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Prognostic Factors, Disparity and Equity Variables Impacting Prognosis in Bone Sarcomas of the Hand: SEER database review

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Abstract

Background: Primary sarcomas originating from the bones of hand and wrist are rare but carry a significant burden of morbidity.

Methods: National Cancer Institute's (NCI) Surveillance, Epidemiology and End Result (SEER) database from 1975–2017 was queried to report incidence and survival data in 237 patients in the US. Kaplan-Meier and Cox Regression were used to determine the prognostic factors affecting survival. Chi square test was used to assess the correlation.

Results: Incidence of hand and wrist sarcoma was 0.017 per 100,000 persons in 2017 and has not significantly changed since 1975 ($p>0.05$). Disease-specific 5-year and 10-year survival for the entire cohort was 90% and 84%, respectively. On multivariate analysis race 'others', histology other than 'osteosarcoma', grade other than 'undifferentiated' and size '<6cm' were predictors of worse disease-specific survival. Cross tabulation of race with other significant prognostic factors on univariate analysis revealed a significant correlation of race with every other significant prognostic factor except for grade.

Conclusions: The current study is an analysis of a population-based registry reporting incidence and survival data for patients with sarcoma of hand and wrist. Independent prognostic factors include race, histology, grade and size. There is lack of improvement in survival over the last four decades.

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Availability of Data and Material: Available at https://seer.cancer.gov/data-software/

Introduction

Primary osseous malignancies of the hand and wrist are extremely rare[1] and are associated with significant morbidity[2]. Anatomical and biomechanical complexity of hand and wrist, with critical neurovascular elements adjacent to osseous and musculo-tendinous structures constitute unique surgical challenges[3]. Surgical challenges include preservation of essential anatomy to maintain function and dexterity[4,5] while achieving local tumor control with negative margins[6]. The data regarding epidemiology and prognostic factors governing the outcomes for bone sarcomas of the hand and wrist is scarce[7]. Given the rarity of the disease, most of the data is limited to small case series emanating from single-centers[2,4,8–16]. Data from single-center studies is susceptible to selection bias. Population based registries have been employed to elaborate the epidemiological features of soft tissue sarcoma affecting the upper extremity in the US[17] and Europe[18]. The National Cancer Database (NCDB) has also been utilized to investigate the characteristics of osteosarcoma affecting the upper extremity[19–21]. However, population-based data regarding osseous sarcoma of the hand is lacking. Osteosarcoma, chondrosarcoma, Ewing sarcoma and malignant giant cell tumor of bone (GCTB) constitutes the majority of malignancies affecting the osseous structures of hand and wrist.

In the current study we have queried National cancer institute's (NCI) Surveillance, Epidemiology and End Result (SEER) database to extract and analyze the data regarding bone sarcomas of the hand and wrist in the US from 1975–2017. SEER is the only comprehensive source of population-based data in the US and is regarded as a standard of quality among the cancer registries around the world with a case completeness of 98%[22]. We have limited our analysis to the hand and wrist in order to elucidate the unique characteristics of the disease process affecting this intricate anatomical area.

Materials and Methods:

The cohort of cases for the current study was isolated using the NCI's SEER program[22]. Presently, SEER collects the data from 18 registries covering approximately 35% of the US population. We isolated a total of 237 cases with primary location as 'small bones of the upper limb' and histologic ICD-O-3 codes for osteosarcoma (9180–6/3, 9192–4/3, and 9200/3), chondrosarcoma (9220–1/3, 9230–1/3, and 9240–3/3), malignant giant cell tumor of bone (9250/3) and Ewing sarcoma (9260/3). The information was extracted from three different datasets within the SEER database (9 registries from 1975–2017, 13 registries from 1992–2017 and 18 registries from 2000–2017). Information regarding patient demographics, grade, stage, size, cause of death, year of diagnosis, surgical and radiation treatment, and survival time until death or loss to follow-up was identified. Information regarding socioeconomic status (SES) and insurance was extracted using the custom SEER census tract level and rurality database from 2000–2016[23]. Patients with no insurance were grouped together with patients on Medicaid. This was done as patients presenting with no insurance to a healthcare facility are enrolled in Medicaid[24]. Small area SES was analyzed as a composite index calculated by SEER using the method described by Yost et al.[25]. Census tract-level SES indicator variables of median household income, median house value, median rent, percentage of the population below 150% of the poverty line, an education

index, percentage of the population with working class occupations and percentage of population older than 16 years in the workforce without a job were utilized[25]. The data is presented as quintiles; group 1 representing the lowest SES and group 5 representing the highest SES. Patients with missing data were excluded from each respective univariate and multivariate analysis.

