

A Systematic Review on Breast Angiosarcoma

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Abstract:

Breast angiosarcoma is an uncommon and aggressive mesenchymal malignancy originating from the endothelial cells of blood or lymphatic vessels. It accounts for a very small percentage of all breast cancers and soft tissue sarcomas. This malignancy manifests in two principal forms: primary angiosarcoma, which arises *de novo* in the breast parenchyma, typically in younger women; and secondary angiosarcoma, which is more common and usually develops in older women as a consequence of prior radiation therapy for breast cancer (radiation-induced angiosarcoma or RIBAS) or chronic lymphedema. Both forms are characterized by aggressive clinical behavior and a generally poor prognosis. Diagnosis is often challenging due to varied and sometimes subtle clinical presentations, non-specific imaging findings, and pathological subtleties that can mimic benign vascular lesions or other malignancies. Histopathological examination with immunohistochemical markers, particularly CD31 and MYC (for secondary forms), is crucial for confirmation. Treatment predominantly involves surgical excision with the goal of achieving wide negative margins, often a mastectomy. The roles of adjuvant radiotherapy, especially in RIBAS, and systemic therapies (chemotherapy, targeted therapy, immunotherapy) are still evolving and lack definitive consensus due to the disease's rarity and paucity of large-scale prospective trials. Prognostic factors include tumor grade, size, margin status, patient age, and tumor type (primary vs. secondary). High rates of local and distant recurrence contribute to unfavorable survival outcomes. This systematic review aims to synthesize the current understanding of breast angiosarcoma, covering its classification, epidemiology, clinical features, diagnostic approaches, treatment modalities, prognostic indicators, and future research directions, to provide a comprehensive overview for clinicians and researchers.

Keywords — Angiosarcoma, Malignancy, CD31, MYC, RIBAS

I. INTRODUCTION

1.1. Definition and Overview of Breast Angiosarcoma

Angiosarcoma (AS) of the breast is a rare malignant tumor of mesenchymal origin, arising from the endothelial cells that line blood vessels or lymphatic vessels within the breast parenchyma or the overlying skin (1, 2, 5, 14). The term "angiosarcoma" itself is derived from the Greek words "angios," meaning vessel, and "sarcoma," meaning a flesh tumor, which directly reflects its vascular endothelial cell lineage (2). This vascular origin is fundamental to its biological behavior, particularly its propensity

for rapid growth, local infiltration, and hematogenous spread, which contributes to its aggressive clinical course and often challenging management (1, 6). Breast AS accounts for approximately 1% of all soft tissue sarcomas and represents a very small fraction, estimated between less than 0.04% to 0.2%, of all malignant breast neoplasms (1, 2, 7, 14). Despite its overall rarity as a breast malignancy, the breast is recognized as one of the more common anatomical sites for angiosarcomas to develop when considering all locations in the body where these sarcomas can occur (5, 15, 30).

1.2. Rarity and Clinical Significance

The extreme rarity of breast angiosarcoma poses substantial challenges in clinical practice and research. This low incidence makes it difficult to conduct large-scale, prospective, randomized clinical trials, which are essential for establishing high-level evidence to guide treatment. Consequently, current treatment guidelines are often based on retrospective studies, small case series, or expert consensus, leading to a lack of universally standardized management protocols (17).

The clinical significance of breast angiosarcoma is disproportionate to its incidence, primarily due to its aggressive biological behavior, high rates of local and distant recurrence, and generally poor prognosis, even when multimodality treatment approaches are employed. A particularly noteworthy trend is the increasing incidence of secondary angiosarcoma, especially radiation-induced angiosarcoma (RIBAS). This rise is an iatrogenic consequence observed in patients who have undergone breast-conserving therapy (BCT) combined with adjuvant radiation for primary breast carcinoma. While BCT has improved cosmetic outcomes and quality of life for many breast cancer survivors, it carries a small but significant long-term risk of inducing this aggressive secondary malignancy. This "paradox of progress," where an advancement in treating a common cancer leads to a rare but serious secondary cancer, underscores the need for long-term surveillance of BCT recipients and ongoing research into mitigating this risk.

The combination of rarity and aggressiveness creates a difficult cycle: the scarcity of cases hinders robust research, and the lack of strong evidence perpetuates uncertainties in treatment, which in turn impacts the ability to improve the typically poor outcomes. This scenario highlights the critical need for collaborative research efforts and the development of novel therapeutic strategies.

1.3. Scope of the Review

This systematic review aims to consolidate and synthesize the current body of knowledge regarding breast angiosarcoma. The review will cover its definition, classification into primary and secondary forms (including radiation-induced and lymphedema-associated subtypes), and underlying etiology. Epidemiological aspects, such as incidence, prevalence, and identified risk factors, will be

discussed. A detailed account of the clinical presentation of both primary and secondary breast angiosarcoma will be provided, followed by an examination of diagnostic modalities, including imaging techniques and biopsy procedures. The histopathological features crucial for diagnosis, including key immunohistochemical and molecular markers, will be outlined. Current treatment strategies, encompassing surgical management (mastectomy versus breast-conserving surgery, margin status, axillary lymph node dissection), radiotherapy (adjuvant, neoadjuvant, and definitive), and systemic therapies (chemotherapy, targeted agents, and immunotherapy), will be comprehensively reviewed. Prognostic factors influencing patient outcomes, patterns of local and distant recurrence, and overall survival rates will be analyzed. The review will also address the significant challenges encountered in the diagnosis and management of this rare malignancy. Finally, current clinical guidelines will be summarized, and promising future research directions, including the development of novel therapies and biomarkers, will be highlighted. The overarching goal is to provide a comprehensive and up-to-date resource for clinicians, pathologists, radiologists, and researchers involved in the care of patients with breast angiosarcoma.

2. Classification and Etiology

Breast angiosarcoma is broadly classified into two main categories: primary and secondary, each with distinct etiological factors, clinical contexts, and, increasingly, recognized molecular characteristics (1, 2).

2.1. Primary Breast Angiosarcoma

Primary breast angiosarcoma arises *de novo*, meaning it develops spontaneously within the breast parenchyma without any identifiable precursor lesion or a history of prior therapeutic interventions such as radiation to the breast or significant chronic lymphedema. These tumors originate from the endothelial cells of the intrinsic blood vessels of the breast tissue itself (2). Clinically, primary AS is more frequently observed in younger women, typically presenting between the ages of 30 and 50, with a median age at diagnosis often cited around 35 to 40 years.

The precise etiology of primary breast angiosarcoma remains largely unknown. While some older

literature has anecdotally suggested potential links to trauma or localized lymphedema, there is a lack of definitive, robust data to substantiate these as causative factors for the primary form (2). More recent molecular studies have begun to shed light on potential genetic drivers. Notably, primary breast angiosarcomas have been found to be more likely associated with somatic mutations in the *PIK3CA* gene and other components of the PI3K/AKT/mTOR signaling pathway. This etiological ambiguity for primary AS stands in stark contrast to the more clearly defined risk factors associated with secondary forms, a distinction critical for understanding their pathogenesis and for guiding research into preventative measures, which are currently not feasible for primary AS due to its idiopathic nature.

2.2. Secondary Breast Angiosarcoma

Secondary breast angiosarcoma develops as a direct consequence of previous therapeutic interventions or pre-existing conditions, most notably prior radiation therapy for an earlier breast cancer or in the context of chronic, long-standing lymphedema. Unlike primary AS, which typically arises within the breast parenchyma, secondary lesions commonly originate in the dermal and subcutaneous layers of the skin overlying the breast or chest wall, particularly within the previously irradiated field or the area affected by lymphedema. These tumors generally affect older women, with a median age at diagnosis around 67 to 71 years, and there is usually a significant latency period between the initial insult (e.g., radiation therapy) and the development of the angiosarcoma.

2.2.1. Radiation-Induced Breast Angiosarcoma (RIBAS)

RIBAS is the most common form of secondary breast angiosarcoma and is strongly linked to a history of adjuvant radiotherapy administered for the treatment of a primary breast carcinoma. The incidence of RIBAS, though still low, is estimated to be less than 0.3% among patients who have received adjuvant radiotherapy for breast cancer. These tumors typically manifest after a considerable latency period, with a median time from radiation exposure to RIBAS diagnosis ranging from 5 to 10 years, although cases have been reported from as early as 3 years to over 20 years post-radiation.

The diagnostic criteria for radiation-induced sarcoma, originally proposed by Cahan and later adapted by Arlen et al. for soft tissue sarcomas including RIBAS, are often applied. These criteria generally include: the sarcoma arising within a previously irradiated field, a latency period of at least several years (commonly ≥ 3 years) between radiation exposure and sarcoma development, and histological confirmation of sarcoma that is distinct from the original irradiated malignancy.

The pathogenesis of RIBAS is thought to involve radiation-induced DNA damage and genomic instability in the endothelial cells within the irradiated volume. It has been proposed that at lower radiation doses (e.g., <50 Gy), sublethal DNA damage may lead to mutations and instability, promoting malignant transformation over time, whereas higher doses (e.g., >50 Gy) are more likely to induce apoptosis (1). This dose-response hypothesis suggests that minimizing the volume of healthy tissue exposed to radiation and optimizing radiation doses could be important in mitigating the risk of RIBAS, a critical consideration in modern radiotherapy planning. Molecularly, RIBAS is frequently characterized by the amplification of the *MYC* oncogene.

2.2.2. Lymphedema-Associated Angiosarcoma (Stewart-Treves Syndrome)

Lymphedema-associated angiosarcoma, classically known as Stewart-Treves syndrome, develops in the setting of chronic, persistent lymphedema. Historically, this was most often described in the upper extremity of women who had undergone radical mastectomy with axillary lymph node dissection for breast cancer, leading to severe arm lymphedema (2). The first description dates back to 1948 by Stewart and Treves (2). While radical mastectomy is less common now, this type of angiosarcoma can still occur in any area of long-standing lymphedema, including the breast or chest wall, following breast-conserving surgery if significant axillary lymph node dissection results in chronic lymphedema (2).

