



Epidemiology and survival factors for sarcoma patients in minority populations: a SEER-retrospective study

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ABSTRACT

Background: Epidemiologic studies have demonstrated race as a predictor of worse oncological outcomes. To better understand the effect of race on oncological outcomes, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to determine what treatment courses are provided to minority patients and how this impacts survival.

Materials and methods: A retrospective review of bone and soft tissue sarcoma cases was performed using the SEER database for a minimum 5-year survival rate (SR) using Kaplan-Meier curves. Categorical variables were compared using Pearson's χ^2 test and Cramer V. Kaplan-Meier curves were used to determine survival rates (SR) and Cox regression analysis was used to determine hazard ratios (HRs).

Results: Races that had an increased risk of death included Native American/Alaska Native (NA/AN) [hazard ratio (HR): 1.36, 95% confidence interval (CI): 1.049–1.761, $p = 0.020$] and Black (HR = 1.17, 95% CI: 1.091–1.256, $p < 0.001$). NA/AN individuals had the lowest SR (5-year SR = 70.9%, 95% CI: 63.8–78.0%, $p < 0.001$). The rate of metastasis at diagnosis for each race was 13.07% — Hispanic, 10.62% — NA/AN, 12.77% — Black, 10.61% — Asian/Pacific Islander (A/PI), and 9.02% — White individuals ($p < 0.001$). There were increases in the rate of metastasis at diagnosis and decreases in rates of surgical excision for Hispanic and Black patients ($p < 0.001$).

Conclusion: Race is determined to be an independent risk factor for death in NA/AN and Black patients with sarcomas of the extremities. Access to healthcare and delay in seeking treatment may contribute to higher rates of metastasis upon diagnosis for minority patients, and decreased rates of surgical excision could be associated with poor follow up and lack of resources.

Key words: soft tissue sarcomas; incidence; demographics; oncology; epidemiology; chemotherapy; radiotherapy

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Introduction

In the United States, racial differences in oncological outcomes have been reported for almost all cancer types [1]. There has been a growing call to identify and address these health disparities both in clinical practice and in research. Sarcomas ac-

count for 1% of all adult solid malignant neoplasms [2], and their multimodal presentation and non-specific symptoms can contribute to low physician suspicion and delayed diagnosis [3]. Given their poor prognosis and progressive stage development, the epidemiology of sarcoma subtypes and differential impact across racial categories should be mon-

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itored. Previous studies have demonstrated racial disparities for treatment and survival among patients with primary extremity bone and soft-tissue sarcoma (BSTS) [4–6]. The rarity of BSTS makes them difficult to study, and single institution reports are not able to generate large scale representative data.

To determine the most updated information on the scope of racial disparities in survival and treatment among patients with sarcoma of the lower extremity, we used the Surveillance, Epidemiology, and End Results (SEER) database [7]. This database represents the largest population-based sarcoma registry and allows for generation of a large-scale generalizable subset of data to document current health disparities in oncological prevalence and treatment. The purpose of this project was to determine how race acts as an independent risk factor for survival outcomes in patients with BSTS of the extremities and to evaluate if significant differences exist in treatment options provided to minority groups.

Materials and methods

A retrospective review of malignant bone and soft tissue sarcoma cases was performed using the latest version of the SEER database, released in April 2021 to assess cases from January 2000 to December 2017. Only cases with at least five years of follow up data were included. Patients were classified by demographic characteristics including age, gender, race/ethnicity, and year of diagnosis; tumor characteristics were classified by primary site, tumor size, location, depth, grade, laterality, staging [American Joint Committee on Cancer (AJCC) 8th edition], radiation, chemotherapy, metastasis at diagnosis; and overall survival (OS) was assessed.

