

Primary and secondary angiosarcoma of the breast

Tania K. Arora¹, Krista P. Terracina¹, John Soong², Michael O. Idowu², Kazuaki Takabe¹

¹Division of Surgical Oncology, Department of Surgery, ²Department of Pathology, Virginia Commonwealth University School of Medicine and the Massey Cancer Center, Richmond, VA 23298-0011, USA

Correspondence to: Kazuaki Takabe, MD, PhD, FACS. Division of Surgical Oncology, Department of Surgery, Virginia Commonwealth University, PO Box 980011, West Hospital 7-402, 1200 East Broad Street, Richmond, Virginia 23298-0011, USA. Email: ktakabe@vcu.edu.

Abstract: Angiosarcoma is a rare soft tissue tumor of the breast. It occurs in both a primary form without a known precursor, and a secondary form that has been associated to a history of irradiated breast tissue. These forms differ in many ways including median age, precipitating factors, and presentation. Both forms have a malignant behavior and a poor prognosis. The endeavor of this paper is to review what is known about the presentation, diagnostic and therapeutic modalities to date.

Keywords: Breast; cancer; aggressive; radiation; rapid growth



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Introduction

Angiosarcoma (AS) of the breast is rare, accounting for 1% of all soft tissue breast tumors (1). It presents as primary tumors of the breast or as secondary lesions that are most commonly associated with previous radiotherapy. Primary AS has been observed in women age 30-50 years presenting with poorly defined masses. It accounts for <0.04% of malignant neoplasms and typically arises in the parenchyma of the breast with occasional skin involvement (1-3). In contrast, secondary AS presents in older women (median age 67-71 years) following a median of 10.5 years after radiotherapy for breast cancer (1,4-6). The median latency to presentation after radiotherapy in seven series ranges from 5 to 10 years (1). Although a causal relationship between radiation exposure and AS has not been established, multiple case reports support the increased risk for AS following adjuvant radiotherapy (7-9). It has been proposed that at radiation doses >50 Gy apoptosis occurs while at <50 Gy DNA damage and instability result. Sarcomas frequently occur at the edge of radiation fields where doses and tumor necrosis may be heterogeneous (4,5). When associated with chronic lymphedema and outside a radiated field, AS in an edematous limb after mastectomy and radiotherapy is referred to as Stewart-Treves syndrome (1,3).

Since the first case of breast AS was presented in 1907

by Borrmann and the first case of secondary AS described in 1987 by Body *et al.*, attempts have been made to correlate histological features and patterns of growth with outcome (2,4,5). The overall rarity of the condition has limited assessment of prognostic factors and best therapeutic options. As the diagnosis of early breast cancer increases it is expected that there will be a similar increase in the incidence of secondary AS. This literature review will clarify what is known to date about breast angiosarcoma and the salient features that differ between primary and secondary angiosarcoma. Literature search was conducted using the PubMed database, with search terms “angiosarcoma” and “breast”. Results were limited to English language papers and humans with a result of 532 titles. All 242 papers published within the past 20 years had title and abstract reviewed for relevance to our topic of interest. Additional older studies cited by previous reviews were also examined, and findings are summarized.

Presentation and diagnosis

Women with primary AS usually present with a palpable mass, fullness or swelling in the breast, which at times can be rapidly growing. Large masses have been reported leading to platelet sequestration and the hemorrhagic manifestations of Kasabach Merrit syndrome (2,10).



Figure 1 (A) Macroscopic appearance of the right breast affected by secondary angiosarcoma eight years after adjuvant radiation. Note enlargement and discoloration of the right breast; (B) Advanced disease with discolored nodular lesions; (C) Local recurrence three months after complete removal with negative margins.

Secondary AS, on the other hand, presents as painless bruising that is frequently multifocal but can present with a mass. It is often neglected because of its seemingly innocent appearance (4). There are other varied descriptions of the presenting signs including purplish discoloration, eczematous rash, hematoma-like swelling, and diffuse breast swelling (5) (*Figure 1*).

Mammogram and ultrasound do not have pathognomonic characteristics in AS which are seen with adenocarcinoma, and nodules, particularly in younger women, these findings may be mistakenly labeled benign. Though there is some evidence that mammographic findings may raise suspicion for this diagnosis (11), multiple studies have demonstrated the ability of magnetic resonance imaging (MRI) to identify patterns of malignancy in AS. AS characteristically results in hyperintensity displayed on T2 images and a rapid initial intense phase followed by washout (12,13). MRI has been demonstrated to be able to detect lesions that were occult to mammography (13).