The latency period for lymphedema-associated angiosarcoma is typically longer than that for RIBAS, often averaging around 10 years or more after the onset of chronic lymphedema (2). The underlying mechanisms are thought to involve chronic

inflammation, impaired immune surveillance, and local tissue changes within the lymphedematous region, creating a microenvironment conducive to malignant transformation of lymphatic or vascular endothelial cells. Similar to RIBAS, lymphedema-associated angiosarcomas also frequently exhibit *MYC* gene amplification (3). The connection between chronic inflammation and cancer development is a well-recognized phenomenon in other organ systems, and its role in lymphedema-associated AS suggests that factors beyond simple lymphatic stasis, such as altered cytokine profiles and immune cell dysfunction in the affected tissues, may contribute to oncogenesis.

2.3. Molecular Characteristics

Distinct molecular alterations are increasingly recognized in breast angiosarcomas, often correlating with their classification as primary or secondary. These molecular features are not only crucial for accurate diagnosis but also hold promise for the development of targeted therapies.

Key Genetic Alterations: A significant molecular distinction lies in the genetic drivers of primary versus secondary angiosarcomas. Secondary angiosarcomas, encompassing both RIBAS and lymphedema-associated types, are very frequently characterized by amplification of the *MYC* oncogene, which is located on chromosome 8q24. This *MYC* amplification is considered a hallmark of these secondary lesions and serves as an important diagnostic marker, helping to differentiate them from atypical vascular lesions that can occur post-radiation (23). In contrast, primary breast angiosarcomas are less likely to show *MYC* amplification. Instead, they are more commonly associated with somatic mutations in the *PIK3CA* gene and other genes within the PI3K/AKT/mTOR signaling pathway. Mutations in *KDR* (encoding VEGFR2, a key receptor in angiogenesis) and the tumor suppressor gene *TP53* have also been reported in angiosarcomas, though their specific prevalence in primary versus secondary breast subtypes requires further clarification.

This molecular dichotomy (*MYC* in secondary AS vs. *PIK3CA* in primary AS) has profound implications. Diagnostically, *MYC* testing (via FISH or IHC) can be invaluable in confirming secondary AS, especially when histopathological features are

ambiguous in post-radiation settings (23). Therapeutically, these distinct genetic alterations suggest different vulnerabilities. For instance, therapies targeting the PI3K/AKT/mTOR pathway might be more relevant for *PIK3CA*-mutated primary angiosarcomas, whereas strategies aimed at *MYC* or its downstream pathways could be explored for secondary forms.

Immunohistochemical

Markers:

Immunohistochemistry (IHC) plays a pivotal role in confirming the endothelial differentiation of angiosarcomas and distinguishing them from other spindle cell or epithelioid malignancies. Key endothelial markers include:

- **CD31 (PECAM-1):** This is widely regarded as the most sensitive and specific immunohistochemical marker for endothelial cells and is consistently expressed in angiosarcomas.
- **CD34:** Another commonly used endothelial marker, CD34 is often positive in angiosarcomas, but its expression can be more variable than CD31, and it is less specific, as it can be found in other mesenchymal tumors. In some contexts, such as distinguishing epithelioid angiosarcoma from carcinoma, a pattern of CD31 positivity with CD34 negativity can be diagnostically useful.
- **Factor VIII-related antigen (von Willebrand Factor):** This marker is also indicative of endothelial origin and can be helpful, particularly in confirming the diagnosis in poorly differentiated tumors.
- **Fli-1 and ERG (ETS-related gene):** These are nuclear transcription factors that are highly sensitive and specific for endothelial differentiation. ERG, in particular, is expressed in the vast majority of vascular tumors, including angiosarcomas.
- **D2-40 (Podoplanin):** This marker is more specific for lymphatic endothelium and may be expressed in angiosarcomas with

lymphatic differentiation, or in lymphangioma-like areas (13).

Proliferation Markers:

- **Ki-67 (MIB-1):** The Ki-67 proliferation index is a measure of the percentage of tumor cells actively dividing. A high Ki-67 labeling index (e.g., values such as 40% reported in some cases (11, 14)) generally correlates with higher tumor grade, increased mitotic activity, and a more aggressive clinical course.

Other Relevant Markers:

- **MYC (protein):** Overexpression of MYC protein, detectable by IHC, correlates with MYC gene amplification and is a characteristic feature of secondary angiosarcomas.
- **Cytokeratins (e.g., AE1/AE3):** Angiosarcomas are typically negative for cytokeratins, which helps in distinguishing them from carcinomas, especially poorly differentiated or epithelioid variants (14).
- **Melanocytic Markers (e.g., S-100 protein, HMB-45, Melan-A):** These markers are negative in angiosarcomas and are used to exclude malignant melanoma in the differential diagnosis of poorly differentiated or epithelioid tumors.

The judicious use of this panel of IHC markers, in conjunction with careful morphological assessment and relevant molecular tests like MYC amplification analysis, is essential for the accurate diagnosis and classification of breast angiosarcoma.

Table 1: Comparative Features of Primary and Secondary Breast Angiosarcoma

Feature	Primary Breast Angiosarcoma	Secondary Breast Angiosarcoma (RIBAS & Lymphedema-Associated)
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Etiology	De novo, largely unknown	Prior radiation therapy, lymphedema
Median Age at Diagnosis	Younger (30s-40s, median ~35-40 yrs)	Older (median ~67-71 yrs)
Typical Clinical Presentation	Palpable breast mass, often rapidly growing	Skin changes (bruising, discoloration, plaques, nodules), swelling
Common Anatomic Location	Breast parenchyma	Dermal/subcutaneous layers of skin in affected area
Key Molecular Markers	More often PIK3CA mutations	Frequently MYC amplification
Typical Latency Period	Not applicable	5-10+ years post-radiation/lymphedema onset
General Prognosis	Poor, grade-dependent	Generally poor, often more aggressive

3. Epidemiology

The epidemiology of breast angiosarcoma is characterized by its overall rarity but also by distinct trends related to its primary and secondary forms.

3.1. Incidence and Prevalence

Angiosarcoma, across all anatomical sites, is an uncommon malignancy. Data from the US Cancer Statistics (USCS) indicate that the overall US incidence of angiosarcoma doubled between 2001 and 2019, reaching an age- and sex-adjusted rate of 3.3 cases per 1,000,000 person-years in 2019. A slight decrease to 3.0 cases per 1,000,000 person-years was observed in 2020, a change potentially influenced by reduced diagnostic activities during the early COVID-19 pandemic.

When focusing on breast angiosarcoma, it remains a very rare subset of all breast cancers, accounting for approximately 0.04% to 0.2% of cases (2, 7, 14). The incidence of primary breast angiosarcoma is particularly low, estimated at around 0.0005%. However, a significant epidemiological trend has emerged: the incidence of angiosarcomas affecting the skin, subcutaneous tissue, and breast (analyzed

as a group) showed an increase of 1.7% per year between 2001 and 2019, reaching 2.3 cases per 1,000,000 person-years.

Crucially, this increase in angiosarcoma incidence among women is predominantly driven by cases of secondary breast angiosarcoma that occur as a second or later malignant neoplasm. For these secondary breast angiosarcomas, the Annual Percentage Change (APC) in incidence was +2.7%. In contrast, the incidence of primary breast angiosarcoma has remained stable over the same period. This shifting epidemiology strongly points to iatrogenic factors, particularly the increased use of breast-conserving therapy (BCT) with adjuvant radiation for primary breast cancer, as the main contributor to the rising overall numbers of breast angiosarcoma. Several studies corroborate that secondary angiosarcomas constitute the majority of breast angiosarcoma cases. For instance, one study involving 904 patients with breast angiosarcoma found that 65.4% were secondary. Another large dataset indicated that 71.9% of 2705 female breast angiosarcomas were classified as secondary. The prevalence of post-irradiation angiosarcoma specifically has been reported in some series to be between 0.05% and 0.16% of irradiated breast cancer patients, with potentially higher figures noted in cohorts with longer follow-up durations (38).

3.2. Risk Factors

The risk factors for breast angiosarcoma differ significantly between its primary and secondary forms.

For Secondary Breast Angiosarcoma:

- **Prior Radiation Therapy:** This is the most well-established and significant risk factor. The risk is associated with radiation delivered for a previous breast cancer, typically as part of BCT. The risk appears to be cumulative over time, potentially continuing to increase for up to 30 years after radiation treatment.
- **Chronic Lymphedema:** Long-standing, chronic lymphedema is another major risk factor. This is classically associated with Stewart-Treves syndrome, developing in an arm after radical mastectomy and axillary

lymph node dissection, but can also occur in the breast or chest wall if chronic lymphedema is present.

- **Age:** Older age at the time of initial breast cancer treatment is associated with an increased risk of developing secondary angiosarcoma. This contrasts with primary angiosarcoma, which typically affects younger individuals.
- **Race:** Studies have indicated that White race is an independent risk factor for the development of secondary angiosarcoma among breast cancer survivors. The majority of angiosarcoma patients in US-based studies are identified as non-Hispanic White (3).
- **Characteristics of Initial Breast Cancer and its Treatment (for RIBAS):**
 - **Type of Surgery:** Lumpectomy (as part of BCT, which invariably includes radiation) is a risk factor, as opposed to mastectomy without radiation.
 - **Axillary Lymph Node Removal:** Axillary dissection, which can contribute to lymphedema, is also a risk factor.
 - **Tumor Characteristics:** An initial invasive breast tumor (as opposed to in situ carcinoma) has been linked to higher risk.
 - **Laterality:** An intriguing finding from one study is an association with left-sided primary breast cancer. The reasons for this are not fully understood but may relate to historical radiation techniques or anatomical factors.

For Primary Breast Angiosarcoma:

- The etiology is largely unknown.

- **Genetic Predisposition (Rare):** While most cases are sporadic, rare associations with germline mutations in genes like *BRCA1* and *BRCA2* have been reported. Certain hereditary syndromes such as neurofibromatosis, Maffucci syndrome, and Klippel-Trenaunay syndrome are associated with an increased risk of angiosarcomas in general, but their specific contribution to primary breast AS is not well defined.
- **Other Potential Factors (Less Defined for Breast AS):**
 - **Chemical Exposures:** Exposure to substances like vinyl chloride, thorium dioxide, arsenic, radium, and anabolic steroids has been linked to angiosarcomas at various sites, though a specific link to primary breast AS is not strongly established in the provided materials.
 - **Hypertension and Diabetes:** These conditions have been noted as risk factors for secondary soft tissue sarcomas generally, but their role in primary or even secondary breast AS specifically needs more investigation.

