ORIGINAL ARTICLE

Distant metastasis – free interval and overall survival in breast sarcoma: a single-institution retrospective study

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Summary

Introduction: Breast sarcomas (BS) are rare malignant tumors with aggressive behavior and limited evidence guiding outcome assessment. Data on distant metastasis–free interval (DMFI) in this population are scarce. This study aimed to describe oncologic outcomes and clinicopathologic characteristics in patients with BS treated with curative intent.

Methods: Patients with primary or secondary breast sarcoma treated at a single tertiary cancer center between 2013 and 2025 were retrospectively analyzed. Patients with metastatic disease at diagnosis were excluded. DMFI was the primary endpoint, and OS was the endpoint. Survival outcomes were estimated using Kaplan–Meier methodology and presented descriptively.

Results: Twenty-six patients met the inclusion criteria. Angiosarcoma was the most common histologic subtype, predominantly occurring as secondary disease after prior breast radiotherapy. Median DMFI was not reached during follow-up, with 71.5% of patients remaining metastasis-free at 3 years, whereas median OS was 31 months with a 3-year OS of 46.9%. Patients with higher pathological T stage, larger tumors, tumor necrosis, younger age, and narrower resection margins tended to demonstrate shorter DMFI. Differences in overall survival were most pronounced according to resection margin status.

Conclusions: Tumor burden–related factors, tumor necrosis, and surgical margin width showed clinically relevant differences in metastasis-related outcomes and survival in breast sarcoma. Adequate surgical resection remains critical in this rare and heterogeneous disease.

Keywords: breast sarcoma, distant metastasis–free interval, overall survival, surgical margins, angiosarcoma

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INTRODUCTION

Breast sarcomas (BS) are rare malignant tumors of mesenchymal origin, accounting for less than 0.1% of all breast malignancies (1, 2, 3). They are characterized by aggressive biological behavior, limited responsiveness to adjuvant therapies, and high propensity for local recurrence and distant metastatic spread, which largely determines long-term outcomes. Unlike epithelial breast cancers, breast sarcomas typically disseminate hematogenously, and distant metastases represent a major cause of disease-related mortality. (4, 5). Breast sarcomas may be classified as primary or secondary. Primary tumors arise de novo from the breast or associated soft tissues. Sometimes they may be associated with hereditary cancer syndromes, including Li-Fraumeni syndrome, familial adenomatous polyposis, neurofibromatosis type 1, and hereditary retinoblastoma (6). Secondary breast sarcomas most often develop as a rare late complication of postoperative breast irradiation or in the setting of chronic lymphedema, with radiation-associated angiosarcoma representing the most common histologic subtype (7, 8).

Complete surgical excision with negative margins is the mainstay of treatment for BS, whereas the roles of adjuvant radiotherapy and systemic therapy remain incompletely defined (1, 4, 9,10). Evidence supporting these practices primarily derives from small retrospective series and institutional reports (11, 12).

Given these limitations, institutional analyses are essential to improve understanding of disease behavior and prognostic factors. This study aimed to describe oncologic outcomes and to characterize clinicopathologic features in relation to distant metastasis–free interval (DMFI) and overall survival (OS) in patients with BS treated with curative intent.

MATERIALS AND METHODS

Patients and data

This retrospective cohort study was conducted on patients treated at a tertiary cancer center between January 2013 and September 2025. Eligible patients had a histopathologically confirmed diagnosis of primary or secondary BS arising within the breast or breast-associated soft tissues, underwent curative-intent surgical treatment at our institution, and had no evidence of distant metastases at diagnosis. Patients were required to have complete clinical, pathological, treatment, and follow-up data available for analysis. Patients with metastatic disease at presentation, palliative-intent treatment, primary treatment performed outside our institution, isolated chest wall sarcomas without breast involvement, or incomplete medical records were excluded from the study. Clinical, pathological, treatment, and follow-up data, including patient age, tumor characteristics, surgical procedures, radiotherapy and systemic therapy parameters were retrieved from medical records and pathology reports. This study was reviewed and approved by the Ethics Committee of the Institute for Oncology and Radiology of Serbia, approval number 01-1/2025/3282.

