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CLINICAL TRIAL

Extent of resection and role of adjuvant treatment in resected localized breast angiosarcoma

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Abstract

Background Localized breast angiosarcoma (LBA) is a rare condition with no prospective clinical trials guiding the management of afflicted patients. Management of LBA and the resulting outcomes on a nationwide scale has not been previously examined.

Methods The National Cancer Data Base (NCDB) from 2004 to 2014 identified resected LBA patients. Treatment patterns were compared between three time periods (2004–2007, 2008–2011, and 2012–2014). Demographic and tumor characteristics, as well as treatments received—extent of surgery and adjuvant therapies—were analyzed for association with overall survival after adjustment for covariates.

Results 826 resected localized breast angiosarcoma patients were identified. Mastectomy was the most common surgical approach (86%); over 60% of patients did not receive adjuvant therapies after surgery. On multivariate analysis, tumor grade, tumor size, and surgical margins were associated with worse survival. Extent of surgery (mastectomy versus lumpectomy) and radiation therapy use were not associated with improved survival. Adjuvant chemotherapy was associated with improved survival in patients with primary tumors 5 cm and greater.

Conclusions The extent of surgery is not associated with improved survival in women with LBA, and patients may consider breast-conservation surgery. Adjuvant therapies are not associated with improved survival, with the exception of possible role of adjuvant chemotherapy in large primary tumors (5 cm or greater). Further clinical studies are needed to determine the impact of these treatments on local control, progression-free survival, and patients' quality of life. Until then, the findings of our analysis will form basis for the multi-disciplinary discussion of management of women with LBA.

Keywords Localized breast angiosarcoma · Radiation therapy · Chemotherapy · Mastectomy · Lumpectomy · National cancer database

Introduction

Localized breast angiosarcoma is a rare disease, with an incidence of 1/2000 (0.05%) primary breast malignancies; it is most frequent in women between ages 20 and 50 with no previous cancer history [1, 2], however, it can also arise in the setting of prior irradiation. Although up to 12% of breast angiosarcomas are diagnosed either during or shortly after pregnancy, the majority of these tumors do not express estrogen and progesterone receptors [3]. Histological assessment of this malignancy in the past has not been shown to provide prognostic value [4, 5]. Physicians face the dilemma of whether to manage localized breast angiosarcoma as a soft tissue sarcoma or breast carcinoma. The predominant management has been surgical [6], with either mastectomy or lumpectomy, and the role of adjuvant therapies—systemic chemotherapy and radiation therapy—is unknown due to the rarity of this disease and paucity of clinical data. To address this void in the evidence-based care, the following nationwide analysis was performed to assess trends in patterns of care and clinical outcomes.

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Methods

Data source

The data source for this study was the National Cancer Data Base (NCDB). The NCDB is a hospital-based cancer registry sponsored jointly by the American College of Surgeons and the American Cancer Society. Comprised of more than 1400 facilities accredited by the American College of Surgeons' Commission on Cancer, the NCDB contains de-identified data on 70% of all newly diagnosed cancers in the United States (US) [7]. The NCDB includes data on radiation therapy (i.e., dosage, technique, target) not contained in the surveillance, epidemiology, and end results (SEER) database [7, 8].

Inclusion and exclusion criteria

The NCDB was used to identify breast angiosarcoma patients in the US treated from 2004 to 2014 having undergone surgical resection. Patients with metastatic disease at diagnosis were excluded, as were patients who did not undergo surgery or whose surgical status was unknown. Disease was stratified by grade, tumor size, nodal status (negative versus positive), extent of resection (mastectomy versus lumpectomy), and surgical margin status (negative versus positive). Mortality analysis excluded patients with fewer than 3 years of follow-up as of 2014, the final year of analysis.

Data collection

Demographic data for age, race, gender, income, geographic location, facility type (academic/research facility, comprehensive cancer center, community, integrated network), primary payer (Medicare, Medicaid, other government, private, no insurance), education (< 14% high school graduates in the region), region of the United States (East/Atlantic, Central, West), income, and medical comorbidities (the overall comorbidity burden was calculated using the Deyo comorbidity index, an adapted Charlson comorbidity index) were analyzed in this study [9, 10].

