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ORIGINAL ARTICLE – BREAST ONCOLOGY

Multidisciplinary Intervention in Radiation-Associated Angiosarcoma of the Breast: Patterns of Recurrence and Response to Treatment

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ABSTRACT

Background. Radiation-associated angiosarcoma (RAAS) of the breast is an aggressive malignancy affecting 1 in 1000 breast cancer patients. This study aimed to determine differences in treatments and outcomes for RAAS initially managed through a sarcoma multi-disciplinary team (SMDT) compared with an outside center (OC) and to describe outcomes after recurrence.

Methods. Patients with a diagnosis of breast RAAS between 2004 and 2019 were identified from our sarcoma database. Clinicopathologic characteristics, recurrence patterns, and factors predictive of survival were assessed. Differences in local recurrence-free survival (LRFS) and disease-specific survival (DSS) were estimated using Kaplan-Meier and compared using the log-rank test.

Results. Surgery was performed for 49 women with RAAS, who had a median age of 74 years (range 41–89 years). Primary management was performed by SMDT for 26 patients and by OC for 23 patients. Radical mastectomy and reconstruction were performed for 96% of the SMDT group versus 17% of the OC group (p = 0.00001). The proportion patients who received chemotherapy, radiation, or both was 42.3% in the SMDT group and 0% in the OC group. During a median follow-up period of 26 months, recurrence was experienced by 38% (10/26) of the SMDT cohort and 83% (19/23) of the OC cohort (p = 0.002). The 3-year LRFS was better in the SMDT cohort (59.3% vs 31.8%; p = 0.019). Of the 29 recurrences 16 received chemotherapy and 6 received radiation, surgery, or both. At the last follow-up visit, 20 patients were in first remission, 1 patient was in second remission, 8 patients were alive with disease, and 20 patients had died of disease.

Conclusion. Initial treatment by SMDT was associated with more extensive surgery, multimodal treatments, and a better 3-year LRFS. Patients with breast RAAS likely benefit from early referral and treatment by an SMDT.

Radiation-associated sarcoma is defined as a sarcoma arising in a previously irradiated field that differs pathologically from the primary malignancy after a latency period of at least a few years.[1] These criteria have been updated to include tumors that arise adjacent to the radiation field with a minimum latency period of 6 months.[2]

Radiation-associated angiosarcoma of the breast (RAAS), a soft tissue sarcoma of endothelial cell origin,[3] is a specific, rare, and late complication of adjuvant radiotherapy for breast cancer. Patients with RAAS have a poor

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prognosis, with a 3-year locoregional-free survival (LRFS) reported to be 54% and a corresponding 5-year overall survival (OS) ranging from 27 to 62.6%.[4–11]

Radiation-associated sarcoma is estimated to affect 1 in 1000 patients treated with adjuvant radiotherapy for breast cancer[12,13] and develops with a median latency of 7 years after radiation therapy (RT).[7,14] Given both the widespread use of RT and the excellent survival rates for early-stage breast cancer, the incidence of RAAS in the breast appears to be increasing.[15]

Commonly, RAAS presents as purple nodules or ulceration arising in irradiated tissue, often mistaken for bruising.[16] These tumors also are frequently associated with multi-focality, with satellite lesions occurring adjacent to the tumor.[17] Because RAAS is believed to be a regional defect secondary to radiation, the entire irradiated field thus is potentially at risk.[18] Aggressive and infiltrative, RAAS has a high tendency to metastasize but with limited lymph node involvement.[19–23]

Morphologically, RAAS is identical to primary angiosarcomas of the breast, but RAAS almost always arises in the dermis, whereas primary angiosarcomas tend to arise in the breast parenchyma.[19] Overall survival is significantly shorter for patients with RAAS than for patients with sporadic angiosarcoma,[24,25] suggesting a different pathobiology.

Primary treatment of RAAS involves wide surgical resection of this dermal sarcoma,[26] with the role of chemotherapy and radiation evolving. After optimal resection, few data exist to guide oncologists in knowing how to treat local and/or distant recurrence. Thus, as with other sarcomas, the optimal management of RAAS likely will be achieved with referral to a high-volume center.[27–29] We therefore sought to describe the management and outcomes of RAAS in a large single-institution series to determine whether the locus of initial care (high-volume sarcoma multidisciplinary center or outside center) had an impact on the outcomes for women with RAAS, and to report the outcomes for patients experiencing local recurrence, distant recurrence, or both managed by multidisciplinary care.

METHODS

Patients

All consecutive patients with a diagnosis of RAAS of the breast between 2004 and 2019 were identified from our prospectively annotated sarcoma database at Princess Margaret Cancer Centre (PM) and Mount Sinai Hospital (MSH). Ethics approval was obtained from the institutional review board at both sites, and informed consent was obtained from all the study subjects.