Treatment

All patients included in this analysis underwent complete diagnostic evaluation and oncologic treatment at our institution. Surgical management consisted of wide local excision or mastectomy, with axillary lymph node surgery performed when clinically indicated. Decisions regarding the overall treatment strategy, including the extent of surgery and the use of adjuvant radiotherapy and/or systemic therapy, were made at a multidisciplinary breast tumor board meeting.

Follow-up and long-term outcomes

Patients were followed every 3 months during the first postoperative year, every 6 months from years 2 to 5, and annually thereafter. The primary study endpoint was DMFI, defined as the time from completion of primary treatment to the first clinically or radiologically confirmed distant metastasis. Overall survival was a secondary endpoint and was defined as the time from completion of primary treatment to death from any cause.

Statistical analysis

Categorical variables were presented as absolute and relative frequencies, whereas continuous variables were summarized using descriptive statistics, including mean, median, standard deviation (SD), and range. Survival outcomes (DMFI and OS) were estimated using the Kaplan-Meier method and presented as median survival times and survival rates at selected time points. Due to the limited sample size, no formal comparative or multivariable analyses were performed, and the results are presented descriptively. All statistical analyses were conducted using R software (version 4.3.1 (2023-06-16 ucrt)— "Beagle Scouts"; Copyright (C) 2023 The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit)) (available at: www.r-project.org; downloaded: 21 August 2023).

RESULTS

Patients and treatment

Between January 2013 and September 2025, 26 patients treated at our institution met the inclusion criteria for the present study. Patient's clinicopathological and treatment

Table 1. Clinicopathological and treatment characteristics of the study cohort.

PATIENT CHARACTERISTICS		PATIENT CHARACTERISTICS	
Age (years)		**Enlarged LN**	
Mean (SD)	61.3 (12.2)	Yes	1 (3.9%)
Median (Range)	60.5 (35-92)	No	25 (96.1%)
CCI		**Follow up (months)**	
Mean (SD)	1.69 (1.49)	Mean (SD)	28.2 (28.9)
Median (Range)	2 (0-6)	Median (Range)	20 (2-113)
Previous BC			
Yes	16 (61.5%)	TREATMENT CHARACTERISTICS	
No	10 (38.5%)		
Previous RT		**Breast surgery**	
Yes	14 (53.8%)	WLE	3 (11.5%)
No	12 (46.2%)	Mastectomy	23 (88.5%)
Laterality		**Axillary dissection**	
Right	17 (65.4%)	Yes	4 (15.4%)
Left	9 (34.6%)	No	22 (84.6%)
CTS (mm)		**Reconstruction**	
Mean (SD)	74.1 (60)	Yes	6 (23.1%)
Median (Range)	60 (15-300)	No	20 (76.9%)
Localization		**Adjuvant CT**	
CQ	10 (38.5%)	Yes	3 (11.5%)
ULQ	4 (15.4%)	No	23 (88.5%)
LLQ	4 (15.4%)	**Adjuvant RT**	
LMQ	3 (11.5%)	Yes	4 (15.4%)
UMQ	5 (19.2%)	No	22 (84.6%)
Total	26 (100%)	**Total**	26 (100%)

Abbreviations: SD – standard deviation; CCI – Charlson comorbidity index; BC – breast cancer; RT – radiotherapy; CTS – clinical tumor size; mm – millimeter; CQ – central quadrant; ULQ – upper lateral quadrant; LLQ – lower lateral quadrant; LMQ – lower medial quadrant; UMQ – upper medial quadrant; LN – lymph node; WLE – wide local excision; CT – chemotherapy.

data are shown in **Table 1**. All patients were females. The cohort consisted predominantly of older patients, many with a history of prior breast cancer and radiotherapy, consistent with secondary BS. Tumors were generally large and clinically node-negative at presentation. Surgical treatment was primarily mastectomy, with axillary procedures used selectively, and adjuvant therapies applied on an individualized basis.

