Open Access ORIGINAL ARTICLE

Clinicopathological Features and Prognosis of Primary Breast Sarcoma: A Single Centre Retrospective Study

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ABSTRACT

Objective: This study aims to describe clinicopathological characteristics and outcomes of primary breast sarcoma (PBS) and the relevance of clinical and pathological characteristics with the outcomes.

Methodology:

Study Design: Retrospective longitudinal study

Place and duration of study: Department of Medical Oncology Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore from January 1995 to August 2021.

Patients aged 18 years and older were included in the study. Individuals with primary or secondary angiosarcoma or cystosarcoma phyllodes were not included. The hospital information system was used for collecting data, and data was collected for 27 patients meeting inclusion study criteria.

Results: Twenty-seven patients were treated with surgery, seven out of 27 patients (25.90%) received adjuvant chemotherapy and 2 patients (7.40%) received chemotherapy on a palliative intent. The remaining (66.70%, n=18) did not receive chemotherapy. Twenty-four out of 27 patients (88.90%) received radiation therapy; intent was adjuvant in the entire cohort. Median PFS was 18 months with 74.01% of patients having no progression at their last follow-up. The median OS was 23 months. Adjuvant radiotherapy was associated with a significant overall survival benefit (P-value: 0.05). Adjuvant chemotherapy was not associated with a significant survival benefit (P-value: 0.5). Age, tumor size, and disease status (localized disease) conferred a non-significant trend towards a better outcome.

Conclusion: Adjuvant radiotherapy is the only factor that affects the outcomes of this disease. Further multicentred and preferably prospective studies with a larger number of patients are required to define disease characteristics and patient outcomes of primary breast sarcoma in Pakistan.

Keywords: clinical characteristics, outcomes, prognosis, primary breast sarcoma (PBS)

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [3,4] Critical analysis and manuscript review; [5,6] Data analysis; Manuscript Editing.

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Article info:
Received: December 3, 2023
Accepted: December 31, 2023

Cite this article. Ullah N, Naeem BS, Jhatial AM, Wahab A, Shahid R, Khan M, Asim S, Siddiqui N. Clinicopathological Features and Prognosis of Primary Breast Sarcoma: A Single Centre Retrospective Study. J Islamabad Med Dental Coll. 2023; 12(4): 324-330.
DOI: https://doi.org/10.35787/jimdc.v12i4.1087

Funding Source: Nil
Conflict of interest: Nil

Introduction

Soft tissue primary breast sarcoma (PBS) is a rare entity with an incidence rate of 4.6 cases/million. It is different from the more common breast cancers by being mesenchymal in origin, while the former are epithelial in origin.[1] And it is different from

phyllodes tumors of the breast which consist of both connective tissue stroma (mesenchymal) and epithelial components.[1] Breast sarcomas can be primary or de-novo, associated with certain genetic predisposition syndromes, and exposure to arsenic, vinyl chloride, or alkylator compounds. Genetic syndromes associated with breast sarcoma are Li Fraumeni syndrome, familial adenomatous polyposis, and neurofibromatosis type 1.[2,4] Sarcomas can be therapy-related, arising secondary to radiotherapy for breast cancer, lymphomas, or other thoracic malignancies.[5]

PBS is a disease of middle age and usually affects patients in their fifties and sixties with a median age of 55-59 years.[6] Primary breast sarcoma can mimic adenocarcinoma of the breast in clinical presentation; however, it has a high risk of recurrence and a dismal prognosis as compared to the adenocarcinoma variety. After diagnosis with a core or excisional biopsy, it is staged according to the American Joint Committee on Cancer (AJCC) system for soft tissue sarcomas including grade of tumor, size, nodes, and distant metastases.[7] Tumor size, grade of differentiation, histopathologic type, and resection margin status determine prognosis with tumor size > 5 cm, poor differentiation, high grade, angiosarcoma variety, and positive resection margins being the factors determining poor outcomes. Treatment is surgery with the aim of negative resection margins with median overall survival reported to be around 63.5%.[8] As compared to epithelial breast cancers, sarcoma of the breast has a worse prognosis.[9]

Pakistan is a low-income country, with limited resources and limited patient awareness, and most of the patients of PBS are treated by surgeons at small non-cancer centers and they are not referred to oncologists or cancer centers for adjuvant treatment or follow-up. In addition, many of the patients present with advanced diseases, where any treatment is not feasible, and thus, they are referred to general hospitals for the best supportive care. This is the reason there is a small number of patients in our study spanning over almost a quarter century. This study aims to describe clinicopathological characteristics and outcomes of primary breast sarcoma and the relevance of clinical and pathological characteristics with the outcomes in our locality. The primary objectives of this study are to determine PFS and OS and the secondary objective is the association of the clinical and pathological characteristics with PFS and OS.

