Breast sarcoma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging

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Literature review current through: **Oct 2023.**
This topic last updated: **Oct 20, 2021.**

INTRODUCTION

Breast sarcomas are rare, histologically heterogeneous nonepithelial malignancies that arise from the connective tissue within the breast [1]. They can develop de novo (primary), after radiation therapy (RT), or in the setting of lymphedema of the arm or breast after treatment of another malignancy (therapy related, secondary) [2-6]. Although the clinical features of breast sarcoma mimic those of breast carcinoma in some ways, therapy and prognosis differ dramatically.

This topic review will cover the epidemiology, risk factors, clinical features, diagnosis, and staging of breast sarcoma. Treatment and prognosis are discussed elsewhere, as are other nonepithelial breast tumors, including breast lymphomas, phyllodes tumors (including cystosarcoma phyllodes), and desmoid tumors of the breast. (See "Breast sarcoma: Treatment" and "Phyllodes tumors of the breast" and "Desmoid tumors: Epidemiology, molecular pathogenesis, clinical presentation, diagnosis, and local therapy", section on 'Breast desmoids' and "Overview of the pathobiology of the non-Hodgkin lymphomas", section on 'Introduction'.)

EPIDEMIOLOGY

Breast sarcomas are rare; they account for less than 1 percent of all breast malignancies [7] and less than 5 percent of all soft tissue sarcomas [8]. In data compiled from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), the annual incidence of breast sarcomas was 4.6 cases per million women [9].

The specific incidence of secondary, therapy-related breast sarcomas is difficult to discern. Secondary or treatment-related breast sarcomas most frequently arise following breast cancer treatment with radiation therapy (RT). However, the absolute magnitude of the risk of a secondary breast sarcoma in women who undergo RT for breast cancer appears to be small (table 1).

Angiosarcoma is the specific sarcoma type that is associated most strongly with treatment for a previous breast cancer. In a population-based study in Los Angeles County, the adjusted relative risk of developing an angiosarcoma for women with a prior diagnosis of breast cancer compared with women without breast cancer was 59 (95% CI 22-153) [10]. Furthermore, women who receive RT as a component of breast cancer treatment have a 9- to 16-fold increase in the relative risk of developing an angiosarcoma relative to those treated with other modalities [6,11]. However, despite these high relative risks, the absolute magnitude of risk for a treatment-related angiosarcoma after RT remains small (table 1). The association between ionizing RT and breast sarcomas is discussed in more detail below. (See 'Ionizing radiation' below.)

The average age at presentation is 45 to 50 years (range 17 to 89) [7,9,12-15]. The vast majority of primary breast sarcomas arise in women, although cases are described in men [16]. Men accounted for 1.5 percent of cases of breast sarcoma in a compilation of published reports [17].

Primary breast angiosarcomas tend to occur in somewhat younger women; the average age at diagnosis is under 40 years in most series [10,18-21]. In contrast, the average age of occurrence for treatment-related angiosarcomas is older (median 64, range 44 to 84 years) [18,20,22]. This may be related, at least in part, to the increased prevalence of epithelial breast cancer in older patients. Information about the latency period between RT and the development of radiation-associated breast sarcomas is found below. (See 'Ionizing radiation' below.)

RISK FACTORS

A causative factor for the formation of primary soft tissue sarcomas cannot be identified in many patients with primary breast sarcomas [23]. In contrast, secondary breast sarcomas are

associated with prior radiation therapy (RT) and conditions causing chronic lymphedema [2-6,11,24]. (See "Radiation-associated sarcomas" and "Breast cancer-associated lymphedema".)

There is no proven association between breast implants and breast sarcomas in humans. (See "Complications of reconstructive and aesthetic breast surgery", section on 'Anaplastic large cell lymphoma' and "Implant-based breast reconstruction and augmentation", section on 'Concerns over breast implants'.)

Ionizing radiation

Classification of radiation-associated sarcoma — Ionizing radiation is a well-documented risk factor for secondary breast sarcoma. The classification of a tumor as a radiation-associated sarcoma generally requires that the following criteria be met [25]:

- Evidence of an initial malignant tumor of a different histology than the putative radiation-associated sarcoma
- Development of the sarcoma in an irradiated field
- A prolonged latency period (typically >4 years) between the two malignancies

Secondary or treatment-related breast sarcomas most frequently arise following breast cancer treatment with RT, either as part of breast-conserving therapy or after mastectomy [25-30]. However, secondary breast sarcomas can also follow RT for other malignancies (eg, lymphoma) when the breast and/or chest wall are included in the irradiated field [4].

