Prognostic Determinants Analysis and Nomogram for Bone Malignant Vascular Tumors: A Surveillance, Epidemiology and End Results (SEER) Analysis

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Background: The aim and objective of our investigations were to explore the prognostic value of various clinical and pathological factors of bone malignant vascular tumors and establish a nomogram for their outcome predictions.

Material/Methods: All data of primary bone malignant vascular tumors (MVTs) patients were randomly selected from the Surveillance, Epidemiology and End Results (SEER) database. However, selected patients were clinically diagnosed with various cancers during 1988–2015. The potential prognostic factors were analyzed using SPSS (Windows, version 22.0). All prognostic factors were combined to formulate a nomogram to predict the overall survival (OS).

Results: A total of 266 selected patients were included in our study. In the univariate model, age (P<0.001), sex (p=0.0255), primary site (P<0.001), surgery (P<0.001), histologic type (P<0.001), metastasis (p=0.000), and pathological grade (P<0.001) were statistically significant for patient survival. The results of Cox analysis revealed that age ($\geq 64$) HR: 3.636, 95% CI [1.955–6.762], p=0.000, the primary site in skull HR: 2.6, 95% CI [1.584–4.268], p<0.001, without surgery HR: 1.473 95% CI [1.239–1.751], p<0.001, metastasis HR: 3.076 95% CI [1.983–4.771] p=0.000, and high malignant grade HR: 1.802, 95% CI [1.032–3.04], p=0.045, and high malignant grade HR: 3.029, 95% CI [2.101–4.366], p=0.003 were independent unfavorable prognostic factors. Angiosarcoma had highest mortality rate among all vascular malignancies. The nomogram predicting overall survival achieved a C-index of 0.694 (95% CI 0.631, 0.745) in the SEER cohort.

Conclusions: Surgery can significantly increase OS survival time for bone MVTs, and low-grade malignancy is a significant factor for OS. However, advanced age, tumor metastasis, primary site in skull, AS, and male sex are predictors of poor prognosis.

MeSH Keywords: Bone and Bones • Bone Neoplasms • Nomograms • Prognosis • SEER Program

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Background

Vascular malignancy is rare and can occur in the liver, lung, skin, bone, spleen, pleura, and lymph nodes [1–4]. Due to the presence of complex vessels within bone, vascular tumors have a higher incidence rate. Due to its low incidence rate, little is known about the pathogenesis and progression of this tumor, and further investigations are urgently needed to clarify the possible risk factors, pathogenesis, and progression of this tumor [5]. Vascular malignancy can be classified into various pathological types, including angiosarcoma (AS), hemangioendothelioma (HE) and its epithelioid variant (EHE), or hemangiopericytoma (HP) [6,7]. EHE is regarded as the most common type. In 1982, the concept of vascular malignant tumor EHE was first proposed by Enzinger and Weiss. EHE has characteristic pathological features and progresses faster than angiosarcoma [8,9]. EHE is the most common malignant vascular tumor, accounting for 2% of soft-tissue tumors. Although there is a higher incidence of AS in vascular tumors, these patients generally have a better prognosis. The most common primary sites of AS are the neck (37%) and head (52%), followed by the breasts and extremities. In addition, AS in bone is extremely rare and accounts for only 1% of ASs, especially in the vertebral column [10]. AS consists of vascular channels with histological features arranged by endothelial cells with huge nuclei, nuclei, and incremental mitosis [11]. The cell of EHE is fusion form and ovoid, and the cells are surrounded by irregular, anastomotic, fissured, or branching vascular lumen [12]. Histopathological examination of EHE substantially revealed 2 types of tissue structures – dilated blood vessels and spindle cells. Reticular sclerosis staining clearly showed that individual cells and groups of cells were distinctly surrounded by reticular fibers [13]. HP is considered to be tightly packed, round-to-fusiform cells, around a well-developed, elaborate, branching “staghorn” vasculature [14]. The staghorn appearance is histologically characterized by irregular vascular channels with branches of different sizes. Nucleoli are usually single and have well-dispersed chromatin formation. Given there is no typical clinical symptom or imaging feature in the early-stage of MVTs in bone, most patients are clinically diagnosed in the end-stage and have poor outcomes. There is no clear evidence or studies systematically describing the clinical characteristics of the disease. Many researchers and clinicians have insufficient knowledge and more data is needed on the possible causes, risk factors, and clinical treatment options for patients [15–17]. The current data volume is actually too small to make meaningful statistical descriptions. The SEER database has been widely used for clinical studies of rare tumors, including chondrosarcoma. Therefore, we used the largest and most accurate tumor database in the United States to collect more data.