Statistical analysis

We used R version 3.4.4 to perform the statistical analysis. Descriptive analysis was used to show patterns of treatment based on tumor size, margin status, and type of resection, using Chi-square test to test the significance of categorical variables and the Cochrane–Armitage test for trend for the association between categorical and ordinal variables. The survival time was estimated on those with at least 3 years of follow-up after diagnosis using the number of months between the date of diagnosis and date on which the patient was last contacted or had died. Univariate and multivariate logistic regression analyses were used to assess the risk of death from breast angiosarcoma based on demographic and disease characteristics. Significance was defined as a two-sided P value less than 0.05, based on the likelihood ratio test. A multivariable model consisting of patient age, tumor size, tumor grade, and surgical margins was used to generate adjusted survival curves using the conditional method and forest plots for level-specific risk by treatment type for surgical margins and tumor size.

Results

Demographics of breast angiosarcoma patient population

The NCDB contained 826 breast angiosarcoma patients in the US from 2004 to 2014 having undergone surgical resection, and 600 of them had at least 3 years of follow-up. The mean age of these patients was 65.7 (SD 16.5) years; all were women. The vast majority (87.2%) were white, 47 (5.7%) were African-American, and 30 (3.6%) were Hispanic; the remaining 29 (3.5%) were categorized as "other." The most common insurance was Medicare (449; 54.4%), followed by private insurance (298; 36.1%), Medicaid (4.5%), other government insurance (3.1%), and no insurance (1.9%). 48.7% of patients had median household income of at least $46,000, and 58.5% of patients had a high school diploma. Patients were most commonly treated at an academic/research facility type (354; 42.9%), with 314 (38%) treated at comprehensive cancer centers; 80 (9.7%) were treated at community hospitals.

Of the 676 patients for whom tumor size was recorded, 305 (45.1%) had tumors greater than 5 cm, 226 (33.4%) had tumors between 2 and 5 cm, and 145 (21.4%) had tumors 0–2 cm. Of the 227 patients for whom lymph node status was available, 96% had negative nodes; the remaining patients had positive nodes. For the 797 patients with surgical margin status recorded, 730 (92%) were resected with negative margins; the remaining 8% had positive margins. Regarding extent of resection, 116 patients (14%) received lumpectomy, with the remaining 86% receiving mastectomy (Table 1).

Treatment of localized breast angiosarcoma over time

Over 60 percent of US patients with localized breast angiosarcoma over the past decade have been treated with surgery

Table 1 Treatment of resected localized breast angiosarcoma over time ($n=826$); numbers expressed in percent form

Treatment modality	2004–2007 ($n=286$)	2008–2011 ($n=314$)	2012–2014 ($n=226$)
Surgery only	67.1	66.9	61.1
Surgery + radiation	14.3	7.0	13.3
Surgery + chemotherapy	15.0	19.4	19.0
Surgery + radiation + chemotherapy	3.5	6.7	6.6
Surgical modality			
Mastectomy	84.9	85.9	87.2
Lumpectomy	15.1	14.1	12.8

Table 2 Impact of tumor size on surgical modality for localized breast angiosarcoma

Surgical modality	0–20 mm tumor ($n=145$) (%)	20–50 mm tumor ($n=226$) (%)	50 + mm tumor ($n=305$) (%)	*P* value[a]
Mastectomy	71.0	86.3	93.7	**< 0.001**
Lumpectomy	29.0	13.7	6.3	

Bold represents the statistically significant value

[a]Cochrane–Armitage test for trend

alone (Table 1), with less than 25% receiving systemic chemotherapy, and even fewer receiving radiation therapy. Over 85% of women were treated with mastectomy (Table 1), with tumor size significantly impacting the surgical decision ($P<0.001$) (Table 2), as well as receipt of radiation therapy ($P=0.001$) (Table 3). After lumpectomy, 25% of patients received radiation therapy, comparing to 16% after mastectomy ($P=0.017$). There was a trend in higher use of radiation therapy in the case of positive resection margins (25.4% vs. 16.3%, $P=0.086$).

Demographic and tumor characteristics associated with mortality

On univariate analysis, age ≥ 80, Medicaid and Medicare insurances, Charlson–Deyo comorbidity scores of 1 and 2, tumor size greater than 2 cm, higher tumor grades, and positive surgical margins were associated with worse overall survival. After adjustment, Medicaid insurance (HR 2.03, $P=0.042$), tumor grades (for grade 3 HR 1.57, $P=0.047$; for grade 4 HR 1.87, $P=0.011$) (Fig. 1a), tumor size greater than 2 cm (for 2–5 cm HR 1.89, $P=0.004$; for ≥ 5 cm HR 2.48, $P<0.001$) (Fig. 1b), and positive surgical margin (HR 2.36, $P<0.001$) (Fig. 1c) remained associated with worse overall survival (Table 4).

