

Management of Breast Sarcoma



Cary Hsu, MD^{a,*}, Susan A. McCloskey, MD^b, Parvin F. Peddi, MD^c

KEYWORDS

• Breast • Sarcoma • Multidisciplinary • Surgery • Radiation • Chemotherapy

KEY POINTS

- The natural history and biologic behavior of breast sarcomas is similar to sarcomas at other sites.
- Total mastectomy is frequently necessary because of tumor size and anatomic considerations, but partial mastectomy does not compromise outcomes if adequate margins can be attained.
- Lymph node metastases occur rarely; thus, routine axillary surgery provides no benefit and is not indicated.
- Adjuvant chemotherapy and radiation are considered for high-risk patients, particularly those with large and/or high grade sarcomas.

Breast sarcoma is a rare clinical entity that represents less than 1% of all breast malignancies and less than 5% of all sarcomas.^{1,2} The published literature on breast sarcomas is predominantly composed of single institution retrospective analyses and case reports. These studies include patients with a wide variety of histologies, treated over many decades with great variability in surgical approaches, and inconsistencies in the use of adjuvant therapies. Owing to the rarity and heterogeneity of breast sarcomas, there are no published randomized trials that validate any particular treatment strategy. However, the literature in aggregate does provide valuable information about the biology and natural history of the disease. The anatomic site is an important variable and certainly influences the clinical decisions for this disease process. This paper discusses the management of breast sarcoma in the context of the studies that have defined current practices.

Disclosure Statement: The authors have nothing to disclose.

^a Department of Surgery, Baylor College of Medicine, One Baylor Plaza, MS 390, Houston, TX 77030, USA; ^b Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA 90095, USA; ^c Division of Hematology & Oncology, Department of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, USA

* Corresponding author.

E-mail address: Cary.Hsu@bcm.edu

Surg Clin N Am 96 (2016) 1047–1058

<http://dx.doi.org/10.1016/j.suc.2016.05.004>

surgical.theclinics.com

0039-6109/16\$ – see front matter © 2016 Elsevier Inc. All rights reserved.

CLINICAL PRESENTATION AND INITIAL EVALUATION

Primary breast sarcomas occur almost exclusively in female patients and are typically diagnosed in the fifth or sixth decades of life. Most patients present with a solitary, firm, well-circumscribed, painless breast mass. In contrast with patients with benign soft tissue masses of the breast, patients often report a history of rapid growth over several months.^{1,3} Historically, breast sarcomas are relatively large at the time of presentation with a median size of 5 cm, although it seems likely that smaller lesions will be detected increasingly as the use of routine screening mammography continues to increase.

Secondary breast sarcomas infrequently develop after prior treatment with external beam radiation for conditions such as non-Hodgkin lymphoma or breast carcinoma with a reported incidence rate of 0.2% for breast cancer patients. The peak incidence is approximately 5 to 10 years after radiotherapy, but the range is substantial. A wide array of histologic subtypes has been reported and these sarcomas are morphologically identical to primary sarcomas by histopathologic analysis. It has been noted that patients with radiation-induced sarcomas tend to present with more advanced disease than patients with primary sarcomas; this may be related to delay in diagnosis because physical examination is often difficult because of changes after radiotherapy. Angiosarcoma is the most common postradiation secondary breast sarcoma and has a median latency period of 6 to 7 years.⁴⁻⁶ Radiation-associated angiosarcoma typically develops in cutaneous tissues and presents as skin discoloration and thickening, which may be subtle in the earliest stages of the disease.⁷

The initial evaluation for primary breast sarcoma includes standard diagnostic imaging used for women presenting with a breast mass. This evaluation includes mammography, ultrasonography, and occasionally breast MRI. Most often, mammograms reveal masses with a round, oval, or lobular shape. Approximately 30% of the mammograms demonstrate architectural distortion without a discrete mass. Calcifications or spiculated lesions are uncommon, but occasionally seen. On ultrasound imaging, most breast sarcomas are hypoechoic and without posterior attenuation. On MRI, breast sarcomas are heterogeneously hypointense on T1-weighted images and hyperintense on T2-weighted images. Intense enhancement is seen after contrast administration. Imaging findings associated with breast sarcoma have considerable overlap with findings that may be seen in breast carcinoma; thus, imaging alone is not diagnostic.⁸

Definitive diagnosis is critical because the management of epithelial malignancy is profoundly different and because the histologic subtype of the sarcoma may influence clinical decisions. Fine-needle aspiration cytology is of little usefulness and is inadequate for determining the subtype or grade of the lesion. Determination of histologic subtype and grade can almost always be achieved with image-guided core needle biopsy.^{9,10} In the rare instance that a core biopsy is not able to provide a histologic diagnosis, incisional biopsy can be considered. Surgical biopsy incisions must be oriented in a manner such that the biopsy scar can be removed completely during the definitive surgical resection. Meticulous attention to hemostasis is paramount because postoperative hematomas may disseminate malignant cells throughout the biopsy cavity. Occasionally, small and presumably benign lesions are excised and return with the unexpected diagnosis of sarcoma; in this situation, the excision must be regarded as inadequate even if the operative report and pathology report suggest that the lesion has been completely removed.