For this study, RAAS was defined as a pathologically confirmed angiosarcoma arising in a previously irradiated field of a patient with a history of breast cancer. Pathology review was performed by a dedicated soft tissue sarcoma pathologist.

All the patients, irrespective of where they received initial treatment for RAAS (PM/MSH or outside center), underwent discussion and review at a sarcoma multi-disciplinary cancer conference (MCC) once they presented to our institution. Consistent with other multidisciplinary centers, our sarcoma multidisciplinary team (SMDT) is composed of pathology, radiology, surgical, medical, and radiation oncology as well as plastic and reconstructive surgery dedicated to the treatment of sarcoma. The outside centers (OCs) included community and/or peripheral hospitals without sarcoma expertise.

Surveillance was performed every 4 months with computed tomography (CT) of the chest, abdomen, and pelvis together with a detailed physical exam for the first 2 years. After 2 years, surveillance after treatment was increased to a 6-month interval with CT of the chest, abdomen, and pelvis and physical examination.

Study Criteria

The date of diagnosis was defined as the date RAAS was histologically confirmed. The patients were classified into the SMDT cohort if their primary RAAS was treated in our sarcoma center (PM/MSH) and into the OC cohort if they were initially treated elsewhere outside a sarcoma setting. Surgery was defined as a limited resection if less than the entirety of the previously irradiated skin was removed (via either lumpectomy or simple mastectomy), and as radical mastectomy (RM) if the patient had all the irradiated skin, residual breast tissue, and underlying pectoralis muscle (if involved) removed with immediate reconstruction (as required given the extent of resected skin secondary to previous radiation fields) using a pedicled muscle or myocutaneous flap.

The clinicopathologic and treatment data included age at diagnosis, grade, size, margin status, use of RT, chemotherapy, and radicality of surgery. Race and ethnicity data were unavailable because they are not routinely collected in the database nor in the patients' medical records and therefore were not included.

Outcome Analysis

The primary end point of the study was disease-specific survival (DSS), defined as the time from the diagnosis of RAAS to the time of death from RAAS. The secondary end

points were recurrence-free survival (RFS), locoregional recurrence-free survival (LRFS), margin status (*R*0, microscopically negative; *R*1, microscopically positive, macroscopically negative; *R*2, macroscopically positive), patterns of recurrence, treatment characteristics, and factors predictive of survival. The study defined RFS as the time from the first diagnosis of RAAS to the time of the first recurrence (local or distant) and LRFS as the time from the first diagnosis of RAAS to the time of the first recurrence at the primary site or regional lymph nodes. Surviving patients and those lost to follow-up evaluation were censored on the date of the last follow-up visit.

Survival curves were constructed using the Kaplan-Meier method and compared with the log-rank test using SPSS version 24. Clinicopathologic features were compared using chi-square, Fisher's exact test, and Student *t* test as tests of statistical analysis. Alpha was set to be lower than 0.05 for all analyses.

A uni- and multivariate Cox regression analysis was used to investigate the following potential prognostic variables of DSS: age, location of initial treatment (SMDT vs OC), radicality of surgery, and use of neoadjuvant chemotherapy. The results of these analyses are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

RESULTS

Patient Characteristics

During a period of 15 years, 51 patients with RAAS of the breast were identified. Of these 51 patients, 49 had a surgical resection. The remaining two patients were not surgical candidates due to comorbidities and therefore were excluded from the subsequent analysis (Table 1).

The medium latency period for RAAS after RT for primary breast cancer was 8 years (range 3–27 years). The median age at RAAS diagnosis was 74 years (range 41–89 years). Records were available for the initial course of radiation for 27 of the 49 patients. For these patients, all plans called for delivery of radiation to the whole breast at a median total dose of 42.4 Gy (range 40–66 Gy) in a median of 16 fractions (range 16–33 fractions). The initial breast cancer of 18 patients (all within the SMDT cohort) was treated at MSH/PM, with the remainder treated at OCs.

At the time of the initial RAAS diagnosis, one patient presented with concurrent axillary lymph node disease that was in fact metastatic breast cancer. No patient in this study presented with distant metastases based on CT of the chest, abdomen, or pelvis.

Treatment of Initial RAAS

Of the 49 patients, 29 (59.2%) underwent radical mastectomy (RM), and 20 (40.8%) had simple mastectomy or lumpectomy. For the SMDT cohort, RM was performed much more commonly than for the patients in the OC cohort (96.1% [25/26] vs 17.4% [4/23]; $p = 0001$). One patient was treated with axillary dissection for upfront nodal involvement, which final postoperative pathology confirmed to be a breast cancer recurrence.