Impact of treatment modality on survival

The extent of surgical resection (lumpectomy versus mastectomy) was not associated with improved survival by either univariate or adjusted Cox analysis (Table 4; Fig. 2a). Addition of radiation therapy was not associated with improvement in overall survival by either univariate or adjusted Cox analysis. On subgroup analysis, after adjustment for age, tumor grade, and tumor size, radiation therapy was not associated with improved overall survival in patients with both negative and positive resection margins (Fig. 3). On univariate analysis, addition of chemotherapy was associated with improved survival (HR 0.72, $P=0.042$), but lost its significance after adjustment for covariates (HR 0.74, $P=0.074$). On subgroup analysis, addition of chemotherapy was associated with improved overall survival in patients with localized breast angiosarcoma ≥ 5 cm (Fig. 4).

Table 3 Demographics impacting utilization of radiation therapy for resected localized breast angiosarcoma

	0–20 mm tumor ($n=145$) (%)	20–50 mm tumor ($n=226$) (%)	50 + mm tumor ($n=305$) (%)	*P* value*
Surgery with RT	11.1	17.3	23.6	**0.0011**
Surgery without RT	89.0	82.7	76.4	
	Negative margins ($n=730$) (%)	Positive margins ($n=67$) (%)		*P* value**
Surgery with RT	16.3	25.4		0.086
Surgery without RT	83.7	74.6		
	Lumpectomy ($n=116$) (%)	Mastectomy ($n=707$) (%)		*P* value**
Surgery with RT	25.0	15.6		**0.017**
Surgery without RT	75.0	84.4		

