6)	Not reached	–
Baseline regional nodal and/or distant metastatic disease absent	47	5	97.6 (83.9–99.7)	84.1 (65.2–93.2)	84.1 (65.2–93.2)	Not reached	
Baseline regional nodal and/or distant metastatic disease present	6	3	83.3 (27.3–97.5)	44.4 (6.6–78.5)	44.4 (6.6–78.5)	26	0.024
Limb-sparing surgery	45	9	90.3 (76.1–96.3)	75.0 (56.8–86.4)	75.0 (56.8–86.4)	Not reached	
Amputation	8	2	100.0	60.0 (12.6–88.2)	60.0 (12.6–88.2)	Not reached	0.904

OS: Overall survival; CI: Confidence interval. Log-rank p values refer to the corresponding two-group comparison; blank cells indicate the companion group in the same comparison.

Table 5. Parsimonious Cox proportional-hazards model and penalized sensitivity analysis for overall survival

Model	Variable	HR	95% CI	p
Conventional Cox	Age, per year	0.979	0.939–1.020	0.305
Conventional Cox	Baseline regional nodal and/or distant metastatic disease	6.85	1.31–35.79	0.023
Firth-penalized Cox sensitivity analysis	Baseline regional nodal and/or distant metastatic disease	7.36	1.41–34.58	0.020

The conventional model included 53 patients with classifiable baseline disease status and 8 deaths and was adjusted for age. Residual-based proportional-hazards checks were non-significant for age ($p=0.651$) and baseline regional nodal and/or distant metastatic disease ($p=0.693$). Because of sparse events, a Firth-penalized Cox model was used as a sensitivity analysis. The penalized estimate is reported for the principal exposure. HR: Hazard ratio; CI: Confidence interval.

CI, 1.41–34.58; $p=0.020$); age remained non-significant (HR per year, 0.978; 95% profile-likelihood CI, 0.941–1.020; $p=0.280$). Schoenfeld-residual rank-correlation checks did not indicate violation of the proportional-hazards assumption for age ($p=0.651$) or the composite advanced-disease variable ($p=0.693$) (Table 5).

OS did not differ significantly between limb-sparing surgery and amputation (log-rank $p=0.904$) (Fig. 3c). Five-year OS was estimated at 75.0% (95% CI, 56.8–86.4%) after limb-sparing surgery and 60.0% (95% CI, 12.6–88.2%) after amputation. Given the strong baseline treatment-selection imbalances, this exploratory comparison should not be interpreted as evidence of therapeutic equivalence.

The association between baseline regional nodal and/or distant metastatic disease and poorer OS remained present in the forearm-only subgroup ($n=54$; log-rank $p=0.016$) and in the soft-tissue-sarcoma-only subgroup ($n=53$; $p=0.044$), consistent with the direction of the primary finding, although precision remained limited by the small number of patients with baseline advanced disease.

DISCUSSION

This multicenter study provides a patient-level analysis of forearm sarcomas after explicit exclusion of carcinoma and other diagnoses that could not be confidently classified as sarcoma. The principal finding was that baseline regional nodal and/or distant metastatic disease was associated with substantially poorer OS in Kaplan-Meier and univariable Cox analyses and remained associated with mortality after age adjustment. A Firth-penalized Cox sensitivity analysis produced a similar effect estimate, although the small number of exposed patients and deaths resulted in wide CIs and limits the precision of the adjusted association.

The adverse association of baseline regional nodal and/or distant metastatic disease with survival is consistent with the broader extremity sarcoma literature, in which systemic disease burden and tumor biol-

ogy are major determinants of outcome.[10–13] In the present cohort, the composite group comprised 3 patients with regional nodal disease only and 3 with distant pulmonary metastases, with no patient having both at baseline. Regional nodal involvement and distant metastasis are biologically distinct states; they were combined only because each component was too uncommon for stable separate survival modeling. Accordingly, the composite estimate should be interpreted as a marker of baseline advanced disease rather than as a distant-metastasis-specific effect.