Reconstruction After Radical Mastectomy

Of the 30 patients who had RM, 27 (90%) underwent immediate reconstruction (96.1% [25/26] by SMDT and 50% [2/4] at OC). The details of reconstruction are available for those treated by SMDT. The pectoralis muscle, chest wall, or both were resected in 16 (61.5%) of the 26 patients. For 24 of the 25 patients, reconstruction was completed using a pedicled flap. A latissimus dorsi flap was most frequently used (18/25) (either myocutaneous or muscle with split-thickness skin graft), followed by a rectus abdominis myocutaneous flap (4/25), with only two free flaps (deep inferior epigastric artery perforator flaps) in the entire cohort.

Multidisciplinary Treatment of RAAS

Chemotherapy was administered to 10 (38.5%) of 26 patients in the SMDT cohort vs 0 (0%) of 23 patients in the OC cohort ($p = 0.0008$). All 10 patients received paclitaxel in the preoperative setting. The decision to offer neoadjuvant chemotherapy was made in a multi-disciplinary MCC to facilitate surgery, decrease local and distant recurrence, or both. Of the 10 patients, 9 completed chemotherapy as determined by the response plateau (median, 3 cycles; range 2–5 cycles). One patient had to stop chemotherapy due toxicity after three cycles. All 10 patients who received neoadjuvant chemotherapy went on to complete surgery. A single SMDT patient with an *R*1 margin received adjuvant RT, and no patients received chemotherapy or RT in the OC group.

Pathologic Evaluation of RAAS

Data on surgical margins were available for 46 of the 49 patients. Of the 46 patients, 43 (93.5%) had an *R*0 resection, and 3 (6.9%) had an *R*1 resection. There were *R*1 margins for one patient in the SMDT group and two patients in the OC group. No *R*2 resections were performed in either group.

All 10 patients who received chemotherapy (100%) had a pathologic response to treatment. Two of the patients

TABLE 1 Clinical characteristics, treatment, and outcome in RAAS of the breast at the first diagnosis

	SMDT (n = 26)	OC (n = 23)	p value
Age at diagnosis (years)			
Mean	72	72	0.85
Median	73.5	75	
Range	56–89	41–89	
Grade of tumor			
1	4	4	0.37
2	3	4	
3	7	10	
Unknown	12	5	
Size (cm)			
< 5	4	8	0.09
> 5	17	8	
Unknown	5	7	
Margin status			
*R*0	25	18	
*R*1	1	2	
*R*2	0	0	
Unknown	0	3	
Surgery			
Radical resection: *n* (%)	25 (96.2)	4 (17.4)	0.00001
Limited resection: *n* (%)	1 (3.8)	19 (82.6)	
Neoadjuvant chemo	10 (38.5)	0 (0)	0.0008
Outcome			0.035
No evidence of disease (NED)	18	8	
Alive with disease (AWD)	5	4	
Died of disease (DOD)	3	10	
Died of other cause (DOC)	0	1	
3-Year LRFS: % (95 CI)	59.3 (22.1–140.7)	31.8 (16.3–47.3)	0.019
3-Year RFS: % (95 CI)	47.8 (25.3–70.3)	26.8 (0.6–53)	0.149
3 year DSS: % (95 CI)	79.8 (55.8–103.8)	67.7 (32.2 – 103.2)	0.25

RAAS radiation-associated angiosarcoma, *SMDT* sarcoma multi-disciplinary team, *OC* outside center, *NED* no evidence of disease, *AWD* alive with disease, *DOD* died of disease, *DOC* died of other cause, *LRFS* local recurrence-free survival, *CI* confidence interval, *RFS* recurrence-free survival, *DSS* disease-specific survival

(20%) had a complete pathologic response with no viable tumor present, whereas one patient (10%) had a near complete response with only scattered cells of viable tumor, and seven patients (70%) had a partial pathologic response).

Disease Outcome

At a median 26-month (range 4–182 months) follow-up visit, 35 (71.4%) of the 49 patients were alive, and 26 (53.1%) had no evidence of disease (NED) from RAAS. The 26 patients comprised 18 patients (69%) from the SMDT cohort and 8 patients (35%) from the OC cohort (p = 0.016).

The SMDT cohort had a higher 3-year LRFS than the OC cohort (59.3% vs 31.8%; p = 0.019; Fig. 1). The SMDT group also had a trend toward a higher 3-year DSS and RFS than the OC group (Fig. 1), but it did not reach statistical significance (79.8% vs 67.7%; p = 0.25 and 47.8% vs 26.8%; p = 0.149, respectively). Radical mastectomy was associated with a better 3-year DSS (83% vs 63%; p = 0.041; Fig. 2).