Patient age was converted to a categorical variable (0–14, 15–40, 40–59, ≥60) for the purpose of analysis. We chose this stratification to align with adolescent and young adult population demographics being defined at 15–39[26,27]. Staging categories of local, regional and distant disease were used according to SEER staging system[28]. Tumor size was also converted into a categorical variable (≤6 cm, >6 cm) considering the distribution of tumor size in the cohort.

SEER* Stat software (version 8.3.8, NCI) was used to analyze incidence rates which were age adjusted and normalized using the 2000 US Standard population using the dataset '9 registries 1975–2017'. Statistical analysis was performed using SPSS Statistical package version 27.0 (SPSS Inc., Chicago, IL). Chi-square test was used to make correlations between categorical variables. Log-rank test was utilized for categorical values to gauge the effects of demographic, clinical, pathological and treatment variables. A multivariate analysis was carried out for determination of independent prognostic factors using the Cox proportional hazards model.

Results:

A total of 237 patients were extracted from the SEER database from 1975–2017. The demographics of the cohort are shown in Table 1. Most of the cases (51.1%) were diagnosed from 2005–2017. The most common age group was 40–59 years. Almost half of the patients were male (49.8%). A majority of the cohort was Caucasian (86.3%) and non-Hispanic (84.2%). The most common grade was 'low' (41.4%) and the most common stage was localized (55.6%). A small proportion of the entire cohort was ≥ 6 cm in size (25 cases, 15.9 %). Chondrosarcoma was the most common histologic diagnosis (64.1%) followed by osteosarcoma (17.7%), Ewing sarcoma (10.1%) and malignant GCTB (8%). Malignant GCTB: a rare diagnosis among bone malignancies of the axial skeleton, shows a predilection for hand and wrist. A majority of the patients underwent surgical resection (87.7%). Of those undergoing surgical resection, 30.9% underwent amputation and limb salvage was performed among the rest. Information regarding radiotherapy (6.8%) and chemotherapy (23.8%) was available only for a fraction of the cohort, precluding any meaningful analysis.

The incidence of bone sarcoma of hand and wrist was 0.017 cases per 100,000 persons in 2017 and has not changed significantly since 1975. Annual percentage change (APC) could not be calculated (Figure 1A). Age adjusted incidence shows a late peak after 60 years of age (Figure 1 B).

The five and ten-years disease specific survival for the entire cohort was 90% and 84% respectively (Table 2, Figure 2A). Stratified by the year of diagnosis, 10-year DSS improved from ~75% for 1975–1994 to ~90% for 1995–2017 (Table 2). Univariate and multivariate

analyses of the entire cohort are summarized in Table 2 and 3 respectively. Of note, osteosarcoma arising from hand and wrist was found to have better prognosis when compared to osteosarcoma arising from the rest of the axial skeleton. On univariate analysis, 'female' sex (p=0.016), 'white' race (p=0.032), 'low' grade (p<0.001), 'localized' stage (p<0.001), histological subtype of chondrosarcoma or malignant giant cell tumor (p<0.001), and surgical resection (p<0.001) were significantly associated with improved survival. Of note SES or insurance status are of no prognostic significance for patient with bone sarcoma of hand and wrist.

On multivariate analysis (Table 3), 'others' race, 'undifferentiated' grade, histopathologic subtype other than 'osteosarcoma', and size of primary tumor '≥ 6cm' were independent predictors of worse outcomes. Corresponding Kaplan-Meier curves are shown in Figure 2B & C and Figure 3 A&B.

A cross table was made between race and other prognostic factors achieving significance to analyze the racial disparity in outcomes (Table 4). Chi square was used to assess the correlation. A significant association was observed between race and stage, size, histology and surgical resection.

Discussion

Bone sarcomas of the hand and wrist are rare but have been associated with significant morbidity[4,7,22]. This is the first investigation to report incidence and prognostic factors governing the outcomes in osseous sarcomas of the hand and wrist. Traditionally a value of <0.1% has been quoted as the incidence of hand malignancies[1,29]. This is the first report of a population-based estimate of incidence of osseous sarcomas of hand and wrist (0.017 cases per 100,000 persons, Figure 1a) as well as the age adjusted incidence showing peak incidence in the 6th decade of life (Figure 1b).

