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Epithelioid hemangioendothelioma of bone: A survival analysis of 50 cases from the SEER database (1992–2016)

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Abstract

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor that may arise in bone. The purpose of this investigation was to determine the clinicopathological features and outcomes of osseous EHE in a large patient series, and to assess whether survival is impacted by demographics, tumor characteristics, or treatment factors. This was a retrospective review of the Surveillance, Epidemiology and End Results (SEER) database from 1992 to 2016. Kaplan-Meier was used to estimate overall survival (OS) and disease-specific survival (DSS). A Cox regression model was used to identify prognostic factors. Fifty patients from 1992 to 2016 with a median age of 54.5 years (IQR, 37–67) were reviewed. For location, 46% ($n = 23$) of tumors arose from the appendicular skeleton while 38% ($n = 19$) occurred within the axial skeleton (overlapping EHE: 16%, $n = 8$). Of the cases with recorded treatment factors, 54.8% ($n = 23$) had surgery, 26% ($n = 13$) received radiation, 22% ($n = 11$) were treated with chemotherapy, and 26% ($n = 13$) had surgery plus radiation. The 5-year OS probability was 49.2% (95% CI, 23.6–70.6), and the 5-year DSS probability was 63.9% (95% CI, 33.0–83.5). No surgery (surgery: HR, 0.262; 95% CI, 0.07–0.9); $p = 0.041$) and age older than 50 years (HR, 4.117; 95% CI, 1.1–15.4; $p = 0.035$) were negative prognostic factors of disease-specific mortality after controlling for confounding variables. There was no association between disease-specific mortality and adjuvant or multimodal therapy. The prognosis of EHE of bone is less than favorable, and the 5-year DSS probability of 64% emphasizes the intermediate grade nature of this tumor subtype. Surgical treatment, when feasible, is associated with a better prognosis.

Keywords

Epithelioid hemangioendothelioma, prognosis, outcomes, survival, vascular tumors

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Introduction

Epithelioid hemangioendothelioma (EHE) is a vascular tumor that exists on a spectrum of histologic heterogeneity. Although EHE more commonly arises from soft tissues, it may rarely occur in bone. It is estimated that EHE accounts for less than 1% of all primary bone tumors, and due to its rarity, there is a paucity of data describing the clinicopathological features and outcomes of these patients.[1–5]

EHE of bone must be differentiated from other primary vascular tumors of bone such as epithelioid hemangioma and epithelioid angiosarcoma. These tumors typically appear as permeative lesions with peripheral sclerosis on radiography, though distinguishing EHE relies on pathognomonic immunohistochemical findings.[6,7] In addition, EHE of bone often behaves more aggressively than a

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benign epithelioid hemangioma, though historically less so than an angiosarcoma. For the management of EHE of bone, wide surgical excision has demonstrated favorable local control according to the literature.[8–11] Depending on the anatomical location, however, the functional loss may preclude a wide resection, and in these cases the use of chemotherapy or radiation has shown limited benefit.[11,12]

The purpose of this investigation was to review a cohort of osseous EHE patients within the United States. This study sought to identify prognostic factors of overall survival (OS) and disease-specific survival (DSS) in order to improve the management of this rare tumor. We hypothesized that younger patients, tumors without metastatic disease, and those amenable to surgical resection would exhibit improved survival profiles.

Materials and methods

Selection

Patients were selected from the Surveillance, Epidemiology and End Results (SEER) database. SEER*Stat version 8.3.6.1 (National Cancer Institute, Bethesda, MD, USA) was accessed.[13] Inclusion criteria were histologically confirmed EHE of the bone and joints diagnosed between 1975 and 2016. Cases were filtered by Histologic International Classification of Diseases for Oncology, Third Edition (ICD-O-3) code for: 9133/3, and by diagnostic confirmation according to SEER.[14] Site and Morphology: Bone and Joints' was used to screen by location. Tumors were then grouped by location (appendicular vs axial), and given the small number of cases, we included EHE of overlapping and unspecified anatomical origin not limited to one site.