Recurrence was experienced by 29 of the 49 patients including 10 (38.5%) of 26 patients who had undergone initial treatment by SMDT and 19 (82.6%) of 23 patients who did not (p = 0.002). The median time to recurrence was 9 months (range 2–93 months). Of the 29 patients who had a first recurrence, 25 (86.2%) had a locoregional recurrence (LRR) alone, 1 (3.4%) had a distant recurrence

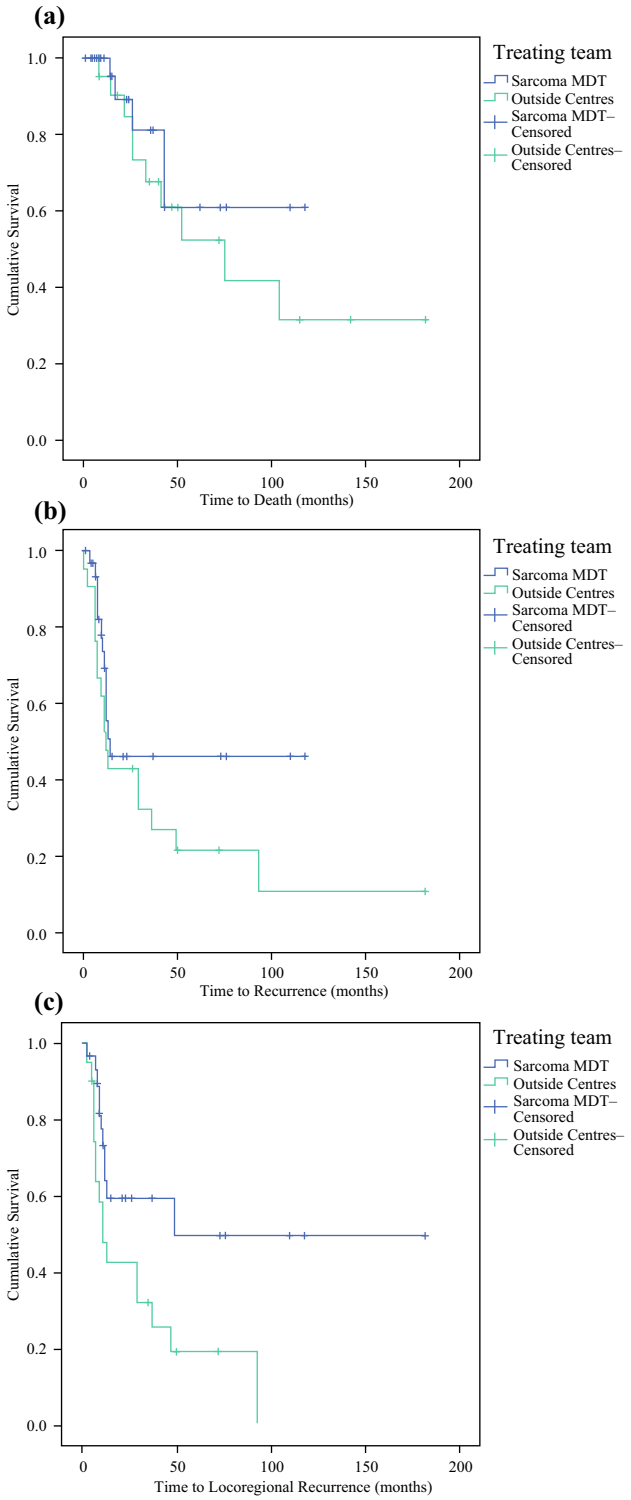

FIG. 1 Radiation-associated angiosarcoma outcome analysis. Kaplan-Meier survival curves for patients treated by the sarcoma multi-disciplinary team (SMDT) were compared with those for patients treated by an outside center (OC). **a** Disease specific survival ($p = 0.259$). **b** Recurrence-free survival ($p = 0.149$). **c** Locoregional recurrence-free survival ($p = 0.019$)