Bold represents the statistically significant value

*Cochrane–Armitage test for trend

**Chi-Square test

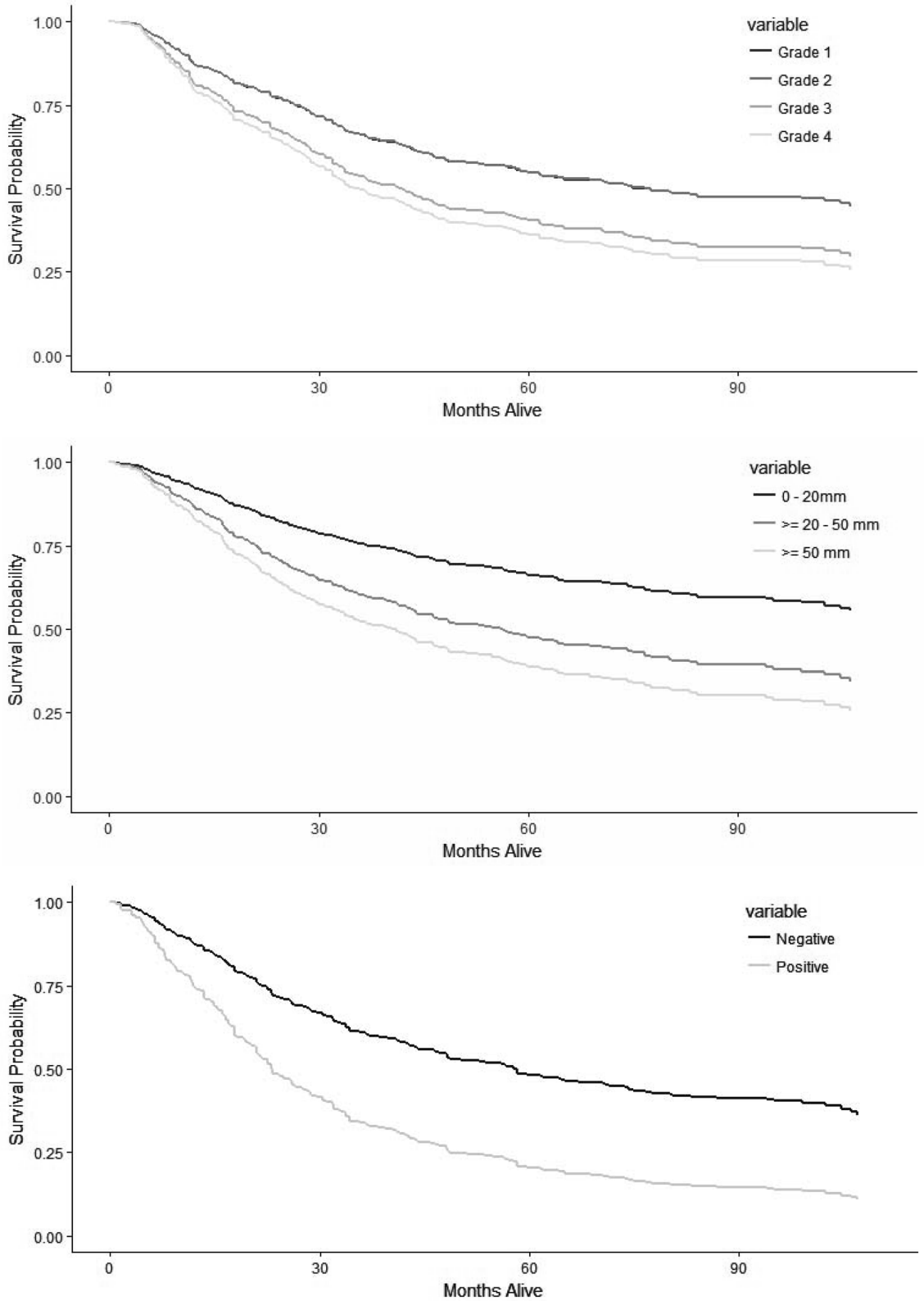

Fig. 1 Survival analysis after adjustment for covariates for 600 patients diagnosed with non-metastatic resected localized breast angiosarcomas by **a** tumor grade, **b** tumor size, and **c** margin status

Table 4 Cox analysis for overall survival in localized breast angiosarcoma diagnosed between 2004 and 2011

Variable	Univariate Cox models		Adjusted Cox models[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years				
18–49	Reference		Reference	
50–64	0.72 (0.47, 1.10)	0.133	0.80 (0.41, 1.55)	0.507
65–79	1.29 (0.90, 1.85)	0.163	1.11 (0.54, 2.26)	0.774
≥ 80	2.53 (1.74, 3.68)	< 0.0001	1.96 (0.93, 4.10)	0.075
Race/ethnicity				
White, non-hispanic	Reference		Reference	
Black, non-hispanic	1.30 (0.84, 2.03)	0.245	1.02 (0.60, 1.71)	0.945
Hispanic	0.61 (0.29, 1.29)	0.198	0.53 (0.23, 1.20)	0.129
Unknown/other	0.64 (0.30, 1.35)	0.239	0.64 (0.29, 1.38)	0.255
Insurance				
Private	Reference		Reference	
Uninsured	1.00 (0.37, 2.74)	0.994	1.13 (0.40, 3.17)	0.816
Medicaid	2.05 (1.12, 3.77)	0.02	2.03 (1.02, 4.01)	0.042
Medicare	2.10 (1.63, 2.71)	< 0.0001	1.41 (0.93, 2.14)	0.109
Other/missing	0.85 (0.39, 1.84)	0.678	0.68 (0.30, 1.54)	0.357
Income, per year				
≥ $46,000	Reference		Reference	