Limb-sparing surgery was the predominant definitive procedure, consistent with contemporary management of extremity sarcoma when adequate oncologic resection can be achieved.[4,5] The present study did not demonstrate a survival difference between limb-sparing surgery and amputation. Importantly, the amputation group had larger and uniformly deep tumors and substantially greater chemotherapy exposure, indicating strong confounding by indication. Accordingly, the surgical comparison is descriptive and should not be interpreted as a comparative-effectiveness estimate.

Chemotherapy and RT were intentionally treated as descriptive treatment-pattern variables rather than baseline survival exposures because treatment timing and indications were heterogeneous. This approach avoids attributing post-baseline or selectively administered therapies to baseline prognosis. The lack of a treatment-effect analysis should not be interpreted as evidence for or against benefit from chemotherapy or RT, whose roles depend on histology, stage, grade, resectability, and multidisciplinary treatment strategy.[10,12,13,15–17]

The distal upper extremity contains compact, functionally critical anatomy, and oncologic resection may require sacrifice or reconstruction of tendons, nerves, vessels, or soft tissue.[6–9,18] Although the present study focused on oncologic outcomes, standardized functional outcome measures were not systematically collected. Future prospective multicenter studies should integrate local control, functional out-

comes, patient-reported outcomes, and survival to better characterize the trade-offs between oncologic adequacy and extremity function.

Restricting the cohort to histologically coherent sarcomas and performing patient-level rather than record-level analysis strengthens the internal validity of the current study. The forearm-only and soft-tissue-sarcoma-only sensitivity analyses showed the same direction of association for baseline regional nodal and/or distant metastatic disease, although statistical precision remained limited by the rarity of the disease and the small number of outcome events.

Limitations of the Study

This study has several limitations. First, its retrospective design introduces selection bias, missing-data bias, and residual confounding. Second, only 11 deaths occurred overall and only 8 deaths entered the complete-case adjusted model; although a Firth-penalized Cox sensitivity analysis was used to reduce sparse-data bias, adjusted effect estimates remain imprecise. Third, baseline regional nodal and/or distant metastatic status was missing or indeterminate in six patients, and complete-case analysis was used without imputation. Fourth, regional nodal disease and distant metastasis were combined into a composite baseline advanced-disease variable because only 3 patients had each component; these disease states may have different biologic and prognostic implications. Fifth, histologic grade could not be analyzed, and a uniform stage system/edition could not be verified retrospectively; stage was therefore not used for primary inference. Sixth, chemotherapy and RT timing, dose, and regimen were heterogeneous and were not modeled as causal baseline exposures. Seventh, the 2008–2025 study period spans changes in imaging, systemic therapy, RT planning, pathology classification, and reconstructive practice. Eighth, local recurrence was reported descriptively because complete recurrence-time data and competing-risk modeling were not available. Finally, standardized functional outcome measures were not systematically collected.

CONCLUSION

In this multicenter patient-level cohort of forearm sarcomas assembled after exclusion of carcinoma and other non-sarcoma and uncertain diagnoses, baseline regional nodal and/or distant metastatic disease was associated with substantially poorer OS. The association persisted after age adjustment and in a Firth-penalized sparse-event sensitivity analysis, but the wide CIs re-

quire cautious interpretation. Limb-sparing surgery was the predominant definitive strategy. The absence of a survival difference between limb-sparing surgery and amputation should be interpreted cautiously because of pronounced treatment-selection bias. Larger histology-specific collaborative cohorts are needed to refine prognostic estimates and integrate oncologic outcomes with standardized functional measures.

Ethics Committee Approval: The study was approved by the Ankara Etlik City Hospital Ethics Committee (no: AEŞH-BADEK1-2025-661, date: 24/12/2025).

Informed Consent: This is a retrospective, multicenter cohort study.

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