Diagnosis is often made by FNA or Core Needle Biopsy (CNB) as imaging is often equivocal. Excessive bleeding after FNA or biopsy may be evidence of the presence of this highly vascular tumor (14). In cases of secondary AS, skin punch and incisional biopsy have been recommended (5). On histopathological analysis the lesions are notable for irregular vascular formations evident on with hyperchromatic and irregular nuclei. The diagnosis can be clarified by immunohistologic staining for the endothelial marker CD31, the most sensitive and specific indicator of angiogenic proliferation; however, the lesions will also stain positive for the vascular markers Factor VIII, and Fli1, and will usually at least be weakly positive for CD34 (15-17) (*Figure 2*).

Metastatic spread of angiosarcoma is thought to be primarily hematogenous; however, isolated case reports of

lymphatic spread do exist (18,19). Pulmonary metastasis is the most likely distant site (3,20); however, there are multiple case reports of irregular patterns of metastasis from mammary AS including metastasis to the cecum presenting with GI bleeding (21), lesions developing in the tonsils (22), the buttock (23), the oropharynx (24), and the heart (25).

Surgical treatment

Due to the infrequent incidence of this disease, there are no randomized trials comparing wide local excision or a breast conserving approach with mastectomy. Breast conserving therapy has been utilized but is only recommended for small lesions if there is an excellent chance of achieving negative margins. Total mastectomy alone or with axillary node dissection is the preferred surgical treatment. The necessity for axillary nodal dissection is unclear at present as nodal metastasis is not common in AS. In a review of 280 patients with primary angiosarcomas from ten studies, 75% underwent mastectomy, 25% underwent breast conservation and 42% underwent axillary node dissection in combination with one of the previously mentioned breast procedures. Of those studies that reported nodal involvement, this was present in less than 10% of patients (2).

In one of the largest series of secondary AS focused on surgical treatment, 31 of 35 patients underwent surgery (4). Four patients did not undergo surgery because of metastases or locally advanced disease. Mastectomy was performed in 24 patients and 7 local excisions (some patients had previous mastectomy). Though they determined that mastectomy was more likely to result in an R0 resection (defined in this study as a margin of >2 cm), 14 of the 23 patients with an R0 resection developed local recurrence within six months. In another series the deep margin was the most commonly

