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Epidemiology of Angiosarcomas in Kentucky, 2000-2019

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Epidemiology of Angiosarcomas in Kentucky, 2000-2019

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Abstract

Background/Objective: Angiosarcomas are rare, highly aggressive malignant soft-tissue sarcomas of vascular or lymphatic origin. The purpose of this study is to describe geographical distribution of angiosarcoma in Kentucky and to examine the epidemiology of angiosarcoma in Kentucky from 2000 to 2019, including the most common sites where angiosarcomas occurred and risk factors affecting survival.

Methods: A sample of 246 angiosarcoma patients was received from the Kentucky Cancer Registry (KCR). Kaplan-Meier curves were produced to examine overall survival, as well as survival by age, insurance type, tumor size, and SEER site. A Cox proportional hazards regression analysis was conducted to estimate hazard ratios for death. A choropleth map was created featuring numerical case counts and cases per 100,000 population to visualize the geographic distribution of angiosarcoma incidence by counties in Kentucky.

Results: The mean overall survival time observed in this sample was 50.2 months. Jefferson County had the highest case count (59), while Livingston County had the highest rate of angiosarcoma cases (21 per 100,000). The most common SEER sites among these cases were soft tissue, breast, and other non-epithelial skin. Patients 80 years old and younger had a decreased risk of death.

Conclusions: Patients older than 80 years old have significantly poorer overall survival than the other age groups, patients with angiosarcoma of the liver, lung and bronchus, and miscellaneous malignancies have a significant increased risk of death compared to other SEER sites, and there is a significant difference between the probabilities of death and SEER site, as well as insurance type.

Introduction

Angiosarcomas are rare, highly aggressive malignant soft-tissue sarcomas of vascular or lymphatic origin. Overall survival ranges from 30-50 months and the five-year survival rates are between 10-50% [1—3]. Angiosarcoma can develop in various areas of the body, including cutaneous regions of the head and neck, breast, viscera, and bone [6, 10]. This form of cancer is commonly presented as cutaneous lesions but can also present as lesions within the deep soft tissues, breast, bone, and organs, including the heart, spleen, and liver [8, 10]. It is also common for angiosarcomas to metastasize to various sites such as bone, brain, liver, and lung, with some cases having two or more metastatic sites [1, 21].

Risk factors associated with angiosarcoma include chronic lymphoedema, which is swelling in the body's tissues, history of radiation, environmental carcinogens such as vinyl chloride, thorium dioxide, and arsenic, and genetic syndromes (e.g., Li Fraumeni syndrome) [3—5, 9]. Roughly 90% of cases of angiosarcoma that are associated with lymphoedema occur following a mastectomy, which is known as Stewart-Treves Syndrome [7, 12]. Mutations in the *POT1* gene have also been associated with cardiac angiosarcomas, which can be passed on through families [20].

With history of radiation treatment being one of the key risk factors associated with angiosarcoma, it is important to study regions with a high burden of cancer. The state of Kentucky ranks first in all-site cancer incidence and mortality, with cancer being one of the leading causes of death, specifically in the Appalachian region [11]. An angiosarcoma cluster was identified among men who worked at the BF Goodrich facility in Louisville, Kentucky before 1972, which was later attributed to vinyl chloride

exposure [5]. Besides that previous study, however, there is little published research on angiosarcoma in Kentucky, and most is focused solely on angiosarcoma of the liver associated with vinyl chloride exposure [17—19]. The purpose of this study is to examine the epidemiology of angiosarcoma in Kentucky from 2000 to 2019, including major risk factors, the most common sites where angiosarcomas occurred, and characteristics associated with poor survival.

Methods

This study was reviewed and approved by the University of Kentucky Medical Institutional Review Board (IRB).

