Review

Malignant Mesenchymal Tumors of the Breast: Current Challenges and New Perspectives

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Review

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Abstract: Mesenchymal tumors of the breast constitute a rare and heterogeneous group of neo- plasms, representing only 0.5% to 1% of all breast tumors. Originating from the mesen- chymal tissues, these tumors include various histological subtypes. Malignant mesenchy- mal tumors are particularly aggressive characterized by a high likelihood of local recur- rence and a generally poor prognosis. The rarity of these tumors has impeded the devel- opment of comprehensive clinical studies leading to a lack of standardized diagnostic protocols and treatment guidelines. This review provides a thorough synthesis of the cur- rent knowledge on breast mesenchymal tumors with a specific focus on malignant vari- ants such as phyllodes tumors and breast sarcomas. It addresses the diagnostic challenges faced by clinicians, evaluates current therapeutic strategies and emphasizes the crucial role of surgical treatment. Additionally, it examines the evolving roles of chemotherapy and radiotherapy in enhancing patient outcomes.

Keywords: mesenchymal tumors; breast neoplasms; phyllodes tumors; breast sarcomas; therapeutic approaches; surgical treatment; chemotherapy; radiotherapy; prognosis; local recurrence

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1. Introduction

Breast cancer is primarily known for its epithelial origins, yet a rare and diverse group of tumors arises from mesenchymal tissues, representing only 0.5% to 1% of all breast tu- mors. These mesenchymal tumors are characterized by a wide array of histological sub- types, including benign and malignant forms. Among these, malignant mesenchymal tu- mors are particularly concerning due to their aggressive behavior, high rates of local re- currence and overall poor prognosis.

Malignant mesenchymal tumors of the breast, which include variants such as phyllodes tumors and primary breast sarcomas, present unique challenges in both diagnosis and treatment. Their rarity often leads to limited clinical experience, resulting in insufficient data to establish robust management protocols. Most available studies are retrospective and small-scale making it difficult to derive standardized diagnostic criteria or treatment guidelines. Consequently, clinicians are often faced with uncertainty in the clinical man- agement of these tumors leading to heterogeneous practices and outcomes.

The distinct biological behaviors of malignant mesenchymal tumors require a tailored approach to treatment that diverges from conventional breast cancer therapies. This review aims to bridge the gap in knowledge by synthesizing current insights into the diagnosis and management of these aggressive tumors. We will focus on the complex nature of malignant mesenchymal tumors, looking at the diagnostic challenges clinicians encounter and assessing current treatment options, especially the important role of surgery. Additionally, we will explore the evolving roles of chemotherapy and radiotherapy, assessing their impact on patient outcomes and identifying unmet challenges that require further investigation.

By improving our understanding of malignant mesenchymal tumors of the breast, this 76review aims to shed light on new insights and emphasize the urgent need for standardized treatment protocols, ultimately enhancing patient care in this difficult area of oncology.

2. Phyllodes Tumors

Phyllodes tumors (PT) of the breast are neoplasms composed of epithelial and stromal elements [4].

They were first described in 1938 by Johannes Müller as phyllodes cystosarcomas [5].

The term "phyllodes" refers to the "leaf-like" appearance these lesions exhibit on histopathological examination due to their stromal component, rich in spindle cells mixed with glandular elements lined by epithelial and myoepithelial cells [6].

They are characterized by rapid dimensional growth and often present as fibroadenomas on initial radiological examinations (ultrasound and mammography); cytological examination via fine needle aspiration and histological examination via core biopsy may sometimes be inadequate to distinguish a PTs from a fibroadenoma reliably [7].

Excisional biopsy is recommended for diagnostic purposes in cases of rapid growth of fibroadenoma-like lesions, which exhibit variable biological behavior. Based on histopathological characteristics, PTs are categorized as benign (60–75%), borderline (15–20%), or malignant (10–20%) [8].

Less aggressive forms behave similarly to fibroadenomas, though they have a greater likelihood of local recurrence (LR). Conversely, malignant tumors can metastasize to distant sites and may occasionally transform histologically into sarcomatous lesions.

According to the 2019 WHO histopathological classification, MPTs are characterized by increased stromal cellularity and atypia, with >10 mitoses per 10 high-power fields (10 HPF), exuberant stromal growth, and infiltrative margins[9].

National Comprehensive Cancer Network (NCCN) guidelines recommend radical excision of the lesion with ≥1 cm negative margins. Axillary lymph node metastases are rare; therefore, sentinel lymph node biopsy and/or axillary lymphadenectomy are not indicated unless the lymph nodes are suspected at clinical staging [10].

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2.1. EPIDEMIOLOGY AND RISK FACTORS

PTs represent approximately 0.3–0.9% of all breast neoplasms. Among all PTs, malignant ones constitute 10-20% of cases, with an annual incidence of 2.1 cases per million women [11].

Due to the rarity of these neoplasms, epidemiological data are limited. The median age of onset is 45 years (range 10-82 years) [12].

High-grade malignant forms are more common in patients older than the median age [13].

In men, PTs are generally associated with gynecomastia [9].

No etiological or risk factors have been described for the development of these neoplasms except for Li-Fraumeni syndrome, a rare autosomal dominant condition characterized by the development of multiple tumor types [14].

2.2. DIAGNOSIS

PTs are a complex type of breast lesions that pose challenges for diagnosis

They often mimic fibroadenomas radiologically [6,15–17].

On mammography, they appear as a well-circumscribed, hyperdense or isodense, round- or oval-shaped mass [6,15,16] with rapid growth and large dimensions.

Ultrasound may show hypoechoic, heterogeneous, or complex cystic and solid echo patterns [16].

Features such as lobulated shape, heterogeneous internal echo pattern and absence of microcalcification are significant sonographic features used to favor PTs over fibroadenomas [6,15].

Specific sonographic features, such as liquefaction and a heterogeneous inner echo, may indicate a higher risk of MPT of the breast [18] .

On Magnetic Resonance Imaging (MRI), PTs appear as oval, well-circumscribed, isointense on T1-weighted images and heterogeneously hyperintense on T2-weighted images [15] due to the presence of cysts, necrosis, or septations, which may be related to the tumor's rapid growth .

Some MRI findings can help determine the risk of malignancy. Non-circumscribed margins, cystic components, irregular cyst walls, peritumoral edema, low signal intensity on T2-weighted images, and low apparent diffusion coefficient (ADC) are correlated to higher histologic grade, presence of stromal hypercellularity, hemorrhagic infarction, and necrosis on histopathology [16].