The development of secondary angiosarcoma appears to be a multifactorial process. While radiation exposure or chronic lymphedema are the primary inciting events, other patient-specific elements such as age, race, and possibly underlying genetic susceptibilities or comorbidities likely modulate an individual's risk. The observation regarding left-sided tumors, for example, warrants further epidemiological study to determine if it represents a true association or a statistical anomaly, and if true, to understand the underlying basis.

4. Clinical Presentation

The clinical manifestations of breast angiosarcoma vary considerably depending on whether the tumor is primary or secondary, and can often be subtle or

mimic benign conditions, contributing to diagnostic challenges (1, 5).

4.1. Symptoms of Primary Breast Angiosarcoma

Primary breast angiosarcoma, typically occurring in younger women (median age 35-40 years), most commonly presents as a distinct, palpable breast mass. This mass is often described as painless, although it can sometimes be tender, and may exhibit rapid growth or appear ill-defined on palpation. The average diameter of such masses at diagnosis can be substantial, often in the range of 4.6 to 5.9 cm (12). In addition to a discrete mass, patients may notice a more diffuse fullness or swelling of the affected breast. While skin changes are more characteristic of secondary angiosarcoma, primary lesions that are large or superficially located can occasionally involve the overlying skin. These changes might include localized skin thickening, a discolored rash, or an area with a bruised appearance. Due to the highly vascular nature of these tumors, a bluish discoloration of the skin may sometimes be observed (12).

A rare but serious presentation associated with very large primary angiosarcomas is the Kasabach-Merritt syndrome. This syndrome is characterized by consumptive coagulopathy due to platelet trapping within the large vascular tumor, leading to thrombocytopenia and hemorrhagic manifestations. The presentation of a palpable breast mass in a younger woman, an age group where breast cancer is less frequent and breast tissue is typically denser, can sometimes lead to a delayed diagnosis if a high index of suspicion for malignancy, including rare entities like angiosarcoma, is not maintained. The reduced sensitivity of mammography in this demographic can further contribute to such delays.

4.2. Symptoms of Secondary Breast Angiosarcoma (especially RIBAS and Lymphedema-Associated)

Secondary breast angiosarcoma, which includes radiation-induced (RIBAS) and lymphedema-associated forms, typically occurs in older women with a history of prior breast cancer treatment and presents predominantly with cutaneous manifestations. The onset is often insidious, and the initial skin changes can appear deceptively benign, frequently leading to neglect by both patients and physicians and consequently delaying diagnosis.

The hallmark symptoms involve changes in the skin of the irradiated breast, chest wall, or lymphedematous area:

- **Bruising or Ecchymosis:** Painless, often multifocal, flat or slightly raised areas of bruising or ecchymotic patches are highly characteristic, particularly for RIBAS. These lesions can easily be mistaken for simple bruising from minor trauma, which is a common reason for diagnostic delay.
- **Skin Discoloration:** Patients may develop purplish, violaceous, or reddish discolored patches or rash-like areas on the skin.
- **Plaques or Nodules:** The skin lesions can evolve into raised, firm plaques or discrete nodules, which may be bluish or reddish.
- **Skin Thickening or Induration:** Diffuse thickening, induration, or a peau d'orange appearance of the skin within the previously irradiated field or in an area of chronic lymphedema is another common sign.
- **Telangiectasia-like Lesions:** Some lesions may resemble clusters of dilated blood vessels (23).

In addition to these skin changes, diffuse swelling of the breast or arm is a common feature, especially in cases associated with lymphedema. While cutaneous signs predominate in secondary AS, a discrete palpable mass, which may or may not be painful, can also occur. Pain in the affected area or nipple region has also been reported.

The often subtle and "innocent-appearing" nature of these early skin changes in patients with known risk factors (prior radiation, chronic lymphedema) highlights the critical importance of maintaining a high index of suspicion. Any new, persistent, or evolving skin lesion in an irradiated breast or a lymphedematous limb should be considered potentially malignant and promptly evaluated with a biopsy to rule out angiosarcoma. Early recognition and diagnosis are paramount, as delays can significantly worsen the already challenging prognosis of this aggressive disease.

5. Diagnosis

The diagnosis of breast angiosarcoma is often challenging due to its rarity, varied clinical presentation, and frequently non-specific imaging findings. A definitive diagnosis relies on histopathological examination of tissue obtained via biopsy, supported by immunohistochemical studies.

5.1. Imaging Modalities

Imaging plays a role in detecting suspicious lesions, assessing the extent of disease, and guiding biopsies, but no single imaging modality has pathognomonic features for breast angiosarcoma.

- **Mammography:** Mammographic findings in breast angiosarcoma are often non-specific and can be misleading (1, 5, 15, 16, 31, 37). Lesions may present as an ill-defined mass, sometimes without typical malignant features like spiculations or suspicious calcifications (12). In some instances, particularly with low-grade tumors or in the dense breast tissue common in younger women (typical for primary AS), mammography may be entirely negative or interpreted as benign (e.g., BI-RADS 2). For secondary AS, which often manifests primarily with skin changes, mammography may only show skin thickening or increased breast density, and it frequently fails to identify the dermal and subcutaneous extent of the disease. Consequently, false-negative mammography results are common, especially in the context of RIBAS where post-treatment changes can obscure subtle findings.
- **Ultrasound (US):** Ultrasound findings are also highly variable. Angiosarcomas may appear as a heterogeneous mass or region with hyperechoic, hypoechoic, or mixed echogenicity. Disruption of the normal breast architecture is a common feature (15, 16, 37). Color Doppler imaging often reveals hypervascularity within the lesion, reflecting its vascular nature, and spectral Doppler may demonstrate an arterial flow pattern.

However, some angiosarcomas can be diffuse or poorly marginated on ultrasound (12). Similar to mammography, ultrasound can fail to correctly diagnose angiosarcoma in a significant proportion of cases and may not be particularly useful in distinguishing the causes of skin changes seen in secondary angiosarcoma.

- **Magnetic Resonance Imaging (MRI):** MRI is generally considered the most sensitive imaging modality for evaluating suspected breast angiosarcoma, particularly for determining the extent of the lesion and guiding surgical planning. Typical MRI findings include:

- **Morphology:** Lesions often appear as large, lobular, or irregularly shaped masses with indistinct or infiltrative borders (12).
- **Signal Characteristics:** Low-grade tumors tend to be hypointense on T1-weighted images (T1W) and markedly hyperintense on T2-weighted images (T2W) (11, 12). High-grade angiosarcomas may exhibit heterogeneous signal intensity, with irregular areas of hyperintensity on T1W images, which can correspond to hemorrhage or venous blood lakes within the tumor (12, 15, 16, 37). Fat-suppressed T2W sequences often show heterogeneous hyperintensity (11).
- **Dynamic Contrast Enhancement (DCE-MRI):** Angiosarcomas, especially high-grade lesions, typically demonstrate rapid and intense heterogeneous enhancement in the early phase after contrast administration, often followed by a

washout pattern (type 3 kinetic curve) in the delayed phase.

- **Diffusion-Weighted Imaging (DWI):** Lesions may show restricted diffusion, appearing hyperintense on DWI sequences (11).
- **Other Findings:** MRI may also reveal associated findings such as thickened mammary vessels adjacent to the tumor (11) or peritumoral edema, which can appear as circumferential hyperintensity on STIR (Short Tau Inversion Recovery) images (12). MRI demonstrates higher accuracy in diagnosis compared to mammography and ultrasound, especially for primary AS, and is better at assessing the true extent of disease, including detecting lesions that may be occult on other imaging modalities. It is the preferred imaging method for evaluating suspected RIBAS. Despite its advantages, the non-specific nature of some findings means that even MRI cannot definitively diagnose angiosarcoma without histological confirmation.

- **Positron Emission Tomography (PET) Scan:** PET scans, typically using 18F-FDG (fluorodeoxyglucose), are primarily used for staging angiosarcoma by detecting regional lymph node involvement (though uncommon) and distant metastases. FDG uptake can be seen in primary tumors and metastatic sites such as the pleura, heart, and liver (12).

The non-specific and often misleading findings on mammography and ultrasound underscore the importance of MRI in the diagnostic workup of suspected breast angiosarcoma. Early recourse to MRI, particularly when clinical suspicion is high (e.g., characteristic skin changes in an irradiated

breast or a rapidly enlarging mass in a young woman), can be crucial for timely diagnosis and appropriate management planning.

5.2. Biopsy Techniques

Histopathological examination of a tissue sample is mandatory for the definitive diagnosis of breast angiosarcoma, given the often equivocal nature of clinical and imaging findings. The choice of biopsy technique depends on the nature and location of the lesion.

- **Fine Needle Aspiration (FNA):** While FNA cytology can be performed, it has significant limitations in the diagnosis of angiosarcoma. It may yield false-negative results in a substantial percentage of cases, particularly for primary AS, due to sampling error or difficulty in interpreting cytological features of this complex tumor. However, one potential clue from FNA can be excessive bleeding from the aspiration site, which may suggest the highly vascular nature of the tumor. Due to its low sensitivity, FNA is generally not the preferred method if angiosarcoma is suspected.
- **Core Needle Biopsy (CNB):** CNB is generally the recommended initial biopsy technique for palpable breast masses or image-detected lesions suspicious for angiosarcoma. It provides a larger tissue sample than FNA, allowing for more accurate histological assessment of architecture and cellular atypia, as well as for essential immunohistochemical staining. CNBs are often performed under ultrasound guidance to ensure accurate targeting of the lesion (14).
- **Skin Punch Biopsy or Incisional Biopsy:** For secondary angiosarcomas that present predominantly with cutaneous lesions (e.g., RIBAS or lymphedema-associated AS), a skin punch biopsy or a small incisional biopsy of the affected skin is often the most appropriate and effective method for obtaining diagnostic tissue. In cases of

RIBAS with clear cutaneous manifestations, a biopsy of the involved skin is usually sufficient for diagnosis.

Important Considerations for Biopsy: When performing any biopsy for suspected sarcoma, it is crucial that the biopsy tract be planned in such a way that it can be completely excised en bloc with the definitive surgical specimen if malignancy is confirmed (40, 46). Careful attention to hemostasis is also important due to the vascularity of these tumors. Given the often infiltrative and sometimes multifocal nature of angiosarcoma, multiple biopsies from different areas of a suspicious lesion or surrounding tissue may occasionally be necessary to capture the diagnostic features and assess the extent of involvement (40).