As with sarcomas at any location, the risk of a radiation-associated breast sarcoma generally increases with higher doses of RT [27,31]. In addition, the risk of secondary sarcoma is higher when patients are irradiated as children than as adults, particularly in those receiving both RT and chemotherapy [32]. (See "Second malignancies after treatment of classic Hodgkin lymphoma", section on 'Bone and soft tissue cancer' and "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Radiation therapy and chemotherapy'.)

Radiation exposure in breast cancer survivors — The early detection of breast cancer through mammographic screening, and improvements in adjuvant therapy have increased the number of breast cancer survivors who are potentially cured of their disease and live long enough to develop late effects of treatment, which include secondary malignancies such as therapy-related sarcomas. (See "Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse", section on 'Risks associated with radiation therapy'.)

Although women who undergo RT for breast cancer have an increased risk of in-field sarcomas that persists for 20 to 30 years, the absolute magnitude of the risk appears to be small (table 1) [2,6,11,33-37]. The average latency period for secondary sarcomas after RT for breast carcinoma is approximately 10 to 11 years, but it may be as long as 44 years and as short as six months [3-5,33,38-41]. The latency period is shorter for angiosarcomas, which tend to occur four to eight years posttreatment [5,10,22,41-45].

It is not known whether newer radiation techniques, such as intensity-modulated RT (IMRT; which decreases the volume of breast tissue exposed to high RT doses but increases the volume exposed to low doses of irradiation [46]) or hypofractionated regimens, may influence the risk of a radiation-associated sarcoma. (See "Radiation therapy techniques for newly diagnosed, non-metastatic breast cancer".)

The potential benefit of RT in the treatment of breast carcinoma usually outweighs the small risk of a treatment-related sarcoma [6]. Nevertheless, the risk is real, and in some cases, it may impact a patient's choice of therapy. As an example, women who have inherited mutations in the ataxia-telangiectasia mutated (*ATM*) gene, which are associated with an increased risk of radiation-associated sarcoma, may choose to avoid breast-conserving therapy, opting instead for mastectomy. (See 'Inherited conditions' below and "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer" and "Ataxia-telangiectasia", section on 'Malignancy'.)

Lymphedema — Chronic arm or breast edema increases the risk of sarcoma after breast cancer treatment, particularly angiosarcoma. Angiosarcomas can also develop in extremities with chronic lymphedema of any etiology [47].

Lymphangiosarcomas of the upper extremity, breast, and axilla arising in women with chronic lymphedema after breast cancer therapy were initially described by Stewart and Treves, and this syndrome is now designated Stewart-Treves syndrome [24]. Such women typically present with longstanding extensive arm edema after mastectomy and axillary lymph node dissection, although it may occur after RT alone (due to axillary lymph node sclerosis) and is most common in patients who undergo both axillary RT and surgery. (See "Clinical features and diagnosis of peripheral lymphedema".)

Inherited conditions — As with other soft tissue sarcomas, there are rarely some predisposing genetic conditions for breast sarcoma, including Li-Fraumeni syndrome, familial adenomatous polyposis (FAP) and its variants, or neurofibromatosis type 1 (NF1) [48]. (See "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Genetic predisposition' and "Li-Fraumeni syndrome" and "Clinical manifestations and diagnosis of familial adenomatous polyposis" and

"Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis", section on 'Soft tissue sarcomas'.)

Environmental factors — Besides ionizing irradiation, environmental exposures linked to sarcomas in general include arsenic compounds, vinyl chloride, herbicides, immunosuppressive agents, and in the case of Kaposi sarcoma, HIV and human herpes virus 8 (HHV-8). (See "AIDS-related Kaposi sarcoma: Clinical manifestations and diagnosis" and "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Radiation therapy and chemotherapy' and "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Industrial chemicals'.)

Although exposure to chemotherapy, particularly alkylating agents, has been implicated in radiation-associated sarcomas, a systematic review of nine studies found no evidence that chemotherapy is a contributing risk factor for radiation-associated breast sarcoma, at least in adults [25].