Data sources

Patients in this study included those diagnosed with angiosarcoma (International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) morphological code 9120) from 2000-2019 in Kentucky. Cases diagnosed on autopsy or by death certificate were excluded, resulting in a sample of 246 patients. The Kentucky Cancer Registry (KCR), the population-based central cancer registry for the Commonwealth of Kentucky and a Surveillance, Epidemiology, and End Results (SEER) site, provided the following information for all eligible cases: sex, age at diagnosis, race, date of diagnosis, SEER site, Appalachian residency, vital status, tumor grade, tumor size, county at diagnosis, and insurance status. All Kentucky health care facilities that either diagnose or treat cancer patients are required to report each case of cancer using the Cancer Patient Data Management System (CPDMS), which was developed by KCR. Each year, data from KCR have been submitted to the North American Association of Central Cancer Registries (NAACCR) for an evaluation of completeness, accuracy, and timeliness.

Statistical analysis

Descriptive analyses were conducted for the following independent variables: sex (male/female), age (<65, 65-80, >80), race (white, black, other), date of diagnosis, survival status (alive/deceased), SEER site, county of residence at diagnosis, tumor grade (I+II, III, IV), and tumor size (<10 cm/≥10cm), insurance status, and Appalachian residency.

A choropleth map was created featuring numerical case counts and cases per 100,000 population to visualize the geographic distribution of angiosarcoma prevalence by counties in Kentucky. This map was created using QGIS software, version 3.16.

Kaplan-Meier curves were produced to examine overall survival, as well as survival by age, insurance type, tumor size, and SEER site. A Cox proportional hazards regression analysis—including all independent variables described above—was conducted to estimate hazard ratios for death. The survival interval variable was created by calculating the interval of time (in months) from the date of diagnosis to the date of last contact or death. The survival interval and vital status were then multiplied to complete survival analysis. Significance was set at $p<0.05$. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc, Cary NC).

Results

Patient Characteristics

After excluding cases diagnosed on autopsy or by death certificate, there were a total of 246 individuals diagnosed with angiosarcoma (ICD-O-3 morphological code 9120) during the study period, 2000-2019, in Kentucky. Of these, 40.2% were between the ages of 65 and 80, 53.7% were female, and 97.1% were white. The most common SEER site

among these cases was soft tissue, including the heart (39.8%). Histologically, 17.5% of tumors were grade IV, which grow and spread faster than lower grades. More than half of the tumors (54.5%) were of unknown grade. Just over half (56.1%) of tumors were less than 10 cm. A majority of patients were from non-Appalachian counties (76.0%). A total of 201 (81.7%) deaths were recorded. The most common insurance carrier among patients was Medicare (63.4%), which patients are eligible for at age 65. The mean age of patients in this sample was 67.42 years old.