2.3. PATHOLOGY ASSESSMENT

PTs are rare biphasic fibroepithelial neoplasms of the breast, accounting for 0.3% to 1% of all primary breast tumors. Their biological behavior can vary significantly, ranging from benign to malignant, with a notable tendency for LR and, in malignant cases, the potential for metastasis. Approximately 10% to 15% of PTs are classified as malignant. The World Health Organization categorizes PTs as benign, borderline, or malignant based on factors such as stromal cellularity, stromal overgrowth, nuclear atypia, mitotic activity, tumor margins, and the presence of malignant heterologous elements [19].

Benign PTs generally have well-defined borders with slight protrusions into surrounding tissue and a bland, uniform stroma that may resemble an intracanalicular fibroadenoma. Key diagnostic features of benign PTs include a cellular stroma with a subepithelial distribution, a low mitotic count of fewer than 5 mitoses per 10 high-power fields, and a varied stroma that can include hyalinized or myxoid areas.

Borderline tumors, according to the WHO classification, have intermediate characteristics, exhibiting microscopic invasion at the tumor margins along with moderate cellularity and pleomorphism. While borderline tumors may recur locally, they rarely metastasize [2].

MPTs are characterized by significant nuclear pleomorphism, diffuse stromal cellularity, stromal overgrowth (where the epithelial component is absent in at least one low-power field), the heightened mitotic activity of more than 10 mitoses per 10 HPFs, and infiltrative borders. Malignant heterologous elements indicate malignancy, even if other features are absent.

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Differentiating MPTs from pure or metastatic sarcomas can be quite challenging. There is a notable risk of distant metastasis—reportedly up to 16%—especially to the lungs and bones, while involvement of the axillary lymph nodes is rare

Histological factors associated with distant metastases include tumor size over 7 cm, infiltrative borders, marked stromal overgrowth, high stromal cellularity, >5 mitoses per 10 HPFs, and necrosis. MPTs are often resistant to chemotherapy, and the prognosis for metastatic cases is poor [13,20] .

The immunohistochemical analysis indicates that benign PTs display low positivity for p53, Ki-67, CD117, EGFR, p16, and VEGF, with an increasing positivity in MPTs. Other Authors have defined stroma-rich PT with a bland appearance as typical CD34 positive, while high-grade MPT usually show loss or lesser grade of CD34 staining [21].

The majority of MPTs however show some degree of CD34 positivity. Genetic studies have shown that benign and borderline PTs exhibit minimal genetic alterations. In contrast, MPTs frequently display specific genetic changes, such as gains on chromosome 1q, losses on chromosome 13q, and deletions on chromosome 9p21, which are associated with the loss of p16INK4A expression. Additionally, mutations in genes such as TP53, RB1, NF1, PIK3CA, and ERBB4 have been found in MPTs, suggesting potential therapeutic targets. Additionally, mutations in genes such as TP53, RB1, NF1, PIK3CA, and ERBB4 have been found in MPTs, suggesting potential therapeutic targets.

In conclusion, accurate histological assessment of PTs, along with immunohistochemical and genetic analyses, helps differentiate between benign, borderline, and MPT. This comprehensive approach guides appropriate clinical intervention and contributes to improved patient outcomes [7,8,21–23].

2.4. SURGICAL TREATMENT

Surgical excision is the recommended treatment for operable MPTs [6,15,16,24–26].

As for other breast tumors, the choice of surgery should take into account both oncological and cosmetic outcomes [2,6,15,24].

If an adequate margin and a good cosmetic outcome can be obtained with a wide excision, breast-conserving surgery should be the first choice of treatment.

NCCN guidelines recommend at least a 1 cm excision margins if preoperative assessments suggest the presence of a borderline or MPT, while wide margins are not required for excision of benign PTs [10,16,17,26,27] .

However, the evidence of a closer margin at final pathology should be discussed in a multidisciplinary context, as according to NCCN guidelines, mastectomy is not an absolute indication in these cases [6,10,28–33].

Mastectomy is recommended when the preoperative surgical assessment estimates the inability to obtain adequate margins without causing cosmetic deformities that would be unacceptable to the patient [10,13,15,16,26,34,35] While tumor size is not associated with LR [7,36], most studies agree that patients with evidence of narrow surgical margins at final pathology have higher LR rates than those with negative margins [6,21,31,32,37–40].

These include a systematic review and meta-analyses of 9234 individual cases (18% of these patients having MPT where a positive surgical margin was significantly associated with a higher LR risk (OR 6.85; 95% CI 1.58–29.64) [24,27].

However, a meta-analysis of 4 studies including 162 patients demonstrated no differences in LR between ≥ 1 cm and < 1 cm margins [29,41].

In current NCCN guidelines, there are no clinical scenarios in which axillary staging is recommended [10] , so there is no indication to perform axillary surgery[10,15,16,20,42–44].

A palpable lymphadenopathy is noted in 10%-15% of patients presenting with MPT but is usually reactive to tumor necrosis and infected or ulcerated skin lesions, with <1% of lymph nodes being pathologically involved [45].

 doi:10.20944/preprints202501.2276.v1

2.5. ADJUVANT RADIOTHERAPY

There is no strong consensus on whether RT improves overall survival (OS) or disease-free survival (DFS) in patients with MPT, particularly those with low-grade or completely excised tumors.

Current guidelines from the NCCN and the European Society for Medical Oncology (ESMO) suggest that radiotherapy may be considered for patients with MPT that have high-risk features, such as positive surgical margins, tumor size greater than 5 cm, or high-grade pathology [10,46].

Conflicting evidence further complicates the utility of adjuvant RT in MPTs. Retrospective studies have suggested that while RT may reduce LR rates, it does not appear to confer a significant survival benefit [47].

These findings underscore the role of margin status in the decision to administer RT, suggesting that it may primarily serve as a tool for local control rather than improving long-term survival outcomes.

Pooled analyses and large database studies are essential for accurately assessing the role of therapies in rare diseases, where survival outcomes are challenging to evaluate among a heterogeneous population [48].

The primary large database analyses regarding the role of radiotherapy in malignant tumors are derived from studies utilizing the Surveillance, Epidemiology, and End Results (SEER) database. The first analysis, published in 2006, examined a total of 821 patients and found that only 76 (9%) received adjuvant radiotherapy. The administration of RT has become more common since the year 2000 [20].

A recent update of SEER analysis published in 2024, reported results of a larger cohort of 2261 patients, who were diagnosed and treated in the last two decades.

In this larger cohort, at least 20% of patients (20,12%) underwent radiotherapy. Results showed that in terms of OS and breast cancer-specific survival, RT did not have a significant impact [49].