HISTOLOGIC CLASSIFICATION

As with other non-breast soft tissue sarcomas, primary breast sarcomas are histologically heterogeneous. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Histopathology'.)

Histologic review by an experienced soft tissue pathologist is critical in making the diagnosis and determining histologic type. Evaluation of type distribution in the breast is limited not only by the rarity of the disease, but also by heterogeneity in the way these tumors have been classified [7,9]. Disparate classification schemes have often been used, obscuring distinctions in clinical course and prognosis among the different histologic entities, as illustrated by the following observations:

- Some authors exclude malignant phyllodes tumor (cystosarcoma phyllodes) from breast sarcoma studies because these tumors have a benign epithelial component in addition to a malignant mesenchymal component. Others classify malignant phyllodes tumors as a type of breast sarcoma because of the similar survival and clinical course [7,9,12,49]. Phyllodes tumors of the breast are considered separately. (See "Phyllodes tumors of the breast".)

- Some series include carcinosarcomas of the breast (metaplastic carcinoma), which represent various combinations of poorly differentiated ductal adenocarcinoma, and mesenchymal (sarcomatous) and other epithelial cell (eg, squamous) components. However, most clinicians classify and treat these tumors as an aggressive variant of ductal

adenocarcinoma rather than a sarcoma. (See "Pathology of breast cancer", section on 'Metaplastic carcinoma'.)

In general, in series that are inclusive of all typical sarcoma types, angiosarcomas and undifferentiated pleomorphic sarcomas (formerly included in a broad category that was termed malignant fibrous histiocytoma) comprise the major types. Subsets of undifferentiated/unclassified soft tissue sarcomas include the pleomorphic, round cell, and spindle cell variants. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Histopathology'.)

In one large series of 991 patients with nonangiosarcoma breast sarcoma in the National Cancer Database, the histologic subtype distribution was as follows [50]:

- Sarcoma, not otherwise specified – 26 percent
- Spindle cell sarcoma – 14 percent
- Leiomyosarcoma – 12 percent
- Giant cell sarcoma – 10 percent
- Stromal sarcoma – 6 percent
- Malignant fibrous histiocytoma – 6 percent
- Fibromyxosarcoma – 4 percent
- Dermatofibrosarcoma protuberans – 3 percent
- Fibrosarcoma – 3 percent
- Undifferentiated – 3 percent
- Liposarcoma – 3 percent
- Pleomorphic liposarcoma – 2 percent
- Others – 8 percent

This distribution of histologies included a large number of "not otherwise specified," which further emphasizes the importance of pathologic review by a sarcoma pathologist. Many such histologies have been reclassified or are able to be refined with the use of additional immunohistochemical staining or molecular diagnostics. Other series also indicate the diversity of histologies that can present in the breast and include such additional histologies including solitary fibrous tumor and osteosarcoma [13]. (See "Solitary fibrous tumor" and "Osteosarcoma: Epidemiology, pathology, clinical presentation, and diagnosis".)

In series that include angiosarcomas and particularly those with a high percentage of therapy-related breast sarcomas, angiosarcomas are the most common tumor type [14,15,41,51]. Angiosarcomas comprised almost one-half of all histologic subtypes in series of secondary breast sarcomas [6,11,41].

Angiosarcomas are sometimes referred to as either lymphangiosarcomas or hemangiosarcomas (derived from lymphatic and capillary endothelium, respectively). As this distinction can be quite difficult histologically and is not always clearly defined, both subtypes will be referred to collectively as angiosarcomas for the purpose of this review.

Angiosarcomas have a poor prognosis relative to other subtypes; they behave in a locally aggressive fashion and often metastasize to distant sites. Although there is no apparent prognostic relevance for other histologic subtypes, histology-specific treatment is becoming more commonplace. (See "Breast sarcoma: Treatment", section on 'Outcomes'.)

Grading — The features that are used to assign a histologic grade of differentiation are the extent of tissue differentiation, the mitotic count, the presence or absence of necrosis, cellularity, and pleomorphism. Histologic grade is an important prognostic factor for soft tissue sarcomas, including those arising in the breast. One exception is that the importance of grade in the prognosis of angiosarcoma is disputed. Although some series indicate a better prognosis for low-grade tumors [52-55], others do not [21,56], and grading is generally not recommended for angiosarcoma [57,58]. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Histologic grade' and "Breast sarcoma: Treatment", section on 'Outcomes'.)