Material and Methods

Data source and selection

The data were gathered from the Surveillance, Epidemiology, and End Results (SEER) database, the world’s largest publicly accessible cancer registry, maintained by the National Cancer Institute [18]. Pathology reports are an important source of SEER data. The extracted pathological data were combined with data from other sources into the final case record. These sources included patient records, reports collected from independent diagnostic imaging and chemotherapy clinics, and death certificates. We used the incidence rate of SEER in the version 18 Registration Research Database. The end date of follow-up for this version of the database was the end of 2015. We found 266 cases of angiocentric vascular tumor of bone based on ICD-0-3. Each patient’s demographic features and the clinico-pathological characteristics were carefully selected, including age, sex, race, metastasis, primary site, histologic type, marital status, tumor grade, surgery, and chemotherapy and radiation performed. In addition, the SEER database uses a 4-grade system to define the grading of the lesion: grade I (well-differentiate), grade II (moderately differentiated), grade III (poorly differentiated), and grade IV (undifferentiated). The SEER database also reports OS, defined as the period from first diagnosis until death. The X-tile program (Yale University, New Haven, CT, USA) was used to identify the best cutoff of age, and it determined the proper cutoff value based on the minimum p values obtained from log-rank chi-square statistics for continuous age. Survival curves were constructed using Kaplan-Meier analysis, and their deviations were carefully evaluated by log-rank test. The Pearson chi-square test was performed to analyze categorical variables, and the 2-sample t test was performed to analyze continuous variables. The survival curves of OS were compared by log-rank test in various groups with the Kaplan-Meier method. For adjustment for baseline variables during the comparison, we generally applied a Cox proportional hazard model, which included all potential prognostic factors obtained from the SEER database. All statistical analyses were performed using the statistical software package SPSS (Windows, version 22.0, BM Corp., Armonk, NY, USA), and p values <0.05 were considered statistically significant.

Results

Patient descriptions

The comprehensive clinical features of all 266 patients are shown in Table 1. We included 160 (60.1%) men and 106 (39.9%) women, with a mean age of 58.45 years (median 61 years). There were 230 whites, 23 blacks, and 13 people of other ethnic groups. There were 140 patients clinically diagnosed
**Table 1.** Patient characteristics and univariate analysis of prognostic factors affecting overall survival.