All statistical analysis was performed using the statistical software SPSS (version 28) [8]. Overall and 5-year survival rates were determined for the entire series; Kaplan-Meier curves were used to analyze overall OS. Survival was defined as the time from initial diagnosis to time of patient death. Categorical variables including race/ethnicity (Hispanic, Non-Hispanic Native American/Alaskan Native, Non-Hispanic Black, Asian/Pacific Islander, and Non-Hispanic White), treatment variables, and disease characteristics were compared using

Pearson's Chi-Square test and Cramer V. Cox regression analysis was used to determine hazard ratios (HRs) that compared the risk of death between categorical variables.

Results

Demographic characteristics

There were 28,521 patients with soft tissue and bone sarcoma in the extremities that met our inclusion criteria. The median age was 52.58 years with a standard deviation (SD) of 23.045. The cohort was 45.1% female and 54.9% male. Most of the cohort (65%) was White, with 0.6% Native American and Alaskan Native (NA/AN), 6.5% Asian/Pacific Islander (A/PI), 11.3% Black (B), and 15.5% Hispanic. Of the entire cohort, 8.7% of patients were found to have metastasis at the time of diagnosis.

Tumor characteristics

The most common tumor classification was liposarcoma (15.7%), followed by malignant fibrous histiocytoma (11%), and osteosarcoma (10.9%). Disease characteristics included a mean tumor size of 221 mm with a standard deviation of 177 mm ranging from 2–987 mm.

Treatment

The rate of surgical excision performed for each race was: 87.31% — Hispanic, 87.79% — NA/AN, 89.23% — A/PI, 86.35% — B, and 88.73% — White individuals. Significant differences were found when comparing overall rates of surgical excision for Hispanic vs. White ($p < 0.001$), and White vs. B ($p < 0.001$).

We expect different survival rates between cohorts that require different treatment regimens and expect to see decreased survival among patients requiring more extensive treatment. We wanted to compare the survival rates between racial groups of cohorts undergoing chemotherapy and radiation to evaluate if minority groups requiring adjuvant/neoadjuvant treatment had worse outcomes than non-minority groups requiring adjuvant/neoadjuvant treatment. Risk of death associated with adjuvant and neoadjuvant treatment varied between races with statistically significant increases for NA/AN ($p = 0.060$), B ($p < 0.001$), White ($p < 0.001$), and Hispanic ($p < 0.001$) when

comparing risk of death associated with receiving radiation. Chemotherapy was associated with increased risk of death for NA/AN ($p < 0.001$), A/PI ($p < 0.001$), Hispanic ($p < 0.001$), Black ($p < 0.001$), and White ($p < 0.001$).

Oncological outcomes

Races that had an increased risk of death when compared to White included: NA/AN [HR = 1.36, 95% confidence interval (CI): 1.049–1.761, $p = 0.020$] and B individuals (HR = 1.17, 95% CI: 1.091–1.256, $p < 0.001$) (Fig. 1). NA/AN individuals had the lowest survival rate (5-year SR = 70.9%, 95% CI: 63.8–78.0% with an overall SR = 58.4%, 95% CI: 49.0–67.8%), followed by B (5-year SR = 72.9%, 95% CI: 71.3–74.5% with an overall SR = 65.4%, 95% CI: 63.2–67.6%), Hispanic (5-year SR = 75.7%, 95% CI: 74.3–77.2% with an overall SR = 58.4%, 95% CI: 49.0–67.8%), A/PI (5-year SR = 77.2%, 95% CI: 75.2–79.2% with overall SR = 68.4%, 95% CI: 65.4–71.3%) and White (5-year SR = 76.8%, 95% CI: 76.2–77.4% with overall SR = 69.1%, 95% CI: 68.1–70.1%). These differences in SR were significant between races ($p < 0.001$).

The rate of individuals with metastasis at diagnosis for each race was: 10.62% — NA/AN, 10.61% — A/PI, 13.07% — Hispanic, 12.77% — B, and 9.02% — White individuals. There were significant differences in the rate of patients with metastasis at diagnosis between Hispanic vs. White ($p < 0.001$) and B vs. White ($p < 0.001$).