CLINICAL FEATURES AND DIAGNOSIS

Breast sarcomas most often present as a unilateral, well-defined, large, painless, firm mass within the breast; they are rarely bilateral. They are usually larger in size than are epithelial breast cancers (median size 5 to 6 cm) and are often characterized by a rapid increase in size [5,9,59].

Breast skin and the nipple-areola complex are only rarely involved by breast sarcomas [60-62]. However, angiosarcomas are the exception; they may be associated with skin thickening, erythema, or skin discoloration with an overlying bluish tint [9,42]. These findings are sometimes mistaken for cellulitis or a hematoma. (See 'Differential diagnosis' below.)

Therapy-related angiosarcomas have a distinct appearance, presenting as single or multiple ecchymotic macular or purplish papular cutaneous lesions in the breast (picture 1) or an edematous upper extremity. Clinically, breast sarcomas often exhibit more rapid growth than do epithelial breast cancers. As with other breast sarcomas, tumor size can be quite large, ranging from 1.5 to 30 cm (median 5 to 6 cm) [7,9,13,53,63].

Diagnosis — A breast sarcoma may be suspected based on physical examination and/or imaging. However, the findings may be similar to those of a primary breast cancer or a benign entity, and accurate tissue diagnosis requires a biopsy.

Imaging — Findings on mammography are nonspecific; calcifications and spiculation are usually absent. In a series of 24 women with primary breast sarcomas, the predominant mammographic finding was a noncalcified oval mass with indistinct margins [64]. Some tumors may be mistaken for benign lesions, such as fibroadenomas [23,65]. The mammogram may be negative even in the setting of a large palpable mass or skin changes [66-69]. Therapy-related sarcomas may be more difficult to detect mammographically because of postsurgical or postradiation changes, but nodular masses may be present (image 1).

Once the tumor is diagnosed as a breast sarcoma, breast magnetic resonance imaging (MRI) is often helpful to more closely examine disease extent preoperatively, particularly in locally advanced tumors near the chest wall. Malignant tumors typically display rapid contrast enhancement with washout characteristics [64,67,70-73]. The borders are often indistinct, and enhancement is inhomogeneous [64]. The MRI appearance of an angiosarcoma is characteristic, with low signal intensity on T1-weighted images but high signal intensity on heavily T2-weighted images, suggesting the presence of vascular channels containing slow-flowing blood [74,75].

MRI can also provide information on the extent of disease within the skin (image 1), as well as the presence or absence of involvement of the deep fascia and pectoralis muscle, which is important in planning the surgical approach [67,70-72,74].

However, as with other imaging modalities, MRI can underestimate the extent of disease. In particular, cutaneous angiosarcomas are not well visualized with any imaging modality, including MRI. If clinical suspicion for disease is high based on physical examination despite normal imaging findings, a diagnostic tissue biopsy should be pursued.

Biopsy — Incisional, excisional, and core needle biopsy all can provide a definitive diagnosis. Core biopsy is generally considered the procedure of choice. If sarcoma is suspected, fine needle aspiration (FNA) is strongly discouraged as it has a low diagnostic accuracy for sarcoma and a false negative result may lead to a delay in diagnosis. In addition, determination of histologic type and grade is seldom possible with FNA. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Biopsy'.)

For cutaneous lesions concerning for angiosarcoma, multiple punch biopsies of the skin may provide a diagnosis (picture 2). The available data are insufficient to assess the accuracy of this approach. The specimen should be taken from the darkest and most infiltrated area.

Laboratory studies — Serum chemistries and tumor markers are of no value in establishing a diagnosis of breast sarcoma.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a primary breast sarcoma includes other primary breast tumors, including inflammatory breast cancer; ductal adenocarcinoma; phyllodes tumor of the breast; breast lymphoma; metastases to the breast from other primary sites; and other benign breast disorders, such as sclerosing adenosis or fibroadenoma. Angiosarcomas with skin discoloration may be mistaken for cellulitis or a breast hematoma. Patients with suspicious findings of discoloration should have a follow-up clinical evaluation within two weeks. If skin findings have not improved or have worsened, then immediate punch biopsy should be performed.