Data from a total of 198 patients were initially extracted from SEER. Of the 198 total patients, 148 were excluded (extraskeletal EHE: $n=145$; no diagnostic confirmation: $n=3$) (Figure 1). Information on the remaining 50 cases was recorded using variables such as: demographics, initial metastases (regional or distant by location), management characteristics including surgery (amputation, limb/salvage or non-amputation resection, or local tumor excision/partial resection), use of radiation therapy and/or chemotherapy, and survival.[14] As EHE typically occurs in younger patients, age was converted to a categorical variable that we considered conceptually meaningful (<50 years, or greater or equal 50 years). Primary tumor location was categorized as appendicular (including hip/shoulder), axial (including ribs/clavicle), or other (unspecified and overlapping location) according to SEER.[14] Cases of overlapping disease were inferred to indicate multifocal EHE of bone given they did not have a single primary site. Tumor stage was classified according to the American Joint Committee on Cancer (AJCC) criteria, and were either stage I or IV.[15] The size (cm) was recorded for cases with available data, however given the limited number of cases that recorded size, a separate analysis by AJCC size criteria was not possible.

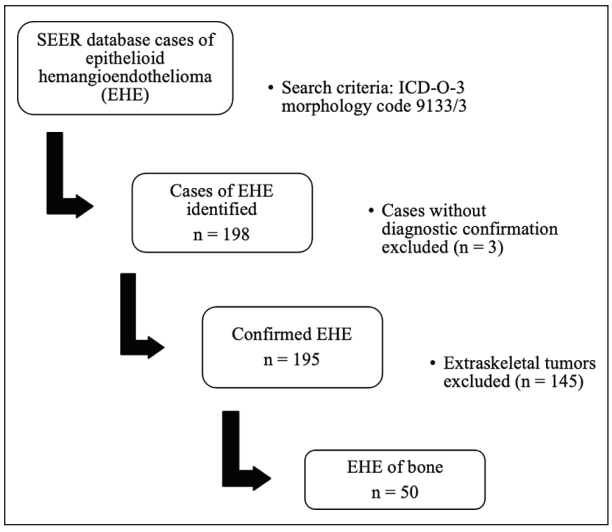

Figure 1. Study flowchart. EHE: epithelioid hemangioendothelioma; SEER: Surveillance, Epidemiology and End Results database.

Statistical analyses

Demographic and clinicopathologic data were analyzed using descriptive statistics. Continuous variables of interest were represented as the mean or median with range, interquartile range (IQR), or standard deviation (SD). OS and DSS were estimated using Kaplan and Meier (e.g. log rank) methods. An adjusted Cox proportional hazards model of regression was used to assess the predictive influence of individual variables on DSS and OS. Only variables with significant univariable influence were included in the final multivariable model, and all variables were tested for univariable significance. Statistical significance was set to a $p < 0.05$, and all analyses were conducted on SPSS version 26.0 (IBM Corp, Armonk, NY, USA).

Results

Demographics

Patient demographics are summarized in Table 1. Of the 50 cases of EHE of bone, there was slight male predominance ($n=29$, 58%), and the majority were Caucasian ($n=40$, 80%). The median age was 54.5 years (interquartile range [IQR], 37–67 years), and there was a relatively equal proportion of patients younger than and older than or equal to 50 years of age ($n=22$, 40%; $n=28$, 56%), respectively. The primary tumor location was most frequently the appendicular skeleton ($n=23$, 46%), followed by the axial skeleton ($n=19$, 38%), and overlapping or other ($n=8$, 16%). For tumors that recorded AJCC stage, nine (18%) tumors were stage I, while 11 (22%) were stage IV. There were a large number of cases that had missing data regarding the AJCC stage ($n=30$, 60%). Of the cases with recorded treatment factors, 54.8% ($n=23$) had surgery, 26% ($n=13$)

Table 1. Demographics, tumor characteristics, and treatment details.