Historically, there have been inconsistencies and some controversy in the reporting and classification of breast sarcomas. Many of the published series include patients

with histologies such as dermatofibrosarcoma protuberans, carcinosarcoma, and malignant phyllodes tumors, which fall outside of the strict clinicopathologic definition of sarcoma.¹¹ The most common histologic subtypes reported in the literature are angiosarcomas followed by pleomorphic sarcomas (previously called malignant fibrous histiocytoma); these 2 subtypes account for approximately 50% of the cases in most series.^{11–14} Fibrosarcoma, stromal sarcoma, osteogenic sarcoma, liposarcoma, and leiomyosarcoma are also represented in many of the series, but at a lower frequency.

Once the diagnosis of sarcoma has been established, appropriate cross-sectional imaging is indicated for operative planning and to rule out distant metastatic disease. Either computed tomography or MRI with an appropriate contrast agent provides anatomic information necessary to guide surgical resection. Cross-sectional imaging should also include the chest because the lungs are the most common site of metastasis for the majority of breast sarcomas. In a Radiology Diagnostic Oncology Group study, computed tomography and MRI were equally accurate in the local staging of soft tissue neoplasms with no difference in the ability to detect involvement of bone, joint, and neurovascular structures.¹⁵ ¹⁸F-fluorodeoxyglucose PET is considered investigational in the treatment of sarcomas, but its role is rapidly expanding. PET scans can provide useful information in staging and restaging, distinguishing between benign and malignant disease, assessing for both local and distant recurrence, and monitoring responses to systemic and regional therapy.¹⁶

MULTIDISCIPLINARY MANAGEMENT

Data are limited regarding management in general and particularly limited with regard to optimal adjuvant therapies. Effective treatment requires thorough pretreatment planning and coordinated care by an experienced, multidisciplinary team of physicians. This team should include surgical oncologists, reconstructive surgeons, medical oncologists, radiation oncologists, pathologists, and radiologists. A number of studies have documented patient benefit from the improved treatment of rare tumors, including soft tissue sarcomas, at specialty centers.^{17,18} An additional benefit of a multidisciplinary approach is that it gives patients with large, high-grade sarcomas the opportunity to be enrolled in protocol-driven therapy, which may answer important clinical questions and drive the field forward. Many of these protocols involve the administration of neoadjuvant therapy (chemotherapy, targeted therapies, radiation therapy) to high-risk sarcomas.

SURGICAL MANAGEMENT

Complete surgical excision is of foremost importance in achieving local control and the only potentially curative therapy for breast sarcomas. The objectives of surgical resection are straightforward: complete removal of the tumor with microscopically negative margins, preservation of function, and secure wound closure. Skin incisions are typically made along the longest axis of the tumor. The skin surrounding the prior biopsy sites should be removed en bloc with the specimen because seeding of malignant cells along the biopsy tract has been reported.¹⁶ With angiosarcoma as an exception, direct extension of the tumor into the skin is uncommon, but when it occurs, the involved skin is taken en bloc with the rest of the specimen. If the mass is large, a generous incision should be used to facilitate a wide resection. When surgical drains are used, they should exit the skin near the resection bed because the drain tract will need to be included in the radiation portals if adjuvant radiation is used.

Soft tissue sarcomas typically expand spherically along tissue planes and compress surrounding tissues creating a pseudocapsule of surrounding tissue; malignant cells

can penetrate this pseudocapsule.^{19,20} As such, there continues to be controversy in defining what constitutes an adequate margin of resection. Historically, sarcoma operations were described in which the entire anatomic compartment housing the tumor was resected. This has been abandoned and the current practice is to obtain a negative margin by dissecting through adjacent, uninvolved tissues away from the tumor. In general, a microscopically negative margin, or R0 resection, is considered adequate. For trunk and extremity sarcomas, there are conflicting data on whether margins wider than microscopically negative offer superior local control.^{21–24} Currently, a margin of greater than 1 cm has been encouraged when feasible for all soft tissue sarcomas.²⁵ This question has not been addressed specifically for breast sarcomas, but a margin of greater than 1 cm is also recommended.³ In contrast with most other breast sarcomas, angiosarcomas are often multicentric and infiltrative; these tumors frequently extend well beyond radiographically or grossly discernable boundaries. A widely negative margin is notoriously difficult to achieve for angiosarcomas; thus, it has been suggested that a 3-cm clinical margin (the gross distance from visible or palpable abnormality) may be more appropriate for this histologic subtype.³