When comparing the OS rates for primary sites of extremity sarcoma (bone vs. soft tissue vs skin sarcoma), all races had significantly increased risk of death with sarcoma in the bone and soft tissue when compared to sarcoma of the skin ($p < 0.001$) (Tab. 1). All races, besides B individuals, had increased risk of death with bone tumors compared to soft tissue tumors, while B individuals had slightly increased risk of death with soft tissue over bone (Tab. 1).

Differences in the rate of patients with metastasis at diagnosis was observed compared to the majority group for Hispanic vs. White ($p < 0.001$) and Black vs White ($p < 0.001$). 13.07% of Hispanic patients, 10.62% of Native American/Alaskan Native patients, 12.77% of B patients, 10.61% of A/PI, and 9.02% of White patients had metastasis upon diagnosis.

Hispanic individuals with resected stage I, II, and IV tumors had a higher risk of death when receiving chemotherapy when compared to those who did not receive it (Tab. 2). White individuals with resected stage I and IV tumors, and non-resected stage II tumors also had a higher risk of death with chemotherapy. Black individuals with stage IV tumors, regardless of surgical removal, had an increased risk of death with chemotherapy (Tab. 2). White individuals with resected stage I and IV tumors and non-resected stage I and II tumors had an increased risk of death with radiation therapy (Tab. 2).

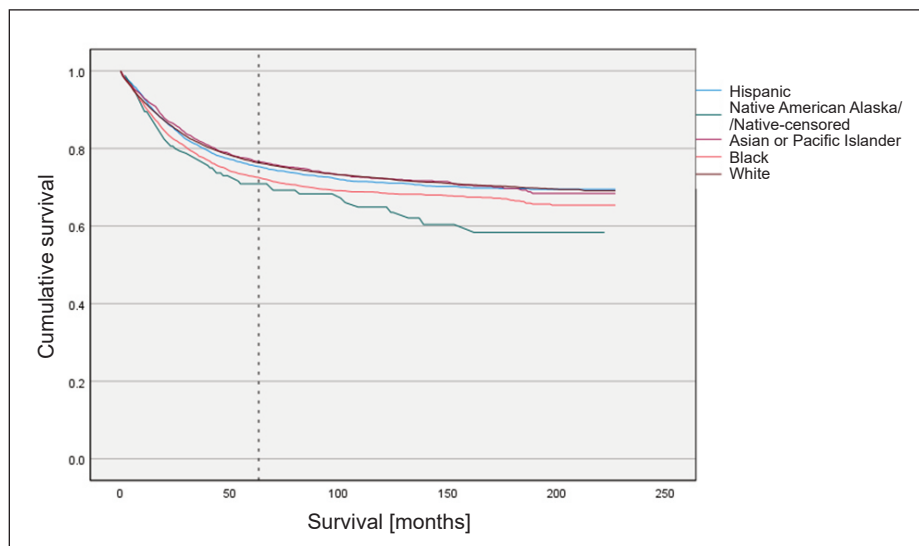


Figure 1. Overall survival rate compared between races with the 5-year mark labeled by the dotted line on the graph

Table 1. Primary site, laterality, and hazard ratios

Primary site		Hazard ratio*		95% CI		p-value
		Lower CI	Upper CI	Lower CI	Upper CI	
Hispanic	Bone	35.729	11.477	111.235		< 0.001
	Soft tissue	27.738	0.900	1.030		< 0.001
Asian/Pacific Islander	Bone	15.495	4.930	48.701		< 0.001
	Soft tissue	11.644	3.736	36.292		< 0.001
Black	Bone	8.190	5.005	13.401		< 0.001
	Soft tissue	8.221	5.080	13.304		< 0.001
White	Bone	12.829	9.552	17.229		< 0.001
	Soft tissue	11.792	8.816	15.774		< 0.001

