Incidence and outcomes of cutaneous angiosarcoma: A SEER population-based study

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Background: Cutaneous angiosarcoma (CAS) is a rare, malignant tumor of vascular mesenchymal origin accounting for less than 1% of all sarcomas.

Objective: To examine epidemiologic trends and outcomes in CAS.

Methods: In this retrospective, population-based study, patients with CAS were identified from the Surveillance Epidemiology and End Results database. Age, sex, and race-standardized incidence rates (IRs) were calculated. Survival was assessed with Kaplan-Meier curves and Cox proportional hazards models.

Results: Of 811 patients with CAS, 43% had a prior primary cancer. CAS IR for patients without prior primary cancers dropped from 5.88 per 100,000 in 1973 to 1984 to 2.87 per 100,000 in 2005 to 2014. In those with prior primary cancers, IR rose from 0.03 per 100,000 in 1973 to 1984 to 2.25 per 100,000 in 2005 to 2014. On multivariate analysis, patients older than 70 years of age had a higher risk of death compared with those younger than 50 years (hazard ratio, 2.16; 95% confidence interval 1.33-3.57; P = .002), and distant disease was associated with increased risk of death compared with localized disease (hazard ratio, 1.50; 95% confidence interval, 1.11-2.03; P = .008). Receipt of surgery and/or radiation therapy was not associated with survival.

Limitations: Potential selection and miscoding bias, retrospective nature.

Conclusion: CAS rates are rising among those with other prior primary cancers. Survival is not affected by current therapeutic strategies, highlighting the need for additional treatment options. (J Am Acad Dermatol 2020;83:809-16.)

Key words: angiosarcoma; cutaneous; disease-specific survival; incidence; outcomes; SEER.

Cutaneous angiosarcoma (CAS) is a rare, malignant tumor of vascular mesenchymal origin that accounts for less than 1% of all sarcomas.[1,2] CAS occurs more often among elderly men, usually in the head and neck area.[3] Clinically, it presents as an enlarging bruise-like lesion with poorly defined margins and may present with ulceration; hemorrhage; fungation; and blue, purple, or

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red nodules.[1,3-6] CAS can often be mistaken for other benign atypical vascular lesions, infection, chronic cellulitis, edema, and scarring alopecia.[2] It can occur after chronic lymphedema or radiation and can also be secondary to foreign material retention, arteriovenous fistulas, and immunosuppression; however, the majority of cases are de novo.[6-15] Treatment is generally surgical with or without adjuvant/neoadjuvant radiation. Chemotherapy is used for advanced regional or metastatic disease.

Because of the rarity of CAS, the majority of studies in the literature are based on case reports and case series.[5,9-12,16-28] The aim of this study is to provide an update on epidemiologic trends and outcomes in CAS.

CAPSULE SUMMARY

- Cutaneous angiosarcoma (CAS) is a rare, malignant tumor of vascular mesenchymal origin.
- CAS age-, sex-, and race-adjusted incidence rates are dropping for patients without prior cancers but rising among those with other cancers before CAS. Surgery and/or radiation do not improve survival, highlighting the need for new therapeutic options.

METHODS

The Surveillance Epidemiology and End Results (SEER) database is a national registry funded by the National Cancer Institute since 1971 that collects data on specific regions of the United States, covering approximately 28% of the population.[29] We used the SEER-18 registry, which includes data from Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco—Oakland, California; Seattle, Washington—Puget Sound; Utah; Los Angeles, California; San Jose—Monterey, California; rural Georgia; the Alaska Native Tumor Registry; greater California; greater Georgia; Kentucky; Louisiana; and New Jersey.[30] Use of SEER-18 is exempt from institutional review board approval.

Cohort identification

In this retrospective, population-based study, SEER*Stat, version 8.3.4 (National Cancer Institute, Bethesda, MD), was used to identify patients diagnosed with CAS using the International Classification of Diseases for Oncology, third edition, morphologic code (9120). Patients were further divided based on whether they had a previous non-CAS cancer.

Primary outcomes of interest were age-, sex-, and race-adjusted incidence rates (IRs) of CAS and CAS-specific survival. For CAS-specific survival, covariates of interest were presence of a previous primary cancer, age at diagnosis, sex, race, decade of diagnosis, primary tumor site, tumor size, pathologic grade, extent of disease, and therapy. The secondary outcome was to determine the effects of specific therapy on disease-specific survival.