The breast is a relatively favorable site for surgical management of sarcoma. For the majority of patients, there are no critical bony or neurovascular structures limiting the planned resection. Extensive soft tissue resections can often be undertaken with no disability and without the need for complex closure. There is considerable flexibility in the ability to tailor a mastectomy incision to center and orient it directly over the long axis of the tumor. In most reported series, the vast majority of patients presenting with primary breast sarcomas presented with resectable disease and had microscopically negative margins after surgery.^{14,26–28}

Total mastectomy had long been regarded as the gold standard in surgical therapy for breast sarcomas.²⁹ Subsequently, numerous institutions have published retrospective analyses indicating that a wide excision to negative margins provides comparable local control in selected patients.^{12–14,27,30–32} From a practical standpoint, the operative options will be dictated by the size and location of the tumor, the patient's breast size, and patient preference. Because the median presenting size of breast sarcomas is greater than 5 cm, mastectomy is often the most straightforward way to achieve the goal of a wide margin; however, selected patients can be managed safely with partial mastectomy. Surgical clips should be placed to mark the boundaries of the resection bed and any margins of concern; this may facilitate the planning of radiation portals if it is determined that adjuvant radiation therapy is indicated.

Frozen section analysis tends to be unreliable for mesenchymal malignancies, particularly when they are low to intermediate grade, and is not routinely used to assess margin status. Occasionally, we find frozen section useful when looking at a focal margin of interest in the setting of a high-grade lesion. If close or positive margins result after resection, reexcision or a completion mastectomy (if partial mastectomy was performed) should be undertaken if it can be accomplished without prohibitive morbidity. Likewise, breast sarcoma patients previously treated with nononcologic resections for presumed benign disease or resection with undocumented margins should be considered for reexcision or mastectomy, because such patients are likely to harbor residual disease from the initial operation.^{33,34}

Soft tissue sarcomas are known to spread via the hematogenous route; thus, lymph node involvement is exceedingly rare.³⁵ As alluded to previously, reported series of breast sarcoma patients often span many decades and include an era in which axillary lymphadenectomy was performed routinely for all malignant lesions of the breast. It is well-documented that breast sarcoma patients who underwent axillary lymphadenectomy rarely had positive lymph nodes and most frequently this was seen in the context

of disseminated disease.^{11–14,27} Axillary lymphadenectomy confers no survival benefit.^{12,36} Furthermore, for patients undergoing axillary dissection, the size of the radiation portal must be extended to include the axillary lymph node basin and this increases the risk of treatment-associated morbidity, particularly lymphedema.³⁷ There are histologic subtypes of sarcoma with potential for spread to the regional lymph nodes, particularly angiosarcoma, rhabdomyosarcoma, clear cell sarcoma, synovial sarcoma, and epithelioid sarcoma.^{35,38} The axilla should be evaluated with axial imaging preoperatively. If nodal metastases are suspected, a biopsy should be obtained because reactive lymphadenopathy may be seen in up to 25% of breast sarcoma patients.³⁹ If axillary lymph node metastases are confirmed or if the primary tumor extends into the axilla, axillary lymphadenectomy should be part of the comprehensive treatment strategy. Otherwise, there are no indications for routine sentinel lymph node biopsy or axillary lymphadenectomy.

Reconstructive surgeons play a critical role in the surgical management of breast sarcomas and should be engaged early in the process of formulating the plan of care. Sarcoma surgery frequently results in complex wounds. When large or recurrent tumors are resected, there may not be adequate redundancy in the native tissues to close the incision primarily. In addition, sarcoma patients frequently receive radiation therapy, which compromises wound healing. The reconstructive surgeon brings expertise and a sophisticated array of techniques, from primary closure to free tissue transfer, to reliably restore integrity and form after extensive resection procedures.⁴⁰ Increasingly, breast reconstruction is being undertaken for breast sarcoma patients. The full range of reconstructive procedures used for epithelial breast cancers have been used, including oncoplastic techniques, breast implants, and local and free tissue flaps.⁴¹ Importantly, breast reconstruction for sarcoma patients can be accomplished with low complication rates and without compromising the oncologic outcomes.²⁸ For patients with epithelial breast cancers, reconstruction has been shown to improve body image, sense of physical well-being, and quality of life; it is suspected that the same is true for sarcoma patients. Crosby and colleagues⁴¹ have reported an extensive experience with reconstruction for breast sarcoma and have proposed an algorithm for clinical decisions regarding reconstructive options; the authors suggest that delayed, autologous tissue reconstruction minimizes complication rates and results in the best outcomes. Subtleties exist in patient selection, timing, and choice of reconstructive procedure; having a plastic surgeon involved in the multidisciplinary planning will help to identify patients who are appropriate candidates for breast reconstruction.