*compared to skin as sarcoma primary site; CI — confidence interval

Table 2. Chemotherapy, radiation, and associated hazard ratios

Chemotherapy		Stage	Hazard ratio*	95% CI		p-value
Race/Factor				Lower CI	Upper CI	
Hispanic	No surgery	I	0.433	0.084	2.239	0.318
		II	0.385	0.127	1.166	0.091
		IV	0.827	0.510	1.256	0.443
	Surgery	I	1.95	1.266	1.611	< 0.001
		II	1.048	0.872	1.26	< 0.001
		IV	1.232	1.082	1.403	< 0.001
Asian	No Surgery	I	0.035	n/a	n/a	0.593
		II	0.115	0.011	1.179	0.069
		IV	0.894	0.445	1.795	0.894
	Surgery	I	5.660	1.656	19.344	0.006
		II	1.184	0.743	1.888	0.477
		IV	2.141	0.849	5.400	0.107
Black	No surgery	I	1.647	0.168	16.115	0.032
		II	0.569	0.211	1.532	0.265
		IV	0.512	0.289	0.906	0.021
	Surgery	I	1.402	0.492	3.997	0.528
		II	1.119	0.772	1.621	0.553
		IV	2.940	1.756	4.924	< 0.001
White	No surgery	I	1.998	0.945	4.222	0.070
		II	0.558	0.352	0.885	< 0.001
		IV	0.718	0.554	0.930	0.012
	Surgery	I	4.352	3.040	6.230	< 0.001
		II	1.050	0.895	1.230	0.550
		IV	3.635	2.757	4.793	< 0.001
Radiation		Stage	Hazard ratio**	95% CI		p-value
Race/Factor				Lower CI	Upper CI	
White	No surgery	I	3.112	1.572	4.652	0.002
		II	0.603	0.384	0.822	0.028
		IV	1.025	0.789	1.261	0.852
	Surgery	I	2.637	1.881	3.393	< 0.001
		II	1.059	0.908	1.210	0.466
		IV	1.752	1.348	2.156	< 0.001

*compared to groups not receiving chemotherapy; **compared to groups not receiving radiation; CI — confidence interval

Male sex was also associated with increased risk of death. When comparing risk of death between sexes among different minority groups, an increased risk of death was observed in males for Hispanic (HR = 1.428, 95% CI: 1.266–1.611, $p < 0.001$), Native American/Alaskan Native (HR = 1.950, 95% CI: 1.116–3.409, $p = 0.019$), A/PI (HR = 1.048, 95% CI: .872–1.26, $p = 0.616$), Black (HR = 1.232, 95% CI: 1.082–1.403, $p = 0.002$), White (HR = 1.192, 95% CI: 1.124–1.264, $p < 0.001$).

It is a known risk factor that increased age at time of diagnoses is associated with worse outcomes for sarcomas. We wanted to determine if this risk was amplified among minority groups, i.e., if increased age at diagnoses was associated with greater risk of mortality in minority groups than in non-minority groups. Risk of death associated with increased age of 1 year at the time of diagnosis was observed for Hispanic (HR = 1.004, 95% CI: 1.001–1.006, $p = 0.006$), Native American/Alaskan Native (HR = 1.006, 95% CI: 0.994–1.017, $p = 0.353$), Asian or Pacific Islander (HR = 1.004, 95% CI: 1.000–1.008, $p = 1.004$), and Black (HR = 1.012, 95% CI: 1.009–1.015, $p < 0.001$) compared to white patients (HR = 1.015, 95% CI: 1.014–1.017, $p < 0.001$). Figure 2 summarizes the major statistically significant HRs associated with race, increased age, and male sex, see Supplementary File — Table S1 for all individual significant and non-significant values for all compared variables.