In conclusion, while adjuvant radiotherapy may be beneficial for certain high-risk patients with MPT—particularly those with positive margins or high-grade histology—the evidence supporting its universal application remains limited. Prospective trials and long-term follow-up studies are needed to refine the guidelines and better delineate which subgroups of patients will benefit most from RT after excision. Until then, treatment decisions should be personalized, carefully considering tumor biology, surgical outcomes, and patient preferences.

2.6. SYSTEMIC TREATMENT

The role of chemotherapy for MPT is controversial and should only be considered after consultation with an expert center.

Many investigators have confirmed the low efficacy of monochemotherapy (Cyclophosphamide, Ifosfamide, Doxorubicin). Currently, treatments typically involve doxorubicin and ifosfamide, and are similar to those for soft tissue sarcoma (STS), as this combination showed the most activity and greatest impact on survival [44].

Neoadjuvant therapy appears to hold a similar significance, yet some recent case reports indicate that aggressive treatment with alkylating agents should be pursued when feasible[50] .

Approximately 20% of patients with MPT develop metastases. Generally, research on systemic therapy is limited to small case reports and series that often highlight positive outcomes. However, in practice, patients appear to receive less benefit from chemotherapy, experiencing relatively short durations of response compared to those with more common sarcoma histologies [51].

Given the rarity of the disease, new therapeutic possibilities are yet to be explored in phase II/III trials. Again, a case report shows the potential of a small molecule targeted to VEGFR2 like apatinib. Specifically for this case, the patient had undergone surgery at the primary site and at lung metastases and subsequent chemoradiotherapy with paclitaxel. At disease progression, apatinib was able to reduce the lung mass and increase the patient's survival by 8 months, until she was lost to follow-up. Obviously, further cohort and prospective trials are needed to identify a subset of patients suitable for apatinib in the clinical treatment of PTs [52].

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3. Primary Breast Sarcoma

Breast sarcomas comprise a heterogeneous group of non-epithelial neoplasms. They are rare tumors, accounting for <1% of breast neoplasms and <5% of soft tissue sarcomas. The annual incidence is approximately 4.5 cases per million[53].

They originate from the connective tissue of the breast and can be classified as primary and secondary. Clinically, they mostly present as unilateral lesions with ill-defined margins and fixation to underlying planes, often rapidly growing [3].

The average size at diagnosis is larger compared to epithelial tumors, with a mean diameter of about 3 cm at the time of pathological analysis, although lesions up to 40 cm in diameter have been described [54].

The overlying skin and the nipple-areola complex are rarely infiltrated, except for cases of angiosarcoma where thickening, erythema, and/or red-violet discoloration of the skin overlying the lesion may occur [55].

PBS, like sarcomas in other body sites, are poorly responsive to chemo- and radiotherapeutic treatments, although the role of the latter is still debated; currently, the main treatment remains radical surgical excision [56,57].

Due to the rarity of these neoplasms, current knowledge on the subject is based on case reports and retrospective studies from limited samples [58].

3.1. EPIDEMIOLOGY AND RISK FACTORS

Malignant breast sarcomas predominantly affect women, with a peak incidence in the fifth to sixth decades of life, although they can occur at any age [59].

The most common subtype is angiosarcoma, which accounts for approximately 30-50% of breast sarcomas [60,61].

In some patients, genetic factors (e.g., Li-Fraumeni syndrome or Neurofibromatosis type 1) and environmental factors (exposure to radiation, vinyl chloride, alkylating agents, immunosuppressive agents) may be implicated [54], while chronic lymphedema after mastectomy and axillary lymph node dissection is a reported risk factor for the onset of lymphangiosarcoma (Stewart-Treves syndrome) [62].

Unlike carcinomas, breast sarcomas are less influenced by hormonal factors like estrogen, although some subtypes may express hormone receptors.

3.2. PATHOLOGIC ASSESMENT

PBS are histologically heterogeneous: an accurate estimate of subtype distribution is hindered not only by the rarity of these neoplasms but also by the different modalities with which they are classified [63].

Currently, the classification referred to is that established by the WHO in 2020 [3].

In case series including all subtypes of PBS, angiosarcoma and undifferentiated pleomorphic sarcoma (previously known as malignant fibrous histiocytoma) constitute the main variants[64].

Subcategories of undifferentiated/not otherwise specified sarcomas include pleomorphic sarcoma, round cell sarcoma, and spindle cell sarcoma[65].

In a Canadian national case series of 991 patients with PBS - excluding angiosarcoma - the distribution of histological subtypes was as follows: unspecified sarcomas 26%, spindle cell sarcoma 14%, leiomyosarcoma (LMS) 12%, giant cell sarcoma 10%, stromal sarcoma 6%, malignant fibrous histiocytoma 6%, myxoid fibrosarcoma 4%, dermatofibrosarcoma protuberans 3%, fibrosarcoma 3%, undifferentiated sarcoma 3%, liposarcoma (LPS) 3%, pleomorphic liposarcoma 2%, others 8%[66].

Grading represents an essential prognostic factor in sarcomas, including those of mammary origin: the elements considered for grading are the extent of tissue differentiation, mitotic count, presence/absence of necrosis, cellularity, and pleomorphism; angiosarcoma is an exception for which the literature results are conflicting [67].

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Primary breast angiosarcoma, although relatively rare, is the most common PBS. It may develop spontaneously but is more usually seen in patients who received radiotherapy to the affected breast. Angiosarcomas are rare aggressive malignant tumors derived from endothelial cells and histologically they show poorly formed irregular vascular channels infiltrating the stroma with pleomorphic hyperchromatic endothelial cells exhibiting high mitotic activity. These tumors often have hematoma-like areas due to extensive vascular proliferation and infiltrative growth without well-defined borders. Additional features include the presence of epithelioid cells in some variants and frequent hemorrhage. Angiosarcomas must be differentiated from benign vascular lesions like hemangiomas which show well-formed vascular channels lined by regular endothelial cells and lack significant atypia and mitotic activity. Tumour cells are positive with a wide range of endothelial markers such as CD31, CD34, D2-40, and ERG [68].

In postradiation angiosarcoma a strong and diffuse nuclear positivity (14), with a loss or reduced expression of H3K27me3 can be observed [69,70].

Pseudosarcomatous lesions such as nodular fasciitis and proliferative myositis can mimic sarcomas histologically but are benign reactive processes. Nodular fasciitis presents with loose myxoid stroma plump spindle cells with abundant cytoplasm often in a tissue culture-like growth pattern and common mitotic figures without atypical forms. Proliferative myositis is characterized by ganglion-like giant cells and a more prominent fascicular growth pattern.