RADIATION THERAPY

Several single institutions have reviewed their experience with the treatment of primary breast sarcoma and, owing to exceedingly small numbers and heterogeneity in treatment selection, no definitive conclusions have been reached regarding the role of adjuvant radiation therapy. However, general conclusions regarding outcomes and specific risk factors for local recurrence have been informative.

Investigators at MD Anderson Cancer Center examined outcomes among 59 patients over 43 years with primary breast sarcoma, 16 of whom underwent segmental resection and 38 of whom underwent mastectomy. Four of 16 received radiation after segmental mastectomy and 13 of 38 received radiation after mastectomy. Owing to small numbers, no differences were detected by treatment modality; however, the authors did report that 14% failed locally after segmental resection alone versus 0% after segmental resection followed by radiation and 34% and 13% failed after

mastectomy alone versus after mastectomy followed by radiation, respectively. Based on these findings, along with the findings that tumor size and surgical margins were significantly predictive of local failure, the investigators concluded that radiation is likely indicated for larger tumor size and positive margins.²⁶ Investigators at the National Institutes of Health observed no local failures among 10 patients with high-grade sarcoma who were treated with mastectomy and postoperative radiation with a median follow-up of 99 months, thus concluding that radiation therapy should be used for high-grade breast sarcomas.⁴² Investigators at Princess Margaret Hospital in Toronto examined disease-specific and overall survival outcomes among 78 patients with breast sarcoma over 32 years. Twenty-six patients received radiation and 52 did not. In examining factors affecting prognosis, extent of surgery was not predictive of survival or local recurrence, but margin status was a significant predictor of local recurrence and radiation dose (>48 vs <48 Gy/no radiation therapy) significantly impacted cause-specific survival. The authors concluded that optimal outcomes were achieved with margin-negative surgical resection and that either lumpectomy or mastectomy achieved excellent local control if negative margins were achieved. This series stressed the importance of radiation given to appropriate dose.³¹ The Institute Gustav-Roussey experience reviewing outcomes among 83 patients with breast sarcoma treated over 37 years similarly concluded that radiation may improve outcomes and should be considered for large and/or high-grade breast sarcomas or after conservative surgery.¹⁴ Washington University investigators examined outcomes among 13 patients treated over 20 years with primary breast sarcoma and concluded that radiation should be considered in all cases owing to high rates of local recurrence, 54% in their series.²⁷ Most recently, Dutch investigators published a 35-year retrospective review examining outcomes among 42 patients with primary breast sarcoma in which they concluded size and grade to be prognostic and suggested high rates of observed local recurrence warrant aggressive surgery and consideration of postoperative radiation.⁴³ Finally, a Rare Cancer Network series exploring outcomes and prognostic factors in breast sarcomas suggested management should mirror that of extremity sarcoma.¹²

Thus, published series are suggestive of a role for radiation therapy in the setting of documented prognostic factors for local failure, which include close/positive surgical margins, high grade, and larger tumor size (most commonly >5 cm). Radiation has been used after both segmental resection and mastectomy in the presence of these risk factors and, unlike in the setting of epithelial breast malignancies, radiation therapy is typically not indicated for sterilization of microscopic nodal disease owing to the infrequency of nodal metastases. These considerations are in line with those used to guide decision making for extremity sarcoma and, indeed, radiation therapy recommendations for breast sarcoma are often extrapolated from general principles of radiation therapy for extremity sarcomas. Prospective randomized data have demonstrated that radiation therapy significantly improves local control for extremity soft tissue sarcoma.^{44,45}

Regarding preoperative radiation therapy, there are no specific data to guide its use in the treatment of primary breast sarcoma, but it may be used for large or inoperable tumors at presentation and may also be of value in terms of optimizing target localization for radiation planning and potentially decreasing late effects of radiation. Preoperative versus postoperative radiation has been studied in the setting of extremity sarcoma and equivalent efficacy has been documented; however, there are toxicity tradeoffs with preoperative radiation associated with increased short-term wound complications but fewer long-term complications, including fibrosis, edema, and joint stiffness.^{46,47} These tradeoffs can certainly be weighed in the multidisciplinary management of primary breast sarcoma.

Regarding radiation therapy delivery specifics, treatment fields have generally encompassed the anatomic breast borrowing from field design principles for epithelial breast malignancies. In terms of nodal coverage, it has been traditionally advisable that sarcoma fields encompass the surgical bed given the possibility of seeding surgical scars. Thus, although axillary dissection is not recommended owing to infrequency of nodal spread, if an axillary dissection was performed, consideration for extending the radiation fields to encompass the axillary surgical bed is advisable.²⁶ Regarding dose, Princess Margaret investigators among others advise microscopic tumorocidal dose of 50 Gy to the whole breast and at least 60 Gy to the tumor bed.³¹ Extrapolating again from management principles for extremity sarcoma, the dose should be escalated according to margin status with doses of greater than 60 Gy recommended for microscopically or macroscopically positive margins. In the preoperative setting, 50 Gy has been used conventionally.