EHE of bone (*n* = 50)	Appendicular (*n* = 23)	Axial (*n* = 19)	Other (*n* = 8)
	Frequency (%)	Frequency (%)	Frequency (%)
Age (years) at diagnosis[c]	45 (15–77)	66 (30–86)	57.5 (19–74)
Age group (years)			
<50	15 (65.2)	4 (21.1)	3 (37.5)
⩾50	8 (34.8)	15 (78.9)	5 (62.5)
Sex			
Male	17 (73.9)	8 (42.1)	4 (50.0)
Female	6 (26.1)	11 (57.9)	4 (50.0)
Race			
White	19 (82.6)	14 (73.7)	7 (87.5)
Distant metastasis			
Yes	4 (17.4)	4 (21.1)	1 (12.5)
No	10 (43.5)	8 (42.1)	1 (12.5)
Missing	9 (39.1)	12 (63.2)	6 (75.0)
AJCC stage[a]			
Stage I	4 (17.4)	4 (21.1)	1 (12.5)
Stage IV	5 (21.7)	5 (26.3)	1 (12.5)
Missing	14 (60.9)	10 (52.6)	6 (75.0)
Size (cm)[d]	4.14 (2.6)	4.68 (2.77)	
Lymph node metastasis			
Yes	1 (4.3)	1 (5.3)	1 (12.5)
No	13 (56.5)	10 (52.6)	1 (12.5)
Missing	9 (39.1)	11 (57.9)	6 (75.0)
Surgery			
Yes	14 (60.9)	8 (42.1)	1 (12.5)
No	6 (26.1)	8 (42.1)	5 (62.5)
Missing	3 (13.0)	3 (15.8)	2 (25.0)
Procedure[b]			
Local excision	3 (13.0)	1 (5.3)	1 (12.5)
Partial resection	1 (4.3)	5 (26.3)	
Wide resection/limb salvage	5 (21.7)	2 (10.5)	
Amputation	5 (21.7)		
Radiation			
Yes	6 (26.1)	6 (31.6)	1 (12.5)
No	17 (73.9)	13 (68.4)	7 (87.5)
Chemotherapy			
Yes	3 (13.0)	4 (21.1)	4 (50.0)
No/unknown	20 (87.0)	15 (78.9)	4 (50.0)

EHE: epithelioid hemangioendothelioma.
[a]American Joint Committee on Cancer sixth or seventh edition depending on year of diagnosis.
[b]According to the SEER variables.
[c]Median (range).
[d]Mean (standard deviation).

received radiation, 22% ($n = 11$) were treated with chemotherapy, and 26% ($n = 13$) had surgery plus radiation.

Overall survival

The 5-year probability of OS was 49.2% (95% confidence interval [CI], 23.6–70.6). OS was examined as a function of univariable demographics and tumor characteristics. On univariable analysis, only age greater than 50 years at diagnosis was associated with a higher mortality risk (hazard ratio [HR], 1.099; 95% CI, 1–1.2; $p = 0.04$). There were no other negative or positive prognostic factors identified.

Disease-specific survival

Long-term DSS was higher than OS, with a 5-year probability of survival of 63.9% (95% CI, 33.0–83.5). On Kaplan-Meier, axial and appendicular EHE demonstrated improved DSS compared to tumors of overlapping or unspecified anatomical origin (Figure 2). This group of