Methodology

Study Overview: This was a retrospective study aiming to study PFS and OS and the association of clinical and pathological characteristics on PFS and OS of PBS.

Ethical approval: The data was collected and analyzed after getting approval from the institutional review board governing research procedures of our institute on the 29th of September 2021 (EX-29-09-21-01).

Study criteria: Patients of both genders aged 18 years and above, who were diagnosed with PBS and treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore from January 1995 to August 2021 were included in the study. Patients diagnosed to have cystosarcoma phyllodes and primary or secondary angiosarcoma of the breast were excluded.

Study procedure: Data was collected from the hospital information system (HIS) of our institute, using a keyword search for sarcoma and breast. Patients with cystosarcoma phyllodes were excluded because of the presence of epithelial components. Patients with primary or secondary angiosarcoma were also excluded. The diagnosis was based on the origin of the tumor from the stroma of the breast and morphology and immunohistochemistry consistent with sarcoma. Tumor grade was based on cellular pleomorphism, mitoses, and the necrotic component. A total of 34 patients were identified, out of which only 27 were

treated and subsequently followed up at our hospital. Clinical (patient and disease factors), treatment, and follow-up details were extracted from electronic patient records. Data was further stratified according to age, gender, tumor histology, tumor grade, TNM stage, treatment history of surgery, radiation and chemotherapy, duration of follow-up, and status on the last follow-up.

Statistical analysis: The data were tabulated and analyzed using SPSS for Microsoft Windows, version 21.0 (IBM Corp., Armonk, NY). Age was described as median and stratified in two groups; up to 40 years and above 40 years of age. Frequencies were tabulated as percentage for gender, clinical presentation, histopathology, disease status, tumor size, treatment with chemotherapy and intent, treatment with surgery, extent of surgery and margin status, treatment with radiotherapy and intent, recurrence, and site of recurrence. For outcome analysis, different diagnoses were unified to primary breast sarcoma as inspired by the classification of soft tissue neoplasms of extremities by WHO. Survival outcomes including PFS and OS were obtained by the Kaplan-Meyer curve and p values were calculated using the log-rank test.

Results

Patient Characteristics: The median age was 40 years, 59.30% (n=16) up to 40 years of age and 40.70% (n=11) above 40 years. Two out of 27 (7.40%) patients were male with a female-to-male ratio of 50:4.

Clinical characteristics: Out of 27, 81.5% (n=22) had localized, 7.40% (n=02) locally advanced and 11.10% (n=03) metastatic disease at presentation. At presentation tumor size was <5 cm for 44.40% (n=12), all but one patient with localized disease. Tumor size was >5 cm for 55.60% (n=15), one of them with locally advanced and 02 with distant metastatic disease at presentation. The median tumor size was 6.5 cm.

(Table 1).

Histopathology: This was a very heterogeneous population with 22.20% (n=06) patients of Fibrosarcoma, 18.50% (n=05) of Leiomyosarcoma, 14.80% (n=04) of High-Grade Sarcoma, 11.10% (n=03) of Spindle Cell Sarcoma, 7.40% (n=02) each of Myxofibrosarcoma and Metaplastic Spindle Cell Sarcoma. The rest consisted of Undifferentiated Liposarcoma, Undifferentiated spindle cell sarcoma, Rhabdomyosarcoma, Carcinosarcoma with osteoid differentiation, and Pleomorphic Liposarcoma (one of each, 3.40%, n=1). (Table 1).

Patient and disease characteristics		No(n)	Percentage (%)
Age	Up to 40 years	16	59.3%
	Above 40 years	11	40.7%
Gender	Female	25	92.6%
	Male	02	07.4%
Presentation	Painless lump	14	51.9%
	Painful lump	08	41.6%
	Post lumpectomy	05	18.5%
Laterality	Left	15	55.6%
	Right	12	44.4%
Histopathology	Fibrosarcoma	06	22.2%
	Leiomyosarcoma	05	18.5%
	High Grade Sarcoma	04	14.8%
	Spindle Cell Sarcoma	03	11.1%
	Myxofibrosarcoma	02	07.4%
	Metaplastic Spindle Cell Sarcoma	02	07.4%
	Undifferentiated Liposarcoma	01	03.4%
	Undifferentiated spindle cell sarcoma	01	03.4%
	Rhabdomyosarcoma	01	03.4%