Angiosarcoma of the breast is a subtype that is most often radiation induced and thus special consideration is given. Cumulative radiation dose and associated toxicity is a consideration but not prohibitive of reirradiation. A systematic review published by Dutch investigators in 2014 examined treatment and prognostic factors of radiation-associated angiosarcoma. Data for 222 patients across 74 publications were included in the review. Seventeen percent ($n = 37$) of patients in the series received reirradiation, 30% of whom received hyperthermia with radiation. The 5-year local recurrence rate was improved in those patients receiving radiation, 34% versus 57%.⁶ This and other single institution series indicated local recurrence approximating 60% for surgery alone for treatment of radiation associated angiosarcoma, thus justifying consideration of reirradiation.^{48,49} In addition to examining reirradiation for the treatment of radiation-associated sarcoma, more novel reirradiation approaches including hyperthermia and hyperfractionation have also been explored and have shown promise.^{50,51}

CHEMOTHERAPY

There are no prospective trials specifically assessing the benefit of adjuvant chemotherapy in breast sarcomas. Therefore, treatment recommendations for breast sarcomas are generally derived from trials on all soft tissue sarcomas or from retrospective studies. In a retrospective study of 60 patients with primary breast sarcoma treated at MD Anderson, adjuvant chemotherapy and/or radiotherapy was associated with prolonged disease-free survival ($P = .015$).¹³ Other retrospective studies have not shown a similar benefit, although they included phyllodes tumors that are thought to be even less responsive to chemotherapy than breast sarcomas.^{12,52} Adjuvant chemotherapy is therefore considered on an individual basis depending on patient age, comorbidities, tumor grade, and size. Given the unclear response rate to chemotherapy, we recommend neoadjuvant therapy only for large, high-grade sarcomas for which obtaining a negative margin may be challenging. However, limited data indicate that patients presenting with unresectable breast sarcomas are not likely to become surgical candidates after neoadjuvant chemotherapy.¹⁴ Similar to other sarcomas, the recommended regimen is generally anthracycline and ifosfamide based. We recommend treatment on a case-by-case basis for high-grade sarcomas larger than 5 cm.

Radiation-induced sarcomas represent a particularly challenging subset of breast sarcomas because reradiation can be controversial given cumulative risk of toxicity, thereby leaving chemotherapy as the only option in addition to surgery. In one retrospective study of 95 patients with radiation-induced angiosarcoma at MD Anderson, adjuvant chemotherapy reduced risk of local recurrence significantly ($P = .0003$).⁴

Chemotherapy regimens varied and included ifosfamide, anthracyclines, taxanes, and gemcitabine. In another retrospective study in France of 80 patients with radiation-induced sarcoma, 42% of which were in the breast, no benefit was seen with the addition of chemotherapy to surgery.⁵³

Angiosarcomas also deserve special mention, given their unique susceptibility to taxane chemotherapy. They represent less than 0.05% of all breast cancers and are not related to radiation therapy.⁵⁴ Taxanes are generally ineffective in sarcomas. However, in a phase II trial of 50 patients with inoperable angiosarcomas, 49% of whom had breast angiosarcomas, weekly paclitaxel resulted in a median overall survival of 19 months.⁵⁵ Similar results were seen in several other prospective and retrospective studies.^{56–58} Weekly taxol is more active than therapy given every 3 weeks in 1 report, similar to studies in breast and gynecologic cancers.⁵⁶ Doxorubicin is also active, similar to other sarcomas.⁵⁹ It is unclear which chemotherapy is more efficacious for treatment of angiosarcomas and either is a reasonable option. Neoadjuvant chemotherapy is considered frequently for angiosarcomas because of the potential for chemosensitivity and the difficulty associated with achieving a negative margin with up-front surgery.^{60,61}

CLINICAL OUTCOMES AND PROGNOSTIC FACTORS

There is considerable variability in reported clinical outcomes. The range for 5-year overall survival is 55% to 73% and the range for 5-year disease-free survival is 29.2% and 68%.¹ Many of the series have small numbers of patients and each series has considerable variability in the histologic subtypes that are represented. Furthermore, there is substantial variability in the treatment administered. Studies have most consistently identified size,^{11–14,26,27} tumor grade,^{12,14} and margin status^{12,14,26,62} as important prognostic factors for disease-free and overall survival. Angiosarcoma has frequently been reported as a histologic subtype with a particularly poor prognosis; however, in 2 series from MD Anderson, patients with angiosarcoma actually had a relatively favorable prognosis.^{12–14,26} The 5-year survival rate for radiation induced sarcomas is in the range of 27% to 48% and the poor prognosis has largely been attributed to a higher proportion of patients presenting with advanced clinical stage disease.⁷ It seems likely that there is more to the biology of radiation-induced sarcomas than delayed diagnosis; indeed, genetic alterations unique to radiation-induced angiosarcomas have been characterized.⁶³