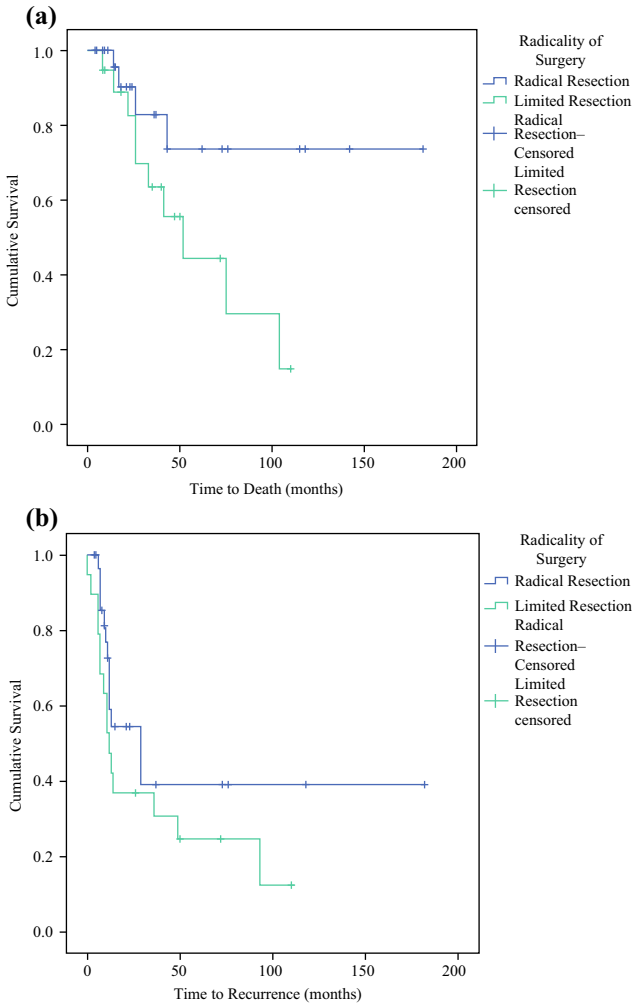

FIG. 2 Radiation-associated angiosarcoma outcome analysis. Kaplan-Meier survival curves for patients treated with radical resection at surgery compared with those for patients treated with limited resection. **a** Disease-specific survival ($p = 0.041$). **b** Recurrence-free survival ($p = 0.151$)

(DR), and 3 (10.3%) had both an LRR and a DR (Fig. 3, Table 2).

Of 43 patients with documented *R*0 resections, 23 experienced local failures. Although the resection performed was an *R*0, the local recurrence rate was notably higher for the patients who underwent surgery at an OC rather than by SMDT (77.8% [14/18] vs 36% [9/25]), likely because it was a more limited surgical resection. One of the three patients with *R*1 resection had adjuvant radiotherapy after resection and was alive with NED at the last follow-up visit (after 21 months). The remaining two patients with *R*1 resections experienced recurrence. The one patient had locoregional recurrence and was alive with disease at the last follow-up visit (after 5 months), and the other patient had both locoregional recurrence and distant pulmonary metastases and subsequently died of disease. Of the 10

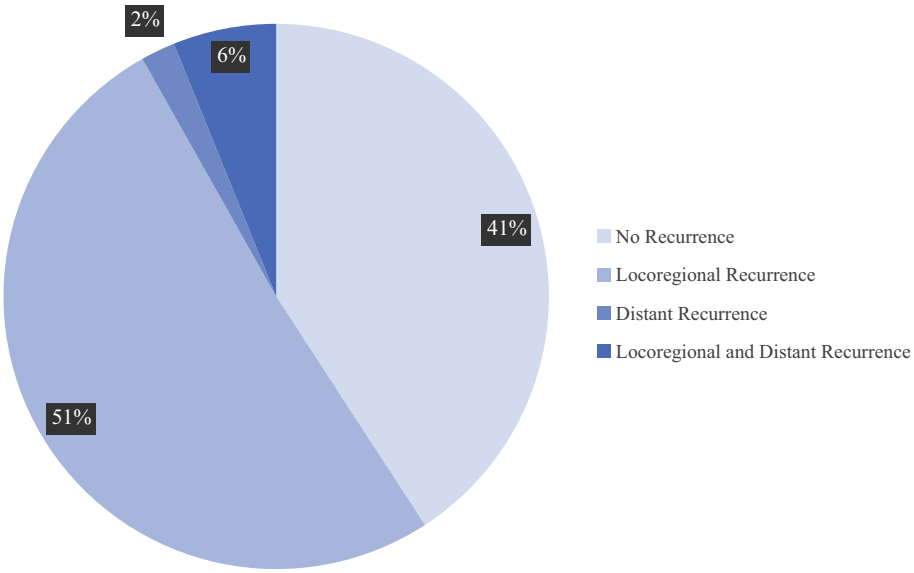

FIG. 3 Site of first recurrence of radiation-associated angiosarcoma (RAAS) (n = 49)

patients who had neoadjuvant chemotherapy, 7 (70%) did not experience recurrence, including those with a complete or near-complete pathologic response.

Treatment of First and Subsequent Recurrence

For the 29 patients who had a first recurrence of their angiosarcoma, the median time to recurrence was 9 months (range 2–93 months). The treatments included surgery for 10 patients, chemotherapy for 16 patients, and radiotherapy for 8 patients (detailed later and in Table 2). A median 26-month follow-up assessment found that 24% (7/29) of the patients who had a first recurrence were alive without evidence of disease.

Of the 10 patients treated with surgery, 7 had surgery alone, and 3 had multimodal treatment (Table 2). A median 45-month (range 14–142 months) follow-up assessment found 4 of these 10 patients with NED. Two of the remaining six patients were alive with disease (AWD), and four had died of disease (DOD).