Discussion

This data represents the most updated epidemiological survival, treatment, disease, and demographic statistics on BSTS of the extremities in the United States. The decreased rate of surgical excision observed in Hispanic and Black populations is consistent with previous epidemiological studies demonstrating lower incidence of surgery for Black patients with all major surgical procedures, including excision of breast, lung, and colorectal cancer [9, 10]. It has also been shown that these disparities are observed independently from insurance status [11]. Many reasons have been proposed for this consistently observed difference in treatment across cancer subtypes, including hospital and personal factors such as misconceptions about surgery, lack of financial resources to cover other cancer costs, and lack of access to trained sur-

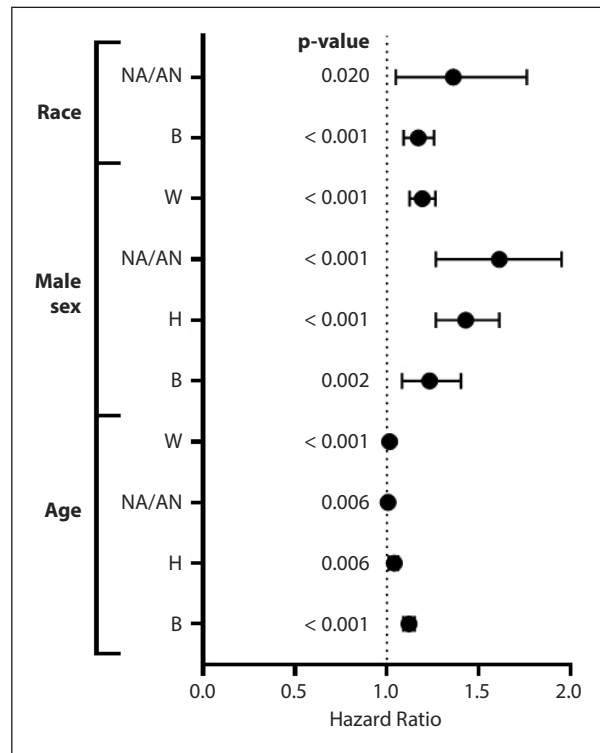


Figure 2. Hazard ratios (HRs) of Black (B) (HR = 1.17) and Native American/Alaska Native (NA/AN) (HR = 1.36) compared to White race (W); HR of male sex compared to female for W (HR = 1.611), NA/AN (HR = 1.611), Hispanic (H) (HR = 1.428), and B (HR = 1.232) race; HR of increased age of 1 year for W (HR = 1.015), NA/AN (HR = 1.006), H (HR = 1.004), and B (HR = 1.012) race

geons [12]. Regardless of the underlying cause, our results show that further research needs to be done to address the difference in surgical procedure rates in minority patients with BSTS.

Our study also demonstrated an independent increased risk of death for NA/AN and Black race among patients with primary extremity SBTS, as well as decreased overall and 5-year survival. We propose that the decreased rates of surgical excision in minority patients play a large role in the difference of survival outcomes.

Our results are consistent with historical trends of BSTS survival outcomes in minority patients [13]. A previous analysis of Black race as independent predictor of mortality using registry data up to 2003 showed an HR of 1.39 (95% CI: 1.13–1.70) [14], and another analysis including data up to 2012 demonstrated an HR of 1.24 (95% CI: 1.12–1.36) [4]. Our study showed Black race to be an independent risk factor with an HR of 1.17 and included more recent data than the previously two men-

tioned studies (through 2017). Thus, we are hopeful that our results represent a continued downtrend in this HR value and by extension health disparities.

We also found increased rate of individuals with metastatic disease at the time of diagnosis in minority groups. Access to early diagnostics and interventions is essential in preventing late stage presentation and improving survival outcomes [15]. A study using the National Cancer Database including data until 2015 showed that insurance status was the most protective factor against metastatic disease in prostate, non-small cell lung cancer, and breast cancer [16]. Even though there are currently no screening tools for sarcomas, delayed access to healthcare once symptoms appear is likely highly influenced by insurance status, which would contribute to increased metastasis at diagnoses for sarcoma patients. Further, it has been found that this factor was not as effective in minority patients with similar insurance status^[17], demonstrating that care access is influenced largely by insurance status, but additional social determinants of health remain obstacles to minority communities.