Age was categorized into <50, 50-69, and ≥70 years. Sex was classified into male or female. Race was divided into white, black, other, and unknown. Year of diagnosis was categorized into four decades: 1973 through 1984, 1985 through 1994, 1995 through 2004, and 2005 through 2014. Tumor site was designated as head and neck, upper portion of the extremities, trunk, lower portion of the extremities, and not specified. Extent of disease was categorized into localized, regional, or distant. Disease-specific survival was calculated as time from diagnosis to death due to disease or end of the observation period. If patients died of causes other than angiosarcoma, they were censored as living.

Statistical methods

Categorical variables are presented as number and percentage, and continuous variables are presented as means and standard deviations. Chi-square tests and *t* tests were used for descriptive statistics. Age-, sex-, and race-adjusted IRs of CAS were calculated according to the 2000 US standard population.

The Cox proportional hazards model adjusted for age, sex, race, year of diagnosis, tumor size, primary site, extent of disease, previous primary cancer, and type of therapy was used to model survival outcomes. Statistical significance was considered at P values less than .05. Data were analyzed using R statistical software, version 3.4.1.[31]

RESULTS

A total of 811 individuals with diagnosis of CAS were identified, of whom 346 had a prior cancer diagnosis (Table I). Patients with a prior primary cancer were more likely to be female ($P < .001$) and white ($P < .001$) and to have received the diagnosis in the last 2 decades. The most common CAS site was the trunk (51%) among those with a prior primary cancer and the head and neck (83%) among those without a prior primary cancer ($P < .001$). Greater tumor size and extent of disease were more common among those with no prior cancer ($P = .01$ and $P = .048$, respectively); however, there were also more patients without tumor size and extent of

Abbreviations used:

CAS: cutaneous angiosarcoma
CI: confidence interval
IR: incidence rate
RT: radiation therapy
SEER: Surveillance Epidemiology and End Results

disease available. The most common cancer preceding angiosarcoma was breast cancer (n = 157, 45.4%), followed by prostate (n = 37, 10.7%), genitourinary (n = 37, 10.7%), gastrointestinal (n = 22, 6.3%), skin (n = 23, 6.6%), and respiratory tract (n = 15, 4.3%) cancers.

The most common treatment modality in patients without or with a previous primary cancer was surgery, at 39.4% and 65.3%, respectively. Patients without a previous primary cancer were more likely to receive combination radiation therapy (RT) and surgery (34.0%) compared with those with a previous primary cancer (12.7%, $P < .001$). Age and pathologic grade did not differ between the 2 groups.

Incidence rates in cutaneous angiosarcoma

The age-, sex-, and race-adjusted IRs of angiosarcoma without a prior primary cancer were highest in the period from 1973 through 1984 among patients younger than 50 years of age (Fig 1, *A*). However, for those older than 70 years of age, incidence of angiosarcoma without a prior primary cancer steadily increased in the last 3 decades. Finally, adjusted incidence dropped between 1973 and 2014.

The age-, sex-, and race-adjusted IRs of angiosarcoma with a prior primary cancer were highest in the last decade among patients aged 70 years and older (Fig 1, *B*). Adjusted incidence steadily increased in all age groups from 1973 to 2014.

Outcomes in cutaneous angiosarcoma

Kaplan-Meier 5-year unadjusted disease-specific survival was not statistically different between patients who had a prior primary cancer (75.8%; 95% confidence interval [CI], 71.8%-79.9%) compared with those who did not (79.6%; 95% CI, 75.3%-84.2%; $P = .15$). Similar trends were found in relative survival of CAS based on presence of a previous primary cancer (Fig 2). Notably, the 3-year relative survival rates were 53.7% for those without and 56.5% for those with a prior primary cancer, whereas the 5-year relative survival rates were 40.3% and 45.8%, respectively.

Table I. Demographic characteristics of patients with cutaneous angiosarcoma based on existence of a prior primary cancer