Two of the largest series provide many insights on the natural history of the disease and it is worth highlighting some of the specific findings. In 2003, Zelek and colleagues¹⁴ reported on 90 primary breast sarcoma patients treated at the Institut Gustave-Roussy. This series spanned approximately 40 years. Nearly 70% of patients had malignant fibrous histiocytomas and 10% had angiosarcomas. Approximately two-thirds of the patients were treated with surgery alone. The 10-year overall survival was 62% and 10-year disease-free survival was 50%. Tumor size and grade were the identified as prognostic factors for survival. The survival curves, stratified by grade and size, paralleled survival curves reported for extremity sarcomas. Most recurrences manifested within 5 years. Most recurrences seen in patients with low-grade sarcomas (7/8) were local (breast or chest wall). In contrast, approximately one-half of the recurrences associated with high-grade sarcomas were to distant sites. All of the patients with distant metastases had lung metastases (and some additional sites as well). Every patient with local recurrence related to grade 1 tumors achieved long-term survival after salvage surgery. In multivariate analysis, poorer survival was observed for patients with angiosarcoma. In 2007, Bousquet and colleagues¹²

reported a retrospective study of 103 patients from the Rare Cancer Network, representing the largest series in the literature. Angiosarcoma was the most common histology in this cohort and represented 41% of the patients in the series. The 5-year overall survival was 55% and 5-year disease-free survival was 44%. Surgical margins of at least 1 cm was a favorable prognostic factor for local control and disease free survival. One-third of the patients underwent breast-conserving surgery and it was noted that the extent of surgery did not affect local failure rates. Angiosarcoma patients in this series had a 10-year disease-free survival of 12% versus 52% for the other histologies combined ($P = .0014$).

SUMMARY

Many issues specific to breast sarcomas have been addressed through observational studies. Most patients in reported series were able to undergo upfront surgery without neoadjuvant therapies and, for many patients, surgery was the only treatment modality. Mastectomy was the most frequently used operation, but partial mastectomy was found to be a safe alternative for patients with smaller tumors. Lymph node metastases are uncommon and thus routine lymphadenectomy is contraindicated. Adjuvant radiation and/or chemotherapy is considered for high-risk patients with the goals of enhancing local control and treating subclinical metastatic disease. The benefits of adjuvant therapies have been difficult to quantify owing to the heterogeneity of the disease and variability in treatments. Angiosarcoma stands out from the other histologic subtypes for the diffuse pattern of growth, multicentricity, cutaneous invasion, chemosensitivity, and prognosis. In general, breast sarcomas demonstrate biological behavior that is similar to sarcomas at other anatomic sites. The rarity and heterogeneity of breast sarcomas will likely preclude study in the context of prospective clinical trials. The current thinking is that sarcomas are better defined by histologic subtype and molecular profile, as opposed to the anatomic site of origin. Development of novel therapies will depend on the discovery of histology-specific strategies that exploit biologic behavior, molecular pathways, and drug sensitivities unique to the sarcoma subtype.

REFERENCES

1. Lim SZ, Ong KW, Tan BK, et al. Sarcoma of the breast: an update on a rare entity. *J Clin Pathol* 2016;69(5):373–81.
2. Pollard SG, Marks PV, Temple LN, et al. Breast sarcoma. A clinicopathologic review of 25 cases. *Cancer* 1990;66:941–4.
3. Al-Benna S, Poggemann K, Steinau HU, et al. Diagnosis and management of primary breast sarcoma. *Breast Cancer Res Treat* 2010;122:619–26.
4. Torres KE, Ravi V, Kin K, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. *Ann Surg Oncol* 2013;20:1267–74.
5. Yap J, Chuba PJ, Thomas R, et al. Sarcoma as a second malignancy after treatment for breast cancer. *Int J Radiat Oncol Biol Phys* 2002;52:1231–7.
6. Depla AL, Scharloo-Karels CH, de Jong MA, et al. Treatment and prognostic factors of radiation-associated angiosarcoma (RAAS) after primary breast cancer: a systematic review. *Eur J Cancer* 2014;50:1779–88.
7. Sheth GR, Cranmer LD, Smith BD, et al. Radiation-induced sarcoma of the breast: a systematic review. *Oncologist* 2012;17:405–18.
8. Surov A, Holzhausen HJ, Ruschke K, et al. Primary breast sarcoma: prevalence, clinical signs, and radiological features. *Acta Radiol* 2011;52:597–601.