When comparing the survival rates for primary sites of extremity sarcoma (bone vs soft tissue vs skin sarcoma), while White, Hispanic, and Asian/PI had increased risk of death with bone tumors compared to soft tissue tumors ($HR_{\text{bone}} > HR_{\text{soft tissue}}$ using HR_{skin} as the control comparison), Black individuals did not follow this same trend and had a slightly increased risk of death with soft tissue sarcomas ($HR_{\text{soft tissue}} > HR_{\text{bone}}$ using HR_{skin} as the control comparison). We interpret these results as a potential indication that in a disease pathology that traditionally has a better prognosis (the five-year relative survival is estimated to be 66.4% for soft-tissue sarcoma and 52.9% for bone sarcoma [18]), Black patients suffer from worse outcomes than patients of other racial groups. Delay time from diagnosis to treatment initiation has been shown to be associated with poorer survival in soft tissue sarcoma specifically [19, 20], thus this data should prompt further investigation into socioeconomic and/or geographical factors that could be associated with delayed treatment initiation.

We also observed several differences in the risk of death between races associated with minority groups being able to access specific treatment regimens. When comparing groups undergoing

treatment with chemotherapy with stage II tumors who did not require surgical resection, White patients had an increased survival compared to patients who did not receive chemotherapy, while Black, Asian, and Hispanic patients showed no difference in survival rates. One theorized explanation for this trend is that if a higher proportion of minority patients who need surgical resection are not receiving the treatment and are receiving chemotherapy only, the survival of these groups will be reduced compared to White patients. Based on the limitations of this study and lack of access to individual patient records, we cannot draw any definitive conclusions based on the trends observed in survival between groups. However, it is important to continue reporting trends on minority outcomes associated with adjuvant/neoadjuvant treatments as we are learning more about the cause of disparate outcomes in minority groups.

We also found that White individuals with stage I tumors undergoing radiation had decreased survival when compared to groups not receiving radiation, both with and without resection. All other races compared had no difference in risk of death regardless of radiation status. While it is expected to observe lower survival rates in patients who undergo radiation (more advanced disease is more likely to require adjuvant and neoadjuvant treatment on a palliative basis), the equal risk of death regardless of adjuvant radiation treatment seen in non-White race groups is a trend that should be studied further in studies with access to more detailed treatment regimens of individual patients.

An additional finding was male gender associated with increased risk of death in all groups except A/PI. Notably, the HR associated with male gender was higher for both Hispanic ($HR_{\text{male}} = 1.232$) and Native American/Alaskan Native ($HR_{\text{male}} = 1.950$) than for White race ($HR_{\text{male}} = 1.192$). It has been shown previously that male gender is a risk factor for development of BSTS, and occupational factors, such as chemical exposure, smoke inhalation, and employment that exposes individuals to heavy machinery that are more likely to impact male patients, have all been implemented as possible causes of this gender disparity [2]. It is well accepted that environmental and exposure are risk factors for developing malignancy, and analysis controlling for income has consistently shown race/ethnicity to be

a significant predictor for environmental exposure [21]. We conjecture that the increased risk seen among minority men could be correlated with increased occupational and environmental exposures in male minority patients.