36,000–45,999	1.08 (0.82, 1.42)	0.582	1.21 (0.87, 1.67)	0.253
30,000–35,999	1.03 (0.75, 1.42)	0.857	1.07 (0.73, 1.58)	0.725
< $30,000	1.27 (0.89, 1.80)	0.185	0.97 (0.63, 1.51)	0.905
Education, percent without high school diploma (%)				
< 14	Reference		Reference	
14–19.9	0.96 (0.73, 1.26)	0.753	0.80 (0.59, 1.10)	0.165
20–28.9	1.10 (0.82, 1.46)	0.523	1.05 (0.73, 1.50)	0.793
≥ 29	1.08 (0.69, 1.68)	0.742	1.32 (0.74, 2.34)	0.35
Facility type				
Comprehensive Cancer Center	Reference		Reference	
Community Cancer Center	1.22 (0.86, 1.73)	0.267	1.13 (0.78, 1.65)	0.52
NCI/Teaching/Research Center	0.88 (0.69, 1.12)	0.29	1.13 (0.88, 1.47)	0.341
Missing	0.83 (0.55, 1.27)	0.399	1.33 (0.62, 2.85)	0.469
Charlson–Deyo comorbidity score				
0	Reference		Reference	
1	1.39 (1.06, 1.82)	0.018	1.24 (0.93, 1.65)	0.15
2	2.28 (1.35, 3.85)	0.002	1.59 (0.91, 2.81)	0.106
Tumor grade				
1	Reference		Reference	
2	1.15 (0.68, 1.93)	0.599	1.10 (0.64, 1.88)	0.736
3	1.97 (1.31, 2.96)	0.001	1.57 (1.01, 2.46)	0.047
4	2.26 (1.46, 3.52)	< 0.0001	1.87 (1.16, 3.03)	0.011
Tumor size, mm				
≤ 20	Reference		Reference	
20–50	1.98 (1.32, 2.97)	0.001	1.89 (1.23, 2.90)	0.004
≥ 50	2.49 (1.68, 3.69)	< 0.0001	2.48 (1.63, 3.79)	< 0.0001
Surgical margins				
Negative	Reference		Reference	
Positive	2.51 (1.80, 3.51)	< 0.0001	2.36 (1.64, 3.40)	< 0.0001
Surgical resection				
Lumpectomy	Reference		Reference	