Table 1. Demographics of Kentucky angiosarcoma patients (N=246), 2000-2019

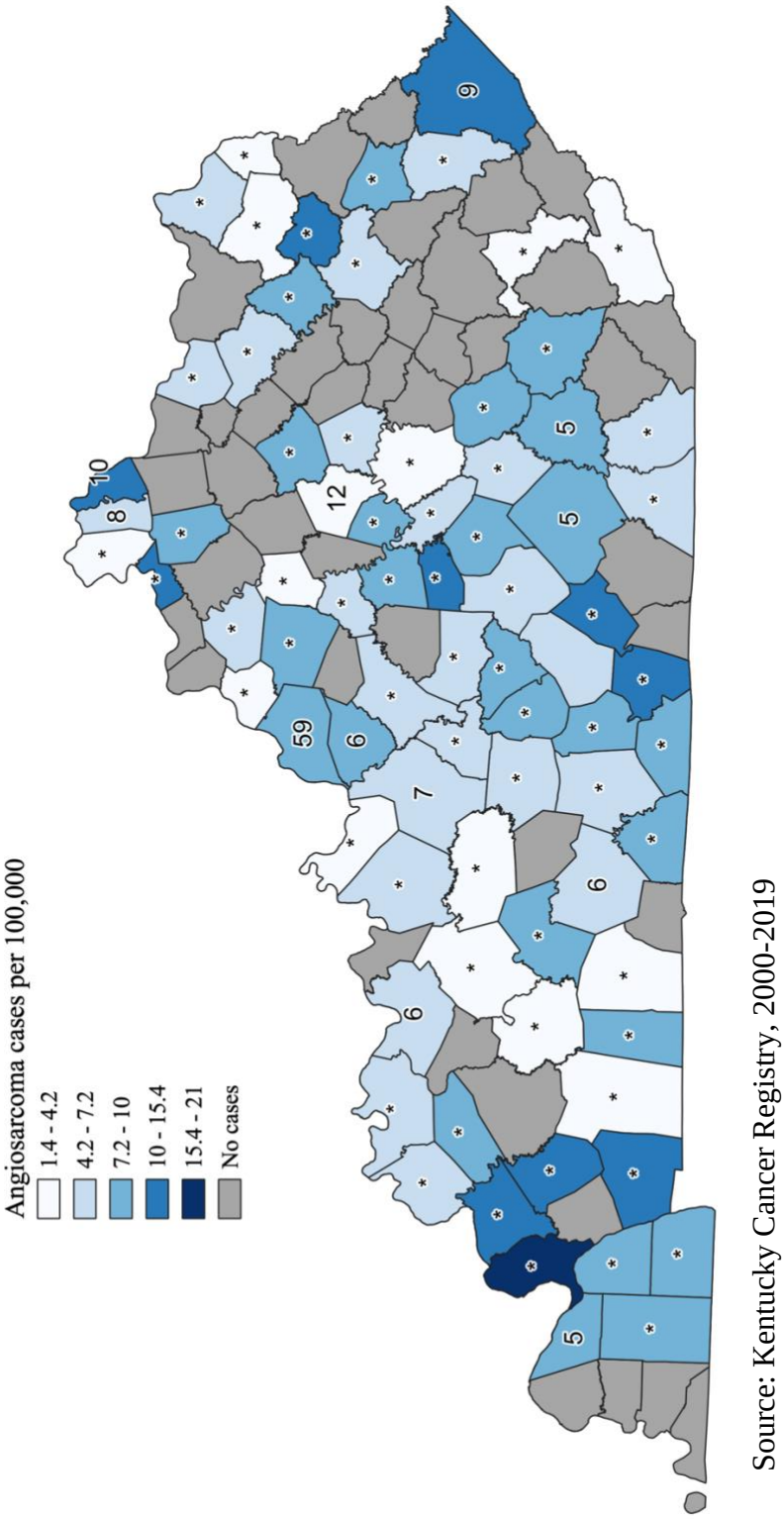
Category	n (%)
Age at Diagnosis	
<65	89 (36.2)
65-80	99 (40.2)
>80	58 (23.6)
Sex	
Male	114 (46.3)
Female	132 (53.7)
Race	
White	239 (97.1)
Black	7 (2.9)
Date of Diagnosis	
2000-2004	53 (21.6)
2005-2009	65 (26.4)
2010-2014	63 (25.6)
2015-2019	65 (26.4)
Site	
Liver	19 (7.7)
Soft tissue (heart)	98 (39.8)
Breast	36 (14.6)
Other non-epithelial skin	44 (17.9)
Lung and bronchus	9 (3.7)
Bones and joints	8 (3.3)
Miscellaneous Malignancy	18 (7.3)
Other	14 (5.7)
Tumor Grade	
I + II	31 (12.6)
III	38 (15.4)
IV	43 (17.5)
Unknown/Missing	134 (54.5)

Tumor Size	
<10cm	138 (56.1)
≥10cm	22 (8.9)
Unknown/Missing	86 (35.0)
Survival Status	
Alive	45 (17.9)
Dead	201 (81.7)
Appalachian	
Yes	59 (24.0)
No	187 (76.0)
Insurance Status	
Private Insurance	49 (19.9)
Medicaid	13 (5.3)
Medicare	156 (63.4)
Not insured	6 (2.4)
Unknown/other	22 (8.9)

Geographic Distribution

Figure 1 displays case counts by county, as well as the incidence rate of cases per 100,000 residents, where cases occurred. (There were 43 counties with no cases.) Jefferson County, home to the state's largest city (Louisville), had the highest case count (59), but Livingston County in western Kentucky had the highest rate of angiosarcoma cases (21 per 100,000).

Figure 1. Angiosarcoma cases in Kentucky by county.