Both entities show rapid growth and high cellularity but lack the atypia and infiltrative behavior of true sarcomas. The differential diagnosis includes low-grade sarcomas like low-grade myxofibrosarcoma which shows more irregular cellular shapes and infiltrative growth[71–73].

Metastases to the breast may mimic other high-grade spindle cell breast lesions. Tumours that metastasize to the breast, showing spindle cell morphology, include melanoma, LMS and sarcomatoid renal cell carcinoma. Careful morphology evaluation, the bilaterality of the neoplastic involvement and clinical history together withan appropriate and focused immunohistochemical panel helps to clarify the diagnosis.

Finally, breast spindle cell lesions represent a broad spectrum of morphologically and clinically overlapping entities, ranging from benign/reactive processes to aggressive malignant neoplasias with different management strategies.

The diagnosis of mesenchymal lesions in the breast relies on a combination of histopathological examination, immunohistochemical staining and molecular studies where necessary Immunohistochemical markers are critical in differentiating between lesions for instance CD34 is useful in distinguishing myofibroblastomas and spindle cell lipomas while cytokeratins can help identify metaplastic carcinoma in the differential diagnosis of PTs. Molecular studies such as fluorescence in situ hybridization FISH or polymerase chain reaction PCR can be employed in challenging cases to detect specific genetic alterations like MDM2 amplification in well-differentiated LPS.

Common challenges include histological overlap between benign and malignant lesions heterogeneity within the same tumor especially in PTs and LPSs and ensuring sufficient tissue sampling for accurate diagnosis Understanding these histological features is essential for pathologists and clinicians as accurate histological assessment guides clinical management ranging from conservative follow-up for benign lesions to aggressive surgical and adjuvant therapy for malignant mesenchymal tumors Continued research and advances in histopathological techniques are critical for improving diagnostic accuracy and patient outcomes.

3.2. DIAGNOSIS

The radiological diagnosis of breast sarcomas utilizes the same modalities as those used for breast epithelial tumors.

Although studies concerning imaging findings in breast sarcomas are limited due to their low incidence, it seems that they have some characteristic radiological findings [54,74].

 doi:10.20944/preprints202501.2276.v1

Breast sarcomas on mammography often appear as a noncalcified hyperdense mass, with indistinct or circumscribed margins borders [54,74,75], findings that may resemble benign fibroadenomas[26,76].

The lack of calcifications and the oval shape of these lesions distinguish them from epithelial tumors; however, these same characteristics are also described in PTs [54].

Furthermore, mammography may appear normal in the presence of a breast sarcomatous lesion[76].

Ultrasound sonography is not specific for radiological diagnosis of breast sarcomas.

Usually they appear as irregular and hyperechoic lesions with no shadowing[74–76], although hypoechoic lesions with indistinctive borders and a posterior acoustic shadow have been described [54].

Contrast-enhanced MRI with contrast is the imaging modality of choice because it allows the identification of suspicious malignant changes (irregularly bordered oval masses with T2 hyperintensity and heterogeneous rapid contrast enhancement and washout)[26,54,75,76].

MRI also allows a proper assessment of the local extension of the disease (showing the extent of involvement of the surrounding skin, fascia, and muscular structures), which are crucial for planning surgery and subsequent radiotherapy[26].

Core biopsy should be performed with needles 16 G or bigger [54],and immunohistochemical analysis of specific cytokeratins should be performed[26,74].

The use of fine-needle aspiration is not recommended because histologic subtype and grade cannot be accurately determined and also for the association with false-negative results[26,74].

All patients with a diagnosis of breast sarcoma should be assessed for distant disease.

Computed tomography (CT) of the chest, abdomen and pelvis, together with a bone scan should be performed. Lungs are the most common site of metastases globally, while angiosarcoma has a propensity for secondary spread to the liver and bone[26].

The role of positron emission tomography (PET) scans remains unclear in the assessment of breast sarcomas[26,54].

3.3. SURGICAL TREATMENT

It is strongly reccomended that breast sarcomas be referred to a sarcoma referral centre to increase OS by investigating clinicopathological features and taking a multidisciplinary approach [26,74].

There is widespread acceptance that surgical resection should be the first modality of treatment for primitive breast sarcoma[54,56,75].

However, the best surgical treatment is still debated, and should be tailored on the individual patient.

The goal of surgery is local control , and mastectomy has been considered the gold standard for many years[26,54,76].

The choice between mastectomy and breast conservative surgery is based on the possibility to obtain negative margins at final histology[26,54,76,77]: in fact, tumor size and excision margin are the two factors that mostly impact survival and recurrence[32,57,59,78–80].

In a study by Wang et al, the 5-year DFS and OS rates for size of tumors <5 cm, 5–10 cm and >10 cm, were 75.0% and 88.9%, 70.8% and 75.0%, and 37.5% and 37.5%, respectively [81].

It is strongly recommended to evaluate the tumor/breast size ratio before surgery to properly perform correct planning of the surgical strategy [56].

While some studies advocate for mastectomy, showing increased OS over conservative surgery, others have demonstrated no significant advantage [63,79–85].

For smaller localized breast sarcomas most authors recommend wide excision with a margin greater than 1 cm [75,76,78].

In the case of angiosarcomas, it is recommended to obtain at least a 3 cm clear margin during surgery since these lesions often have an infiltrative cutaneous disease that extends well beyond the visible tumor [75,76,78].

 doi:10.20944/preprints202501.2276.v1

In this set of patients, mastectomy with delayed reconstruction remains the most prudent surgical approach[54,76].

Because the aesthetic outcome of breast conserving surgery when approaching large resections is often poor, some authors suggest oncoplastic reconstruction with parenchymal rearrangement or reconstruction with local flap as a viable option [76,86].

Sentinel lymph node biopsy is not routinely performed in patients with breast sarcomas, as nodal dissemination is very rare[54,75,76,87].

In a study by Fong et al involving 1772 cases of STS, the rate of nodal metastasis was only 2.6%, while in a study based on the SEER and focused on breast sarcomas, 129 out of 333 patients underwent lymphadenectomy and only six patients (4.7%) were found to have nodal metastases[88,89].

Radical dissection of axillary lymph nodes is appropriate in the presence of histologically proven isolated nodal disease or where the purpose of surgery is local control and symptom relief[54,76].

3.4. ADJUVANT RADIOTHERAPY

Breast sarcomas are rare malignant tumors for which treatment protocols are not well-established.