Characteristics	No previous primary cancer	Previous primary cancer	*P* value
n	465	346	
Age at diagnosis in years, n (%)			.391
<50	37 (8.0)	19 (5.5)	
50-69	134 (28.8)	102 (29.5)	
70+	294 (63.2)	225 (65.0)	
Male sex, n (%)	287 (61.7)	108 (31.2)	<.001
Race, n (%)			<.001
White	392 (84.3)	316 (91.3)	
Black	19 (4.1)	22 (6.4)	
Other	38 (8.2)	8 (2.3)	
Unknown	16 (3.4)	0 (0.0)	
Decade at diagnosis, n (%)			<.001
1973-1984	22 (4.7)	2 (0.6)	
1985-1994	65 (14.0)	24 (6.9)	
1995-2004	139 (29.9)	104 (30.1)	
2005-2014	239 (51.4)	216 (62.4)	
Site, n (%)			<.001
Head and neck	386 (83.0)	120 (34.7)	
Upper extremity	6 (1.3)	19 (5.5)	
Trunk	30 (6.5)	176 (50.9)	
Lower extremity	29 (6.2)	27 (7.8)	
Unspecified	14 (3.0)	4 (1.2)	
Tumor size, n (%)			.011
<1 cm	132 (28.4)	129 (37.3)	
>1 cm	23 (4.9)	22 (6.4)	
Unknown	310 (66.7)	195 (56.4)	
Pathologic grade, n (%)			.229
Well differentiated	30 (6.5)	21 (6.1)	
Moderately differentiated	36 (7.7)	40 (11.6)	
Poorly differentiated	68 (14.6)	53 (15.3)	
Undifferentiated	65 (14.0)	57 (16.5)	
Unknown	266 (57.2)	175 (50.6)	
Extent of disease, n (%)			.048
Localized	241 (51.8)	176 (50.9)	
Regional	108 (23.2)	106 (30.6)	
Distant	40 (8.6)	23 (6.6)	
Unstaged	76 (16.3)	41 (11.8)	
Therapy, n (%)			<.001
Surgery only	183 (39.4)	226 (65.3)	
RT only	50 (1.8)	24 (6.9)	
RT + surgery	158 (34.0)	44 (12.7)	
None/unknown	74 (15.9)	52 (12.0)	

RT, Radiation therapy.

Patients diagnosed between 1985 and 1994 had the lowest 5-year survival rate (65.2%; 95% CI, 56%-75.9%), and those diagnosed between 2005 and 2014 had the greatest 5-year survival rate (82%; 95% CI,

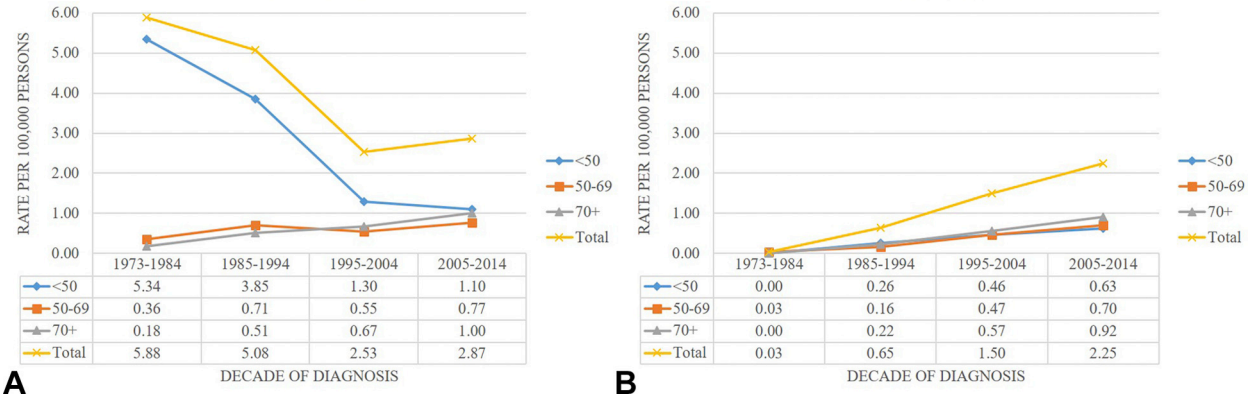

Fig 1. Cutaneous angiosarcoma age-adjusted incidence rates. **A**, Age-adjusted incidence rate of cutaneous angiosarcoma without a previous primary cancer. **B**, Age-adjusted incidence rate of cutaneous angiosarcoma with a previous primary cancer.

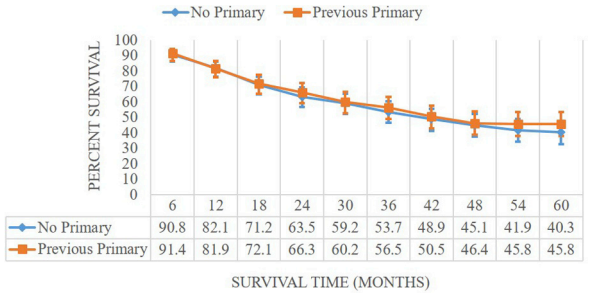

Fig 2. Relative survival of cutaneous angiosarcoma based on presence of a previous primary.