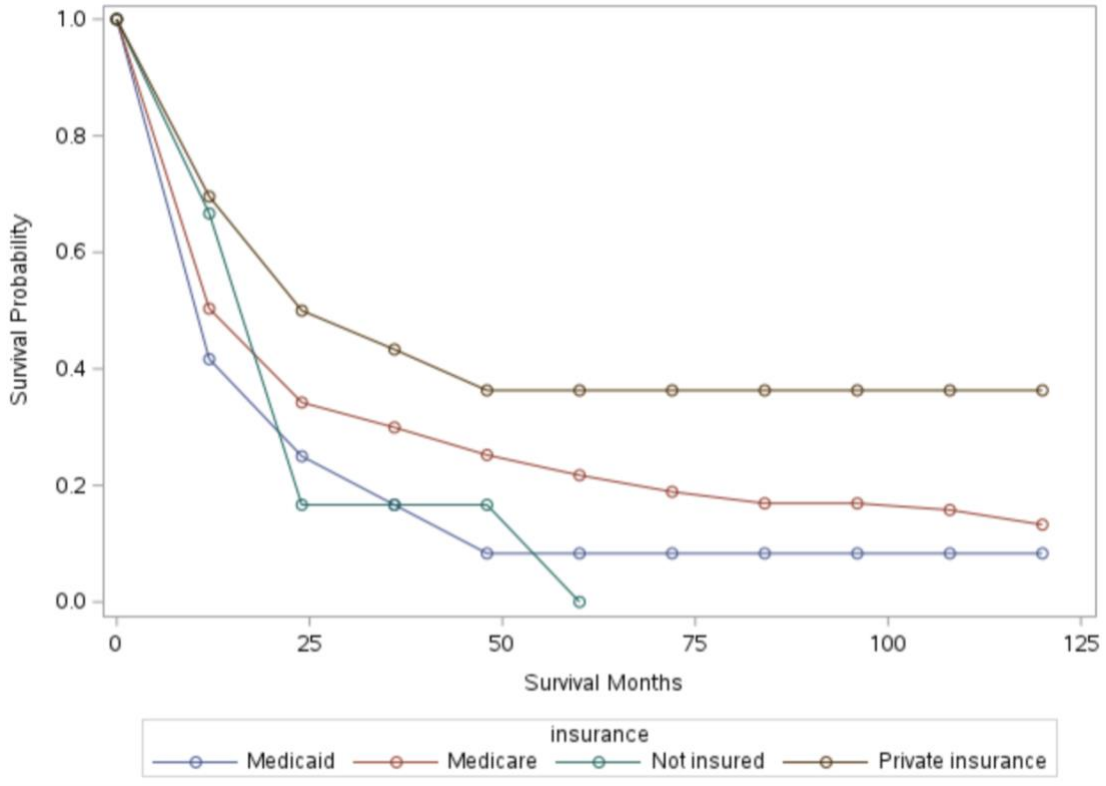
Source: Kentucky Cancer Registry, 2000-2019

Survival Analysis

Based on the Kaplan-Meier estimates, there were significant differences in survival by insurance type, age at diagnosis, tumor size, and SEER site. A log-rank test was performed to analyze the differences in each of the categories of these variables (Table 2). The Cox proportional hazards model showed that patients 80 years old and younger had a lower risk of death compared to those 81 years and older (Table 3). Patients with angiosarcoma of the liver, lung and bronchus, and miscellaneous malignancies had an increased risk of death compared to other SEER sites (Table 3).

Figure 2. Kaplan-Meier method estimated survival in patients with angiosarcoma stratified by (A) insurance type, (B) age at diagnosis (years), (C) tumor size, and (D) SEER site