Due to its rare incidence (<1% of all breast cancer diagnosis), univocal indication for therapies are still under investigation. Adjuvant RT is recommended after a positive margin resection, in tumors larger than 5 cm and in any high-grade sarcoma, because of the high risk of LR[90].

PBS are sometimes associated with p53 mutation and Li Fraumeni syndrome, therefore testing for these pathogenic variants should occur before administering adjuvant RT.

3.5. SYSTEMIC TREATMENT

3.5.1. First-Line Treatments

Even though surgery represents the best approach to breast sarcomas, a certain percentage of these tumors appear locally advanced or unresectable at the time of diagnosis, either because of chest wall invasion or, less commonly, the presence of synchronous distant metastases.

However, the rarity of such diseases accounts for the lack of data on the use of chemotherapy and RT in both the neoadjuvant/adjuvant setting and the metastatic one, dictating decisions based on multidisciplinary and case-specific discussions[91].

PBS have the same clinical history and prognostic factors as sarcomas arising at other sites. Therefore, it is legitimate to use similar treatment strategies[55].

However, as for STS arising at the extremities, the lack of data makes the role of chemotherapy extremely controversial; therefore, decisions must always be taken on a case-by-case basis and in a multidisciplinary setting[51].

Moreover, the response to chemotherapy is utterly variable. Thus, treatment is selected based on each histotype sensitivity[75].

Chemotherapy is especially taken into consideration in treating high-grade lesions or masses with a diameter larger than 5 cm[92].

For the tumors that present distant metastases at the moment of diagnosis, although no specific prospective phase 3 trial exists, chemotherapy is now the gold standard approach[93].

Adjuvant chemotherapy, even if associated with a significant reduction of LR, doesn't improve OS in young patients or in any pathology subgroup. Poor quality of initial surgery is the most important prognostic and predictive factor for the utility of adjuvant chemotherapy in STS. Thus, adjuvant chemotherapy for STS remains an investigational procedure and is not a routine standard of care[94,95].

At the state of the art, for the pbs the standard pre- and post-operative therapy combines anthracyclines (mostly epirubicin) and ifosfamide[96].

Given the high heterogeneity of STS, a tailored therapeutic choice seemed to be best approach. However, in a population of patients with localized high-risk STS, histology-tailored neoadjuvant

 doi:10.20944/preprints202501.2276.v1

therapy was not associated with a better DFS or OS, suggesting that the association of anthracyclines and ifosfamide should remain the regimen to choose whenever neoadjuvant chemotherapy is used in such patients[97].

Specifically, doxorubicin is the core of first-line treatment, and only a few recent studies assess whether it should be administered as a single agent or in combination.

Within the randomized phase III European Organisation for Research and Treatment of Cancer (EORTC) 62012 trial, a total of 455 locally advanced or metastatic, grade 2 or 3 STS patients were randomly assigned to receive either single-agent doxorubicin (75 mg/m2) or doxorubicin (75 mg/m2) with ifosfamide (10 g/m2 over 4 days) with growth factor support. Patients were treated every 3 weeks for a maximum of 6 cycles or until progression. At a median follow-up of 56 months, the OS difference did not achieve statistical significance (14.3 months with the combination and 12.8 months with doxorubicin alone. HR =0.83; P=0.076). Median progression free survival (PFS), however, was 7.4 months with the combination and 4.6 months with doxorubicin alone, for a 26% reduction in risk that was statistically significant (HR =0.74; P=0.003). The objective response rate (ORR) was 26.5% with the combination and 13.6% with doxorubicin. Despite colony-stimulating factor support, the most common grade 3 and 4 adverse events were all more common in the combination than in the doxorubicin alone group: leucopenia (43% vs. 18%), neutropenia (42% vs. 37%), febrile neutropenia (46% vs. 13%), anemia (35% vs. 5%), and thrombocytopenia (33% vs. <1%). The lack of OS advantage but with more toxicities for the combination regimen do not support its routine use in the setting of advanced incurable disease unless there is an immediate need to decrease tumor bulk, improve symptoms or translate into resection[98].

Combinations are more frequently used in specific sarcoma subgroups. A retrospective analysis showed that the association of doxorubicin and dacarbazine has a favorable activity in both ORR and PFS in patients with advanced LMS [99].

Furthermore, the LMS-04 randomised phase III trial - which enrolled 150 patients with LMS in a superiority-aimed study for a first-line association of doxorubicin and trabectedin versus doxorubicin alone - showed a significantly longer median PFS in the investigational arm versus the doxorubicin alone group (12,2 months vs 6,2 months). Nevertheless, the drug combination was associated with a higher, yet manageable, grade of toxicity. The most common grade 3-4 adverse events were neutropenia (13% in the doxorubicin alone group vs 80% in the doxorubicin plus trabectedin group), anaemia (5% vs 31%), thrombocytopenia (0% vs 47%), and febrile neutropenia (9% vs 28%). 12% patients in the doxorubicin alone group and 20% patients in the doxorubicin plus trabectedin group has serious adverse events. Considering the significant increase in PFS, doxorubicin plus trabectedin can still be considered as a first-line treatment of metastatic LMS [100].

3.5.2. New cytotoxic drugs and strategy

Due to doxorubicin's significant toxicities, several types of anthracyclines have been recently tested in first-line treatment for STS. Aldoxorubicin is a novel albumin-binding prodrug of doxorubicin. It contains a carboxylic hydrazone and covalently binds to albumin in the blood until reaching tumour tissue, where the acidic microenvironment breaks the covalent bond with albumin and releases doxorubicin. This allows for greater doses (3.5–4 times the standard doxorubicin dose) of doxorubicin to be administered while reducing its side effects, especially concerning cardiac function[101].

A phase IIb clinical trial randomised 140 patients (ratio 2:1) to receive single agent aldoxorubicin (350 mg/m2; dose equivalent to doxorubicin 260 mg/m2) or doxorubicin (75 mg/m2), administered once every 3 weeks for up to 6 cycles. Aldoxorubicin showed superior efficacy in terms of the primary endpoint, as PFS was significantly increased (5.6 vs 2.7 months; P = 0.02) as was the rate of 6-month PFS (46% and 23%; P = 0.02). Overall tumor response rate was also higher in the interventional arm compared to the control group (25% [20 patients, all partial response] vs 0%) and there were no unexpected events, as adverse events were more frequent with aldoxorubicin but mostly manageable. Specifically, grade 3 or 4 neutropenia was more frequent in the interventional arm (29% vs 12%), but not grade 3 or 4 febrile neutropenia (14% vs 18%). Most importantly, no acute

 doi:10.20944/preprints202501.2276.v1

cardiotoxicity was observed in either arm, although left ventricular ejection fraction lower than 50% occurred in 3 of 40 patients receiving doxorubicin[102].