Table 4 (continued)

Variable	Univariate Cox models		Adjusted Cox models[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Mastectomy	1.20 (0.87, 1.67)	0.273	0.88 (0.61, 1.28)	0.514
Adjuvant therapies				
Surgery only	Reference		Reference	
Radiation	0.96 (0.68, 1.36)	0.827	0.98 (0.67, 1.43)	0.914
Chemotherapy	0.72 (0.53, 0.99)	0.042	0.74 (0.53, 1.03)	0.074
Radiation and chemotherapy	1.03 (0.63, 1.70)	0.892	1.08 (0.60, 1.95)	0.792

[a]Adjusting for age, race, insurance, income, education, facility type, Charlson Score, tumor grade, tumor size, surgical margins, surgical resection and adjuvant surgery therapies

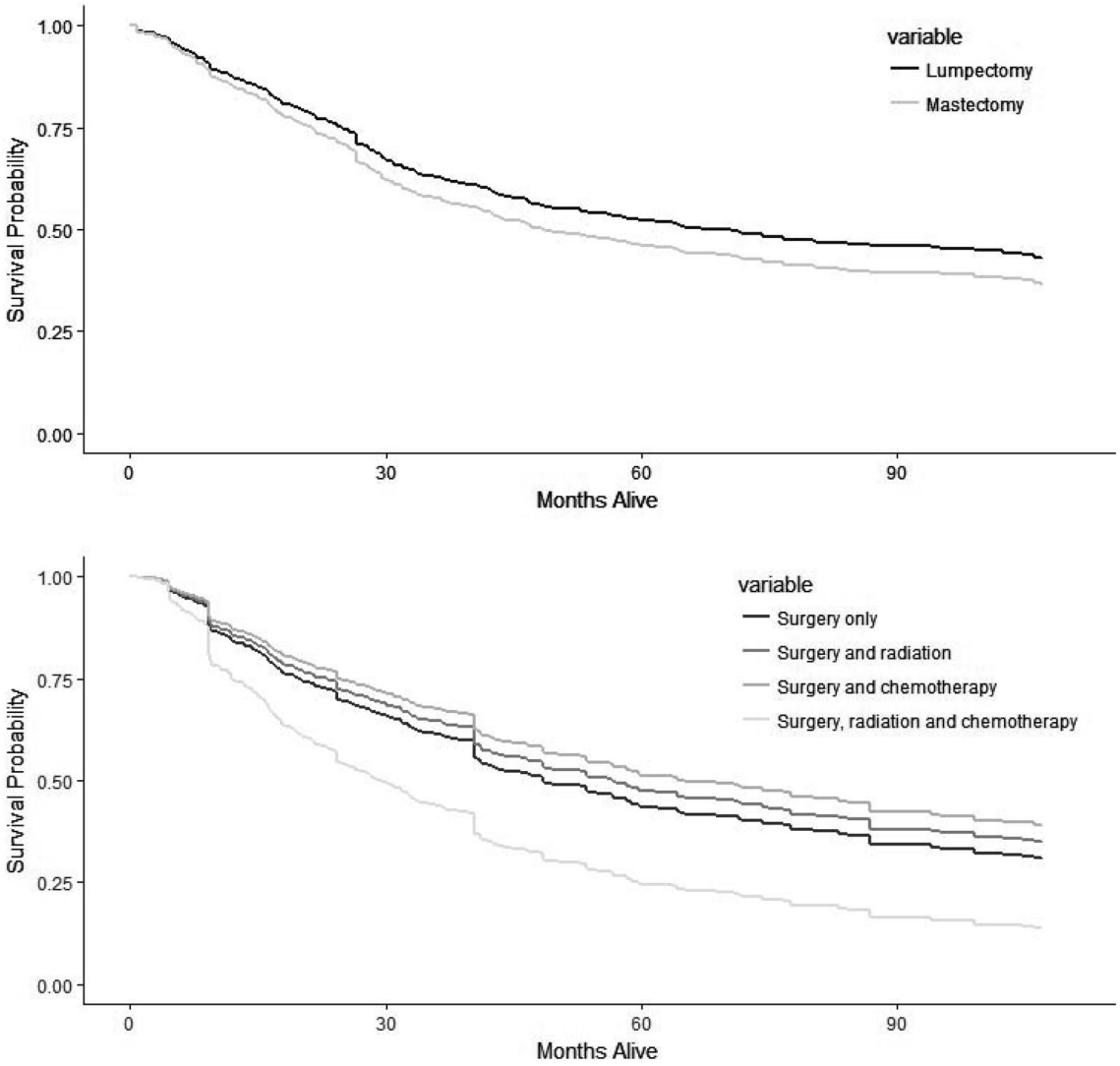

Fig. 2 Survival analysis after adjustment for covariates for 600 patients diagnosed with non-metastatic resected localized breast angiosarcomas by **a** extent of resection and **b** adjuvant therapies received

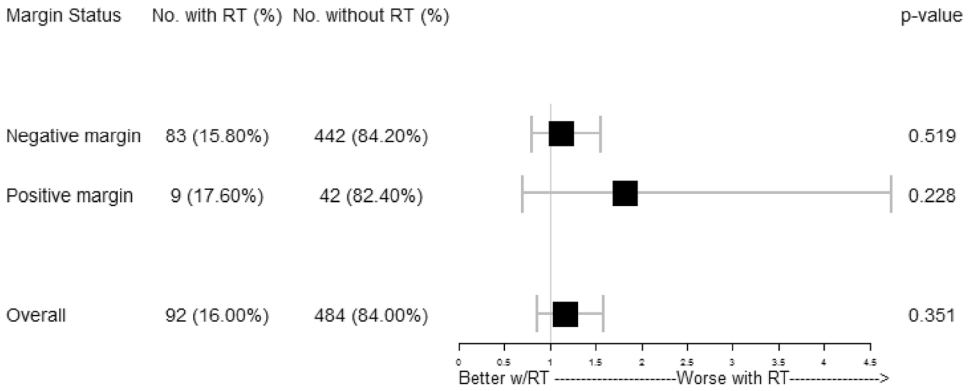

Fig. 3 Association of adjuvant radiation therapy with overall survival in patients with resected localized breast angiosarcoma by surgical margin status, after adjustment for age, tumor grade, and tumor size

Fig. 4 Association of adjuvant chemotherapy with overall survival in patients with resected primary breast angiosarcoma by tumor size, after adjustment for age, tumor grade, and surgical margin

Subgroup analysis of primary breast angiosarcoma patients

Patients whose breast cancer diagnosis was only angiosarcoma, a surrogate for primary breast angiosarcoma versus secondary (i.e., radiation-induced), were analyzed in a subset analysis; 220 of the 826 patients met this criteria. Characteristics comparing primary breast angiosarcoma patients versus the overall breast angiosarcoma pool are listed in Table 5. Neither the modality of breast surgery (lumpectomy vs. mastectomy) nor adjuvant therapies impacted the aforementioned outcomes (larger tumors were more likely to be treated with mastectomy, no significant difference in the use of surgery plus radiation based on surgical type) in the subgroup of patients with primary breast angiosarcoma (Table 6).

Discussion

The rarity of breast angiosarcoma and ensuing paucity of reported studies provides a frustrating challenge for application of evidence-based care. To our knowledge, this is the first and the most comprehensive national cancer database analysis of patients with resected localized breast angiosarcoma.