A



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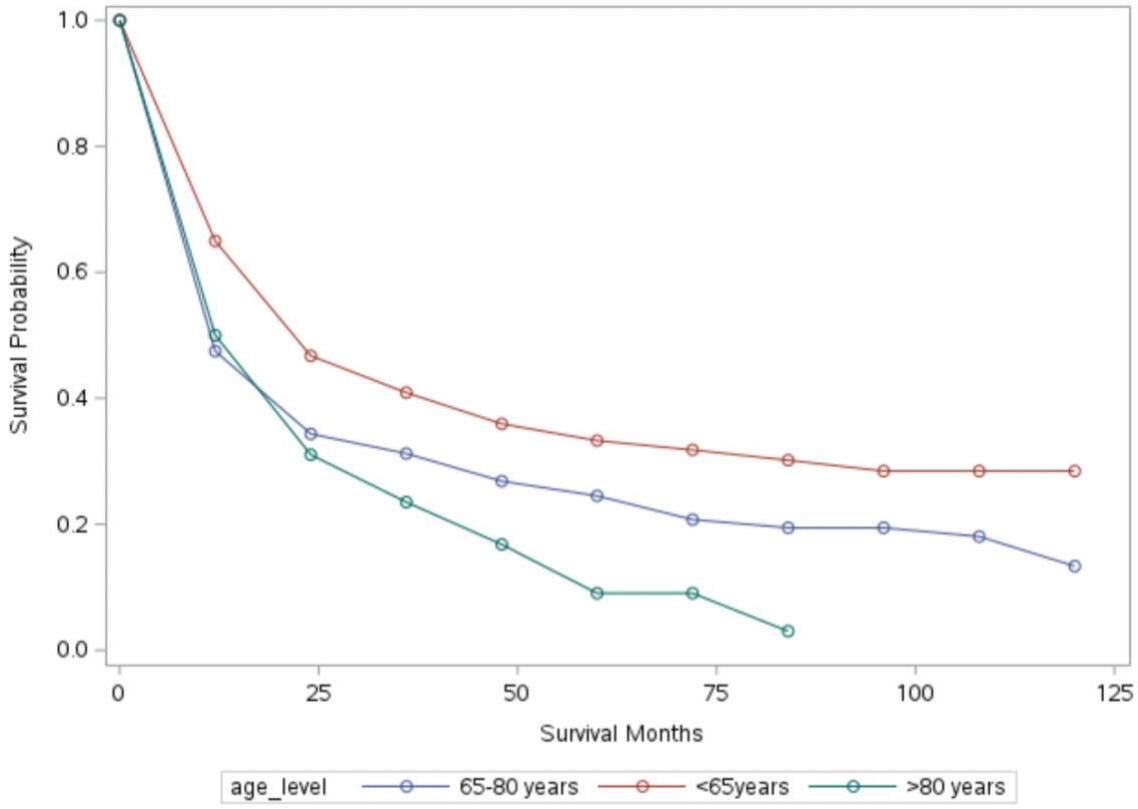
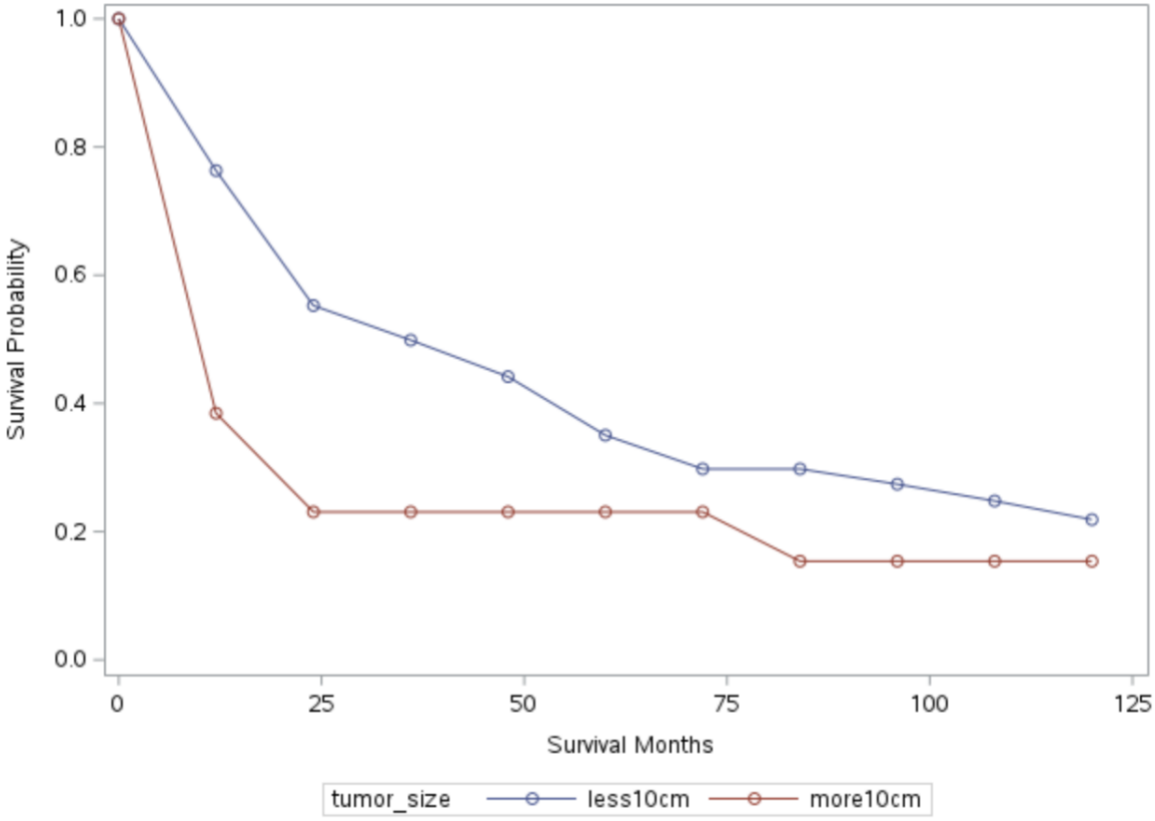