As sarcomas can be therapy-related or recurrent, and considering the impact of a doxorubicin-based treatment on cardiac function, aldoxorubicin is currently a subject of interest in relapsing or progressing tumours. In a pivotal international, multicentre, Phase III trial evaluating PFS as the primary endpoint, 433 patients with relapsed or refractory STS were randomly assigned to receive aldoxorubicin 350 mg/m2 (260 mg/m2 doxorubicin equivalent) every 3 weeks or investigator's choice of treatment including dacarbazine, doxorubicin, pazopanib, ifosfamide, and gemcitabine/docetaxel with GCSF support. Tumour subtypes included LMS (42.2%), LPS (12.8%), synovial sarcoma (9.6%), and other sarcomas (34.9%).

Approximately two-thirds of the patients received prior doxorubicin in both experimental and control arms. The mean cumulative doxorubicin equivalent dose of aldoxorubicin administered was 1,359.8 mg/m2 (range 260–10,920). Aldoxorubicin demonstrated superior median PFS over investigator's choice in patients with LMS or LPS, though there was no difference in the overall cohort. Secondary endpoints included ORR, disease control rate (DCR), OS, and safety.

Although the ORR was twice as high in the doxorubicin arm (8.3 vs. 4.2%, P=0.1106), there was no significant difference in median OS (12.88 months vs. 12.16 months, P=0.8555). There was a trend toward significantly improved ORR in the L-sarcomas group, which also achieved statistically significant DCR (41.7 vs 27.0%, P=0.0161). Globally, there were more high-grade adverse events in the doxorubicin group; however, the incidence of cardiotoxicity – defined by a decrease of 20% or more in left ventricular ejection fraction (LVEF) – was lower (3.8 vs. 8.5%).

Thus, aldoxorubicin represents a viable alternative compared to the standard of care in patients with relapsed or refractory metastatic STS[103].

Within the same molecule class, amrubicin - a third-generation synthetic 9-amino-anthracycline that inhibits topoisomerase II - has been suggested to be less noxious than doxorubicin, particularly regarding cardiac toxicity. Despite phase III trials yet to be conducted on the subject, a phase II multicenter single-arm study was executed to evaluate the efficacy and tolerability of amrubicin in advanced STS. A total of 24 patients received amrubicin (40 mg/m2 for 3 days in 21-day cycles) as a first-line therapy. The best ORR was 13%, the median PFS was 5.8 months, and the median OS was 26 months. Notably, grade 3 to 4 AEs included febrile neutropenia and anemia in 21% of treated patients, but there was no significant cardiac toxicity up to a cumulative dose of 4,800 mg/m2. One patient with metastatic myxoid-liposarcoma (MLPS) with the TLS-CHOP translocation had a durable response, suggesting that further investigation is warranted in this subtype[104].

On the other hand, newer fosfamides, such as evefosfamide and palifosfamide, have yet to show potential. Both the SARC021 and the PICASSO phase III trials compare the combination of either doxorubicin and evofosfamide or palifosfamide respectively to doxorubicin alone. The combination arm registered higher RR but more toxicity in both cases[105,106].

Another frequently used combination to treat metastatic STS is gemcitabine plus docetaxel, considering the superior PFS and OS compared to gemcitabine alone[107].

The GeDDiS trial was a phase III, randomized, multicenter study that compared the combination of gemcitabine and docetaxel with doxorubicin in patients with previously untreated advanced unresectable or metastatic STS. A total of 257 patients were enrolled to investigate the primary endpoint of 24-week PFS, which was identical between the investigational arm (675 mg/m2 of gemcitabine on days 1 and 8 plus 75 mg/m2 of docetaxel on day 8 every 21 days) and the control arm (75 mg/m2 doxorubicin). However, the investigational arm suffered higher toxicity (83.3% vs. 94.6% dose intensity reductions, 55.5% vs. 45.7% dose delays, and 10.2% vs. 0.8% withdrawals due to unacceptable toxicity in the investigational arm and in the control arm, respectively). Furthermore, no difference in efficacy was highlighted in specific histology subgroups, such as LMS [108].

Paclitaxel is an interesting molecule, as it has been proven to have sustained activity in angiosarcomas, which represents a rare yet extremely important histotype among breast sarcomas. Most breast angiosarcomas are secondary to previous RT executed on the same area. In the phase II ANGIOTAX study conducted by a French group, 30 patients were administered paclitaxel

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intravenously as a 60-minute infusion at a dose of 80 mg/m2 on days 1, 8, and 15 of a 4-week cycle. The primary endpoint was the non-progression rate after two cycles. PFS after 2 and 4 months were 74% and 45%, respectively; the median time to progression was 4 months, and the median OS was 8 months. Additionally, naïve patients and pretreated patients has a comparable PFS rate (77% vs 71%). Toxicity was manageable. In conclusion, even considering the limitations of this study, weekly paclitaxel seems to have the potential to be further investigated in future trials[109].

3.5.3. Second-line treatments

Second-line treatments involve molecules with moderate activities compared to doxorubicin and ifosfamide, one of the oldest ever discovered being dacarbazine. In 1987, Borden et al. conducted a randomized trial comparing single-agent doxorubicin and doxorubicin plus dacarbazine, which showed that dacarbazine improved the overall response frequency of doxorubicin from 16%-18% (depending on the schedule of administration) to 30%. This was particularly highlighted in LMSs. However, the toxicity experimented in the combination group was far greater, thus making the results controversial[110].

Dacarbazine's role as a single-agent therapy in a second-line setting is seemingly as old, as in 1991, Buesa et al. demonstrated that a RR of 18% could be achieved in previously treated patients with advanced STS in a phase II study involving 50 patients (44 fully analyzed). 42 of these patients had been exposed to doxorubicin and ifosfamide, and the most represented histologic subtype was LMS (12 patients). However, the duration of response was concise at only 8 weeks. Nonetheless, these data suggest the possible employment of dacarbazine in combination regimens, for instance, in association with gemcitabine[111].

In fact, this combination has exhibited efficacy in terms of PFS and OS, albeit without robust confirmation from larger clinical trials[112].

A real-world data analysis conducted as a retrospective study in a single institution involving 95 patients pointed to a benefit in PFS of 3.5 months and an OS of 14.2 months. Patients with translocated histotypes had better PFS, while those with platelet–lymphocyte ratios (PLRs) surpassing a specific threshold or lower albumin levels had poorer OS. The most represented histotype was again LMS (27.4%) [113].