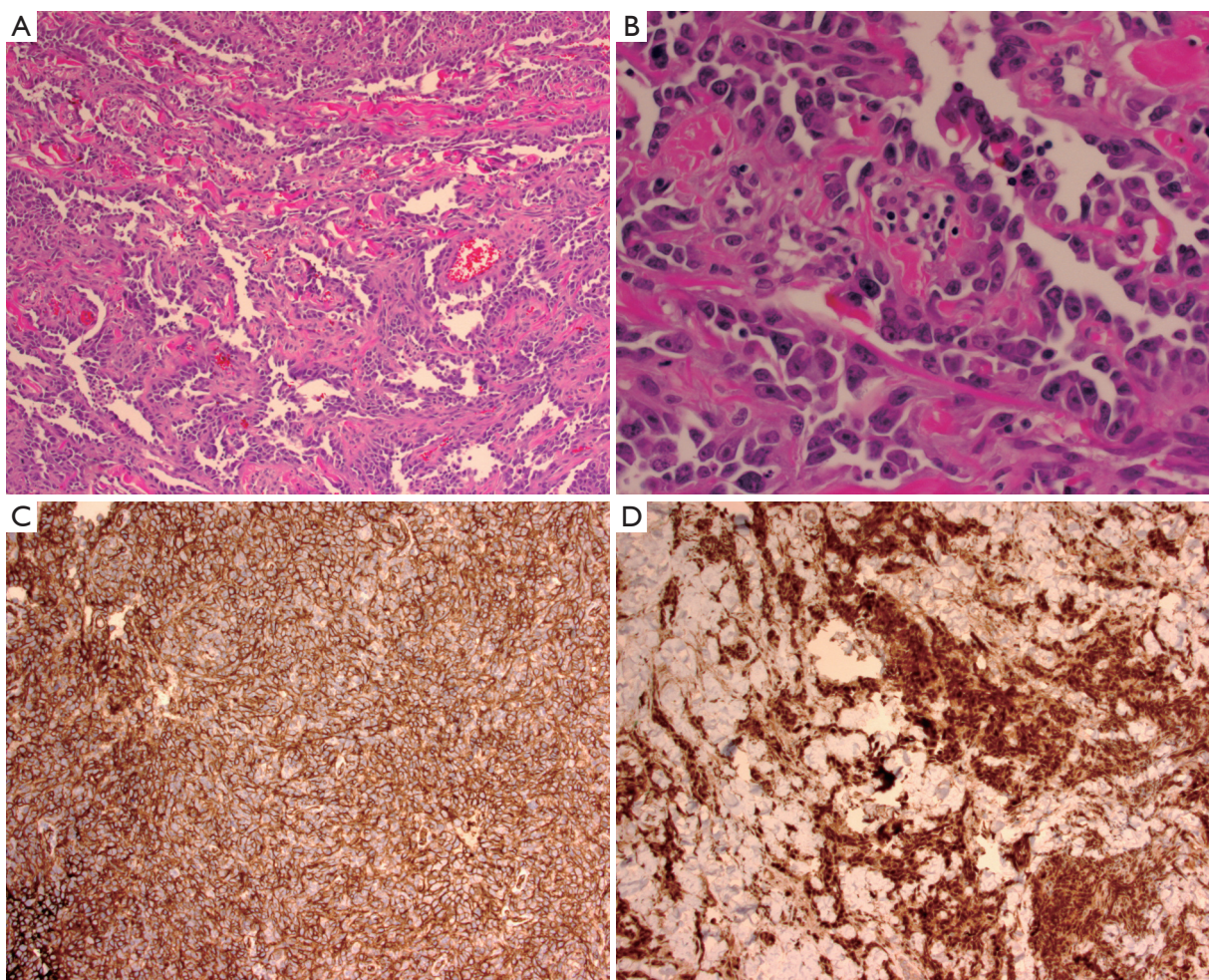


Figure 2 (A) Mammary angiosarcoma (10×) demonstrating vascular channels dissecting through connective tissue and forming anastomotic networks; (B) Higher power showing cytologically atypical endothelial cells with high N:C ratio and large hyperchromatic nuclei (40×); (C) Tumor stains positive for CD31 (10×) and (D) Fli1 (10×).

positive in an incomplete excision suggesting that more aggressive excisions including muscle may be warranted. Many patients in these series required consultation with a plastic surgeon for flap reconstruction (4,5).

Adjuvant treatment

Previous knowledge of treatment for soft tissue sarcomas in general has been applied to AS. The estimated risk of metastases for soft tissue sarcoma has been estimated to be as high as 50%. Some studies suggest that treatment with anthracycline-based chemotherapy can improve both disease free survival (DFS) and overall survival (OS) (8). A meta-analysis of patients treated with doxorubicin and a randomized trial of epirubicin plus ifosfamide demonstrated

longer DFS and OS (26,27). The rate of delivery of chemotherapy can range from 0% to 65% and selection bias of treating more high risk or high grade patients cannot be ruled out (8). In at least two studies, adjuvant chemotherapy had no effect on recurrence free survival or OS (28,29). Taxane based regimens are also gaining prominence in the treatment of angiosarcoma, with a retrospective analysis of 41 patients, published in 2011 among patients with metastatic angiosarcomas from different primary tumor sites demonstrating an improvement in OS from 10.4 to 23.7 months with taxane based regimens compared to non-taxane based adjuvant chemotherapy (30).

Radiation treatment has been used in the adjuvant setting of breast sarcoma with the intent of improving both locoregional control after surgical excision and survival.

In one review of ten series of patients with angiosarcomas of the breast 35% underwent adjuvant radiotherapy (8). Treatment was based on tumor characteristics and the type of surgical treatment (28). Even after mastectomy, radiotherapy has been thought to be beneficial for patient with microscopically positive margins (31). In one series of 14 out of 63 patients treated with radiation either alone or in combination with chemotherapy, there was no correlation to local control or survival (28). In two series, a benefit to the 5 and 10 year recurrence free survival, DFS and OS was seen following radiotherapy (29,32). While there has been suggestion that adjuvant radiotherapy may benefit selected patients, the majority of the data has been based on small retrospective studies that have failed to draw strong conclusions. Utilization of radiotherapy may be limited in many cases of secondary AS, as the breast tissue has already received the maximum dose of radiotherapy (4).

Likewise, the interpretation of the results of adjuvant therapy in secondary AS is limited by the number of cases and the mixed study populations. In a series of 95 patients retrospectively reviewed, adjuvant chemotherapy was found to significantly lower the local recurrence rate; however, did not affect distant recurrence or OS (3). There are few investigations and case reports that have examined the use of (neo)adjuvant paclitaxel, docetaxel, adjuvant vascular endothelial growth factor inhibitors, and hyperfractionated radiotherapy. These therapies show promise but need further examination (1,33-37). Imatinib, a tyrosine kinase inhibitor has also been suggested as a beneficial treatment in radiation-induced sarcoma (38).