The choice of biopsy technique significantly impacts diagnostic accuracy. The high false-negative rate associated with FNA suggests it should be used with extreme caution, if at all, when angiosarcoma is in the differential diagnosis. CNB or incisional/punch biopsies, which yield more substantial tissue, are generally preferred to avoid misdiagnosis or undergrading, given the pathological heterogeneity and subtleties inherent in angiosarcomas.

5.3. Histopathology and Immunohistochemistry

The definitive diagnosis of breast angiosarcoma rests on careful histopathological evaluation of biopsy or excision specimens, supported by a characteristic panel of immunohistochemical (IHC) stains.

Histopathological Features: Angiosarcomas are characterized by the proliferation of atypical endothelial cells that form irregular, inter-anastomosing vascular channels which infiltrate the surrounding breast parenchyma or dermis. The endothelial cells lining these channels typically exhibit cytological atypia, including nuclear hyperchromasia, pleomorphism, and prominent nucleoli. The cells themselves can vary in morphology, appearing rounded, polygonal, spindle-shaped (fusiform), or epithelioid. The tumor often has an infiltrative growth pattern and typically lacks a true capsule.

The histological grade of angiosarcoma is a critical prognostic factor and is typically assessed based on features such as cellularity, degree of nuclear atypia,

mitotic activity, and the presence of necrosis or solid/papillary growth patterns.

- **Well-differentiated (low-grade) angiosarcomas** may show subtle atypia and can closely resemble benign vascular lesions such as hemangiomas or lymphangiomas. They consist of open, anastomosing vascular channels lined by relatively bland endothelial cells. This resemblance can make diagnosis particularly challenging on small biopsy samples.
- **Poorly differentiated (high-grade) angiosarcomas** exhibit more pronounced cellularity, significant nuclear pleomorphism, frequent and atypical mitoses, and may form solid sheets of cells, spindle cell areas, or papillary projections into vascular lumens. Hemorrhage and necrosis are common features in high-grade lesions.

Immunohistochemistry (IHC): IHC is indispensable for confirming endothelial differentiation and distinguishing angiosarcoma from other malignancies, especially in poorly differentiated cases.

- **Endothelial Markers:**

- **CD31 (PECAM-1):** This is considered the most sensitive and specific marker for endothelial differentiation. Strong and diffuse membranous staining for CD31 is a hallmark of angiosarcoma.
- **CD34:** Another commonly expressed endothelial marker, but its expression can be more variable and it is less specific than CD31, as it can also be positive in other mesenchymal cells and some carcinomas. A pattern of CD31 positivity and CD34 negativity can sometimes be seen in epithelioid angiosarcomas and can aid in differentiating them from carcinomas.

- **Factor VIII-related antigen (von Willebrand Factor):** This is a classic endothelial marker, though less sensitive than CD31, it can be useful, particularly in confirming vascular origin in challenging cases.
- **Fli-1 and ERG (ETS-related gene):** These are nuclear transcription factors that are highly sensitive and specific for endothelial differentiation. ERG, in particular, is expressed by virtually all benign and malignant vascular tumors and is a very reliable marker.
- **D2-40 (Podoplanin):** This marker is more specific for lymphatic endothelium. Its expression in an angiosarcoma may suggest lymphatic differentiation or origin (13).

- **MYC:** Overexpression of MYC protein (detected by IHC) or amplification of the MYC gene (detected by FISH) is a key molecular feature of secondary angiosarcomas (both RIBAS and lymphedema-associated forms). This finding is highly valuable in distinguishing secondary AS from primary AS and, importantly, from atypical vascular lesions (AVL) that can occur after radiation therapy. AVLs are typically MYC-negative. The discovery and application of MYC testing has significantly improved diagnostic accuracy in the post-radiation setting, where distinguishing reactive vascular changes from early malignancy was previously very challenging.
- **Ki-67 (MIB-1):** This proliferation marker highlights actively dividing cells. A high Ki-67 labeling index (e.g., >20%, with some reports of 40% or higher (11, 14)) generally indicates increased mitotic activity, correlates with higher tumor grade, and often

implies a more aggressive clinical behavior and poorer prognosis.

• **Markers for Differential Diagnosis:**

- **Cytokeratins (e.g., AE1/AE3, CAM5.2):** Angiosarcomas are typically negative for cytokeratins. This helps to differentiate them from carcinomas, especially when dealing with poorly differentiated or epithelioid tumors (14).
- **Melanocytic Markers (S-100 protein, HMB-45, Melan-A):** These markers are also negative in angiosarcomas and are essential in the workup of poorly differentiated malignant neoplasms to exclude malignant melanoma.

A panel of these IHC markers, interpreted in the context of the H&E morphology and clinical history, is crucial for an accurate and definitive diagnosis of breast angiosarcoma and its subtypes.

Table 2: Diagnostic Modalities for Breast Angiosarcoma

Modality	Typical Findings/Utility	Advantages	Limitations/Challenges
Mammography	Often non-specific; ill-defined mass, skin thickening, or negative. No pathognomonic features.	Baseline imaging, may detect some masses.	Low sensitivity, especially in dense breasts or skin-predominant secondary AS. High false-negative rate.
Ultrasound (US)	Variable: heterogeneous mass (hypo-, hyper-, mixed)	Good for guiding biopsy, or assessing	Non-specific, can fail to diagnose correctly, may not distinguish causes of skin

echogenicity), secondary AS. hypervascular on Doppler, disruption of architecture.

Large, irregular/lobular mass. T1W: low signal (low-grade) or heterogeneous (high-grade, hemorrhagic). T2W: high signal. Rapid, intense contrast enhancement with washout. Restricted diffusion.

Magnetic Resonance Imaging (MRI)

Useful for staging and detecting distant metastases.

Positron Emission Tomography (PET) Scan

FDG uptake in primary tumor and metastatic sites. Minimal atypia, bloody aspirate. High false-negative rate, often insufficient for definitive diagnosis or grading.

Fine Needle Aspiration (FNA) Biopsy

Best for determining lesion extent, detecting occult lesions, higher accuracy than mammo/US. Preferred for RIBAS. Findings can still be non-specific, requiring biopsy. Cost and accessibility.

Core Needle Biopsy (CNB)	Provides tissue architecture for histological and IHC analysis.	More accurate than FNA, provides sufficient tissue for IHC.	Invasive, potential for bleeding. Sampling error still possible in heterogeneous tumors.
Skin Punch/Incisional Biopsy	Diagnostic for cutaneous lesions.	Method of choice for skin-manifested secondary AS (e.g., RIBAS)	Limited to superficial disease; may not represent deeper components if present.

. Treatment Strategies

The management of breast angiosarcoma is complex and typically requires a multidisciplinary approach, involving surgical oncologists, medical oncologists, radiation oncologists, pathologists, and radiologists, preferably at specialized sarcoma centers. Due to the rarity of the disease, treatment strategies are often extrapolated from guidelines for other soft tissue sarcomas, and there is a lack of high-level evidence from large randomized trials specifically for breast angiosarcoma.

6.1. Surgical Management

Complete surgical excision with histologically negative margins (R0 resection) is the cornerstone of curative-intent treatment for localized breast angiosarcoma and offers the best opportunity for long-term local control and survival.

6.1.1. Mastectomy versus Breast-Conserving Surgery (BCS)

The choice between mastectomy and breast-conserving surgery (BCS), also known as wide local excision or lumpectomy, depends on several factors, including tumor size, extent, location (parenchymal vs. dermal), multifocality, and the ability to achieve wide negative margins while preserving an acceptable cosmetic outcome.

- **Mastectomy (Simple or Total):** Mastectomy is generally the preferred

surgical approach for most cases of primary and secondary breast angiosarcoma. This is because angiosarcomas are often infiltrative and can have microscopic extensions beyond the grossly visible tumor, making it more challenging to achieve adequate margins with less extensive surgery. Mastectomy is typically recommended for larger tumors, multifocal disease (common in RIBAS), or when the tumor extensively involves the skin. Studies suggest that mastectomy is more likely to result in an R0 resection compared to BCS. For RIBAS, total mastectomy, sometimes encompassing all previously irradiated skin and underlying tissue, is often necessary.

- **Breast-Conserving Surgery (BCS) / Wide Local Excision:** BCS may be considered as an option for selected cases of small, well-localized primary angiosarcomas, particularly if they are low-grade and there is a high likelihood of achieving wide negative surgical margins without compromising oncologic safety or resulting in an unacceptable cosmetic outcome. However, if BCS is performed, the margins must be unequivocally negative and sufficiently wide. Some evidence suggests that for primary breast angiosarcoma, BCS might lead to increased overall survival, and for secondary breast angiosarcoma, non-inferior overall survival when compared to mastectomy, but these findings require cautious interpretation due to the retrospective nature of the studies and potential selection biases (39). Given the high local recurrence rates associated with angiosarcoma, BCS is generally approached with caution.

6.1.2. Importance of Achieving Negative Surgical Margins

Achieving histologically negative (R0) surgical margins is of paramount importance in the surgical treatment of breast angiosarcoma and is a critical

prognostic factor for local control and survival. Positive or close surgical margins (R1 or R2 resection) are strongly associated with an increased risk of local recurrence and poorer overall outcomes, even if adjuvant radiotherapy is administered.

Defining an "adequate" negative margin can be challenging for angiosarcomas due to their infiltrative growth pattern. While a microscopically clear margin is the minimum goal, some authorities advocate for wider margins, such as >1 cm or even >2 cm, particularly for secondary angiosarcomas where dermal spread can be extensive. The deep margin is often a site of positivity in incomplete excisions, suggesting that resection may need to include underlying fascia or even muscle in some cases to ensure clearance. The diffuse and often multifocal nature of RIBAS makes achieving negative margins particularly difficult, and some surgeons advocate for the excision of all previously irradiated tissue if feasible. If initial surgical margins are found to be positive or very close, re-resection to achieve wider clearance is generally recommended if anatomically possible (40, 46).

A significant challenge in surgical management is the "margin dilemma": despite surgeons' best efforts to achieve clear margins based on gross and sometimes intraoperative assessment, the infiltrative nature of angiosarcoma means that microscopic disease frequently extends beyond the visible or palpable tumor. This is particularly true for secondary AS involving the skin. Even after an apparent R0 resection, local recurrence rates can be distressingly high. This suggests that current methods for margin assessment may be insufficient for this specific tumor biology and underscores the need for improved intraoperative tools or a broader acceptance of more radical resections in selected high-risk cases.