78.4%-85.8%, respectively) ($P < .001$). Localized disease (79.3%; 95% CI, 75.3%-83.5%) was associated with a greater 5-year survival rate compared with those with distant disease (65.1%; 95% CI, 54.3%-78%; $P = .027$). Finally, unadjusted 5-year Kaplan-Meier disease-specific survival did not differ significantly based on treatment modality: surgery (76%; 95% CI, 71.8%-80.5%), RT (76.7%; 95% CI, 67.6%-87.1%), surgery plus RT (80%; 95% CI, 74.5%-86.1%), or no therapy (78.5%, 95% CI, 71.3%-86.4%; $P = .87$). There were also no differences in survival between types of therapy in localized, regional, or distant diseases (data not shown).

On multivariate analysis, patients who were older than 70 years of age had a higher risk of death (hazard ratio, 2.16; 95% CI, 1.33-3.57; $P = .002$) compared with those younger than 50 years (Table II). Those with distant disease were also at increased risk of death 50% (hazard ratio, 1.50; 95% CI, 1.11-2.03; $P = .008$) compared with those with localized disease. Sex, race, presence of a prior primary cancer, decade of diagnosis, tumor location and size, pathologic grade, and treatment modality did not affect survival.

DISCUSSION

In this study, we found that the age-adjusted IR of angiosarcoma among people younger than 50 years of age is decreasing, but it is on the rise for those older than 70 years. Survival was negatively affect by age older than 70 years and distant disease. In addition, there were no differences in survival for patients with a prior primary cancer compared with those without, and therapeutic regimen did not affect survival.

CAS tends to occur in patients older than 60 years of age, with approximately 85% of cases in this age group; approximately 65% of cases occur in those older than 70 years of age. These findings have remained consistent with prior studies.[1,6,20,32] In contrast to prior reports, there was no male predominance overall; however, those without a previous primary cancer were more likely to be male.[6,14,20,32-34] Furthermore, we noted a female predominance in the group with previous primary cancer, which could be explained by the facts that breast cancer was the most common previous primary cancer and that radiation—a risk factor for CAS—is often part of breast cancer treatment. This is supported by the finding of more truncal cancers among patients with a previous primary cancer. Similarly, the higher number of patients who received diagnoses in the last 2 decades could be due to the increased use of RT.

Like other cutaneous carcinomas, angiosarcoma occurred in a primarily white population in this cohort and in prior studies.[2,6] Similar to prior reports, the head and neck was the most common site overall and among those without a prior cancer; however, for patients with a prior cancer, the trunk was the most common area.[20,33] The reason for increased development of CAS on the head and neck has been

Table II. Multivariate analysis adjusting for factors affecting cutaneous angiosarcoma survival

Factors	Hazard ratio	95% CI	*P* value
Primary cancer			
Not primary	ref		
Primary	1.06	0.85-1.32	.592
Age at diagnosis in years			
<50	ref		
50-69	1.55	0.93-2.60	.093
70+	2.16	1.33-3.57	.002
Sex			
Female	ref		
Male	0.93	0.75-1.14	.468
Race			
White	ref		
Black	1.36	0.93-1.98	.11
Other	1.18	0.82-1.69	.368
Unknown	0.31	0.11-0.86	.024
Decade of diagnosis			
1973-1984	ref		
1985-1994	1.30	0.80-2.13	.291
1995-2004	1.04	0.65-1.67	.857
2005-2014	0.70	0.43-1.12	.14
Location			
Head and neck	ref		
Trunk	0.82	0.59-1.13	.221
Upper extremity	1.08	0.61-1.90	.789
Lower extremity	0.97	0.67-1.39	.753
Unspecified	1.00	0.59-1.71	.907
Tumor size			
<1 cm	ref		
≥1 cm	1.37	0.93-2.03	.108
Unknown	1.00	0.79-1.28	.968
Pathologic grade			
Well differentiated	ref		
Moderately differentiated	1.21	0.74-1.96	.446
Poorly differentiated	1.32	0.85-2.06	.217
Undifferentiated	1.38	0.89-2.13	.155
Unknown	1.41	0.94-2.13	.097
Extent of disease			
Localized	ref		
Regional	1.14	0.93-1.41	.213
Distant	1.50	1.11-2.03	.008
Unstaged	1.11	0.84-1.46	.467
Therapy			
None/unknown	ref		
RT only	0.89	0.63-1.26	.521
Surgery only	1.06	0.78-1.42	.724
RT + surgery	0.90	0.65-1.25	.528

CI, Confidence interval; *ref*, reference; *RT*, radiation therapy.