One of the predictors of improved outcome was Caucasian race when compared to 'others' (p=0.032, Table 3). This is a novel finding that has not been reported in the literature to the best of our knowledge[3,7].'Others' include a total of 11 cases (Table 1) with 2 cases identifying as Native American, 2 as Asians, 3 as Filipinos, 1 as Haitian, 2 as Japanese, and 1 Vietnamese. Given the small numbers of patients in each category, it is not possible to generate any meaningful statistic for a particular racial category among others. Similarly, the limited number of non-Caucasian cases may have led to non-significant results observed between race and grade (Table 4). However, there was significant association noted between race and 'stage' (p<0.001), 'size' (p=0.003), 'surgery' (p<0.001) and 'histology' (p<0.001) (Table 4). A higher proportion of 'whites' (104/184) had 'localized' stage at the time of diagnosis as compared to 'others' (2/10). Size was ≥ 6 cm in 3 out of 7 cases among 'others' as compared to 16 out of 135 cases for 'whites'. Surgical resection was performed more often for 'whites' (180/200) as compared to 'others' (5/11). And 'others' had a diagnosis of either osteosarcoma (4/11) or Ewing sarcoma (2/11) more frequently as compared to 'whites' (27/202 and 22/202, respectively). All these confounding factors were controlled for in the multivariate analysis, and 'white' race was still an independent predictor of improved survival. Socioeconomic status as a composite measure and the insurance status

were not found to be of prognostic significance (Table 2). Given the small numbers of cases in categories other than Caucasians, this finding should be interpreted with caution.

Chondrosarcoma was the most common histopathological subtype in our cohort, confirming a previously reported finding[7]. Most of the chondrosarcoma cases in our cohort were either well differentiated / low grade (59/130) or moderately differentiated (56/130). The stage was 'distant' in only 3 out of 141 cases for which the data was available. Chi Square test revealed a p-value of 0.001 and 0.002 respectively, upon cross-tabulation (data not shown). This finding highlights the significant association between histopathological diagnosis of chondrosarcoma and lack of poorly or undifferentiated grade and distant stage. The findings are consistent with previously published literature[7,11].

Osteosarcoma was the second most common histological diagnosis in the cohort of cases with hand and wrist osseous malignancies (Table 1). It was also an independent predictor of poor outcomes on multivariate analysis (Table 3). The five- and ten- years survival for patients with osteogenic sarcoma of the hand and wrist was 0.79, a markedly better 5- and 10- years survival rate for osteosarcoma as compared to other locations[30]. A higher proportion of patients with 'well differentiated/ low' or 'moderately differentiated' grade was seen in the cohort of patients with hand and wrist osteosarcoma compared to patients with osteogenic sarcoma in other locations (38.1% vs. 17.4%, data not shown)[30]. A similar trend was also observed for the 'size' of the primary tumor. This finding is consistent with what other have reported previously in the literature[7,12,14,15,19,20].

Patients with histopathological diagnosis of Ewing sarcoma constituted 10.1% of the current cohort (Table 1). The 5- years survival rate was 0.72 as compared to 0.55 for patients with Ewing sarcoma in other locations[28]. Despite having a lower 5- and 10- years survival rate as compared to osteosarcoma, when controlled for other factors, Ewing sarcoma was not independent predictor of worse outcomes.

AJCC recommends "T" size cut off of 8 cm to be used for appendicular disease[31,32], we however, chose the arbitrary value of 6 cm to stratify the tumor size. Less than 5% of the entire cohort, for which the size information was available, had a size ≥8 cm. The decision was made to facilitate meaningful statistical analysis.

Limitations of the current study include limited information in the SEER database regarding medical comorbidities, clinical course, radiological exams or serological investigations. No information regarding any specific chemotherapy or medical therapy is provided in the SEER database. Accuracy of staging information can be a potential pitfall in all studies based on the database. In the current study, staging information has been extracted out of SEER database as was recorded at the time of reporting by the registry. Lack of any radiological record makes it impossible to verify the stage at diagnosis. There is no information regarding any patient reported outcome measures (PROMs) in the SEER. Especially for sites such as hand and wrist, survival data does not entirely represent the morbidity burden of the disease. Given the rarity of the disease process, small number of patients is another limitation of the current study.