6.1.3. Role of Axillary Lymph Node Dissection (ALND)

Axillary lymph node dissection (ALND) is generally not routinely indicated in the surgical management of either primary or secondary breast angiosarcoma. This is because angiosarcomas, being sarcomas, primarily spread via the hematogenous (bloodborne) route rather than through the lymphatic system. Metastasis to regional lymph nodes is uncommon,

reported in less than 10% of patients with primary breast AS in some series.

ALND should typically be reserved for cases where there is clinical or radiological evidence of axillary lymph node involvement, such as the presence of enlarged, firm, or suspicious palpable nodes, or nodes deemed metastatic on preoperative imaging. Routine prophylactic ALND in the absence of suspicious nodes is not supported by current evidence and would add morbidity without clear oncologic benefit.

Reconstruction

Given the often extensive resections required to achieve negative margins, particularly with mastectomy for larger or diffuse tumors, breast reconstruction is an important consideration. Patients frequently require consultation with plastic and reconstructive surgeons to discuss options, which may include immediate or delayed reconstruction using various techniques, including autologous tissue flaps or implant-based methods. The choice and timing of reconstruction depend on the extent of the defect, patient factors, and the potential need for adjuvant therapies like radiation.

6.2. Radiotherapy (RT)

The role of radiotherapy (RT) in the management of breast angiosarcoma is complex and varies depending on whether the tumor is primary or secondary (RIBAS), and whether RT is being considered in the adjuvant, neoadjuvant, or definitive setting.

- **Adjuvant RT:** Following surgical resection, adjuvant RT is often considered, particularly for patients with high-grade tumors, large tumor size, or positive or close surgical margins, with the aim of reducing the risk of local recurrence. For *primary breast angiosarcoma*, the use of adjuvant RT is largely extrapolated from general principles of soft tissue sarcoma management. Some retrospective studies suggest that it may improve local control. For *secondary angiosarcoma*, especially RIBAS, the role of additional (re-)irradiation is highly controversial and technically challenging. The primary concern is that the tumor itself

is radiation-induced, and the surrounding tissues have already received a significant, often maximal, dose of radiation during the treatment of the initial breast cancer. This limits the tolerance of normal tissues to further radiation and increases the risk of severe acute and late toxicities. Despite these challenges, some studies have reported a decrease in local recurrence rates with adjuvant RT in PRAS, while others have not found a clear survival benefit. Specialized techniques such as re-irradiation combined with hyperthermia, or hyperfractionated accelerated RT regimens, have been explored in an attempt to improve the therapeutic ratio (local tumor control vs. normal tissue toxicity) in this difficult setting, with some reports of success in local control. The "RIBAS radiotherapy conundrum" highlights this difficult balance: RT is a standard tool for local control, but its use in a radiation-induced tumor within a previously irradiated field requires extreme caution, highly specialized expertise, and careful patient selection after weighing potential benefits against substantial risks.

- **Neoadjuvant RT:** Preoperative (neoadjuvant) RT may be considered for patients with large, locally advanced, or borderline resectable angiosarcomas. The goals are to shrink the tumor, potentially sterilize microscopic disease at the tumor periphery, and thereby increase the likelihood of achieving a complete R0 resection with negative margins. Potential advantages of neoadjuvant RT include smaller radiation treatment volumes (as the tumor bed is treated before surgical manipulation widens it), treatment of better-oxygenated (and thus more radiosensitive) tumor tissue, and a theoretical reduction in the risk of intraoperative tumor cell seeding (21).

- **Definitive RT:** In certain situations where surgery is not feasible due to tumor extent, patient comorbidities, or patient refusal, definitive RT may be considered as a primary treatment modality, particularly for localized cutaneous angiosarcomas (21, 25). Radical RT, sometimes using techniques like high-field electron beam therapy for superficial lesions, has shown some promise in prolonging survival in selected patients with localized disease (21). Curative-intent radiotherapy has also been reported for local control in some cases (25).
- **RT Techniques:** RT for angiosarcoma can be delivered using various techniques. External beam radiotherapy (EBRT) is the most common method. Brachytherapy, which involves placing radioactive sources directly into or near the tumor bed, is another option that can deliver a high, localized dose of radiation. Brachytherapy may offer advantages in specific anatomical locations (e.g., near joints, to spare them from EBRT) or by allowing for a shorter overall treatment time compared to a typical 5-6 week course of EBRT (21).

The decision to use RT, the timing (adjuvant vs. neoadjuvant), and the specific technique should be made on an individual basis by a multidisciplinary team, considering all relevant tumor and patient factors.

6.3. Systemic Therapies

Systemic therapies, including chemotherapy, targeted therapy, and immunotherapy, play a role in the management of metastatic breast angiosarcoma and are sometimes considered in the neoadjuvant or adjuvant setting for patients with high-risk, localized disease. However, responses to systemic agents are often modest and of limited duration, and the optimal regimens and sequencing are not well established due to the rarity of the disease.

6.3.1. Chemotherapy

- **Commonly Used Regimens:**

- **Taxanes (Paclitaxel, Docetaxel):** These agents have demonstrated notable activity against angiosarcomas, particularly those of cutaneous origin and RIBAS. Weekly paclitaxel is a frequently used regimen and is listed as a preferred option in NCCN guidelines for soft tissue sarcoma, which are often extrapolated to angiosarcoma (43).
 - **Anthracyclines (Doxorubicin, Liposomal Doxorubicin):** Anthracyclines are standard first-line cytotoxic agents for many types of soft tissue sarcomas, and they have shown activity in angiosarcoma. Doxorubicin is often used as a single agent or in combination with ifosfamide.
 - **Ifosfamide:** This alkylating agent is also used in combination regimens for sarcomas, including angiosarcoma.
 - **Gemcitabine:** Gemcitabine, often in combination with docetaxel, can be an effective option, particularly as a second-line or subsequent therapy.
 - **Other Cytotoxic Agents:** Other drugs that have been used, though typically not as first-line choices, include vinorelbine, cyclophosphamide, etoposide, and cisplatin.
- **Efficacy:**
 - **Adjuvant and Neoadjuvant Settings:** The role of chemotherapy in the adjuvant (post-surgical) or neoadjuvant (pre-surgical) setting for localized breast angiosarcoma is not clearly defined and remains an area of debate. Some retrospective studies have suggested that adjuvant chemotherapy, particularly anthracycline-based regimens, might improve disease-free survival (DFS) and overall survival (OS) in primary breast AS, or reduce local recurrence rates in secondary AS. A retrospective study on neoadjuvant taxane-based chemotherapy for RIBAS reported improved distant metastasis-free survival (DMFS) and OS compared to no neoadjuvant chemotherapy (22). However, other studies have yielded conflicting results, and a consistent, clear survival benefit for adjuvant chemotherapy has not been definitively established across all patient subsets. The response rate to neoadjuvant chemotherapy, when used, is estimated to be around 40-50% with the most active regimens, but toxicity can be significant.
 - **Metastatic Setting:** In patients with metastatic or unresectable angiosarcoma, chemotherapy is the mainstay of palliative treatment. However, response rates to conventional cytotoxic chemotherapy regimens are generally modest, often in the range of 18-25%, and the median progression-free survival (PFS) is typically short, around 4 to 7 months. Responses, when they occur, are frequently not durable.
- ### 6.3.2. Targeted Therapy and Immunotherapy
- The limited success of conventional chemotherapy has spurred interest in novel systemic approaches, including targeted therapies and immunotherapy, particularly as the molecular understanding of angiosarcoma subtypes evolves.
- **Targeted Therapy:**

- **Anti-VEGF Agents (e.g., Bevacizumab):** Given that angiosarcomas are vascular tumors and often overexpress Vascular Endothelial Growth Factor (VEGF), agents targeting the VEGF pathway have been investigated. Bevacizumab, a monoclonal antibody against VEGF, has shown some efficacy in metastatic or locally advanced angiosarcoma, either as a single agent or in combination with chemotherapy. However, results have been mixed; for example, one randomized phase II trial of bevacizumab combined with weekly paclitaxel reported a lower response rate and higher toxicity compared to paclitaxel alone.
- **Tyrosine Kinase Inhibitors (TKIs):**
 - **Pazopanib:** This multi-targeted TKI, which inhibits VEGFR, PDGFR, and c-Kit, is approved for the treatment of advanced soft tissue sarcomas (excluding GIST and adipocytic sarcoma). It has shown some activity in angiosarcoma, but retrospective data suggest that its efficacy may be limited, with a median PFS of around 3 months.
 - **Other TKIs (Sorafenib, Regorafenib, Anlotinib):** These agents, which also target multiple kinases including VEGFR, have generally produced underwhelming results in clinical studies of angiosarcoma.
- **Beta-blockers (e.g., Propranolol):** There is emerging preclinical and clinical evidence suggesting that non-selective beta-blockers like propranolol may have anti-tumor activity in angiosarcomas, particularly cutaneous forms (40, 43). Propranolol is thought to exert its effects by inhibiting beta-adrenergic signaling, which can influence angiogenesis and tumor cell proliferation. It has been granted orphan drug status in Europe for soft tissue sarcoma treatment (40). Further research is ongoing to clarify its role and efficacy.
- **Immunotherapy (Immune Checkpoint Inhibitors - ICIs):**
 - **Rationale:** The rationale for using ICIs in angiosarcoma stems from observations that some subtypes, especially cutaneous angiosarcomas (including those on the scalp and face, which can be UV-induced), may harbor biomarkers associated with response to immunotherapy. These include a high tumor mutational burden (TMB-H), PD-L1 expression on tumor or immune cells, and the presence of specific mutational signatures (e.g., UV damage signature).
 - **Agents:** Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis (e.g., pembrolizumab, nivolumab) and CTLA-4 (e.g., ipilimumab) are being actively investigated. Pembrolizumab is included in NCCN guidelines as a subsequent-line treatment option for unresectable or metastatic angiosarcoma that has progressed

after prior therapy and when no satisfactory alternatives exist (43).