- (See "Clinical features, diagnosis, and staging of newly diagnosed breast cancer".)
- (See "Inflammatory breast cancer: Clinical features and treatment".)
- (See "Clinical manifestations and evaluation of locoregional recurrences of breast cancer".)
- (See "Complications of reconstructive and aesthetic breast surgery", section on 'Anaplastic large cell lymphoma' and "Implant-based breast reconstruction and augmentation", section on 'Concerns over breast implants'.)
- (See "Overview of benign breast diseases".)
- (See "Breast cellulitis and other skin disorders of the breast".)
- (See "Overview of the pathobiology of the non-Hodgkin lymphomas", section on 'Introduction'.)

STAGING

Staging of the extent of tumor spread provides a means for formally assigning prognostic categories and is of enormous value in comparing treatment results from individual treatment centers. Treatment decisions are strongly influenced by the stage at initial diagnosis. The most commonly used staging system for breast sarcomas is the same as that used for sarcomas arising at other sites, from the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) (table 2) [76]. Tumor, node, metastasis (TNM) stage incorporates histologic grade (G), tumor size (T), the presence or absence of lymph node metastases (N), and distant metastases (M) to characterize four stage groupings: I through IV. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Staging'.)

Initial imaging of the primary tumor, to assist in staging, is discussed above. (See 'Imaging' above.)

Nodal status is less informative than it is with epithelial breast cancers. As with soft tissue sarcomas arising at other sites, regional lymph node metastases are uncommon, with the exception of certain histologies, including angiosarcoma. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Regional nodes'.)

All patients should, however, be evaluated for spread of metastatic disease. Computed tomography (CT) of the chest should be obtained for all patients with a primary breast sarcoma, since the lungs are the predominant metastatic site for primary breast sarcoma, similar to the majority of soft tissue sarcomas. Further imaging evaluation for other sites of distant metastases from breast sarcomas is dependent on histology, similar to sarcomas arising from other sites, and is discussed separately. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Evaluation for metastatic disease'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Soft tissue sarcoma".)

SUMMARY AND RECOMMENDATIONS

- Breast sarcomas are primary nonepithelial malignancies arising from the connective tissue within the breast. Sarcomas of the breast can arise de novo (primary) or as a result of treatment for another malignancy (secondary, therapy related), usually with radiation therapy (RT). (See 'Introduction' above.)

- A causative factor cannot be identified in many breast sarcomas. Predisposing genetic conditions can sometimes be identified, but these are uncommon. Secondary or treatment-related breast sarcomas most frequently arise following breast cancer treatment, but they can also be associated with RT for other malignancies in which the breast or chest wall is included in the radiated field. Another contributory factor is chronic lymphedema. (See 'Risk factors' above.)

- Core biopsy is generally considered the procedure of choice for the definitive diagnosis of a breast sarcoma. Fine needle aspiration is strongly discouraged as it has a low diagnostic

accuracy for sarcoma and a false negative result may lead to a delay in diagnosis. For cutaneous lesions, multiple punch biopsies of the skin may provide a diagnosis. (See 'Biopsy' above.)

- Histologic review by an experienced soft tissue pathologist is critical in making the diagnosis and determining histologic type. In general, angiosarcomas and pleomorphic sarcomas are the most frequently occurring types. (See 'Histologic classification' above.)

- Chest computed tomography (CT) should be obtained in all newly diagnosed patients, since the lungs are the predominant metastatic site. Further imaging evaluation for other sites of distant metastases is dependent on histology, similar to sarcomas arising from other sites. (See "Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Evaluation for metastatic disease'.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Thomas F DeLaney, MD, who contributed to an earlier version of this topic review.

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Topic 811 Version 45.0

GRAPHICS

Secondary sarcomas and angiosarcomas after breast cancer radiotherapy

First author, year	Trial design	Follow-up, years	Cumulative total, percent	
			No RT	RT
Sarcoma				
Taghian A; 1991	Cohort*	10	–	0.2
		20		0.4
		30		0.8
Obedian E; 2000	Nonrandomized, cohort*	15	0.2	0.4
Galper S; 2002	Cohort*	11	–	0.4
Yap J; 2002	Case-control¶	15	0.2	0.3
Huang J; 2001	Cohort	–	0.07	0.13
Kirova Y; 2005	Retrospective	5		0.07
		10		0.27
		15		0.48
Angiosarcoma				
Marchal C; 1999	Retrospective		–	0.05
Strobbe L; 1998	Retrospective		–	0.2
Huang J; 2001	Cohort	–	0.005	0.08

RT: radiation therapy.