Postoperative histopathological characteristics, staging, and long-term outcomes

Postoperative histopathological analysis revealed a predominance of high-grade tumors, with angiosarcoma representing the most frequent histologic subtype. Out of 15 patients with angiosarcoma, 13 (86.7%) received previous radiotherapy for breast cancer treatment. On the other hand, only one patient in our cohort developed a tumor other than angiosarcoma after RT (undifferentiated pleomorphic sarcoma). Tumors were generally large and exhibited a high proliferative activity, with tumor necrosis commonly observed. Detailed histopathological characteristics are summarized in **Table 2**. Most patients achieved microscopically negative (R0) resection, although a small proportion had positive margins (n=2).

During follow-up, eight patients experienced distant metastatic progression, while death was recorded in twelve patients. Kaplan–Meier curves for DMFI and OS are shown in **Figure 1**. Median DMFI was not reached during follow-up (95% CI, >39 months), with 71.5% (95% CI: 55.6%-92.1%) patients being metastasis-free after 3 years. The median overall survival was 31 months (95% CI, >20 months) with 3-year OS of 46.9% (95% CI: 28.6%-76.8%).

Clinicopathological characteristics according to outcomes

Continuous variables were explored descriptively across outcome groups. Due to the limited number of events, no formal threshold determination was considered reliable, and results are presented descriptively.

Kaplan-Meier curves indicated differences in DMFI across several clinicopathological subgroups, including tumor size, pathological T stage, tumor necrosis, patient age, and resection margin width. Differences in OS were

Table 2. Histopathological characteristics of the study cohort

HISTOPATHOLOGICAL CHARACTERISTICS			
Sarcoma type		**PTS (mm)**	
Angiosarcoma	15 (57.7%)	Mean (SD)	84.4 (62.4)
Other	11 (42.3%)	Median (Range)	67.5 (20-300)
Ki67 (%)		**pT**	
Mean (SD)	53.3 (24)	T1	12 (46.1%)
Median (Range)	55 (5-95)	≥*T2*	14 (53.9%)
Grade		**Resection margin (mm)**	
I	5 (19.2%)	Mean (SD)	26.8 (14.9)
II	10 (38.5%)	Median (Range)	25 (0-57)
III	11 (42.3%)	**R status**	
Tumor necrosis		R0	24 (92.3%)
Yes	14 (53.8%)	R1	2 (7.7%)
No	12 (46.2%)	**Total**	26 (100%)

Abbreviations: SD – standard deviation; PTS – pathological tumor size; pT – pathological T stage; mm – millimeter.