Among second-line treatments, molecules such as eribulin and trabectedin are mostly targeted at specific subtypes. Eribulin—a microtubule growth inhibitor—is currently approved for use in pretreated patients with recurrent sarcomas. The median OS for eribulin and dacarbazine was 13.5 and 11.5 months, respectively (P=0.017). The OS was significantly improved (15.6 vs. 8.4 months) in LPS cohorts, while no sense was seen in LMS.

Trabectedin is another drug with proven activity for STS that has been investigated as a second-line choice[114].

A phase 3, randomized, multi-centre study compared trabectedin (administered to 345 patients) and dacarbazine (173 patients) in locally advanced, unresectable, or metastatic LMS and LPS. All patients had to have received prior therapy with an anthracycline and at least one additional systemic regimen. In the trabectedin arm, trabectedin (1.5 mg/m2) was administered on day 1 of every 3 weeks, whereas in the dacarbazine arm, dacarbazine (1 g/m2) was administered by intravenous infusion over 20–120 min on day 1 of every 21-day cycle. OS was the primary endpoint, yet the interim analysis indicated no improvement, and PFS was a secondary endpoint. Fortunately, treatment with trabectedin resulted in a statistically significant improvement in PFS, with a PFS of 4.2 months and 1.5 months for trabectedin and dacarbazine, respectively[115].

Another phase III randomized, multicenter, open-label study compared trabectedin to best supporting care (BSC) for heavily pretreated patients with STS. It included 103 adult patients, 60.2% of them with L-STS (LPS/ LMS), who were randomised (1:1) to receive trabectedin 1.5 mg/m2 every 3 weeks or BSC. The primary efficacy endpoint was PFS, which was 3.1 months in the trabectedin arm versus 1.5 months in the BSC arm, with benefits observed across almost all analyzed subgroups, but particularly in patients with L-STS (5.1 versus 1.4 months, P 1⁄4 0.0001). Seven patients (13.7%) in the trabectedin arm (all with L-STS) achieved a partial response, while no objective responses were

 doi:10.20944/preprints202501.2276.v1

observed in the BSC arm. Toxicity was mostly haematological or hepatic and the analysis of the impact of the treatment on the quality of life showed no impairment[116].

Temozolomide, being the prodrug of dacarbazine, is an alkylating agent which interferes with the biosynthesis of purines. This drug showed moderate activity in patients with pretreated sarcomas - and especially LMSs - when administered following a prolonged schedule. However, phase II trials were not followed by phase III studies of temozolomide alone [117,118].

3.5.4. New treatment in the Target therapy Era

Among targeted treatments, pazopanib is a potent and selective tyrosine kinase inhibitor (TKI) that blocks tumor growth and inhibits angiogenesis. The PALETTE trial included most histological types, excluding LPS, and is the first placebo-controlled phase III trial investigating the activity of a TKI on STS. 369 patients with metastatic or progressive disease (according to RACIST 1.0) during the 6 months (or 12 months after adjuvant therapy) before the screening were enrolled. Every patient had been previously treated with anthracyclines and subjected to a maximum of 4 therapy lines. The median PFS was 4.6 months for pazopanib and 1.6 months for placebo. The delta in OS was not significant as it was calculated that showing a projected difference of 3 months would require more than 750 patients[119].

LPS was excluded based on the results of a phase II EORTC 62043 study analysing PFR at 12-weeks, as the LPS cohort was the only one not to reach the progression-free at 12 weeks[120].

Tivozanib – a TKI targeting VEGFR1-3, with activity against PDGFRa/b and cKIT – showed antitumor activity with a promising median PFS and PFS rate at 4 months in a heavily pretreated population of metastatic STS. A Simon two-stage phase II trial was performed using tivozanib given orally at 1.5 mg daily, 3 weeks on 1 week off on a 28-day cycle until disease progression or intolerable toxicity. 58 patients were enrolled and treated with tivozanib. LMS was the most represented STS subgroup (47%) and 27 patients (46%) had received at least 3 lines of therapy prior to study entry. Up to 24 patients (41%) had prior VEGF targeted therapies. Partial response and stable disease were observed in 2 (3.6%) and 30 (54.5%) patients respectively. The 16-week PFS rate was 36.4% and median PFS was 3.5 months. Median OS was 12.2 months. AEs were manageable. Correlative studies demonstrate no correlation between the expression of VEGFR 1, 2 or 3, PDGFRa/b or FGF, and activity of tivozanib[121].

Anlotinib is another TKI targeting VEGFR, FGFR, PDGFR, C-kit, which has shown sensible efficacy in treating STS previously exposed to anthracyclines-based therapies. In a randomised double- blind, placebo-controlled phase IIb trial involving 233 patients and investigating PFS as a primary endpoint, median PFS was 6.27 months in the anlotinib arm versus 1.47 months in the control arm, the difference was very significant, and the risk of disease progression was reduced by 67%[122].

This specific agent has been specifically investigated on long-term administration and as a possible maintenance treatment after first-line chemotherapy.

A retrospective analysis was conducted of patients with advanced sarcomas with measurable target, evaluated using RECIST 1.1, with target lesions measures and PFS as the primary endpoint. 22 patients, 14 of which had previously undergone chemotherapy, were assessed as they had taken anlotinib regularly for > 12 months. The primary diseases included alveolar soft part sarcoma, synovial sarcoma, LMS, and others. 9 patients took anlotinib alone, 13 patients underwent combination treatment, 9 of which with chemotherapy and 4 with immunotherapy (anti-PD-1). Complete remission (CR) was achieved in four (18.18%) cases, partial response (PR) in five (22.73%) cases, and stable disease in 13 (59.09%) cases. The mean PFS for the CR, PR, and stable disease groups was 16.50, 14.50, and 29.31 months, respectively ($p < 0.05$)[123].

Another study addressed the potential of anlotinib as a maintenance treatment after chemotherapy in STS. It involved 49 patients who achieved partial response or stable disease after first-line anthracycline-based chemotherapy and who all received anlotinib as a maintenance treatment. The primary endpoint of PFS was 9.1 months, while the median OS was not reached, and the 1-year OS rate was 98.0%. The best ORR and DCR were 16% and 94%, respectively. Thus, anlotinib exhibits promising efficacy and tolerable toxicity in patients with advanced STS[124].