* Prospective cohort.

¶ From tumor registry.

Modified with permission from: Matesich SM, Shapiro CL. Second cancers after breast cancer treatment. Semin Oncol 2003; 30:740. Copyright © 2003 Elsevier Inc.

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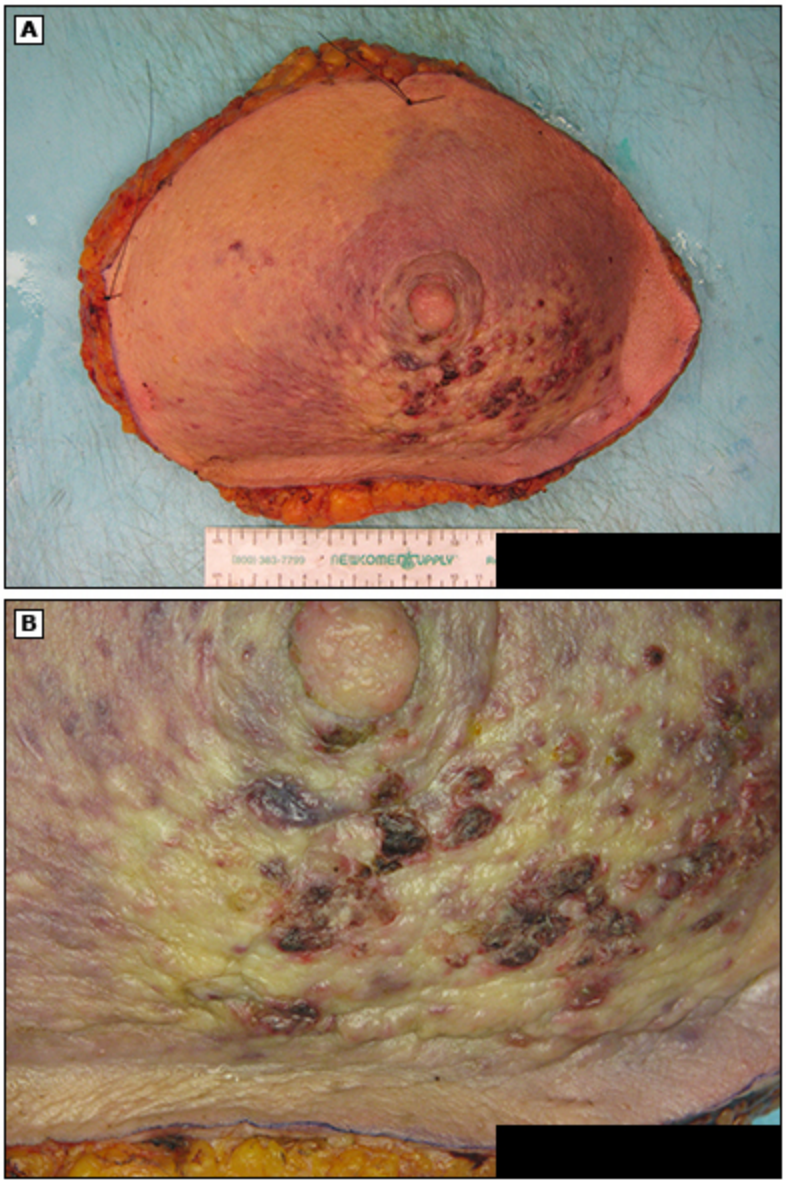
Gross images of breast angiosarcoma