For the 16 patients with a first recurrence who received chemotherapy, 10 of the treatments were given in isolation and 6 as part of multimodal treatment (Table 2). Of these 16 patients, 13 had paclitaxel and 3 had doxorubicin. The median number of treatment cycles was 5 (range 2–10). The last follow-up assessment at a median of 29.5 months found that four patients were alive with NED, three patients were AWD, and 9 had DOD.

One of the eight patients treated with radiotherapy received neoadjuvant radiotherapy, then re-resection. After surgery, this patient had a complete clinical and pathologic response. She was alive with NED at her last follow-up visit at 62 months. Of the seven other patients, one had NED, four were alive with LRR, and 2 had DOD at a follow-up assessment after a median of 24 months (range 7–36 months).

Of the 29 patients, 10 experienced a second recurrence (2 SMDT patients and 8 OC patients) after a median time of 6.5 months (range 3–23 months) from the first to the second recurrence (Table 2). One patient had DR alone, and one patient had both LRR and DR. The remaining eight patients had LRR alone. All but two of the patients underwent additional treatment.

The treatment for isolated LRR included surgery (with negative margins), radiation therapy, and chemotherapy (where surgery, radiation, or both were not feasible). The patients with distant disease underwent chemotherapy ± radiation therapy. One patient was alive at the last follow-up visit with NED (Table 2).

Four patients experienced a third recurrence after a median period of 11 months (range 7–16 months). Two patients experienced LRR, and two patients experienced DR. Both second and third recurrences were more frequent in the cohort initially treated at OC. Treatment of the second and third recurrences are detailed in Table 2. The time to recurrence data is displayed in Fig. 4.

Uni- and Multivariate Analyses of RAAS DSS

The factors associated with decreased DSS included the initial treatment team and the use of neoadjuvant chemotherapy (Table 3). In a multivariable model, only the initial treatment team remained statistically significant (SMDT vs OC; p = 0.02; HR, 0.304; 95% CI, 0.113–0.817).

TABLE 2 Treatment and outcome of recurrences

	SMDT $n = 26$	OC $n = 23$	p values
First recurrence of RAAS (%)			
Total	10/26 (38.4)	19/23 (82.6)	0.0017
Local recurrence	8/10	17/19	
Distant recurrence	1/10	0/19	
Local + Distant recurrence	1/10	2/19	
Treatment			
Surgery alone	1	6	
Surgery/neo-adjuvant RT	1	0	
Surgery/neo-adjuvant chemo	0	2	
Chemotherapy alone	2	8	
RT alone	2	1	
Chemo + RT	3	1	
No treatment	1	1	
Outcome at median follow up of 26 months			
NED	2	5	0.27
AWD	5	4	
DOD	3	10	
DOC	0	0	
Second Recurrence of RAAS			
Total	2	8	0.019
Local recurrence	2/2	6/8	
Distant recurrence	0/2	1/8	
Local +distant recurrence	0/2	1/8	
Treatment			
Surgery alone	0	3	
Chemotherapy + radiotherapy	0	1	
Chemotherapy alone	1	1	
Radiotherapy alone	1	1	
No treatment	0	2	
Outcome at median follow up of 29.5 months			
NED	1	0	
AWD	1	3	
DOD	0	5	
DOC	0	0	
Third recurrence of RAAS			
Total	0	4	
Local recurrence	–	2/4	
Distant recurrence	–	2/4	
Local +distant recurrence	–	0	
Treatment			
Surgery	–	3	
Surgery + radiotherapy	–	1	
Outcome at median follow up of 36.5 months			
NED	–	0	
AWD	–	2	
DOD	–	2	
DOC	–	0	

SMDT sarcoma multi-disciplinary team, *OC* outside center, *RAAS* radiation-associated angiosarcoma, *RT* radiation therapy, *NED* no evidence of disease, *AWD* alive with disease, *DOD* died of disease, *DOC* died of other cause