| Characteristic                  | No (%) of patients | P      |
|--------------------------------|--------------------|--------|
| Age, y, mean±SD                | 58.45±19.15        |        |
| Age group, y                   |                    | 0.000* |
| ≥64                           | 170 (76.5)         |        |
| <64                           | 52 (23.5)          |        |
| Sex                            |                    | 0.0255*|
| Male                          | 138 (62.4)         |        |
| Female                        | 83 (37.6)          |        |
| Race/ethnicity                |                    | 0.052  |
| White                         | 185 (83.7)         |        |
| Black                         | 23 (10.4)          |        |
| Other                         | 13 (5.9)           |        |
| Year of diagnosis              |                    | 0.061  |
| 1988–1995                     | 33 (14.9)          |        |
| 1996–2004                     | 54 (24.4)          |        |
| 2005–2015                     | 134 (60.7)         |        |
| Primary site                   |                    | 0.000* |
| Skull                         | 17 (7.7)           |        |
| bones of the extremities      | 119 (53.8)         |        |
| Spine                         | 62 (28.1)          |        |
| Bones of Body                 | 9 (4.1)            |        |
| Other                         | 14 (6.3)           |        |
| Histologic type                |                    | 0.000* |
| Angiosarcoma                   | 130 (58.8)         |        |
| Hemangioendothelioma           | 28 (12.7)          |        |
| Epithelioid hemangioendotheliomas | 45 (20.4)   |        |
| Hemangiopericytoma             | 18 (8.1)           |        |
| Marital status                 |                    | 0.61   |
| Yes                           | 180 (81.4)         |        |
| No                            | 41 (18.6)          |        |
| Radiation                      |                    | 0.173  |
| Yes                           | 96 (43.4)          |        |
| No                            | 125 (56.6)         |        |
| Metastasis                     |                    | 0.000* |
| Yes                           | 105 (39.5)         |        |
| No                            | 132 (49.6)         |        |
| Unknown                        | 29 (10.9)          |        |
with primary MVTs in bones of the extremities 26 in the skull, 71 in the spine, and 13 in bones of the trunk. For the histological type, AS and EHE accounted for 74.3% of all patients, of which AS accounted for 57.1%. There were 112 (42.1%) cases who received radiation and 154 (57.9%) who did not, 61 (22.9%) received chemotherapy and 205 (77.1%) did not, 153 (57.5%) received surgery and 113 (42.5%) did not. A total of 105 (39.5%) patients were clinically diagnosed with tumors which spread to another organ in the body. There were 201 patients who were married when diagnosed with a malignant vascular tumor and 65 patients were not married. Of all patients, 56 patients were selectively identified as having a low-grade tumor, and 69 patients were diagnosed as having a high-grade tumor. The mean follow-up time was 46.95 months (median 14.0 months; range 1–335 months). X-Plots were constructed, identifying 64 years old as the optimal cutoff point to divide the tested cohort into low and high risk based on OS (Figure 1). Univariate and multivariate analyses were used to identify the potential prognostic factors for overall survival. Univariate analysis results showed that radiotherapy, marital status, and chemotherapy are associated with age (p=0.000), sex (p=0.0255), histological subtype (p=0.000), tumor grade (p=0.000), metastasis (p=0.000), tumor site (p=0.000), and surgery (p=0.000), meaning that these characteristics were strongly associated with OS in the univariate analysis (p<0.05) (Table 1). Then, significant prognostic factors from univariate analysis were used to construct a nomogram for overall survival. 

Table 1 continued. Patient characteristics and univariate analysis of prognostic factors affecting overall survival.

| Characteristic | No (% of patients) | P       |
|----------------|--------------------|---------|
| Chemotherapy   |                    | 0.108   |
| Yes            | 49 (22.2)          |         |
| No             | 172 (77.8)         |         |
| Surgery        |                    | 0.000*  |
| Yes            | 130 (58.8)         |         |
| No             | 91 (41.2)          |         |
| Grade          |                    | 0.000*  |
| I              | 20 (9.0)           |         |
| II             | 27 (12.2)          |         |
| III            | 36 (16.3)          |         |
| IV             | 63 (28.5)          |         |
| Unknow         | 75 (33.9)          |         |

* Indicates statistical significance (p<0.05). Skull – bone of skull and face and associated joints (includes mandible; bones of the extremities – bone, joint and articular cartilage of limbs; spines – vertebral column (includes sacrum and coccyx); bones of body – rib, sternum, clavicle and associated joint.