9. Hoebler I, Spillane AJ, Fisher C, et al. Accuracy of biopsy techniques for limb and limb girdle soft tissue tumors. *Ann Surg Oncol* 2001;8:80–7.
10. Heslin MJ, Lewis JJ, Woodruff JM, et al. Core needle biopsy for diagnosis of extremity soft tissue sarcoma. *Ann Surg Oncol* 1997;4:425–31.
11. Adem C, Reynolds C, Ingle JN, et al. Primary breast sarcoma: clinicopathologic series from the Mayo Clinic and review of the literature. *Br J Cancer* 2004;91: 237–41.
12. Bousquet G, Confavreux C, Magne N, et al. Outcome and prognostic factors in breast sarcoma: a multicenter study from the rare cancer network. *Radiother Oncol* 2007;85:355–61.
13. Gutman H, Pollock RE, Ross MI, et al. Sarcoma of the breast: implications for extent of therapy. The M. D. Anderson experience. *Surgery* 1994;116:505–9.
14. Zelek L, Llobart-Cussac A, Terrier P, et al. Prognostic factors in primary breast sarcomas: a series of patients with long-term follow-up. *J Clin Oncol* 2003;21: 2583–8.
15. Panicek DM, Gatsonis C, Rosenthal DI, et al. CT and MR imaging in the local staging of primary malignant musculoskeletal neoplasms: report of the Radiology Diagnostic Oncology Group. *Radiology* 1997;202:237–46.
16. Schwartz HS, Spengler DM. Needle tract recurrences after closed biopsy for sarcoma: three cases and review of the literature. *Ann Surg Oncol* 1997;4:228–36.
17. Rydholm A. Improving the management of soft tissue sarcoma. Diagnosis and treatment should be given in specialist centres. *BMJ* 1998;317:93–4.
18. Ray-Coquard I, Thiesse P, Ranchere-Vince D, et al. Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas. *Ann Oncol* 2004;15:307–15.
19. Bowden L, Booher RJ. The principles and technique of resection of soft parts for sarcoma. *Surgery* 1958;44:963–77.
20. Kawaguchi N, Ahmed AR, Matsumoto S, et al. The concept of curative margin in surgery for bone and soft tissue sarcoma. *Clin Orthop Relat Res* 2004;(419): 165–72.
21. Baldini EH, Goldberg J, Jenner C, et al. Long-term outcomes after function-sparing surgery without radiotherapy for soft tissue sarcoma of the extremities and trunk. *J Clin Oncol* 1999;17:3252–9.
22. Dickinson IC, Whitwell DJ, Battistuta D, et al. Surgical margin and its influence on survival in soft tissue sarcoma. *ANZ J Surg* 2006;76:104–9.
23. McKee MD, Liu DF, Brooks JJ, et al. The prognostic significance of margin width for extremity and trunk sarcoma. *J Surg Oncol* 2004;85:68–76.
24. Sampo M, Tarkkanen M, Huuhtanen R, et al. Impact of the smallest surgical margin on local control in soft tissue sarcoma. *Br J Surg* 2008;95:237–43.
25. Byerly S, Chopra S, Nassif NA, et al. The role of margins in extremity soft tissue sarcoma. *J Surg Oncol* 2016;113(3):333–8.
26. Barrow BJ, Janjan NA, Gutman H, et al. Role of radiotherapy in sarcoma of the breast—a retrospective review of the M.D. Anderson experience. *Radiother Oncol* 1999;52:173–8.
27. Fields RC, Aft RL, Gillanders WE, et al. Treatment and outcomes of patients with primary breast sarcoma. *Am J Surg* 2008;196:559–61.
28. Toesca A, Spitaleri G, De Pas T, et al. Sarcoma of the breast: outcome and reconstructive options. *Clin Breast Cancer* 2012;12:438–44.
29. Berg JW, Decrosse JJ, Fracchia AA, et al. Stromal sarcomas of the breast. A unified approach to connective tissue sarcomas other than cystosarcoma phyllodes. *Cancer* 1962;15:418–24.