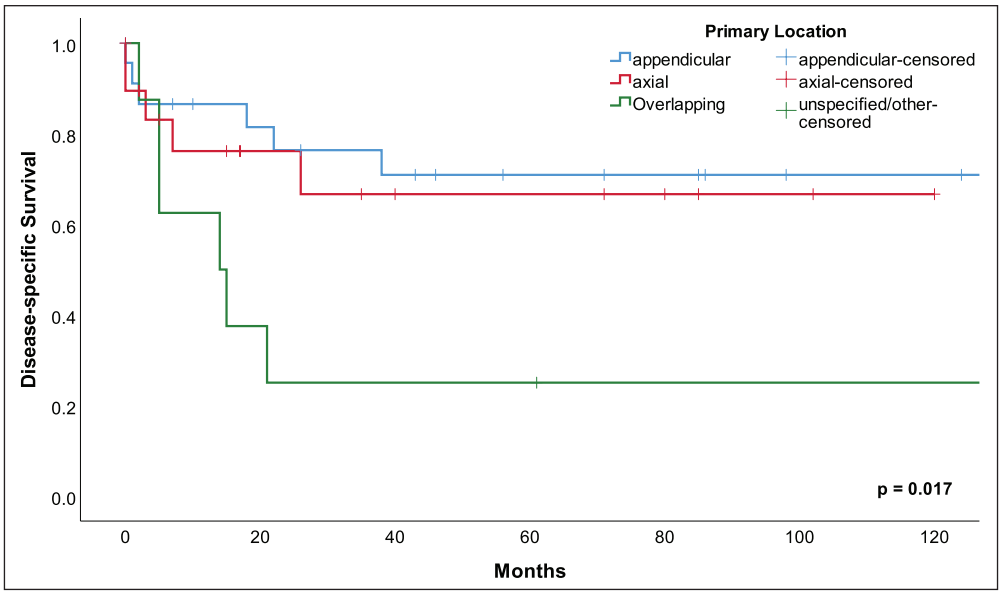

Figure 2. Disease-specific survival by primary tumor location. Overlapping (unspecified) or multicentric EHE of bone are tumors not confined to the appendicular or axial skeleton.

Table 2. Disease-specific survival as a function of demographics, tumor characteristics, and treatment details.

Variable	Univariable HR (95% CI)	*p*-Value	Multivariable HR (95% CI)	*p*-Value
Age group (years)				
Under 50	Ref	Ref	Ref	Ref
⩾50	5.821 (1.6–20.4)	0.006	4.117 (1.1–15.4)	0.035[a]
Surgical procedure				
No	Ref	Ref	Ref	Ref
Yes	0.189 (0.06–0.6)	0.006	0.262 (0.07–0.9)	0.041[a]
Primary location				
Appendicular	Ref	Ref	Ref	Ref
Axial	1.379 (0.4–4.6)	0.599	0.427 (0.1–1.7)	0.245
Overlapping/other	4.165 (1.4–12.6)	0.012	1.631 (0.4–6.2)	0.477
Radiation				
No	Ref	Ref	Ref	Ref
Yes	0.72 (0.2–2.2)	0.566		
Chemotherapy				
No	Ref	Ref	Ref	Ref
Yes	1.529 (0.5–4.4)	0.427		

CI: confidence interval; HR: hazard ratio; Ref: reference variable.
[a]Significant on multivariable analysis only.

"overlapping/other" osseous EHE demonstrated a significantly worse prognosis than appendicular or axial EHE with a median estimated survival of 14 months (95% CI, 0.1–27.8 months; $p=0.017$).

Disease-specific survival as a function of univariable demographics, tumor characteristics, and treatment factors are reported in Table 2. Patients over 50 years of age had a higher risk of disease-specific mortality (HR, 5.821; 95% CI, 1.6–20.4; $p=0.006$), as did tumors not limited to the axial or appendicular skeleton (site, overlapping/other: HR, 4.165; 95% CI, 1.4–12.6; $p=0.012$). Those who underwent some surgical procedure had a significantly improved DSS (surgery: HR, 0.189; 95% CI, 0.06–0.6; $p=0.006$). After controlling for confounding variables using a multivariable model, only age greater than 50 years (HR, 4.117; 95% CI, 1.1–15; $p=0.035$) and no surgical procedure performed (surgery: HR, 0.262; 95% CI, 0.07–0.9; $p=0.041$) retained significance as negative prognostic factors of DSS. There

was no association of disease-specific mortality risk with chemotherapy, radiation, or surgery plus radiation.

Discussion

EHE is a unique vascular tumor composed of epithelioid cells that demonstrate endothelial differentiation. Given the similarity of EHE to other vascular tumors, however, confirming the diagnosis is challenging. Stout[16] were among the first to establish pathologic criteria for diagnosing hemangioendothelioma, which at that point encompassed benign, intermediate, and malignant vascular lesions. Then, Weiss and Enzinger[17] characterized the natural disease course of a specific histologic variant, EHE, highlighting its indolent though somewhat intermediate-grade clinical course. After this depiction of EHE as its own entity in soft tissues, various other reports began to describe its presence within bone.[12,18,19] Given the rarity of primary EHE of bone, however, there are very few studies to inform the modern clinical management of these patients.