Prognostic factors

Like other sarcomas, tumor size and grade, and margin status in relation to prognosis have been of interest. Trends among series indicate higher rates of local failure with positive margin and higher grade. In one series the authors note an improved DFS for grade I and II tumors compared to grade III (39). Other authors have found similar results with significantly improved DFS and OS in low and intermediate grade tumors compared to high grade tumors (28,40). However in one series of 49 patients with primary angiosarcoma of the breast, analysis demonstrated no correlation between grade and survival (41).

Margin status has also been an important influence of local failure that has been examined in several small series. Multiple authors note that recurrences are more common in those patients with positive or close margins, which at

times is in spite of radiotherapy (5,39,42,43).

Studies have demonstrated mixed results in regards to size. Some authors have found that larger size is a negative prognostic factor (3,42,44). Others report that there is no correlation between size and grade or outcome (28,29,39,45).

Prognosis of secondary AS is poor. In a retrospective series of 14 patients over 12 years, incomplete excision was associated with a shorter latency to local recurrence and poor survival. The local recurrence rate was 92% and the median survival time for patients who underwent complete and incomplete excision was 42 and 6 months respectively (5). In one series of 31 patients, in spite of R0 resection, 2/3 developed a local recurrence and median disease specific survival was 37 months (4). In one of the largest series of 33 patients with secondary AS, age greater than 70 and presentation with ecchymosis or violaceous skin were negative predictors of RFS and OS (6). The median survival range reported from seven series is from 15.5-72 months (1). The overall five year survival in various institutional series of primary and secondary AS is 40-55% and 43-88% respectively (1,6).

Summary

Angiosarcoma of the breast in all presentations is rare. The primary and secondary forms are clinically distinct entities (*Table 1*). The median age of primary AS in most series is near 40, 30 years younger than that of secondary AS. The lesions of primary AS usually arise in the parenchyma of non-irradiated breast as opposed to those of secondary AS which arise in the dermal and subcutaneous layers of the skin of radiated fields, 7-10 years post radiation and may not necessarily involve the parenchyma. As the use of breast conservation therapy has increased over the last 30 years, it is assumed that the incidence of secondary AS will likely increase and that a judicious approach to delivery of adjuvant radiotherapy in the treatment of breast cancer should be considered.

The clinical presentation of AS is varied and its sometimes harmless appearance may contribute to a delay and neglect by both patients and physicians. New breast lesions with or without a history of radiation should be evaluated and biopsied for a diagnosis.

As there is no high level evidence on which to base recommendations, no clear consensus exists on the surgical management of AS of the breast. In most series that discuss procedures, the majority of primary AS patients undergo

Table 1 Summary of primary and secondary angiosarcoma of the breast with presentation, diagnosis, treatment recommendations. Levels of evidence utilizing the CEBM guidelines in this table are all level 4

	Presentation	Diagnosis	Surgical management	Chemotherapy	Radiation	Prognosis
Primary	Poorly defined breast mass in the parenchyma, onset age 30-50 years	MRI may be better than US and mammography; must have biopsy confirmation with FNA or CNB	Total mastectomy is most common, although wide local excision may be acceptable. Node dissection is controversial unless clinically positive nodes	Neoadjuvant therapy may assist in changing resectability; adjuvant therapy may increase survival with some studies suggesting no benefit	Hyperfractionated radiotherapy may be beneficial in locoregional control and may improve survival	Positive margin has worse prognosis. Tumor size and grade may contribute to poor prognosis
Secondary	Skin changes in the cutaneous areas, sometimes an isolated mass. Typically 5-10 years after radiotherapy	MRI may be useful but biopsy confirmation is necessary. Skin punch or incisional biopsy useful for cutaneous lesions	Wide local excision or completion mastectomy with goal for negative margins, with or without radical excision requiring chest wall reconstruction, with or without node dissection	Neoadjuvant therapy may assist in changing resectability; adjuvant therapy may increase survival with some studies suggesting no benefit	Hyperfractionated radiotherapy may be beneficial in locoregional control and may improve survival	Positive margin has worse prognosis. Tumor size and grade may contribute to poor prognosis

mastectomy. The management of secondary AS is less clear, as these patients have already undergone surgical management for their original breast cancer. Wide local excision is often reported, but whether or not all irradiated skin is removed is not specified. Furthermore, because the deep margin has been the typical site of margin positivity, the depth of the resection is controversial. Some authors have recommended aggressive resection including removal of muscle (5,6).

It is clear that aggressive treatment of AS of the breast is necessary; however, the role of neoadjuvant, and adjuvant chemotherapy and radiotherapy remains ill-defined. Referral to a specialized center with multidisciplinary care, including plastic surgeons, medical, radiation and surgical oncologists is important to enhance the complicated decision making and to allow for the multimodality therapies necessary in the treatment of this aggressive malignancy.

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