We also saw increased risk of death associated with older age at diagnosis for all races, consistent with what is known about sarcoma prognosis [22]. However, we saw the greatest risk of death in White patients ($HR_{1\text{-year}} = 1.015$), followed by B ($HR_{1\text{-year}} = 1.012$), A/PI ($HR_{1\text{-year}} = 1.004$) and Hispanic ($HR_{1\text{-year}} = 1.004$). Multiple epidemiological studies have shown that minority patients are more likely to be diagnosed with malignancies at a younger age. For example, minority women are 72% more likely to be diagnosed with breast cancer under the age of 50 years when compared to non-minority groups, with a relative HR of 1.72 [23]. It is possible that environmental or other social health determinants contribute to the development of malignancies including sarcomas at a younger age in minority groups, which could explain why the greatest HR associated with increasing age was seen in White patients in our results. It has been shown that oncological studies that report race as a demographic characteristic report a lower average age at diagnosis than studies that do not report race. A systemic review of 261 oncology trials demonstrated a 3-year decreased reported average age at diagnosis in studies that included racial cohort data compared to studies that did not [24]. Our results demonstrate that continued efforts are needed to recruit diverse populations for clinical trials in sarcoma studies.

These results were based on cancer statistics collected from the U.S. population. However, studies on disparities in sarcoma care have shown similar results in other countries, including the Asia-Pacific region and Canada [25]. Disparities in minority cancer outcomes exist across multiple health systems with different payment models. In Australia, indigenous populations have a 40% increased risk of death associated with malignancy as compared to non-indigenous individuals, and similar statistics are seen when considering the native New Zealand population [26, 27]. In the UK, Asian and Black ethnic groups have decreased survival for multiple cancer types when adjusting for comorbidity, age, sex, and income levels [28]. Given that minority populations consistently have dispar-

ities in outcomes across multiple health systems and countries, it is feasible that our results represent a global issue that should be taken into consideration by non-US health systems.

Conclusion

While race is known to be an independent risk factor for a variety of adverse health outcomes, little is known as to how this parameter relates specifically to differences in outcomes and treatment options in BSTS. Given the multimodal presentation of soft tissue sarcomas, it is important to investigate these differences in hopes of better addressing the potential contributors to these health disparities. We do not claim race/ethnicity to be an isolated risk factor due to any inherent physiologic differences between groups, but rather a risk factor due to social and economic disparities associated with minority groups.

This study provides both accurate and generalizable data about 5-year and overall survival rates for BSTS of the extremities and is novel in its assessment of these variables across various racial and ethnic groups. We report that when compared to White patients, Black and Hispanic patients both had increased rates of metastasis at initial diagnosis and decreased rates of surgical excision. Access to medical therapy also varied between groups and, notably, Native American/Alaskan Native patients had worse survival rates when compared to the majority group after surgical treatment. Decreased rates of surgical excision could be associated with poor access to health systems and lack of follow-up. Increased risk of death associated with adjuvant therapies is likely due to the advanced disease at presentation most likely as a result of delay or lack of access to health resources. This study elucidates many statistically significant differences between the prognosis and treatment of sarcoma among various racial groups that can help the medical community better understand and decrease these discrepancies.

Limitations

Limitations of this study include incomplete or missing data from the SEER registry for some case entries. This limited the amount of significant analysis that could be performed, especially in the NA/AN populations which were a very low

percentage of overall cases. A significant limitation of this study is that no assessment of co-morbidity was made due to the nature of the information provided by the SEER registry. Patients who died of other causes were excluded from the survival analysis; however, patients that died from primary tumor or subsequent metastasis may have had unreported comorbidities. We consider this an acceptable limitation as comorbidities are difficult to measure and are not routinely recorded when considering survival for sarcoma patients. Another limitation of this study is that the results should be interpreted in the context of the United States healthcare system, given that SEER provides information on cancer statistics in the U.S. population.

Conflicts of interest and Funding

The authors, their immediate family, and any research foundation with which they are affiliated did not receive any financial payments or other benefits from any commercial entity related to the subject of this article. There are no relevant disclosures. We have no conflicts of interest. The Manuscript submitted does not contain information about medical device(s)/drug(s). All authors significantly contributed to the document and have reviewed the final manuscript.

Author contributions

All authors participated in the study and helped shape the research question, data, analysis, and manuscript.

Ethical permission

All patient identifiers are removed from the SEER database; thus, this study is exempt from Institutional Review Board approval.

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