- o **Efficacy:** Early clinical data from case reports, retrospective series, and phase I/II trials have shown promising and sometimes durable responses to ICIs in a subset of patients with angiosarcoma, including complete responses. These responses appear to be more frequent in cutaneous angiosarcomas, particularly those of the head, neck, and scalp. However, the overall data are still limited, and larger, prospective clinical trials are needed to confirm these findings, identify predictive biomarkers of response, and determine the optimal use of ICIs in the treatment of various angiosarcoma subtypes, including breast angiosarcoma.

The evolving landscape of systemic therapy reflects a gradual shift from broad cytotoxic chemotherapy towards more personalized approaches based on the molecular characteristics and immune microenvironment of the tumor. While conventional chemotherapy remains important, particularly for initial treatment of metastatic disease, the development of effective targeted therapies and immunotherapies holds significant promise for improving outcomes in this challenging malignancy.

Table 3: Overview of Treatment Modalities for Breast Angiosarcoma

Treatment Type	Role/Indication	Key Considerations/Reported Efficacy	Common Toxicities/Controversies
Surgery (Mastectomy)	Primary treatment for most localized primary & secondary	Higher chance of R0 resection.	Cosmesis, reconstruction needs.
AS.			
Larger/multifocal tumors.			
Surgery (Breast-Conserving Surgery - BCS)	Selected small, localized primary AS.	Preserves breast tissue.	Higher local recurrence if margins inadequate. Requires careful selection.
Radiotherapy (Adjuvant)	Post-surgery for high-risk features (positive/close margins, high grade).	May improve local control.	Controversial & challenging for RIBAS (prior irradiation). Normal tissue toxicity.
Radiotherapy (Neoadjuvant)	Large, borderline resectable tumors.	Tumor downsizing, improve resectability.	Delays surgery, acute RT side effects.
Radiotherapy (Definitive)	Unresectable localized disease, palliative.	Local control in select cases.	High doses needed, potential toxicity.
Chemotherapy (Taxanes - Paclitaxel, Docetaxel)	Metastatic disease; (neo)adjuvant for high-risk/RIBAS.	Active, esp. cutaneous AS/RIBAS. NCCN preferred.	Myelosuppression, neuropathy, alopecia.
Chemotherapy (Anthracyclines - Doxorubicin)	Metastatic disease; (neo)adjuvant.	Standard for STS, active in AS.	Cardiotoxicity, myelosuppression.
Targeted Therapy	Metastatic/advanced	Some activity in AS, but	Hypertension, diarrhea, liver toxicity.

(Pazopanib)	STS (2nd line).	limited efficacy.
Targeted Therapy (Bevacizumab)	Metastatic/advanced AS (often with chemo).	Anti-VEGF; mixed results, potential toxicity. Hypertension, bleeding, thrombosis.
Targeted Therapy (Propranolol)	Cutaneous AS (investigational).	Potential anti-proliferative/anti-metastatic effects. Bradycardia, hypotension, fatigue. Still under investigation.
Immunotherapy (ICIs e.g., Pembrolizumab)	Metastatic/unresectable AS (subsequent line).	Promising responses in some, esp. related to cutaneous AS with specific biomarkers (UV signature, TMB-H). Immune-related adverse events. Data still limited, trials ongoing.

7. Prognosis

The prognosis for patients with breast angiosarcoma is generally considered poor, influenced by a variety of clinical and pathological factors. The aggressive nature of the disease, coupled with challenges in diagnosis and treatment, contributes to unfavorable outcomes for many patients.

7.1. Prognostic Factors

Several factors have been identified in the literature as influencing the prognosis of breast angiosarcoma:

- **Tumor Grade:** Histological grade is one of the most consistently reported prognostic factors. High-grade tumors (Grade III or IV, or simply designated "high-grade") are associated with significantly worse disease-free survival (DFS) and overall survival (OS) compared to low-grade (Grade I or II) tumors. Patients with low-grade lesions generally have a more favorable prognosis.
- **Tumor Size:** Larger tumor size, often defined as ≥ 5 cm in diameter, is generally considered a negative prognostic indicator, associated with an increased risk of recurrence and decreased survival. However,

some studies have not found a statistically significant correlation between tumor size and outcome, possibly due to variations in study populations or the overwhelming influence of other factors like grade.

- **Surgical Margins:** The status of surgical margins after resection is a critical determinant of local control and survival. Achieving complete surgical excision with histologically negative (R0) margins is essential. Positive or close margins are strongly predictive of local recurrence and are associated with poorer survival outcomes.
- **Age at Diagnosis:** Older age at diagnosis has been linked to a worse prognosis, particularly in patients with secondary angiosarcoma. Conversely, primary angiosarcoma tends to occur in younger women, and if these tumors are low-grade and completely resected, the prognosis may be relatively better compared to older patients or those with high-grade disease (28).
- **Stage at Presentation:** As with most malignancies, the stage of disease at the time of diagnosis is a major prognostic factor. Patients presenting with localized disease have a better prognosis than those with regional spread (e.g., extensive local infiltration, though nodal involvement is rare) or distant metastatic disease. The presence of metastases at diagnosis confers a very poor prognosis.
- **Primary versus Secondary Angiosarcoma:** Secondary angiosarcoma, particularly RIBAS, is often considered to have a more aggressive clinical course and potentially a worse prognosis compared to primary breast angiosarcoma. However, high-grade primary angiosarcomas can also be very aggressive (28). The poorer outcome in secondary AS may be related to factors such as older patient

age, underlying tissue damage from prior radiation, and often more diffuse or multifocal disease presentation.

- **Clinical Presentation (for Secondary AS):** In some series of secondary angiosarcoma, presentation with ecchymosis or violaceous skin changes has been identified as a negative predictor for recurrence-free survival (RFS) and OS.
- **Anatomic Site/Laterality:** While less consistently reported for breast AS specifically, the primary site of origin can influence prognosis in angiosarcomas generally (27, 28). One study on breast angiosarcoma noted that right-sided tumors were associated with a worse prognosis, although the underlying reason for this observation remains unclear and requires validation (28). For angiosarcomas in general, unfavorable locations like the retroperitoneum are linked to poorer outcomes.
- **Molecular Markers:**
 - **MYC Amplification:** While primarily a diagnostic marker for secondary angiosarcoma, the prognostic significance of MYC amplification itself, independent of other factors like grade and stage, is still under investigation.
 - **Ki-67 Proliferation Index:** A high Ki-67 index, reflecting a high rate of tumor cell proliferation, generally correlates with more aggressive behavior and is likely associated with a poorer prognosis (11, 14).
 - **PIK3CA mutations:** These are more common in primary breast AS (3, 29). Their direct impact on prognosis, independent of tumor grade, is an area for further research.

- **Multifocality:** The presence of multifocal lesions, particularly in RIBAS, is considered an indicator of poor prognosis and can make achieving complete surgical control more challenging.

It is important to recognize that these prognostic factors often interact. For example, a large, high-grade tumor (multiple negative factors) is more likely to have positive margins after surgery, further worsening the prognosis. An older patient with secondary AS presenting with diffuse skin changes faces a confluence of adverse factors. This interplay underscores the complexity of predicting outcomes in individual patients.

7.2. Recurrence Patterns

Breast angiosarcoma is notorious for its high rates of both local and distant recurrence, which are major contributors to its overall poor prognosis.

- **Local Recurrence:** Local recurrence in the treated breast, chest wall, or regional skin is a very common event following initial treatment. The risk of local recurrence is significantly increased by factors such as positive or close surgical margins, higher tumor grade, and secondary angiosarcoma subtype (especially RIBAS). For RIBAS, local recurrence rates are particularly high, with some studies reporting rates of 78% or 61%. The median local recurrence-free interval (LRFI) for RIBAS can be quite short, often around 10 to 12 months after initial surgery. Even with apparently complete resection, the infiltrative nature of the tumor often leads to residual microscopic disease that can give rise to local relapse. Recurrences typically develop within the first two years after primary resection (40).
- **Distant Metastasis:** Distant metastasis is also a frequent occurrence in breast angiosarcoma and is the primary cause of mortality for most patients.
 - **Common Sites of Metastasis:** The lungs are the most common site for

distant spread of breast angiosarcoma. Other frequently involved metastatic sites include the liver, bones, and distant skin or soft tissues. Metastasis to the contralateral (opposite) breast has also been reported (31).

- **Pattern of Spread:** The predominant mode of distant spread for angiosarcomas is hematogenous (via the bloodstream), consistent with their vascular origin. While regional lymph node metastasis is considered less common than in carcinomas, it can occur, particularly with certain histological subtypes like epithelioid angiosarcoma, or in cases with extensive local disease.
- **Unusual Metastatic Sites:** Reflecting their angiotropic nature, angiosarcomas can sometimes metastasize to unusual locations. Case reports have documented metastases from mammary angiosarcoma to sites such as the cecum, tonsils, buttock, oropharynx, and even the heart.

The aggressive behavior of breast angiosarcoma is evident in its dual propensity for both high rates of local recurrence, often due to the challenges in achieving complete microscopic eradication with surgery, and a strong tendency for early distant hematogenous metastasis. This dual threat necessitates a comprehensive treatment strategy that aims for maximal local control (through aggressive surgery and often radiotherapy) while also considering systemic therapies to address micrometastatic disease, although the efficacy of current systemic agents in the adjuvant setting remains limited.

7.3. Survival Outcomes

Survival outcomes for patients with breast angiosarcoma are generally unfavorable, reflecting the aggressive nature of the disease and the challenges in achieving durable disease control.

Reported survival rates can vary widely in the literature, influenced by factors such as disease subtype (primary vs. secondary), tumor grade and stage at diagnosis, patient characteristics, treatment modalities employed, and the length of follow-up in different studies.

- **Overall Survival (OS):** The 5-year OS rates for breast angiosarcoma (combining primary and secondary types) are often cited in the range of 20% to 55% in various series. One general estimate for all angiosarcomas suggests a 5-year survival rate of about 35%.
 - For *primary breast angiosarcoma*, 5-year OS can range significantly, from approximately 43% to as high as 88% in some series, with outcomes heavily dependent on tumor grade and other prognostic factors. Patients with low-grade, localized primary tumors that are completely resected tend to have better survival.
 - For *secondary breast angiosarcoma*, particularly RIBAS, the prognosis is often considered worse. Reported 5-year OS rates for secondary AS are typically in the range of 40% to 55%. However, some studies focusing specifically on RIBAS have reported more sobering figures, such as a 3-year OS rate of only 15.2% in one series. Median OS for RIBAS was reported as 31 months in one study, while another study reported a median OS of 37 months for secondary AS. For patients presenting with or developing metastatic angiosarcoma, the median OS is considerably shorter, often around 7 to 16 months with systemic therapy.