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Anlotinib is also being taken into consideration as a first-line treatment for patients not suitable for chemotherapy. A multicenter, open-label, single-arm, phase II clinical trial done in China involved 39 patients who received 12mg anlotinib once daily for 14 days every 3 weeks until disease progression or unacceptable toxicity, with PFS as a primary endpoint. Median follow-up was 13.4 months. At the data cutoff date, the median PFS and median OS were 7.1 months and 24.3 months, respectively. The PFS at 6 months was 60.0%, and the OS at 12 months was 76.6%. However, of the 37 patients eligible for the evaluation of tumor response, only one achieved confirmed partial response; instead, 30 had stable disease and the DCR was 83.8%. The safety profile was manageable as grade 3 events represented 33.3%[125].

Another interesting small molecule is regorafenib. In a placebo-controlled, randomized phase 2 trial, regorafenib improved PFS for patients with doxorubicin-pretreated advanced nonadipocytic sarcoma. 182 patients were enrolled. In nonadipocytic sarcoma, the PFS was 4.0 months with regorafenib vs 1.0 month with placebo, while the OS was 13.4 months vs 9.0 months. A quality-adjusted time without symptoms of progression or toxicity (Q-TWiST) post hoc exploratory analysis was applied to provide an integrated measure of its clinical benefit and it resulted in a significant improvement[126].

The ANNOUNCE 2 trial aimed to explore the addition of olaratumab (O) to gemcitabine (G) and docetaxel (D) for advanced STS. In Phase 2, patients were randomized 1:1 from two cohorts (O-naïve and O-pretreated) to 21-day cycles of olaratumab (20 mg/kg Cycle 1 and 15 mg/kg other cycles, Days 1 and 8), gemcitabine (900 mg/m2, Days 1 and 8), and docetaxel (75 mg/m2, Day 8). Since the primary endpoint was not reached, no result can be considered statistically significant, yet the combination of O+G+D showed a possible favorable trend in OS in the O-pretreated cohort and other efficacy outcomes in both cohorts[127].

At present, at least 20 clinical trials of PD-1/L1 inhibitor plus chemotherapy in the treatment of sarcomas have been registered and are recruiting. The PD-1 inhibitors used in these clinical trials include camrelizumab, durvalumab, nivolumab, pembrolizumab, retifanlimab, sintilimab, and Toripalimab[128].

Pembrolizumab has meaningful clinical activity in patients with undifferentiated pleomorphic sarcoma or dedifferentiated LPS. One of the first immune checkpoint inhibitors (ICI) trials with positive results was the prospective single-arm phase II trial SARC028, evaluating the anti-PD1 pembrolizumab as a second-line treatment in 80 patients with either STS or bone sarcoma. 80 of 86 patients' responses were analysed in a median follow-up of 17.8 months. ORR was 18% with a median PFS and OS of 18 and 49 weeks, respectively. Among the subtypes represented in the cohorts, LMS and Ewing's sarcoma showed no objective response. 9 (11%) patients (5 in the bone sarcoma group and 4 in the STS group) had treatment-emergent serious adverse events, 5 of whom had immune-related serious adverse events, including adrenal insufficiency, pneumonitis and nephritis[129].

The response of undifferentiated pleomorphic sarcoma (UPS) to pembrolizumab was further confirmed in an expansion cohort of SARC028 with two CRs and 7 PRs in the UPS cohort; however, a response was not seen in the LPS cohort[130].

A pooled analysis of several clinical trials investigating anti-PD-1/PD-L1 immunotherapy in advanced STS reported alveolar soft part sarcoma (ASPS) and UPS were among the highest responders (48.4% and 15.7%, respectively) and LPS and LMS were among the lowest (7.3% and 6.9%, respectively)[131].

Furthermore, combination checkpoint inhibition with nivolumab and ipilimumab was evaluated in previously treated patients with advanced STS in the phase II Alliance A091401 trial and compared to single-agent treatment with nivolumab alone. ORR was 16%, median PFS was 4.1 months and OS was 14.3 months. Better responses were seen with combination therapy, with the best responses being in UPS (33%), LMS (14.2), and AS (33%) [132].

 doi:10.20944/preprints202501.2276.v1

4. Conclusions

Malignant mesenchymal tumors of the breast are rare but extremely aggressive, present- ing significant challenges in both diagnosis and treatment. Due to the lack of standardized guidelines, clinical decision-making remains complex and varies widely. Surgical treat- ment remains the cornerstone of therapy with the primary goal of achieving complete excision to prevent local recurrences and metastases. Surgical options include both breast- conserving surgery and mastectomy, with axillary treatment typically only necessary in cases of biopsy-proven nodal involvement. While the roles of radiotherapy and chemotherapy are still unclear, ongoing research is essential to refine these treatment modalities. The rarity of these tumors complicates the conduction of large-scale studies making it vital for healthcare professionals to adopt a tailored, multidisciplinary approach, especially in high-volume centers specializing in rare malignancies. These settings provide the best opportunity for improving patient outcomes through expertise and collaboration. Ultimately, advancing our understanding of malignant mesenchymal tumors enhancing diagnostic precision and developing comprehensive treatment protocols will be key to improving patient prognoses and managing these challenging malignancies more effec-tively.

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Abbreviations:

The following abbreviations are used in this manuscript:

PTs	Phyllodes Tumors
WHO	World Health Organization
MPT	Malignant Phyllodes Tumors
PBS	Primary Breast Sarcomas
RT	Radiation Therapy
HPF	High-power fields
NCCN	National Comprehensive Cancer Network
MRI	Magnetic Resonance Imaging
ADC	Apparent Diffusion Coefficient
LR	Local Recurrence
OS	Overall Survival
DFS	Disease-free survival
ESMO	European Society for Medical Oncology
SEER	Surveillance, Epidemiology, and End Results
	Breast Cancer-Specific Survival
BCSS	Soft Tissue Sarcoma
STS	Computed tomography
CT	Positron Emission Tomography
PET	Progression Free Survival
PFS	Objective Response Rate
ORR	European Organisation for Research and Treatment of Cancer

 doi:10.20944/preprints202501.2276.v1

EORTC	Liposarcoma
	Leiomyosarcoma
LPS	Left Ventricular Ejection Fraction
LMS	Disease Control Rate
LVEF	Metastatic Myxoid-Liposarcoma
DCR	Platelet–lymphocyte Ratios
MLPS	Best Supporting Care
PLRs	Tyrosine Kinase Inhibitor
BSC	Complete Remission
TKI	Partial Response
CR	Immune Checkpoint Inhibitors
PR	Undifferentiated Pleomorphic Sarcoma
ICI	Alveolar Soft Part Sarcoma
UPS	Olaratumab
ASPS	Gemcitabine
O	Docetaxel
G	
D	

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