Figure 1. (A–C) The image show defining the optimal cutoff values of age via X-tile analysis. (A) The black dot indicates that optimal cutoff values of age have been identified. (B) A histogram and (C) Kaplan-Meier curve were constructed based on the identified cutoff values. Optimal cutoff values of age were identified as 64 years based on survival.
These prognostic factors extracted by univariate analysis were subjected to Cox proportional hazards analysis (Table 2), showing that age <64 years, low-grade malignancy, female sex, diagnosis without metastasis, and receiving surgery were predictors for OS. However, characteristics of the site of onset and pathological types were risk factors for OS, including angiosarcoma and a vascular malignancy of the skull. These findings indicate that people older than 64 years were 3.636 times more likely to be diagnosed than those younger than 64 years (RR=3.636). The relative risk of not receiving surgery was 1.473 times higher than in patients who received surgery (RR=1.473). Metastasis was associated with significantly worsen of OS (No vs. Yes, p=0.000). The relative risk of metastasis was 1.473 times higher in patients without metastasis (RR=3.075). In addition, the data showed the stratification of prognostic factors. The statistical results were age ($\chi^2=18.997, P=0.000$), metastasis ($\chi^2=25.552, P=0.000$), primary site ($\chi^2=20.231, P=0.0035$), sex ($\chi^2=4.033, P=0.0225$), and histological type ($\chi^2=69.2, P=0.0000$), surgery ($\chi^2=20.195, P=0.0008$), and grade ($\chi^2=51.293, P=0.0016$), as shown in Table 2. Kaplan-Meier curves were used to show OS for the full cohort (Figure 2). A nomogram predicting 3- and 5-year overall survival was constructed by incorporating the above independent prognostic factors (Figure 3). The C-index of the nomogram for predicting overall survival was about 0.694 in the SEER cohort.

| Factor          | Category                        | N   | HR (95% CI)          | p-Value |
|-----------------|---------------------------------|-----|----------------------|---------|
| Age (years)     |                                 |     |                      |         |
|                 | <64                             | 120 | Reference            |         |
|                 | ≥64                             | 146 | 3.636 (1.955–6.762)  | 0.000*  |
| Sex             | Female                          | 106 | Reference            |         |
|                 | Male                            | 160 | 1.802 (1.032–3.004)  | 0.046*  |
| Primary site    | Trunk                           | 13  | Reference            |         |
|                 | Limbs                           | 140 | 1.108 (0.595–2.603)  | 0.747   |
|                 | Other                           | 15  | 0.813 (0.508–0.932)  | 0.016*  |
|                 | Skull                           | 26  | 2.600 (1.584–4.268)  | 0.000*  |
|                 | Spine                           | 71  | 0.680 (0.398–1.163)  | 0.159   |
| Metastasis      | No                              | 132 | Reference            |         |
|                 | Yes                             | 105 | 3.076 (1.983-4.771)  | 0.000*  |
|                 | Unknown                         | 29  | 1.557 (1.003-2.417)  | 0.051   |
| Histologic type | Angiosarcoma                     | 152 | Reference            |         |
|                 | Hemangioendothelioma            | 46  | 0.250 (0.129–0.485)  | 0.000*  |
|                 | Epithelioid hemangioendotheliomas| 49  | 0.453 (0.283–0.727)  | 0.001*  |
|                 | Hemangiopericytoma              | 19  | 0.498 (0.265–0.937)  | 0.031*  |
| Surgery         | Yes                             | 153 | Reference            |         |
|                 | No                              | 113 | 1.473 (1.239–1.751)  | 0.000*  |
| Grade           | Low                             | 56  | Reference            |         |
|                 | High                            | 69  | 3.029 (2.101–4.366)  | 0.003*  |
|                 | Unknown                         | 141 | 2.091 (1.364–3.204)  | 0.027*  |

* Indicates statistical significance (p<0.05).

Table 2. Multivariate analysis of prognostic factors in patients with primary malignant vascular tumors of bone.
MVTs are rare primary cancer in the skeleton, with low diagnosis rate and poor prognosis [5,19]. There are no clear investigations for statistical analysis of clinical features; the possible prognostic factors have been unknown until now. A retrospective analysis of 46 patients with malignant vascular tumors in the spine suggested that age, surgery, metastasis, and malignant grade were prognostic factors for overall survival [20]. A multicenter retrospective study of Japanese patients with epithelioid hemangioendothelioma showed that tumor size >3.0 cm is an independent indicator of poor prognosis [21]. In the present study, we applied univariate and multivariate analysis to identify the potential independent prognostic factors based on the SEER database, which are related to OS in patients with bone MVTs. We established a nomogram clinical prediction model based on these significant prognostic factors. The survival rate of specific tumor patients can be calculated individually, having a great value in clinical practice, which is the main advantage of this model. We found the mean age of patients was 58.4 years, which is consistent with previous studies [5]. Furthermore, our results showed that age was a significant independent prognostic factor for OS of MVTs in bone. We applied the X-tile model to identify optimal cutoff values of age. Our analysis strongly indicated that 64 years of age is
Figure 3. Cancer-specific survival nomogram for patients with malignant vascular tumors of bone.