1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
0
25
50
75
100
125
Survival Months
age_level
65-80 years
<65years
>80 years

C


1.0
0.8
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Survival Probability
0
25
50
75
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125
Survival Months
tumor_size
less10cm
more10cm

D

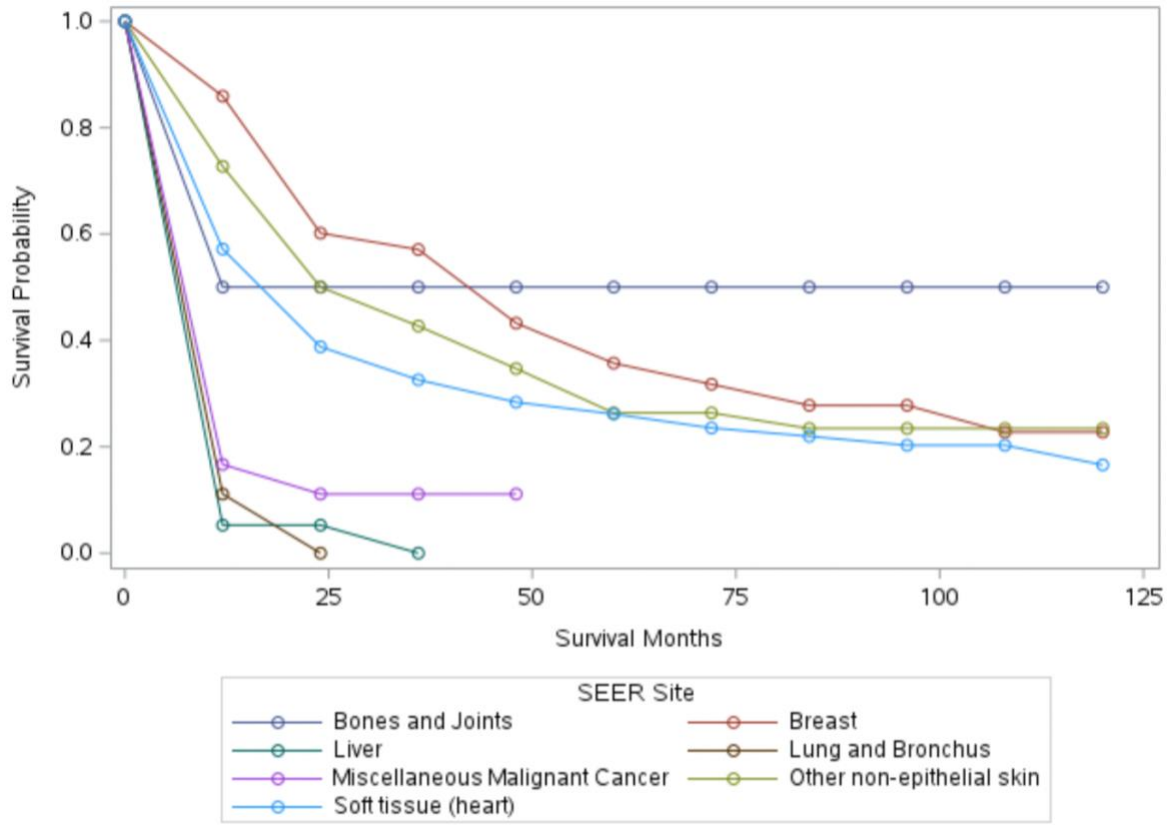

Figure 3. Kaplan-Meier method estimated overall survival in patients with angiosarcoma

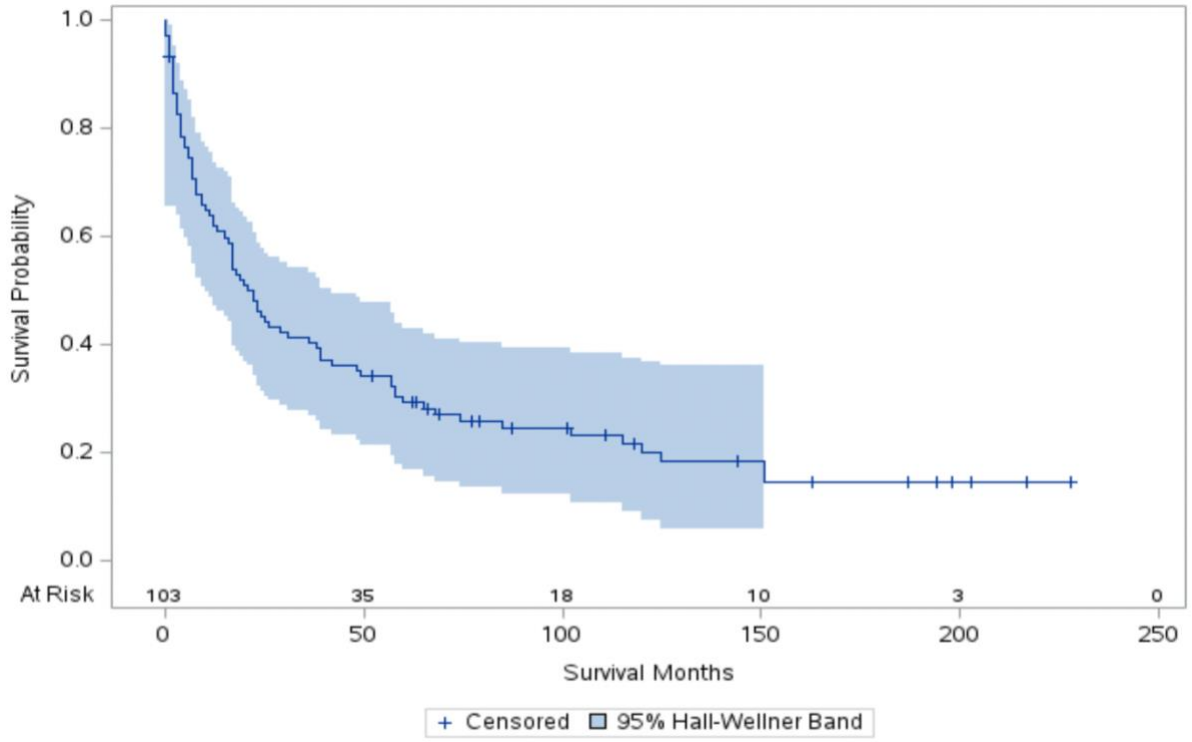

Table 2. Kaplan-Meier method univariate analysis of variables for survival in angiosarcoma patients