- **Disease-Free Survival (DFS):** DFS rates are also generally poor due to the high frequency of local and distant recurrences.
 - For angiosarcomas (mixed sites, including breast), one study reported a 5-year DFS rate of 19.3%. Within the same study, the cohort with breast angiosarcoma specifically had a 5-year DFS of 34.8% (27).
 - For primary breast angiosarcoma, 5-year DFS is highly grade-dependent: it can be as high as 76% for grade 1 tumors but drops sharply to around 15% for grade 3 tumors (31).
 - In a series of angiosarcoma patients treated with (neo)adjuvant chemotherapy, the median DFS from diagnosis was reported as 1.4 years.
- **Impact of Staging and Treatment on Survival:** As expected, patients diagnosed with advanced-stage disease (regional or distant metastases) have significantly worse survival outcomes compared to those with localized tumors. Achieving a complete surgical resection with negative margins (R0 resection) is consistently associated with improved survival. The impact of adjuvant therapies (radiotherapy and chemotherapy) on overall survival is less consistently demonstrated across all studies and patient subgroups, with some studies showing benefit and others not.

The notable heterogeneity in reported survival outcomes for breast angiosarcoma (e.g., 5-year OS ranging from as low as 15% in some RIBAS cohorts to over 80% in selected low-grade primary AS cohorts) reflects several underlying issues. These include the inherent biological diversity of the disease itself (primary vs. secondary, different grades, varying molecular profiles), differences in patient populations across studies (age, comorbidities), variations in treatment approaches

and expertise among institutions, and the statistical limitations imposed by small sample sizes in many retrospective series due to the tumor's rarity. This variability makes it challenging to provide precise prognostic information to individual patients and complicates comparisons of treatment efficacy across different studies. It also underscores the need for larger, multi-institutional collaborative studies and registries to better define prognostic groups and standardize outcome reporting.

Table 4: Significant Prognostic Factors in Breast Angiosarcoma

Factor	Impact on Recurrence/Survival
Tumor Size (e.g., <5 cm vs. ≥5 cm)	Larger size generally associated with worse DFS/OS.
Histological Grade (Low vs. High)	High grade strongly associated with worse DFS/OS and higher recurrence.
Surgical Margin Status (Negative vs. Positive/Close)	Positive/close margins strongly predict local recurrence and worse survival.
Age at Diagnosis	Older age often associated with poorer survival, especially in secondary AS.
Tumor Type (Primary vs. Secondary/RIBAS)	Secondary AS (especially RIBAS) often considered more aggressive with poorer prognosis.
Stage (Localized vs. Regional/Distant)	Advanced stage significantly worsens prognosis.
MYC Status (Amplified vs. Not)	Diagnostic for secondary AS; direct independent prognostic value still under study.
Ki-67 Index (Low vs. High)	High Ki-67 generally correlates with aggressiveness and poorer prognosis.

Clinical Presentation Ecchymotic presentation in (e.g., ecchymosis for secondary AS linked to secondary AS) worse RFS/OS.

Multifocality Multifocal lesions (esp. in RIBAS) indicate poor prognosis.

8. Challenges in Diagnosis and Management

The diagnosis and management of breast angiosarcoma are fraught with numerous challenges, stemming primarily from its extreme rarity, aggressive biological behavior, and the consequent lack of high-level evidence to guide clinical decision-making. These interconnected difficulties contribute to diagnostic delays, suboptimal treatment outcomes, and high rates of recurrence.

- **Rarity of Disease:** Breast angiosarcoma is an exceptionally uncommon malignancy. This low incidence translates to limited experience for many clinicians, making it difficult to recognize and diagnose promptly. Furthermore, the small number of cases hinders the ability to conduct large-scale prospective clinical trials, which are crucial for developing robust, evidence-based treatment guidelines. As a result, much of the current management is based on retrospective data, small case series, or extrapolation from other soft tissue sarcomas.
- **Non-specific Clinical Presentation:** The symptoms of breast angiosarcoma can be vague, varied, and often mimic benign conditions, particularly in the early stages. Primary angiosarcoma may present as a palpable mass, while secondary forms, especially RIBAS, often manifest as subtle skin changes like bruising, discoloration, or a rash. These "innocent-appearing" lesions can be easily misdiagnosed as simple bruising, post-radiation dermatitis, infection, or hematoma, leading to significant diagnostic delays which can be detrimental given the tumor's aggressive nature.

- **Imaging Limitations:** Standard breast imaging modalities such as mammography and ultrasound frequently yield non-specific or even false-negative results for angiosarcoma. Mammography can be particularly unhelpful in young women with dense breasts (typical for primary AS) or when secondary AS presents mainly with skin changes. While MRI is more sensitive in detecting lesions and assessing their extent, its findings can still be equivocal, often requiring biopsy for definitive diagnosis.
- **Pathological Subtleties and Diagnostic Difficulty:** Histopathological diagnosis can be challenging. Well-differentiated angiosarcomas can closely mimic benign vascular lesions like hemangiomas, especially on small biopsy samples. Conversely, poorly differentiated angiosarcomas can resemble other aggressive malignancies such as high-grade carcinomas or melanomas. Accurate diagnosis relies heavily on experienced pathologists and the judicious use of immunohistochemical markers (e.g., CD31, ERG, MYC). Differentiating RIBAS from atypical vascular lesions (AVL) in a previously irradiated field can be particularly problematic without molecular analysis for *MYC* amplification.
- **Lack of Consensus on Optimal Treatment:** Due to the disease's rarity and the limited availability of data from large clinical trials, there is no universally accepted consensus on the optimal treatment strategies for breast angiosarcoma. This applies to the choice of surgical approach (BCS versus mastectomy), the indications and techniques for adjuvant or neoadjuvant radiotherapy (especially in the complex scenario of RIBAS), and the selection and timing of systemic therapies. Treatment decisions are often individualized and based on the collective experience of

multidisciplinary teams at specialized centers.

- **Difficulty in Achieving Negative Surgical Margins:** The infiltrative and often diffuse growth pattern of angiosarcoma makes it exceedingly difficult to achieve wide, truly negative (R0) surgical margins, even with aggressive surgical procedures like mastectomy. The deep margin is a common site of involvement. This difficulty in obtaining clear margins is a major contributor to the high rates of local recurrence.
- **High Recurrence Rates:** Despite aggressive multimodality treatment, breast angiosarcoma is characterized by very high rates of both local recurrence and distant metastasis. This relentless tendency to recur significantly impacts long-term survival and quality of life.
- **Aggressive Nature and Rapid Progression:** The inherent biological aggressiveness of angiosarcoma means that the disease can progress rapidly, often limiting the window for effective intervention and contributing to its poor overall prognosis.
- **Need for Specialized Centers and Multidisciplinary Approach:** Given all these complexities, the optimal management of breast angiosarcoma necessitates referral to specialized sarcoma centers with extensive experience and a dedicated multidisciplinary team. Such teams typically include pathologists, radiologists, surgical oncologists, medical oncologists, radiation oncologists, and plastic/reconstructive surgeons, all with expertise in sarcoma care. However, access to such specialized centers may be limited for some patients.

These challenges are not isolated but rather interconnected, creating a cumulative negative impact. For example, the rarity of the disease (1) can

lead to lower clinician familiarity, which, combined with non-specific presentations (1) and imaging findings (5), can result in diagnostic delays (38). Such delays are particularly detrimental for an already aggressive tumor (6). Even when a diagnosis is made, treatment is complicated by the lack of consensus on optimal strategies (17) and the inherent difficulty in achieving complete surgical eradication due to infiltrative growth (19), ultimately leading to high recurrence rates (19) and poor prognosis. Addressing these multifaceted challenges requires a concerted effort involving improved awareness, enhanced diagnostic tools, collaborative research to establish evidence-based treatment protocols, and centralized care in expert centers.

9. Current Guidelines and Recommendations

Due to the rarity of breast angiosarcoma, specific, high-level evidence-based clinical practice guidelines dedicated exclusively to this entity are scarce. Management recommendations are often extrapolated from guidelines for soft tissue sarcomas (STS) in general, with some nuanced considerations for the unique aspects of breast angiosarcoma, particularly the radiation-induced subtype. Major guideline-issuing bodies like the National Comprehensive Cancer Network (NCCN) in the United States and the European Society for Medical Oncology (ESMO) provide comprehensive guidelines for STS, which serve as the primary reference for treating angiosarcomas, including those of the breast (18, 23, 43, 44, 45, 46).

- **NCCN Guidelines:** The NCCN Clinical Practice Guidelines in Oncology for Soft Tissue Sarcoma are a key resource. While these guidelines cover over 50 histological subtypes of STS, they acknowledge that some are so rare that specific treatment recommendations are limited (44). For angiosarcomas, the NCCN guidelines generally recommend:
 - **Diagnosis:** Confirmation by an experienced sarcoma pathologist is crucial. Biopsy should be carefully planned (44, 46).

- **Localized Disease:** Surgical resection with the aim of achieving wide negative margins is the primary treatment (40, 43, 46). For stage II and resectable stage III disease, preoperative radiation therapy is a category 1 recommendation (40). Postoperative radiation is also an option, particularly if margins are close or positive, or for high-grade tumors (21, 40). The role of adjuvant chemotherapy is not routinely established but may be considered in high-risk situations. For angiosarcoma specifically, paclitaxel is listed as a preferred chemotherapy agent if systemic therapy is indicated (43).
- **Metastatic or Unresectable Disease:** Systemic therapy is the mainstay. Paclitaxel is a preferred first-line option for angiosarcoma. Other options include doxorubicin-based regimens. Pembrolizumab (an immune checkpoint inhibitor) is listed as a subsequent-line treatment option for unresectable or metastatic angiosarcoma that has progressed following prior treatment and when no satisfactory alternative treatments exist (43). The NCCN emphasizes the importance of managing patients with sarcomas at high-volume centers with multidisciplinary expertise (44). Specific guidelines for "Breast Cancer" (33) primarily focus on epithelial carcinomas and do not typically detail the management of rare sarcomas like angiosarcoma, reinforcing the need to consult STS guidelines.
- **ESMO Guidelines:** ESMO, in collaboration with EURACAN (European Reference Network for rare adult solid cancers) and GENTURIS (European Reference Network for genetic tumour risk syndromes), publishes clinical practice guidelines for soft tissue and visceral sarcomas (45, 46). These guidelines also emphasize:
 - **Diagnosis:** Diagnosis in a reference center with sarcoma expertise, including expert pathology review and molecular pathology where appropriate. Core needle biopsy is preferred over open incisional biopsy in most cases (46).
 - **Localized Disease:** Wide surgical excision is the standard of care. Preoperative or postoperative radiotherapy is often recommended for deep, high-grade tumors >5 cm, or when margins are inadequate. The role of adjuvant chemotherapy is generally not recommended outside of clinical trials for most STS subtypes, but angiosarcoma's chemosensitivity, particularly to taxanes, might warrant consideration in high-risk cases, though robust evidence is lacking (24, 46).
 - **Advanced/Metastatic Disease:** Anthracycline-based chemotherapy (e.g., doxorubicin) is a standard first-line treatment. For angiosarcoma, weekly paclitaxel is a recognized active regimen. Pazopanib is an option for non-adipocytic STS in second-line and subsequent treatment (24, 46). ESMO guidelines for "Early Breast Cancer" (35, 36) and "Metastatic Breast Cancer" focus on common epithelial breast cancers and do not provide specific recommendations for angiosarcoma.