hypothesized to be due to chronic exposure to ultraviolet radiation, but vascular density may also play a role.[1,20]

In this cohort, the majority of tumors were less than 1 cm, with smaller tumors found in the population with a previous primary; however, more than half of the tumors did not have measurements available. This is potentially due to difficulty in precise measurements because of the diffuse growth pattern of the tumor. Some prior single-center studies examined tumor size and associated tumors greater than 5 cm with a worse prognosis as compared with smaller tumors, but there are not enough cases with tumor size greater than 5 cm in this cohort to confirm these findings.[6,35] However, for tumors less than 1 cm and those greater than or equal to 1 cm, there was a trend toward improved survival among the smaller tumors on multivariate analysis. Similarly, in a recent analysis of SEER focusing on head and neck cutaneous and non-cutaneous angiosarcoma, increased tumor size was associated with a 1% lower disease-specific survival rate, highlighting the possibility that the effect of tumor size may be minimal.[36]

Information on the IR of CAS is lacking in the literature. We noted a decline in incidence over the last 4 decades among patients without a prior primary tumor; however, incidence has been rising among those with a prior primary cancer. Rouhani et al[37] also noted an increase in CAS incidence between 1978 and 2004; however, they noted a decline in the early 2000s.

Relative survival among patients is 40.3% for those without a prior primary cancer and 45.8% for those with a prior primary cancer. Similar to our study, Rouhani et al[37] reported a 44.9% relative survival for CAS. However, the literature is variable, with prior reports reporting between 12% and 60% 5-year survival and the majority of initial reports showing very poor prognosis.[2,14,28,37-39]

Initial treatment of angiosarcoma involves surgery; however, negative surgical margins are achieved in only 21% to 47% of cases, thus requiring additional radiation, neoadjuvant chemotherapy, and/or adjuvant chemotherapy.[40] For patients with large tumors, treatment with taxanes followed by maintenance chemotherapy is a plausible option.[41,42] Among this cohort, surgery was performed in 73.4% of patients without in 78% of those with a prior primary cancer. Those with a prior primary cancer received additional RT 46% of the time, whereas those without a prior primary cancer received additional RT 16.3% of the time. Furthermore, there were no differences in survival depending on the type of therapy received among this cohort. A prior study examining surgery and RT found no additional benefits of combining the 2 modalities in CAS.[43] Similarly, 2 single-center studies found that surgery and radiation did not affect survival in patients with head and neck CAS.[44,45] In addition, data from the National

Cancer Database and from a single-center study showed no additional benefit of RT in patients who received surgical treatment.[39,46] Another recent study using SEER data similarly found no survival benefit to surgical treatment of head and neck angiosarcoma.[36] Finally, radiation before surgical resection has been attempted, and although well tolerated, there was no survival benefit.[47] In contrast, Guadagnolo et al[48] found that surgery plus RT is a superior therapy compared with either modality alone in patients with CAS on the face and scalp. Other studies examining CAS on the face and scalp similarly noted that surgery plus RT improves local control, overall survival, and disease-free survival compared with either modality alone.[33,40]

In combination with the majority of prior literature, our data show that there is no optimal therapeutic regiment. It is possible that this is due to the inherent biology of the disease, and currently available therapies are not able to modify the natural progression. In addition, it is possible that there are other factors affecting the disease not captured by SEER or other sources or that an additional level of granularity in data collection is needed. Potential future therapeutic options could include chemotherapy, molecular-targeted therapies, and the β-blocker propranolol.[49-57] In addition to these, because of the complex and heterogeneous mutational signature of angiosarcoma, immunotherapy is a potential future treatment.[58] Indeed, a case report showed successful angiosarcoma treatment with pembrolizumab and has shown no progression or new lesions during 8 months of follow-up.[59] Furthermore, most immunotherapy trials for sarcoma showed minimal therapeutic benefit; however, angiosarcoma was not well represented.[57,59,60] Further research into these forms of therapy, as well as other novel therapeutics, is imperative to improve survival among patients with CAS.

The limitations of this study include potential selection bias due to its retrospective nature. The available data are limited, and some patients are lacking important prognostic data such as tumor size. Finally, because of the rarity of CAS, the sample size was relatively small.

CONCLUSION

CAS is a rare, aggressive tumor associated with poor prognosis, especially in individuals older than 70 years of age and with distant disease. The most common tumor location varies based on prior history of another primary cancer. The currently available therapies do not appear to significantly affect survival, highlighting the need for new therapeutic options.

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