EHE of bone typically affects patients in the second through third decade of life, with an estimated age range of 10 to 77 years.[8] Additionally, EHE of bone appears to have an equal predilection for sex, though some small series describe a slight male predominance.[11,12,18,19] The current study found a similar though older median distribution of age (median age: 54 years), along with a higher proportion of males presenting with EHE of bone than females. With respect to anatomical location, EHE of bone most frequently presents within the upper or lower extremity and spine. However, the proportion of appendicular EHE is higher than axial EHE according to the literature (62% vs 10%, respectively).[8,11] The current study using SEER recorded a greater proportion of axial EHE (38%) than has been reported previously, though there was no significant change in survival individually between these (axial) and appendicular tumors.[10,20,21] Interestingly, there was an observed increase risk in disease-specific mortality among older patients. However, older age was also a prognostic factor in overall survival.

A favorable prognosis has been recorded in the majority of data that assess the clinical outcomes of EHE of bone. In two of the largest series to date, the survival of patients with unifocal (unicentric) EHE of bone was 89% and 97%, compared to multicentric EHE of bone that portended a probability of survival of 50% and 74% in each respective review.[11,12] In the current study, however, the disease-specific probability of survival was 64% at 5-years. This survival profile suggests that the outcomes of patients with EHE are more consistent with an intermediate-grade tumor than a low-grade tumor of bone. In earlier literature describing EHE of bone, it was actually thought that multicentric or multifocal disease portended a better prognosis than unifocal EHE.[1,4,22] However, multicentric disease has been reliably associated with worse outcomes in modern reviews. The current study documented eight cases of EHE that fell in the "other/overlapping" category for anatomical location, which likely indicates multicentric disease. Thus, our data are consistent with previous studies that demonstrated poorer outcomes in multicentric disease as these tumors had a significantly worse DSS than either axial or appendicular EHE. Although this significance was not retained on multivariable analysis, these data do contribute evidence for a trend toward worse prognosis in multicentric EHE of bone.

With respect to the management of EHE of bone, complete surgical excision is the treatment of choice. A favorable disease-free progression following surgery has been demonstrated in case reports and small series, in which an emphasis is placed on wide resection.[1,12,23] In the current study, the majority of patients underwent surgical resection of their primary tumor (either partial or local excision, wide non-amputation resection, or amputation). Altogether, the surgical patients demonstrated a significantly improved survival on multivariable analysis, regardless of the procedure performed. Thus, if the tumor is amenable to resection, our data indicate surgical excision should be considered given the clear survival benefit. Additionally, it is also hypothesized that the local recurrence rate of EHE of bone after surgery is about 15%.[24] Given this evidence for local recurrence of EHE of bone, a wide margin resection should therefore be the mainstay of surgical treatment if there is no increase in morbidity or significant functional compromise.

In EHE of bone not amenable to surgical excision, or in instances of multicentric disease or incomplete resection, chemotherapy and/or radiation therapy may be utilized. However, it is difficult to determine the optimal treatment for patients with EHE of bone given its extremely low incidence. In some cases, radiation has been suggested to be of benefit, though complications such as radiation-induced sarcoma must be weighed against the benefit of preventing a systemic relapse.[11] Historically, the possibility of a radiation-induced sarcoma occurs within 5 to 10 years after a latency period following irradiation. Newer evidence suggests that the latency period ranges from 2 to 3 years up to 50 years, with an estimated median ten years.[25] With respect to dosage, typically patients who receive a cumulative dose of 60 Gy are at a higher risk according to the literature, which suggests a dose-dependency.[26] Therefore, as most patients with EHE survive beyond 5 years, a discussion with the patient is warranted. Furthermore, variable patterns of metastasis have been reported in the current literature, and there is approximately a 31% rate of metastatic spread of EHE of bone observed most commonly in the lungs.[8] With respect to chemotherapy for systemic spread, the consensus is also unclear, and the evidence is limited to few reports.[27,28] In the current study, there was no survival advantage afforded by either radiation or chemotherapy alone, nor with radiation plus surgery. We did not assess surgery plus