Limitations and Need for Expert Centers: A significant challenge highlighted by both NCCN and ESMO is the rarity and heterogeneity of sarcomas, including angiosarcoma (44, 45). This makes it difficult to conduct randomized controlled trials to establish definitive treatment protocols for each subtype. Consequently, many recommendations are based on smaller studies, retrospective analyses, or expert consensus. Both guideline bodies strongly advocate for patients with suspected or confirmed sarcomas to be referred to and managed by a specialized multidisciplinary team at a sarcoma reference center or a center with significant expertise in treating these rare tumors. This is crucial for accurate diagnosis, appropriate staging, individualized treatment planning (which may include surgery, radiation, systemic therapy, or a combination), access to clinical trials, and optimal supportive care. The complexity of breast angiosarcoma, particularly RIBAS, further underscores this need, as treatment decisions (e.g., re-irradiation, extensive surgery) require a high level of specialized skill and experience.

In summary, while specific guidelines solely for breast angiosarcoma are lacking, comprehensive STS guidelines from bodies like NCCN and ESMO provide the framework for management. These guidelines consistently emphasize complete surgical resection with negative margins for localized disease, consider perioperative radiotherapy, and outline options for systemic therapy in advanced or metastatic settings, with taxanes being particularly relevant for angiosarcoma. Crucially, they highlight the paramount importance of multidisciplinary care in specialized sarcoma centers to navigate the complexities of this rare and aggressive malignancy.

10. Future Research Directions

The rarity and aggressive nature of breast angiosarcoma, coupled with current treatment limitations, underscore an urgent need for further research across multiple fronts. Future investigations should aim to enhance understanding of its pathogenesis, improve early detection and risk stratification, and develop more effective and less toxic therapeutic strategies.

- **Novel Therapeutic Strategies:**

- **Targeted Therapies Based on Molecular Profiles:** A key area of research is the identification and validation of actionable molecular targets. The distinct molecular landscapes of primary (often *PIK3CA*-mutated) versus secondary (*MYC*-amplified) breast angiosarcomas offer avenues for tailored therapies. Research into inhibitors of the PI3K/AKT/mTOR pathway for *PIK3CA*-mutant primary AS, and strategies to target *MYC* or its downstream effectors in secondary AS, is warranted. Further genomic and proteomic profiling of tumors is needed to uncover additional vulnerabilities. The role of anti-angiogenic agents, beyond current TKIs like pazopanib and sorafenib, needs continued exploration, perhaps with newer generation compounds or combinations. The potential of beta-blockers like propranolol, particularly in cutaneous AS, also merits further investigation in well-designed clinical trials (40, 43).
- **Immunotherapy:** Immune checkpoint inhibitors (ICIs) have shown promise in some angiosarcoma subtypes, especially cutaneous AS with UV mutational signatures or high tumor mutational burden (TMB). Future research should focus on:
 - Identifying reliable predictive biomarkers for ICI response in breast angiosarcoma (e.g., PD-L1 expression, TMB, specific immune cell infiltrates, interferon-gamma signatures).

- Conducting prospective clinical trials of single-agent ICIs and ICI combinations (e.g., anti-PD-1/L1 plus anti-CTLA-4, or ICIs combined with radiotherapy or targeted agents) specifically in breast angiosarcoma cohorts or enriched sarcoma populations.
- Understanding mechanisms of primary and acquired resistance to immunotherapy.
- **Combination Therapies:** Exploring rational combinations of chemotherapy, targeted therapy, immunotherapy, and radiotherapy to enhance efficacy and overcome resistance is crucial. For example, combining taxanes with anti-angiogenic agents or ICIs.
- **Early Detection Methods and Biomarkers:**
 - **Improved Imaging Techniques:** While MRI is currently the best imaging modality, research into advanced MRI sequences, novel PET tracers, or other imaging techniques that can more specifically identify early angiosarcomatous changes or differentiate them from benign post-radiation alterations would be valuable (42).
 - **Blood-Based Biomarkers (Liquid Biopsies):** The development of non-invasive biomarkers for early detection, risk stratification, monitoring treatment response, and detecting minimal residual disease is a high priority (42). This could include circulating tumor DNA (ctDNA) to detect specific mutations (e.g., *PIK3CA*, *MYC* amplification), circulating tumor cells (CTCs), or proteomic/RNA profiles in blood (42). Such biomarkers could be particularly useful for surveillance in high-risk populations (e.g., post-BCT patients, those with chronic lymphedema).
- **Biomarkers for Risk Stratification:** Identifying molecular or immune biomarkers that can better predict the risk of developing secondary AS (especially RIBAS) after breast cancer treatment could allow for personalized surveillance strategies or even preventative interventions in the future. Understanding why only a small fraction of irradiated patients develop RIBAS is key.
- **Understanding Pathogenesis and Resistance Mechanisms:**
 - Further research into the fundamental biology of angiosarcoma development, including the specific cellular and molecular events driving transformation of endothelial cells in primary AS, RIBAS, and lymphedema-associated AS, is needed.
 - Investigating the tumor microenvironment, including the role of immune cells, fibroblasts, and the extracellular matrix, may reveal new therapeutic targets.
 - Understanding the mechanisms of resistance to current therapies (chemotherapy, targeted agents) is essential for developing strategies to overcome it.
- **Prospective Studies, Collaborative Efforts, and International Registries:** Given the

rarity of breast angiosarcoma, progress will heavily depend on collaborative efforts.

- **Multi-institutional Clinical Trials:** Designing and conducting well-powered prospective clinical trials, even if they require international collaboration, is critical to establish the efficacy of new treatments and define optimal management strategies. Adaptive trial designs or basket trials focusing on molecular alterations rather than just histology might be feasible.
- **International Registries and Tissue Banks:** Establishing comprehensive patient registries and tumor tissue banks can facilitate larger-scale epidemiological studies, correlative research, and the identification of prognostic and predictive biomarkers. "The Angiosarcoma Project," a patient-led initiative, is an example of efforts to gather genetic data.
- **Improving Management of RIBAS:** Specific research is needed to optimize the management of RIBAS, including:
 - Defining the true extent of "at-risk" tissue to guide surgical margins.
 - Evaluating the efficacy and safety of novel re-irradiation techniques (e.g., proton therapy, advanced brachytherapy) or combinations with radiosensitizers or systemic agents.
 - Identifying factors that predict which atypical vascular lesions post-radiation will progress to angiosarcoma.

The focus on understanding molecular drivers (like *MYC* and *PIK3CA*) and the tumor immune microenvironment is paving the way for more targeted and potentially more effective therapies

beyond conventional chemotherapy. Similarly, the development of biomarkers for early detection and risk stratification, particularly for secondary angiosarcoma in high-risk populations (e.g., post-radiation patients), could significantly improve outcomes by allowing for earlier intervention (42). Continued investment in these research areas, fostered by collaborative networks, is essential to make meaningful progress against this challenging disease.

11. Conclusion

Breast angiosarcoma, encompassing both primary and secondary forms, remains a rare yet highly aggressive malignancy characterized by significant diagnostic and therapeutic challenges. Primary angiosarcoma typically affects younger women and arises *de novo*, while secondary angiosarcoma, more commonly radiation-induced (RIBAS) or lymphedema-associated, occurs in older women with a history of prior breast cancer treatment or chronic lymphedema (1, 2, 4). The increasing incidence of secondary breast angiosarcoma, linked to the widespread use of breast-conserving therapy with radiation, highlights an iatrogenic component that demands careful long-term surveillance of at-risk populations.

Diagnosis is often complicated by non-specific clinical presentations that can mimic benign conditions, leading to delays, and by imaging findings that lack pathognomonic features. Histopathological confirmation, supported by immunohistochemical markers like CD31 and, for secondary forms, *MYC*, is essential (1, 3, 14). The infiltrative nature of these tumors makes complete surgical resection with wide negative margins—the cornerstone of curative treatment—particularly difficult to achieve, contributing to high rates of local recurrence.

Current treatment strategies are multimodal, typically involving surgery, with consideration for radiotherapy and systemic therapies, especially in advanced or high-risk cases (17, 19, 21, 24). However, due to the disease's rarity, there is a lack of high-level evidence from large prospective trials, and consensus on optimal adjuvant and neoadjuvant strategies, particularly for RIBAS, is limited. The overall prognosis for breast angiosarcoma remains poor, with high rates of both local recurrence and

distant metastasis, primarily to the lungs, liver, and bone. Factors such as tumor grade, size, margin status, patient age, and disease stage significantly influence outcomes (19, 27, 28).

The management of breast angiosarcoma necessitates a highly specialized, multidisciplinary approach within experienced sarcoma centers to navigate these complexities and offer patients the best possible chance of disease control. Future progress hinges on continued research into the molecular pathogenesis of primary and secondary angiosarcomas, the development of novel targeted therapies and immunotherapies based on identified biomarkers, and the establishment of robust methods for early detection and risk stratification. Collaborative international efforts, including prospective clinical trials and comprehensive patient registries, are paramount to improving the understanding and treatment of this challenging disease and ultimately enhancing patient survival and quality of life.

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