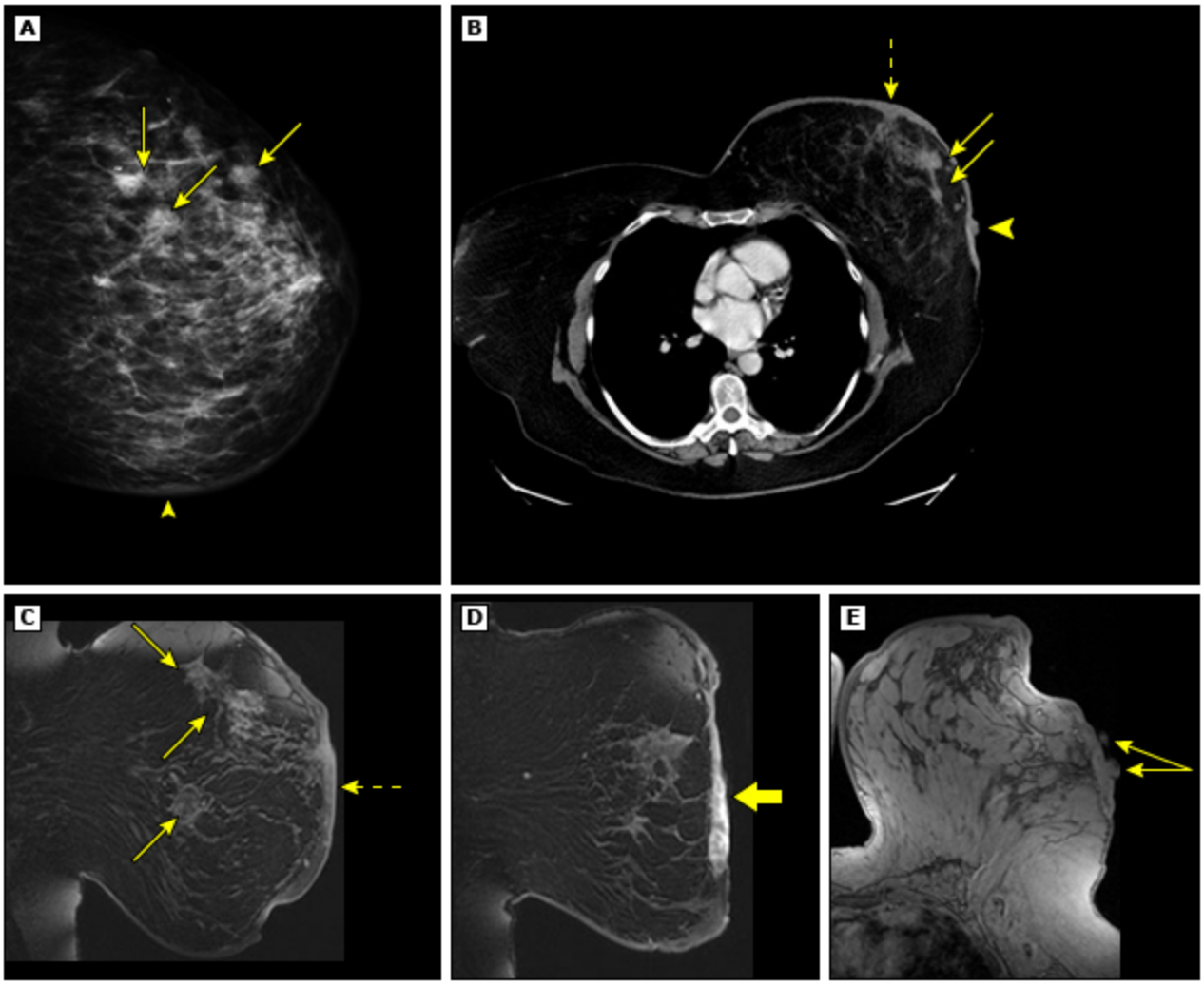
A) Mastectomy specimen from a patient with a radiation-associated angiosarcoma. Note the diffuse purple-blue discoloration of the skin and multiple raised red-black nodules on the skin.

B) A close up image of the nodules which appear to be blood-filled, scabbed, and within an indurated patch.

Courtesy of Drs. Alero Inyang and David Lucas.