	Survival (log-rank P-value)
Age at diagnosis	0.0051
Tumor size	0.0070
SEER site	<0.0001
Insurance type	0.0063

Table 3. Multivariable Cox proportional hazard regression results (N=246)

	Hazard Ratio	Pr>Chi Sq
Age at Diagnosis		
<65	0.4	0.02
65-80	0.5	0.02
>80	Ref	-
Sex		
Male	Ref	-
Female	1.2	0.5
Race		
White	Ref	-
Black	2.6	0.2
Site		
Liver	10.5	<0.0001
Soft tissue (heart)	Ref	-
Breast	0.7	0.3
Other non-epithelial skin	0.9	0.7
Lung and bronchus	18.3	<0.0001
Bones and joints	0.8	0.8
Miscellaneous Malignancy	3.8	0.04
Tumor Grade		
I + II	0.9	0.8
III	0.9	0.9
IV	Ref	-
Tumor Size		
<10cm	0.5	0.1
≥10cm	Ref	-
Appalachian		
Yes	0.98	0.96
No	Ref	-
Insurance Type		-
Medicaid	1.3	0.6
Medicare	0.9	0.9

Private Insurance	Ref	-
Not insured	1.8	0.5

Discussion

Reports in the literature suggest that overall survival for angiosarcomas ranges from 30-50 months [1-3]. The mean overall survival time observed in this sample was 50.2 months (standard error= 5.66, Figure 3). A previous study conducted in the United States found a mean overall survival time of 82.10 (95% CI: 76.48– 87.72) months, which suggests better outcomes in the United States as a whole, compared to Kentucky alone [2].

Our findings were consistent with previous studies showing that sex and race do not affect the overall survival of angiosarcoma patients [1, 13-14]. Patients older than 80 years old had significantly poorer overall survival than the other age groups (Table 3), which was observed in prior studies [1, 2, 15].

By using SEER site coded variables, we were able to determine common sites of angiosarcoma and their survival rates. Patients with angiosarcoma of the liver, lung and bronchus, and miscellaneous malignancies had a significantly higher risk of death compared to other SEER sites (Table 3), and the log-rank test concluded that probability of death varied significantly by SEER site ($p<0.0001$, Table 2). Insurance type has not been previously studied in prior literature regarding angiosarcoma patients. We found that there was a significant difference between the probabilities of death and insurance type ($p=0.0063$, Table 2), however we did not find that any certain type of insurance had an increased risk of death over the other types (Table 3).

Fewer than five cases were observed in Livingston County, which had the highest incidence of angiosarcoma cases per 100,000 residents. A possible explanation for this

finding is that there are several industrial plants, including chemical manufacturers, in Calvert City, Kentucky. This city is technically located in Marshall County but is right on the border of Livingston County. Further study might include exposure assessments among local residents or workers for carcinogens linked to angiosarcoma, such as vinyl chloride, thorium dioxide, and arsenic. Pike county had higher rates compared to the rest of the Appalachian region, which is an interesting finding that needs explanation.

This study has several limitations. First, since this a rare type of cancer, so the sample size was small and precluded some meaningful types of analysis. Second, cases included in this study were diagnosed over a 20-year period and many of the variables' (e.g., tumor grade) definitions have changed over time, or may not have been captured for the entire period (these are shown as unknown or missing in Table 1). Third, the KCR database does not include information on occupational history or personal health history, so little was known about individual factors that might have influenced risk of incidence or death. Lastly, this analysis did not examine different types of treatment or their effect on survival. Ultimately many of these cases had multiple different combinations of treatment for example surgery and chemotherapy, surgery and radiation therapy, or even a mix of all three so it was difficult to examine the effects of one different type of treatment over another.

Conclusions

We conclude that patients older than 80 years old have significantly poorer overall survival than the other age groups, patients with angiosarcoma of the liver, lung and bronchus, and miscellaneous malignancies have a significant increased risk of death compared to other SEER sites, and there is a significant difference between the

probabilities of death and SEER site, as well as insurance type. This study was the first to examine the incidence and survival of all angiosarcomas in Kentucky.

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