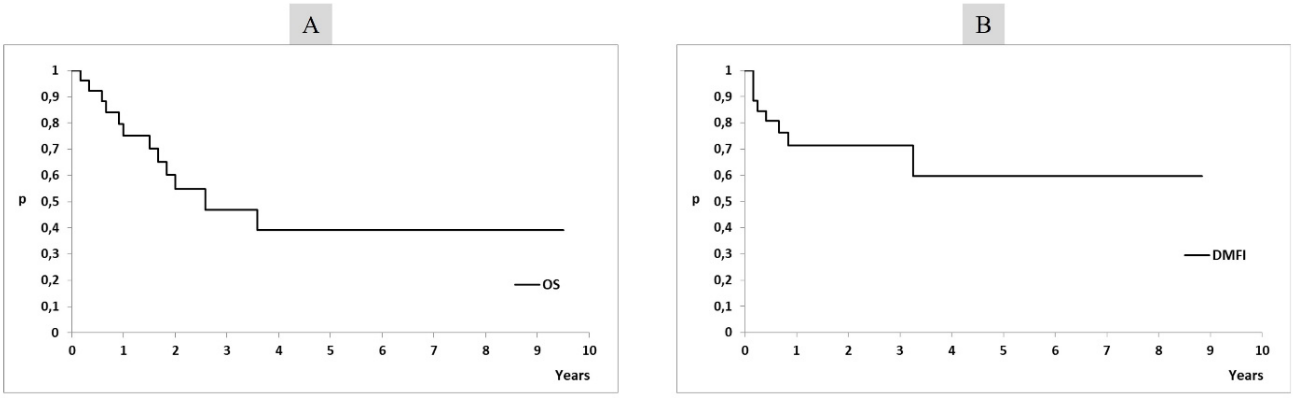

Figure 1. A. Kaplan–Meier estimate of overall survival of the entire study cohort. B. Kaplan–Meier estimate of distant metastasis-free interval of the entire study cohort.

observed across subgroups, particularly according to resection margin status. This parameter demonstrated a similar pattern across both DMFI and OS curves.

DISCUSSION

In this single-institution retrospective cohort of BS patients treated with curative intent, we observed a disease profile characterized by large tumors at presentation, frequent angiosarcoma, often in the context of prior breast cancer radiotherapy. Tumor size at presentation in our cohort exceeded that reported in comparable series (2, 11), while age at diagnosis was consistent with previously published data (2, 11, 13, 14).

This is, to our knowledge, the only study to analyze DMFI in BS patients. The discrepancy between 3-year overall survival and distant metastasis–free rates reflects deaths occurring without documented metastatic disease, most commonly due to aggressive local progression, treatment-related morbidity, or competing comorbidities in older patients. In our cohort, variation in DMFI appeared to be associated with tumor burden–related parameters (pT stage and tumor size), resection margins, tumor necrosis, and patient age. Fields et al. reported increased risk for death, local recurrence, and development of metastases in patients with tumors larger than 5cm in diameter, which is comparable to findings in our cohort (4). Similar results were published by Adem et al in the Mayo Clinic series and literature review (1). These observations are consistent with the broader soft tissue sarcoma literature, which reports that tumor size, necrosis, and features of aggressive biology are commonly associated with metastatic risk and survival across histologic subtypes (15, 16, 17). Because BS series are typically small and biologically heterogeneous, DMFI may provide particularly informative insight into systemic disease behavior. In contrast, overall survival may be influenced by competing risks, salvage treatments, and comorbidities, especially in older patient populations.

In contrast, in our cohort, OS differed primarily by resection margin width, with a consistent pattern across both DMFI and OS. Positive resection margins in other cohorts were associated with significantly worse treat-

ment outcomes (14). In our cohort, only two patients had positive resection margins, with time to death of 4 and 7 months, compared to a median OS of 43 months in R0 patients. The small number of R1 patients precluded further analysis. This supports the longstanding principle that complete surgical resection with negative margins is the cornerstone of sarcoma treatment, emphasized in major guidelines and consistently observed in BS series (2, 9, 12, 18). Although BS predominantly disseminates hematogenously, surgical margin status remains a meaningful surrogate for oncologic clearance, particularly in infiltrative histologies such as angiosarcoma, where microscopic residual disease may drive early recurrence and systemic relapse (19, 20, 21).

Interestingly, older age was accompanied by a parallel, although not statistically significant, trend toward longer OS in our cohort. While counterintuitive, this observation likely reflects the complex, context-dependent influence of age on sarcoma outcomes rather than a direct biological advantage. Given the limited sample size and number of events, these results should be interpreted cautiously and should not be overinterpreted. Notably, prior breast and soft tissue sarcoma studies have not consistently demonstrated a similar association between older age and improved metastasis-related or survival outcomes.