30. North JH Jr, McPhee M, Arredondo M, et al. Sarcoma of the breast: implications of the extent of local therapy. *Am Surg* 1998;64:1059–61.
31. McGowan TS, Cummings BJ, O'Sullivan B, et al. An analysis of 78 breast sarcoma patients without distant metastases at presentation. *Int J Radiat Oncol Biol Phys* 2000;46:383–90.
32. Blanchard DK, Reynolds CA, Grant CS, et al. Primary nonphylloides breast sarcomas. *Am J Surg* 2003;186:359–61.
33. Giuliano AE, Eilber FR. The rationale for planned reoperation after unplanned total excision of soft-tissue sarcomas. *J Clin Oncol* 1985;3:1344–8.
34. Zagars GK, Ballo MT, Pisters PW, et al. Surgical margins and reresection in the management of patients with soft tissue sarcoma using conservative surgery and radiation therapy. *Cancer* 2003;97:2544–53.
35. Fong Y, Coit DG, Woodruff JM, et al. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. *Ann Surg* 1993;217:72–7.
36. Gullett NP, Delman K, Folpe AL, et al. National surgical patterns of care: regional lymphadenectomy of breast sarcomas. *Am J Clin Oncol* 2007;30:461–5.
37. Warren LE, Miller CL, Horick N, et al. The impact of radiation therapy on the risk of lymphedema after treatment for breast cancer: a prospective cohort study. *Int J Radiat Oncol Biol Phys* 2014;88:565–71.
38. Sherman KL, Kinnier CV, Farina DA, et al. Examination of national lymph node evaluation practices for adult extremity soft tissue sarcoma. *J Surg Oncol* 2014;110:682–8.
39. Christensen L, Schiødt T, Blichert-Toft M, et al. Sarcomas of the breast: a clinico-pathological study of 67 patients with long term follow-up. *Eur J Surg Oncol* 1988;14:241–7.
40. Langstein HN, Robb GL. Reconstructive approaches in soft tissue sarcoma. *Semin Surg Oncol* 1999;17:52–65.
41. Crosby MA, Chike-Obi CJ, Baumann DP, et al. Reconstructive outcomes in patients with sarcoma of the breast. *Plast Reconstr Surg* 2010;126:1805–14.
42. Johnstone PA, Pierce LJ, Merino MJ, et al. Primary soft tissue sarcomas of the breast: local-regional control with post-operative radiotherapy. *Int J Radiat Oncol Biol Phys* 1993;27:671–5.
43. Holm M, Aggerholm-Pedersen N, Mele M, et al. Primary breast sarcoma: a retrospective study over 35 years from a single institution. *Acta Oncol* 2016;55(5):584–90.
44. Pisters PW, Harrison LB, Leung DH, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol* 1996;14:859–68.
45. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998;16:197–203.
46. Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol* 2005;75:48–53.
47. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002;359:2235–41.
48. Billings SD, McKenney JK, Folpe AL, et al. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. *Am J Surg Pathol* 2004;28:781–8.

49. Seinen JM, Styring E, Verstaappen V, et al. Radiation-associated angiosarcoma after breast cancer: high recurrence rate and poor survival despite surgical treatment with R0 resection. *Ann Surg Oncol* 2012;19:2700–6.
50. de Jong MA, Oldenburg S, Bing Oei S, et al. Reirradiation and hyperthermia for radiation-associated sarcoma. *Cancer* 2012;118:180–7.
51. Palta M, Morris CG, Grobmyer SR, et al. Angiosarcoma after breast-conserving therapy: long-term outcomes with hyperfractionated radiotherapy. *Cancer* 2010;116:1872–8.
52. Confavreux C, Lurkin A, Mitton N, et al. Sarcomas and malignant phyllodes tumours of the breast—a retrospective study. *Eur J Cancer* 2006;42:2715–21.
53. Lagrange JL, Ramaoli A, Chateau MC, et al. Sarcoma after radiation therapy: retrospective multiinstitutional study of 80 histologically confirmed cases. Radiation Therapist and Pathologist Groups of the Federation Nationale des Centres de Lutte Contre le Cancer. *Radiology* 2000;216:197–205.
54. Bordoni D, Bolletta E, Falco G, et al. Primary angiosarcoma of the breast. *Int J Surg Case Rep* 2016;20S:12–5.
55. Ray-Coquard IL, Domont J, Tresch-Bruneel E, et al. Paclitaxel given once per week with or without bevacizumab in patients with advanced angiosarcoma: a randomized phase II trial. *J Clin Oncol* 2015;33:2797–802.
56. Fury MG, Antonescu CR, Van Zee KJ, et al. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. *Cancer J* 2005;11:241–7.
57. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol* 2008;26:5269–74.
58. Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. *Eur J Cancer* 2008;44:2433–6.
59. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer* 2005;104:361–6.
60. Vorburger SA, Xing Y, Hunt KK, et al. Angiosarcoma of the breast. *Cancer* 2005;104:2682–8.
61. Oxenberg J, Khushalani NI, Salerno KE, et al. Neoadjuvant chemotherapy for primary cutaneous/soft tissue angiosarcoma: determining tumor behavior prior to surgical resection. *J Surg Oncol* 2015;111:829–33.
62. Pandey M, Mathew A, Abraham EK, et al. Primary sarcoma of the breast. *J Surg Oncol* 2004;87:121–5.
63. Guo T, Zhang L, Chang NE, et al. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. *Genes Chromosomes Cancer* 2011;50:25–33.