	Carcinosarcoma with osteoid differentiation	01	03.4%
	Pleomorphic Liposarcoma	01	03.4%
Disease Status	Localized	22	81.5%
	Locally advanced	02	07.4%
	Metastatic	03	11.1%
Tumor Size	< 5cm	12	44.4%
	> 5cm	15	55.6%
Surgery	WLE	09	33.3%
	Mastectomy	12	44.4%
	Modified radicle mastectomy	06	22.2%
Margins	R0	09	33.3%
	R1	18	66.7%
Chemotherapy given	Yes	09	33.3%
	No	18	66.7%
Chemotherapy intent	Curative	07	25.9%
	Palliative	02	07.4%
	None	18	66.7%
Radiotherapy Given	Yes	24	88.9%
	No	03	11.1%
Radiotherapy intent	Curative	24	88.9%
	Palliative	00	11.1%
Recurrence	Yes	09	33.3%
	No	18	66.7%
Site of recurrence	Loco-regional	03	11.1%
	Distant	06	22.2%
	Loco-regional and distant	18	66.7%
Status	Alive	21	88.8%
	Dead	06	22.2%

Table 1: Numerical presentation of patient and disease characteristics and outcomes.

Treatment: All patients were treated with surgery; 33.30% (n=09) patients achieved R0 resection, 66.70% (n=18) patients achieved R1 resection. Majority (44.40%, n=12) of the patients underwent mastectomy, 33.30% (n=09) patients underwent wide local excision (WLE), and 22. 02% (n=06) modified radical mastectomy (MRM). R0 resection was achieved in 4 out of 6 patients who underwent MRM, 2 out of 09 patients who underwent WLE and 1 out of 12 patients who underwent mastectomy. One third (33.30%, n=09) of the patients received chemotherapy, 25.90% (n=07) on an adjuvant intent and 7.40% (n=02) on a palliative intent. The remaining 66.70% (n=18) did not receive chemotherapy. Majority of the patients (88.90%, n=24) received radiation therapy; intent was adjuvant in the entire cohort.

Outcomes

Survival: Median follow up was 25 months (range 2-162 months) with 77.70% (n=21) patients alive on last follow up visit and 22.22% (n=06) dead at a median interval of 18 months. Median OS was 23 months (Figure 1). Radiotherapy was the only factor that significantly affected OS (p-value 0.005). Younger age at presentation (up to 40 years) was associated with a trend towards a better OS (p-value 0.31). Tumor characteristics including disease status at presentation (disease localized to breast, p-value 0.09) and tumor size (<5 cm, p-value 0.1), were also associated with a trend towards better OS. Patients who did not need chemotherapy also showed a trend towards better OS (p-value 0.12)

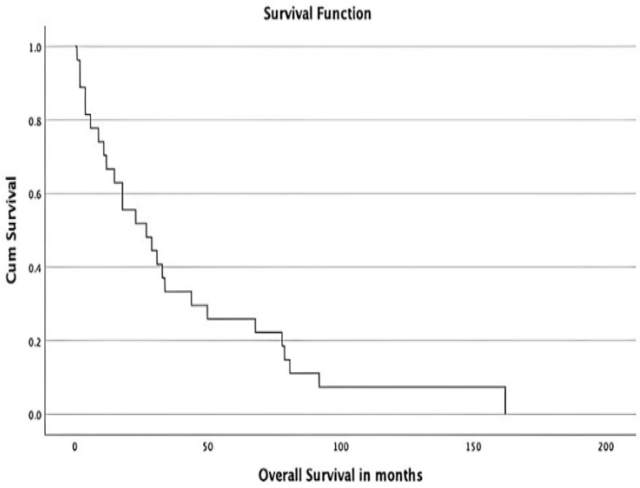

Figure 1: Overall survival in months (median overall survival: 23 months, Confidence interval (95%): 14.56-31.43 months)

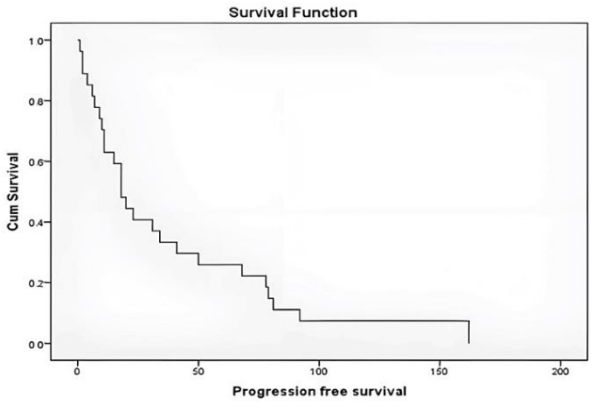

Figure 2: Progression-free survival in months (median progression-free survival: 18 months, confidence interval (95%): 11.6-24.3 months)