Our findings indicate that over the last decade, adjuvant therapies (chemotherapy and radiation therapy) have not been commonly used after resection of localized breast angiosarcoma. Practicing US radiation and medical oncologists endorse utilization of adjuvant therapies to a much larger extent, with the majority supporting trimodality therapy [11]. Patients with localized breast angiosarcoma may not be referred to adjuvant therapy discussion by surgeons. In the absence of prospective clinical data, multi-disciplinary evaluation and management of these patients are important for optimal outcomes and patient satisfaction with care received. Our analysis provides some preliminary evidence that can be cautiously used in these multi-disciplinary discussions, pending validation in prospective studies.

The extent of surgery is not associated with overall survival, and breast-conservation surgery should be considered in these patients similarly to management of breast carcinoma. Adjuvant radiation therapy does not appear to provide a survival advantage, regardless of the extent of surgery and/or resection margin status. With a very small number of patients in our database with positive resection margins, the confidence interval is very large and any conclusion about the role of radiation therapy in this population of patients

Table 5 Overall disease characteristics for all NCDB breast angiosarcoma ($n=826$) versus primary angiosarcoma ($n=220$), NCDB 2004–2011

Variable	Primary breast angiosarcoma ($n=220$) (%)	All localized breast angiosarcoma ($n=826$) (%)
Comorbidity score		
0	182 (82.7)	659 (79.8)
1	32 (14.5)	139 (16.8)
2	6 (2.7)	28 (3.4)
Grade		
1	57 (25.9)	100 (12.1)
2	40 (18.2)	105 (12.7)
3	51 (23.2)	265 (32.1)
4	25 (11.4)	131 (15.9)
Other	47 (21.4)	225 (27.2)
Tumor size (mm)		
0–20	40 (18.2)	145 (17.6)
20–50	64 (29.1)	226 (27.4)
50+	96 (43.6)	305 (36.9)
Unknown/other	20 (9.1)	150 (18.2)
Regional nodal status		
Negative	97 (44.1)	217 (26.3)
Positive	5 (2.3)	10 (1.2)
Unknown/other	118 (53.6)	599 (72.5)
Surgical margins		
Negative	196 (89.1)	730 (88.4)
Positive	15 (6.8)	67 (8.1)
Unknown/other	9 (4.1)	29 (3.5)
Surgical modality		
Lumpectomy	47 (21.4)	116 (14.1)
Mastectomy	173 (78.6)	707 (85.9)
Treatment modality		
Surgery only	105 (47.7)	540 (65.4)
Surgery and radiation	50 (22.7)	93 (11.3)
Surgery and chemotherapy	34 (15.5)	147 (17.8)
Surgery, radiation and chemotherapy	31 (14.1)	46 (5.6)

must be made with utmost care, as radiation therapy is commonly used to decrease the risk of local resection after resection with positive margins. NCDB analysis cannot provide information about the benefit (or lack thereof) of radiation therapy in terms of local control improvement.

Adjuvant chemotherapy's benefit may be limited to patients with large primary tumors, greater than 5 cm in size. This is in line with the current lack of evidence of impact of adjuvant chemotherapy on overall survival from large randomized clinical trials [12], but conflicting reports from single institutions suggesting the benefit for adjuvant chemotherapy in large extremity soft tissue sarcoma [13, 14].

Limitations of this study include its retrospective nature and the possibilities of incomplete/biased data reporting and/or miscoding during data submission to NCDB, as there has been no verification that the NCDB data are representative of the breast angiosarcoma population nationwide. While NCDB contains several important details, important aspects of outcome (local control, distant toxicities) were not available, nor were other important treatment variables (operative surgical approach, treatment isodose lines, Karnofsky performance status, whether patients with axillary lymph node negativity had axillary sampling performed) or the delineation of comorbidities beyond the Charlson/Deyo score. An important shortcoming of the NCDB is the lack of information on surgeon caseload, as for several disease sites (including breast), surgeon volume has been directly associated with morbidity and in-hospital mortality [15–17]. A third limitation is the absence of information on subsequent re-irradiation or progression/development of pathologic factors in the NCDB; in this vein, this study is limited by the

Table 6 Multivariable Cox Models for breast angiosarcoma patients eligible for survival analysis, NCDB 2004–2011