MVTs include a range of pathological types. In addition to its unique histopathological features, some important molecular markers can also be used for early diagnosis and prognostic definition of MVTs. FISH and molecular analysis techniques are widely used to detect the molecular targets of various tumors, which play an important role in clinical and scientific studies.

Nevertheless, a clinicopathological and molecular study of 21 cases of epithelioid hemangiofibroma clearly suggested that all cases were positive for ERG and CD31, which is primarily used to demonstrate the presence of endothelial tissues and to evaluate tumor angiogenesis [26]. FOSB nuclear positivity was displayed in some lesioned endothelial cells. FOS gene rearrangements are most frequently found in EH in the bone by FISH analysis [27–29]. In addition, positive nuclear CAMTA1 is a key tool for diagnosis of epithelioid hemangioendothelioma [30].

The patients with high-grade malignancy also differ in appearance from the less malignant patients, for instance necrosis and invasion of bone tissues. Previous investigations showed that the degree of malignancy is also an important factor affecting prognosis [24], which was also shown in the present study. Patients diagnosed with cancer of low-grade malignancy often live longer and have better quality of life than those with high-grade malignancy. Moreover, surgery is mostly considered as a conventional methods of tumor treatment.
shows surgical management of MVTs patients has a significant effect on patient prognosis. The OS of malignant vascular tumor patients in other organs are more or less prolonged after surgical treatment [31]. Complete resection of the primary tumor site can considerably improve the patient’s prognosis and prolong survival rates [32]. Consequently, curative-intent surgery to remove a primary tumor for patients diagnosed with cutaneous angiosarcoma could become a promising treatment option in the near future [33]. However, several investigations obviously demonstrate that the emphasis on primary hepatic epithelioid hemangioendothelioma is the most beneficial surgical treatment of this tumor [34]. Since blood vessels in bone and surrounding tissues are distinct in different parts, the possibility of vascular malignancy is also diverse. We found malignant hemangiomas in all bones in the SEER database and roughly divided them into the following sections: skull – bone of skull and face and associated joints (includes mandible); trunk bones – rib, sternum, clavicle, and associated joint; spine – vertebral column (includes sacrum and coccyx); and bones of the extremities – bone, joint, and articular cartilage of limbs. According to the statistical results, patients with malignant hemangioma growing in the skull have the shortest survival time, which may be related to the complex vascular network in the brain. External validation is a vital method to address overfitting and to explore the external relevance of the nomogram. Therefore, our remarkable findings can be beneficial to create a new clinical prediction model called a nomogram in the near future.

Our investigations also contain the largest number of cases and most complete clinical features of patients for MVTs in bone. All patients’ data were carefully obtained from the same database; there are unified standards and procedures for evaluation of the patients. However, there are still some limitations in our study. This large-scale retrospective study of 266 patients found that radiotherapy, chemotherapy, and surgery improved survival rates. However, the SEER database does not have complete records on specific surgical methods and other combined treatment measures, leading to the incomplete selection of potential prognostic factors.

Conclusions

We designed and evaluated a prognostic nomogram for patients with primary malignant vascular tumors of bone. The nomogram showed good discrimination ability. As a novel nomogram specific to primary malignant vascular tumors of bone, our model needs to be improved by further research. Our results may be of use in developing bone MVT patient health education and to provide a basis for further investigations.

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Conflict of interests

None.

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