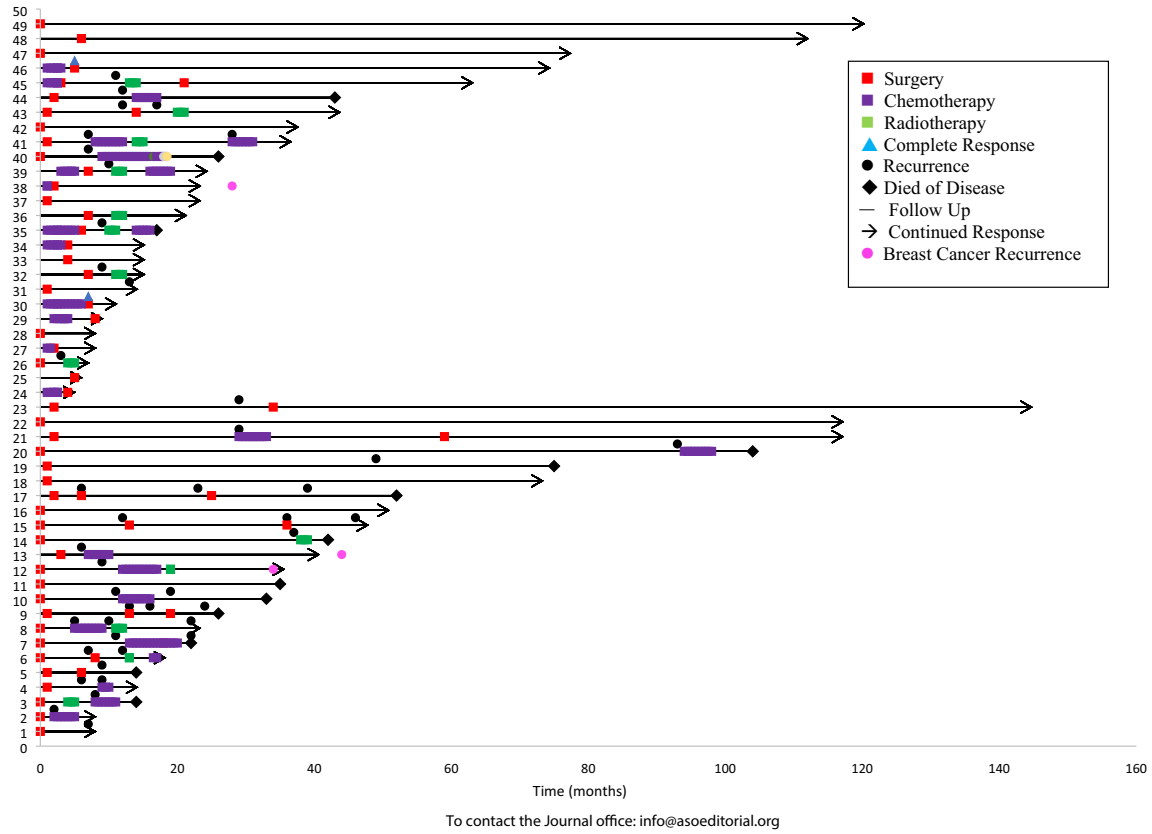

FIG. 4 Swimmers plot showing an individual patient's response and follow-up evaluation. Each bar is one patient treated initially by either the sarcoma multi-disciplinary team (SMDT) or an outside center (OC). Patients 1 to 23 were treated by OC, and patients 24–49 were treated by SMDT. See key for treatment and outcomes

TABLE 3 Uni- and multivariate Cox regressional analyses for prognostic factors of disease-specific survival (DSS)

Variable	*n*	HR	95% CI	*p* value
Univariate analysis				
Age		1.89	0.91–3.94	0.09
<75	26			
>75	23			
Treatment Team		0.31	0.15–0.68	0.02
SMDT	26			
OC	23			
Radicality of Surgery		0.59	0.27–1.29	0.18
Radical resection	29			
Conservative	20			
Use of neoadjuvant chemotherapy		0.41	0.19–0.91	0.03
Neoadjuvant Chemo	10			
No Neoadjuvant Chemo	19			
Multivariate analysis				0.02
Treatment Team		0.304	0.113–0.817	
SMDT	26			
OC	23			

HR hazard ratio, *CI* confidence interval, *SMDT* sarcoma multi-disciplinary team, *OC* outside center, *Sx* symptoms

DISCUSSION

During the past three decades, the use of adjuvant radiotherapy after breast-conserving surgery for breast cancer has resulted in an increasing incidence of RAAS of the breast.[30] This report describes a large series of RAAS patients who had undergone multi-disciplinary management at a dedicated sarcoma center compared with patients who initially had treatment at a non-specialized center. This series expands on the limited literature describing treatment for RAAS. It is unique in describing longitudinal outcomes including patterns and treatments of recurrence and demonstrating that patients can be salvaged even after recurrence or recurrences.

Surgery remains the standard of care in resectable RAAS, and the extent of surgical resection has been demonstrated to have a direct impact on outcomes in RAAS.[23,26,30] An inferior outcome is associated with an *R*1 resection because positive margins have been associated with significant risk for local recurrence,[9] and *R*1 resections have significantly lower levels of survival than *R*0 resections.[23]

In our study, radical mastectomy was superior to lesser surgery, with clear margins and an improved 3-year DSS (83% vs 63%; $p = 0.041$), in keeping with the concept that complete surgical excision of the entire irradiated field likely improves outcomes. We demonstrated that even with an *R*0 resection, rates of local recurrence were substantially lower when a radical resection including the entire irradiated field was performed. Patients treated at a high-volume specialized sarcoma center had a higher likelihood of treatment with radical surgery (96%) than those managed at a non-sarcoma center (17%). These findings highlight the need for guidelines in the management of RAAS and surgical expertise for this rare and complex disease.