Cox models		Primary breast angiosarcoma ($n=154$)		All localized breast angiosarcoma ($n=600$)	
Variable	Level	HR	*P* value	HR	*P* value
Age, years	18–49			Reference	
	50–64			0.78 (0.51, 1.20)	0.262
	65–79			1.31 (0.90, 1.90)	0.155
	80+			2.41 (1.64, 3.56)	< 0.001
Charlson–Deyo score	0	Reference			
	≥ 1	2.38 (1.25, 4.54)	0.009		
Grade	1	Reference		Reference	
	2	1.10 (0.47, 2.62)	0.822	1.05 (0.62, 1.78)	0.847
	3	1.66 (0.84, 3.25)	0.142	1.44 (0.94, 2.20)	0.095
	4	1.38 (0.59, 3.25)	0.456	1.68 (1.06, 2.64)	0.026
Tumor size	≤ 20 mm	Reference		Reference	
	20–50 mm	4.34 (1.44, 13.01)	0.009	1.81 (1.20, 2.74)	0.005
	≥ 50 mm	7.20 (2.49, 20.80)	< 0.001	2.30 (1.54, 3.43)	< 0.001
Surgical margins	Negative	Reference		Reference	
	Positive	5.83 (2.32, 14.67)	< 0.001	2.18 (1.55, 3.07)	< 0.001
Adjuvant therapy	Surgery	Reference			
	Plus RT	0.98 (0.54, 1.78)	0.952		
	Plus chemo	0.45 (0.18, 1.15)	0.094		
	Plus RT and chemo	1.08 (0.48, 2.42)	0.852		

lack of NCDB information on important postoperative factors (average period of postoperative monitoring, event-free survival rate, local recurrence rate, re-excision rate, number of patients to convert from lumpectomy to mastectomy). Given that a main conclusion from this analysis involves the importance of adjuvant chemotherapy for improving the survival of large primary tumors (5 cm or greater), details regarding chemotherapy regimens used would be invaluable; unfortunately these data are likewise not available from the NCDB. Another limitation is that there may be ambiguity regarding whether patients had prior breast cancer and/or breast radiation; to help address this concern, a subgroup analysis of patients with angiosarcoma as their only cancer diagnosis was performed (Table 6). In this analysis, these patients developed disease at a younger age, in line with previous studies examining non-radiation-induced angiosarcoma [18]. Furthermore, this subgroup analysis demonstrated that neither the modality of breast surgery (lumpectomy versus mastectomy) nor adjuvant therapies impacted the aforementioned outcomes in the subgroup of patients with primary breast angiosarcoma. Regardless of the etiology of breast angiosarcoma (primary versus secondary), the treatment decision is always difficult and would still involve all treatment modalities, as the time from breast irradiation is often very long and allows for additional radiation dose. The fact that extent of surgery remained unassociated with improved survival despite positive margin status being associated with improved survival likely means that more extensive resections (i.e., mastectomy) remain unable to provide negative margins for this disease; this finding persisted on subgroup analysis of primary angiosarcoma patients (Table 6). Finally, as with all work derived from the NCDB, this study is derived from predominantly Commission on Cancer-approved hospitals, skewing the data towards hospitals more frequently located in urban locations, more likely to be affiliated with a medical school or residency program, more likely to offer oncology-related services (screening programs, chemotherapy, radiation therapy, hospice/palliative care), less likely to be critical access hospitals, and more likely to have more total beds and perform more operations per year than non-approved hospitals which comprise more than 70% of hospitals identified from the American Hospital Association Annual Survey Database [19].

In conclusion, the extent of surgery is not associated with improved survival in women with localized breast angiosarcoma, and patients may consider breast-conservation surgery, after detailed discussion with expert surgeons and with input from multi-disciplinary tumor boards. Adjuvant therapies are not associated with improved survival, with the exception of possible role of adjuvant chemotherapy in large primary tumors (5 cm or greater). Further clinical studies are needed to determine the impact of these treatments on the local control, progression-free survival, and patients' quality of life. Until then, the findings of our analysis will form the basis for multi-disciplinary discussion of managing patients with localized breast angiosarcoma.

Author Contributions McClelland: conceptualization, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, writing—original draft, and writing—review and editing. Hatfield: investigation, methodology, project administration, resources, software, validation, visualization, and writing—review and editing. Degnin and Chen: data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing—review and editing. Mitin: conceptualization, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing—review and editing.

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Compliance with ethical standards

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Research involving human participants and/or animals All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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