Median PFS was 18 months, with 74.01 % patients having no progression on last follow up (Figure 2)

Discussion

PBS is a rare cohort of mesenchymal tumors; a group of heterogeneous histopathological variants, it has equally heterogeneous clinical outcomes. Herein, we have reported 27 cases registered over 26 years with the biggest number of cases reported from our region so far. Though the classification of PBS is a matter of debate, this disease is sub-classified according to the principles of soft tissue sarcoma involving the trunk and extremities. Berg et al. first reported the term stromal sarcoma to include all soft tissue sarcomas except Cystosarcoma Phyllodes because of an element of the epithelial component in its histological origin.[10] Typically, PBS presents with a progressive, painless mass in one breast in patients in their 50s and 60s with a growth proportionately faster than that of epithelial carcinomas.[11]

Contrary to this, our patient population was younger with a median age at presentation of 40 years. The median tumor size in our report is 6.5 cm while that quoted in contemporary literature is 5 to 6 cm, larger than epithelial breast tumors. Sometimes a tumor may be mistaken for being benign [12] or even absent on Sono-mammography despite a large, clinically palpable mass.[13] A biopsy is the definitive diagnostic modality, and it is the procedure of choice due to its low complication rate and higher diagnostic yield.[14] Our report consists of a heterogeneous population with Fibrosarcoma, Leiomyosarcoma, and High-grade Sarcoma being the most common varieties while contemporary literature reports sarcoma of no special type as the most common tumor type.[7] All patients with breast sarcoma should undergo a computed tomography (CT) scan of the chest to look for metastatic disease because the lungs are the predominant site for metastases for primary breast sarcoma.[15]

Current treatment recommendations are based on small retrospective case reviews and data on soft tissue sarcoma of the trunk and extremities.[7] Surgery is the only potentially curative treatment modality for breast sarcoma with an adequate resection margin being the most important factor determining long-term survival.[7,16] Mastectomy and wide local excision with wide resection margins are considered to be comparable in outcomes with mastectomy preferred for patients with tumor size > 5 cm.[11,17,18] Cosmetic results have been documented to be better with a mastectomy for tumors larger than 5 cm and en-bloc, resection of the chest wall is required for deep-seated tumors.[19] Axillary lymph node dissection is discouraged because of the hematogenous route of dissemination of these sarcomas.[20] However, certain subtypes of sarcomas like Rhabdomyosarcoma, Angiosarcoma, Clear Cell Sarcoma, Synovial Sarcoma, and Epithelioid Sarcoma can disseminate via the lymphatic route. [21] In situations where there are suspected nodal metastases on clinical examination and imaging, an axillary lymph node biopsy must be carried out to rule out the involvement of axillary lymph nodes before going for surgery.[22] The majority of breast sarcomas are unifocal and require margin-negative surgery, irrespective of the extent of surgery, however standard of care for angiosarcoma of the breast is mastectomy.[23] There is controversy on adjuvant treatment to date, with the role of chemotherapy or external beam radiation (XRT) being tumor-type specific or ill-defined due to rarity.

A recent report suggests poor outcomes with chemotherapy probably because it was utilized as a "last-ditch" attempt at disease control in an advanced setting, radiotherapy on the contrary has been shown to improve outcomes, at least in terms of local disease control or palliation, as shown by this report. Our report also concurs with these findings.

As we have observed in our study MRM showed better results in achieving negative margins. Adjuvant chemotherapy had no significant OS benefit, while radiation therapy was associated with better survival as compared to chemotherapy. As it is a single-centered and retrospective study with a limited number of patients, it needs further large randomized prospective studies from our part of the world to shed light on classification, management, and outcomes of the disease.

Conclusion

This study of 27 cases over 26 years demonstrates the need for additional research in areas with scanty PBS data. Biopsy is the definitive diagnostic method, common subtypes include fibrosarcoma, leiomyosarcoma, and high-grade sarcoma. The primary curative treatment is surgery, notably modified radical mastectomy, emphasizing the necessity of clear resection margins for survival. The function of adjuvant therapy is unclear, as radiation improves local control, while chemotherapy offers very modest advantages. The results of the study support the preference for radiation therapy over chemotherapy. To improve our knowledge and management of PBS, larger, prospective, geographically focused studies are needed. Further, prospective studies with larger sample sizes are required to establish the role of patient, disease, and treatment-related factors affecting outcomes in our population.

Conflict of Interest: No conflict of interest. All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

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