In our study, we classified limited resection as a simple mastectomy or lumpectomy and a radical resection as a wide local excision of the previously irradiated skin by mastectomy with or without the removal of the pectoralis muscle (as involved). To excise the entirety of the skin in the previously irradiated field, reconstruction with a pedicled muscle or myocutaneous flap usually is necessary, and careful planning of surgery with sarcoma and reconstructive surgeons is required.

Overall, treatment by a multidisciplinary team trended toward an improved RFS and demonstrated a significant LRFS. Unmeasured factors may be drivers of this finding. For example, more aggressive disease is subsequently referred to an expert center. Also, the OC group had longer follow-up time (median, 35 months; range 8–182 months) than the SMDT group (22 months; range 4–118 months). Additionally, race and ethnicity data were unavailable. Given that RAAS is a rare malignancy, little is known whether certain ethnicities have a greater biologic predisposition in addition to a potentially confounding effect between ethnicity and referral practice patterns. Nonetheless, we demonstrated lower rates of first and second recurrences and no third recurrences for patients initially treated by SMDT rather than OC. Additionally, at the last follow-up visit, 69% of the patients treated by SMDT were alive without evidence of disease, in contrast to only 35% of the patients treated initially at OC. Finally, the SDMT cohort not only received more extensive (radical) surgery than the OC group, but also had neoadjuvant chemotherapy.

Despite an *R*0 resection, 53% of the women still experienced local disease failure, reflecting the aggressive biology of this disease. Although neoadjuvant paclitaxel-based chemotherapy was used for a minority of the patients, the observation that the majority of those treated experienced an almost complete clinical response with a partial or complete pathologic response warrants further study of this approach.

Currently, no consensus exists on the role of neoadjuvant chemotherapy in the treatment of RAAS.[7,21] The incidence of RAAS is low, and no randomized trials have addressed systemic treatment. Previous studies have shown both no benefit from combining adjuvant chemotherapy with surgery[7] as well as a potential role of combining adjuvant chemotherapy with surgery when margins are widely resected.[5,31] Although it remains to be proven, neoadjuvant chemotherapy may be beneficial over adjuvant chemotherapy in the treatment of RAAS. Neoadjuvant treatment causes tumor regression, increasing the likelihood of an *R*0 resection and/or facilitating surgery for previously unresectable lesions.[7]

According to our experience, the response to chemotherapy can be monitored easily by physical examination and the treatment stopped if the patient is non-responsive or a treatment plateau occurs. Our findings suggest that neoadjuvant chemotherapy may play a role in achieving disease-free status when combined with resection and potentially could have an impact on long-term survival. An international randomized trial is needed to better define the role and utility of neoadjuvant chemotherapy for RAAS patients.

Importantly, salvage after recurrence is possible. In the current study, approximately one fourth of the patients, including one with a second recurrence, were alive with NED (median follow-up period, 26 months) after treatment of a first recurrence with radiation, chemotherapy, and/or surgery, demonstrating that these patients can do well after relapse. Interestingly, three patients experienced a recurrence of their initial breast cancer after treatment while having a complete response of their angiosarcoma (Fig. 4).

Sporadic angiosarcoma and RAAS are morphologically identical diseases. However, RAAS is characterized by amplification of the c-MYC oncogene.[32] Behjati et al. [33] identified recurrent mutations in two genes linked to angiogenesis, inactivating mutations to the angiogenesis regulator PTPRB and activating mutations in PLCG1, a tyrosine kinase. PTPRB inhibits VEGFR2, therefore this inhibition promotes angiogenesis. Mutational burden and PD1 expression also have been investigated, but with only limited results. Further genomic studies are needed to understand the molecular basis of this disease and to identify novel therapeutic targets.

Despite improvement in the prognosis for carcinoma of the breast and the consequential rise in the incidence of RAAS, RAAS remains a rare disease.[30] Early referral of patients to a SMDT allows for both consideration of neoadjuvant chemotherapy (including potential trials) and a more radical surgical approach. Additionally, given the high propensity for recurrence, patients with RAAS likely benefit from multidisciplinary management should they experience recurrence given the potential for salvage. Multi-center prospective trials are urgently needed to determine the optimal management of RAAS as well as concurrent guidelines outlining current best practices, including a multi-disciplinary approach, to these rare and highly aggressive malignancies.

DISCLOSURE There are no conflicts of interest.

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