chemotherapy given lower numbers. However, given the lack of large, prospective data regarding the association of multimodal management with survival in EHE of bone, consideration for therapy may be given for multicentric or inoperable disease, or if palliation of symptoms is desired, as is currently done in our institution. Of note, there are considerable toxicities associated with systemic chemotherapy, and therefore an emphasis should be placed on reserving systemic treatment for select cases, especially given the lack of a demonstrable survival benefit. In such cases of EHE of bone as described elsewhere, chemotherapy may consist of doxorubicin along with ifosfamide and mesna, dosed to the appropriate body surface area.[29] However, as noted, the risk of toxicity is high according to Common Terminology Criteria for Adverse Events version 4 criteria.[30] Ultimately, the decision of whether to treat with preoperative or postoperative radiation and/or chemotherapy should be discussed in a multidisciplinary setting. Such groups are often inclusive of radiation and medical oncologists, pathologists, radiologists, and surgical oncologists. Therefore, in the setting of a rare tumor such as EHE of bone, individual input from each of these specialties may permit a more appropriate collaborative treatment approach than would be realized without the assistance of such a group.

There are limitations to the current study, most of which are inherent to studies of large databases such as SEER. One limitation to the conclusions drawn regarding the importance of surgery in these patients is the potential for selection bias. As surgery is the mainstay of treatment, it was likely not performed in cases only when unfeasible, limiting the conclusions drawn by SEER. Second, despite the relatively long-term follow-up, patients are not included in the registry if they seek medical care outside of the states that are included in SEER. This loss to follow-up may affect the true estimations of survival. Additionally, we cannot reliably confirm that each of the eight cases of overlapping EHE was truly multicentric, though given the worse survival profile we suspect these tumors had multiple skeletal involvement. Finally, we acknowledge the inclusion of missing or incomplete data may influence statistical conclusions. For survival, these data were omitted. For chemotherapy, for example, SEER combines "no" and "unknown," which may overestimate the number of cases that actually did not receive chemotherapy. Thus, these data must be interpreted accordingly.

Conclusion

In conclusion, our investigation of EHE of bone using the SEER database is one of the largest to date and found patients with this rare tumor subtype have a prognosis consistent with an intermediate grade rather than low-grade tumor of bone. Patients who are older in age had a significantly worse prognosis than younger patients. Additionally, surgical treatment of EHE of bone resulted in improved survival. Together with existing literature, these data help to inform the optimal management of these tumors, which at this point remains an unmet medical need.

List of abbreviations

SEER, Surveillance, Epidemiology, and End Results; EHE, epithelioid hemangioendothelioma; OS, overall survival; DSS, disease-specific survival; AJCC, American Joint Committee on Cancer.

Author contributions

Study concept and design: S.G., A.T.B.; analysis and interpretation of data: C.A.G.; drafting of the manuscript: C.A.G., S.C.T.; critical revision of the manuscript for important intellectual content: C.A.G., S.G., S.C.T., A.T.B.; statistical analysis: C.A.G.

Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosures

ATB: (BMJ Case Reports: Editorial or governing board; Clinical Orthopaedics and Related Research: Editorial or governing board; exparel/pacira: Stock or stock Options; Journal of Oncology Practice: Editorial or governing board; Journal of Surgical Oncology: ad hoc reviewer; Lancet—Oncology: Editorial or governing board; Musculoskeletal Tumor Society: Board or committee member; Onkos Surgical: Paid consultant; Pediatric Blood and Cancer: Editorial or governing board; Rare Tumors: ad hoc reviewer; Rush Orthopedic Journal: Editorial or governing board; Swim Across America Cancer Research Grant: Research support); SG: (Onkos Surgical: Paid consultant; Stock or stock Options; USMI: Stock or stock Options). C.A.G. and S.C.T. other authors have no pertinent disclosures.

Declaration of conflicting interest

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