The inclusion of both primary and secondary BS in the present analysis warrants specific consideration. In our cohort, 86.7% of angiosarcomas occurred as secondary BS; however, no clear differences in DMFI or OS were apparent between angiosarcoma and other sarcoma subtypes. This finding should be interpreted cautiously, given the limited sample size and number of events. Secondary BS, most commonly radiation-associated angiosarcomas, are recognized as a biologically distinct subgroup, often characterized in the literature as having higher rates of local recurrence and poorer survival than primary sarcomas (20, 22, 23). Nevertheless, prior institutional and population-based studies have frequently analyzed primary and secondary BS together, reflecting the rarity of the disease and the shared clinical challenge of managing aggressive mesenchymal tumors arising in the breast (3, 24). While this approach increases biological heterogeneity, it allows for clinically meaningful evaluation of outcome patterns and prognostic factors across the broader spectrum of BS. Importantly, tumor burden and adequacy of surgical resection, factors identified in the present study, have been consistently reported as dominant determinants of outcome in both primary and radiation-associated BS, supporting the relevance of combined analyses in exploratory outcome research (18, 20).

This study is limited by its retrospective, single-center design and small sample size, which restricts generalizability. The low number of distant metastatic events precluded reliable multivariable modeling; therefore, the analyses were interpreted descriptively. The inclusion of both primary and secondary BS further increases biological heterogeneity, a challenge inherent to studies of rare tumors. In addition, the low number of distant metastatic events limited the ability to perform robust multivariable analyses.

In conclusion, shorter DMFI tended to occur in patients with higher tumor burden–related factors, tumor necrosis, and older age. At the same time, resection margin width showed a consistent relationship with both DMFI and OS. These findings indicate that metastasis-related outcomes may provide complementary information to overall survival regarding systemic disease behavior in this rare and heterogeneous population. Larger, multi-institutional studies are needed to explore these observations further and better define prognostic factors in BS.

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INTERVAL BEZ UDALJENIH METASTAZA I UKUPNO PREŽIVLJAVANJE KOD SARKOMA DOJKE: RETROSPEKTIVNA STUDIJA U TERCIJARNOM CENTRU

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Sažetak

Uvod: Sarkomi dojke (SD) predstavljaju retke, agresivne maligne tumore sa ograničenim dokazima o dugoročnim ishodima lečenja. Cilj ove studije bio je da opiše onkološke ishode i ispita kliničkopatološke faktore povezane sa intervalom bez udaljenih metastaza (DMFI) i ukupnim preživljavanjem (OS) kod pacijenata lečenih sa kurativnom namerom.

Metode: Retrospektivno su analizirani pacijenti sa primarnim ili sekundarnim sarkomom dojke lečeni u jednom tercijarnom onkološkom centru u periodu od 2013. do 2025. godine. Pacijenti sa metastatskom bolešću u trenutku dijagnoze bili su isključeni. DMFI je definisan kao primarni, a OS kao sekundarni ishod. Preživljavanje je procenjivano Kaplan–Majerovom metodom i prikazano deskriptivno.

Rezultati: Ukupno dvadeset šest pacijenata ispunilo je kriterijume uključenja u studiju. Angiosarkom je bio najčešći histološki podtip, uglavnom kao sekundarni tumor nakon prethodne radioterapije dojke. Medijana DMFI nije dostignuta, pri čemu je 71,5% pacijenata bilo bez udaljenih metastaza nakon tri godine, dok je medijana OS iznosila 31 mesec uz trogodišnje OS od 46,9%. Kraći DMFI je tendenciozno uočen kod pacijenata sa višim patološkim T stadijumom, većom veličinom tumora, prisustvom tumorske nekroze, mlađim uzrastom i užim resekcionim marginama. Razlike u OS bile su najizraženije u odnosu na status resekcionih margina.

Zaključak: Tumorsko opterećenje, nekroza tumora i starost bili su povezani sa DMFI, dok je jedino širina hirurških margina bila povezana i sa DMFI i sa OS, naglašavajući značaj adekvatne hirurške resekcije SD.

Ključne reči: sarkom dojke, interval bez udaljenih metastaza, ukupno preživljavanje, hirurške margine, angiosarkom

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