The current study is the largest analysis of incidence, survival and prognostic factors for bone sarcoma of the hand and wrist using the largest source of population-based data in the US. The independent prognostic factors include race, grade, histology, and size of primary tumor. The current findings are clinically significant and distinct.

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Synopsis:

Malignant sarcomas originating from bones of hand and wrist are rare (0.017 per 100,000 people in 2017) and independent predictors of improved survival include race, histology, grade and size.

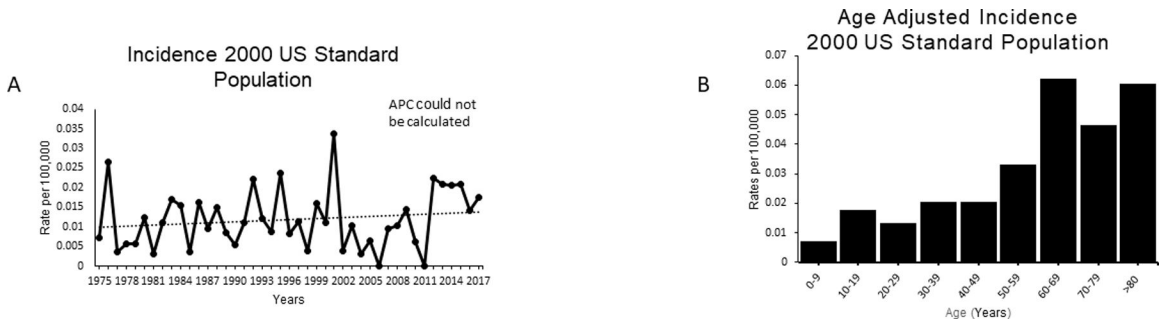

Figure 1:

Incidence data standardized to 2000 US population.

a) Overall incidence from 2000–2017 for the entire cohort of hand sarcoma.

b) Age-adjusted incidence for the entire cohort hand sarcoma.

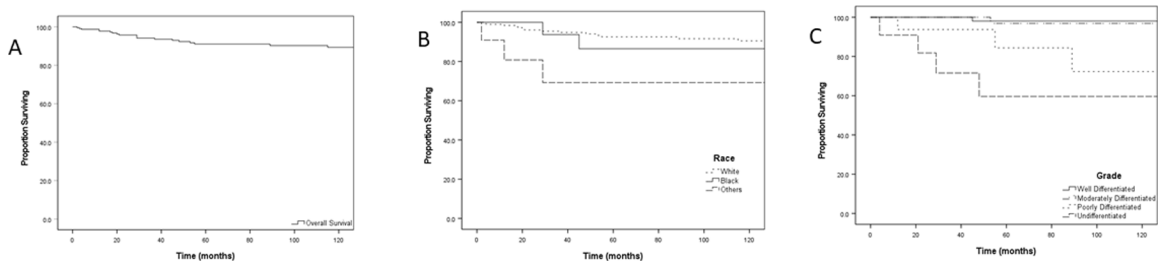

Figure 2:

Kaplan-Meier survival curves for the entire cohort

a) Disease-specific survival of the entire cohort

b) Disease-specific survival stratified by race

c) Disease-specific survival stratified by grade

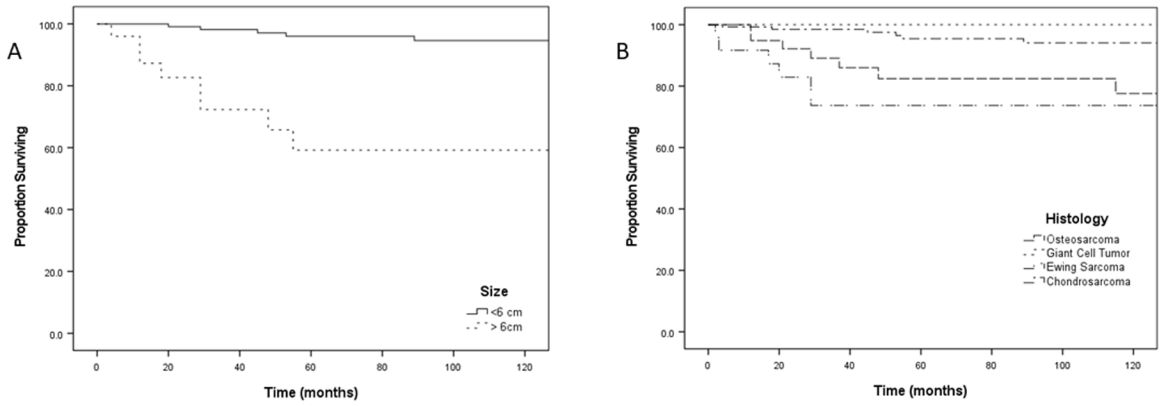

Figure 3:

Kaplan-Meier survival curves for:

a) Disease-specific survival stratified by size

b) Disease-specific survival stratified by histologic subtype

Table 1

Demographics and Clinical Characteristics of the Entire Cohort

			n	Valid 100% of total
Total Patients			237	100
Age				
	0–14 years		21	8.9
	15–39 years		61	25.7
	40–59 years		99	41.8
	≥ 60 years		93	39.2
Sex				
	Male		118	49.8
	Female		119	50.2
Race				
	White		202	86.3
	Black		21	9
	Others		11	4.7
Ethnicity				
	Non-Hispanic		207	84.2
	Hispanic		30	15.8
Grade				
	Low		65	41.4
	Moderate		61	38.9
	Poorly		19	12.1
	Undifferentiated		12	7.6
Stage				
	Localized		120	55.6
	Regional		84	38.9
	Distant		12	5.6
Size				
	<6 cm		132	84.1
	≥6 cm		25	15.9
Histology				
	Osteosarcoma		42	17.7
	Giant Cell Tumor		19	8
	Ewing Sarcoma		24	10.1
	Chondrosarcoma		152	64.1
Surgery				
	Surgery		206	87.7
		Limb Salvage	*143*	*69.1*
		Amputation	*64*	*30.9*
	No Surgery		29	12.3
Radiation Therapy				

		n	Valid 100% of total
	Radiotherapy	14	6.8
	None/Unknown	192	93.2
Chemotherapy			
	Chemotherapy	49	23.8
	None/Unknown	157	76.2
Socioeconomic Status (SES)			
	Group 1	30	21.9
	Group 2	25	18.2
	Group 3	23	16.8
	Group 4	31	22.6
	Group 5	28	20.4
Insurance			
	Medicaid/No Insurance	15	17.9
	Private Insurance	69	82.1
Year of Diagnosis			
	1975–1984	20	8.4
	1985–1994	31	13.1
	1995–2004	65	27.4
	2005–2017	121	51.1

Table 2

Disease-specific survival according to demographic and clinical characteristics (proportion surviving)

		5 year Survival	10 year Survival	p-value
Overall		0.9	0.84	n/a
Age				
	00–14 years	0.83	0.66	
	15–39 years	0.9	0.84	
	40–59 years	0.9	0.85	
	≥ 60 years	0.9	0.9	0.113
Sex				
	Male	0.86	0.76	
	Female	0.94	0.94	**0.016**
Race				
	White	0.91	0.85	
	Black	0.88	0.88	
	Others	0.7	0.7	**0.032**
Ethnicity				
	Non-Hispanic	0.89	0.83	
	Hispanic	0.95	0.95	0.363
Grade				
	Low	0.98	0.98	
	Moderate	0.98	0.98	
	Poorly	0.74	0.74	
	Undifferentiated	0.62	0.62	**<0.001**
Stage				
	Localized	0.98	0.94	
	Regional	0.85	0.8	
	Distant	0.52	0.17	**<0.001**
Size				
	<6 cm	0.95	0.89	
	≥6 cm	0.62	0.62	**<0.001**
Histology				
	Osteosarcoma	0.79	0.79	
	Giant Cell Tumor	1	1	
	Ewing Sarcoma	0.72	0.48	
	Chondrosarcoma	0.95	0.91	**<0.001**
Surgery				
	Surgery	0.92	0.88	
	No Surgery	0.73	0.6	**<0.001**
Radiation Therapy				
	Radiotherapy	1	0.43	

		5 year Survival	10 year Survival	p-value
	None/Unknown	0.89	0.87	0.514
Chemotherapy				
	Chemotherapy	0.86	0.78	
	None/Unknown	0.91	0.86	0.218
Socioeconomic Status (SES)				
	Group 1	0.91	0.91	
	Group 2	0.84	0.84	
	Group 3	0.83	0.83	
	Group 4	0.96	0.96	
	Group 5	0.91	0.91	0.126
Insurance				
	Medicaid/No Insurance	0.82	~	
	Private Insurance	0.94	0.94	0.171
Year of Diagnosis				
	1975–1984	0.89	0.77	
	1985–1994	0.9	0.74	
	1995–2004	0.93	0.93	
	2005–2017	0.86	0.86	0.792

P value shown for Log rank test between variables;

Age: p=0.113 only for age 0–14 vs. > 60; p=0.149 for 0–14 vs. 40–59; p=0.244 for 0–14 vs. 15–39; p= 0.854 for 15–39 vs. 40–59; p=0.621 for 15–39 vs. > 60; p=0.923 for 40–59 vs. > 60.