Graphic 86979 Version 1.0

Mammogram, CT scan, and MRI of angiosarcoma of the breast



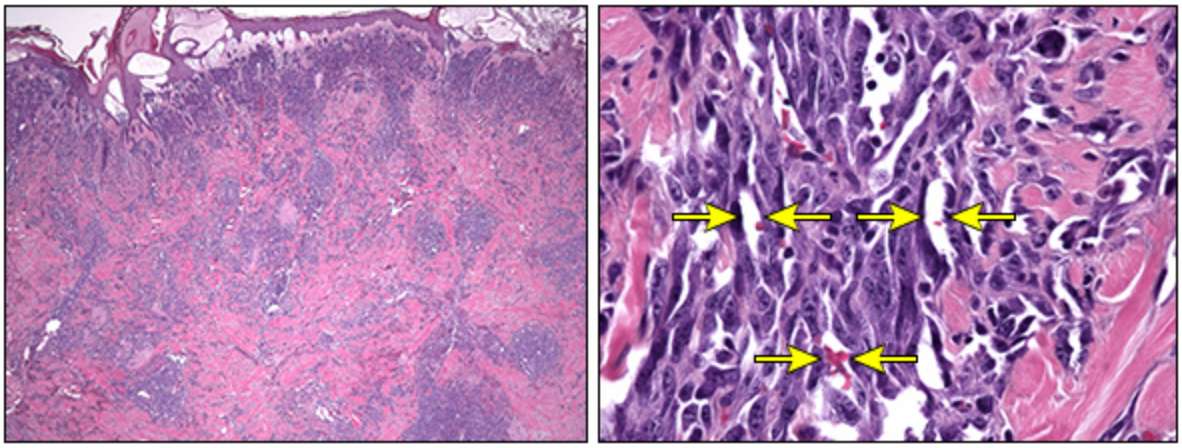
This 55-year-old patient has angiosarcoma of the left breast associated with radiation therapy for breast carcinoma 8 years prior. She presented with breast enlargement and bluish discoloration of the skin that was clinically initially felt to correspond to an "expanding hematoma." The mammogram of the left breast (A) reveals multiple nodular masses (arrows) in the outer part of the breast, with overall increased trabecular background markings and skin thickening (small arrowhead). The CT scan through the mid-chest (B) shows a skin nodule (large arrowhead), breast nodules (arrows), and thickened skin (dashed arrow) of the left breast. There are increased trabecular background markings throughout the left breast. The T1-weighted, fat-suppressed MRI postcontrast images show three suspiciously enhancing masses (arrows in C) and thickened and enhancing skin (thick arrow in D). The T1-weighted MRI image in axial projection (E) shows nodular foci of skin thickening (double arrow).

CT: computed tomography; MRI: magnetic resonance imaging.

Courtesy of Priscilla J Slanetz, MD, MPH, FACR.

Graphic 86977 Version 3.0

Microscopic images of secondary breast angiosarcoma



Left panel reveals a low power view of a photomicrograph of a radiation-associated angiosarcoma. Note the cellular proliferation within the dermis, including pockets of cells, single cells percolating between dermal collagen, and columns of cells that appear to raise the epidermis, forming blisters/nodules (corresponding to the gross appearance of these tumors on the chest wall). Right panel reveals a higher power view of the same tumor showing predominantly spindle cells (and rare epithelioid cells) with large, oval to round vesicular nuclei containing one or more prominent nucleoli and basophilic cytoplasm. These malignant cells form vasoformative channels (arrows) containing erythrocytes.

Courtesy of Drs. Alero Inyang and David Lucas.

Graphic 86926 Version 1.0

Soft tissue sarcoma of the extremities and trunk TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension
Regional lymph nodes (N)	
N category	**N criteria**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
Definition of grade (G)	
G	**G definition**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Prognostic stage groups				
When T is...	**And N is...**	**And M is...**	**And grade is...**	**Then the stage group is...**
T1	N0	M0	G1, GX	IA
T2, T3, T4	N0	M0	G1, GX	IB
T1	N0	M0	G2, G3	II

T2	N0	M0	G2, G3	IIIA
T3, T4	N0	M0	G2, G3	IIIB
Any T	N1	M0	Any G	IV
Any T	Any N	M1	Any G	IV

Tumor differentiation

Tumor differentiation is histology specific and is generally scored as follows:

Differentiation score	Definition
1	Sarcomas closely resembling normal adult mesenchymal tissue (eg, low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (eg, myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400x magnification = 0.1734 mm^2) are assessed using a 40x objective.

Mitotic count score	Definition
1	0 to 9 mitoses per 10 HPF
2	10 to 19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor necrosis

Evaluated on gross examination and validated with histologic sections.

Necrosis score	Definition
0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Contributor Disclosures

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