Race: p=0.032 for Caucasian vs. Other only, Caucasian vs. Black: p=0.795, and Black vs. Other: p=0.172.

Grade: p<0.001 only for Low vs. Undifferentiated and Moderate vs. Undifferentiated; p=0.003 for Low vs. Poorly; p=0.791 for Low vs. Moderate; p=0.018 for Moderate vs. Poorly; p=0.286 for Poorly vs. Undifferentiated.

Stage: p<0.001 for Distant vs. Localized and Regional vs. Localized only; p=0.003 Localized vs. Regional. Histology: p<0.001 only for chondrosarcoma vs. Ewing sarcoma; p=0.150 osteosarcoma vs. Ewing sarcoma; p=0.062 giant cell tumor vs. osteosarcoma; p=0.007 giant cell tumor vs. Ewing sarcoma; p=0.333 giant cell tumor vs. chondrosarcoma; p=0.01 osteosarcoma vs. chondrosarcoma.

Socioeconomic status (SES): p=0.126 only for group 4 vs. group 3 only; p=0.841 for Group 1 vs. Group 2; p=0.426 for Group 1 vs. Group 3; p=0.395 for Group 1 vs. Group 4; p=0.981 for Group 1 vs. 5; p= 601 for Group 2 vs. Group 3; p=237 for Group 2 vs. Group 4; p=0.745 for Group 2 vs. Group 5; p=0.414 for Group 3 vs. Group 5; p=0.432 for Group 4 vs. Group 5

Year of diagnosis: p=0.792 only for 1975–1984 vs. 2005–2017; p=0.215 for 1975–1984 vs. 1995–2004; p=0.994 for 1975–1984 vs. 1985–1994; p=0.204 for 1985–1994 vs. 1995–2004; p=0.447 for 1985–1994 vs. 2005–2017; p=0.2 for 1995–2004 vs. 2005–2017.

Table 3

Multivariate Analysis

		n	Hazard Ratio	95% CI	p-value
Sex					
	Male	54	1.067	0.114–9.999	0.955
	Female	64		Reference Group	
Race					
	White	103	0.002	0–0.572	**0.032**
	Black	9	2.944	0.078–111.012	0.56
	Others	6		Reference Group	
Grade					
	Low	47	0	0–0.153	**0.016**
	Moderate	46	0.001	0–0.293	**0.017**
	Poorly	16	0.021	0–0.964	**0.048**
	Undifferentiated	9		Reference Group	
Stage					
	Localized	69	5.114	0.102–256.003	0.414
	Regional	45	28.427	0.889–909.038	0.058
	Distant	4		Reference Group	
Histology					
	Osteosarcoma	18	0.001	0–0.665	**0.037**
	Giant Cell Tumor	1	0	0.000-~	0.998
	Ewing Sarcoma	2	0	0.000-~	0.997
	Chondrosarcoma	97		Reference Group	
Surgery					
	Surgery	112	2.58E+08	0.000-~	0.982
	No Surgery	6		Reference Group	
Size					
	<6 cm	102	0.024	0.001–0.450	**0.013**
	≥6 cm	16		Reference Group	

~Statistic could not be calculated

Cox proportional hazards model for risk of death from hand and wrist sarcoma

CI: Confidence Interval

TABLE 4

Cross table between race and other significant factors of univariate analysis: Cross-tabulation of race and other factors

	White	Race Black	Others	*p* value
Grade				
Low	56	7	2	
Moderate	57	2	1	
Poorly	14	1	3	
Undifferentiated	10	1	1	0.096
Stage				
Localized	104	12	2	
Regional	73	6	4	
Distant	7	1	4	<0.001
Size				
<6 cm	119	9	4	
≥6 cm	16	6	3	0.003
Histology				
Osteosarcoma	27	9	4	
Giant cell tumor	15	4	0	
Ewing sarcoma	22	0	2	
Chondrosarcoma	138	8	5	<0.001
Surgery				
Surgery	180	18	5	
No surgery	20	3	6	<0.001