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Osteosarcoma of the Upper Extremities: A National Analysis of the US Population

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Abstract. *Background/Aim: Osteosarcoma of the upper extremities is rare, and characteristics in this location have not been described before. We aimed to analyze the characteristics and survival rate of osteosarcoma of the upper extremities. Materials and Methods: A retrospective cohort study was performed by querying the National Cancer Database. Statistical analysis was performed using a multivariate logistic regression model and Kaplan–Meier log-rank tests for survival. Results: A total of 991 patients were diagnosed with osteosarcoma of the upper extremities. Most tumors were osteogenic and osteoblastic (66.8%), larger than 8 cm (47.9%), high grade (64.3%), lymph node-negative (7.9%), and without metastasis to lungs (39.0%). Osteosarcomas of the hand and wrist were less likely to be high-grade when compared to osteosarcomas of the forearm, arm, and shoulder. Conclusion: The results of this study help us to approach patients promptly and avoid total amputation, increasing functionality and prognosis of the disease.*

Bone tumors represent 3-6% of all childhood cancers and 1% of cancers in adults (1). Osteosarcoma is the most frequent primary malignant tumor of the bone defined as the presence of malignant mesenchymal cells that produce osteoid and immature bone (2). It is considered a bimodal tumor, with peaks of incidence during adolescence and after 60 years of age (3). Osteosarcomas in the hand are rare, with an incidence of 0.18% (4). Clinical symptoms include acute pain, localized swelling, and limitation of the joint movement, although the diagnosis is usually delayed or initially mistaken, leading to inappropriate treatments (5). The pathophysiology of the disease is still not clear, but there seems to be a propensity for areas of rapid bone growth (1, 3). It has been described that osteosarcoma originates *de novo*, but could also occur secondary to Paget disease, (6) metastatic disease, and after exposure to ionizing radiation (7). Due to the low incidence of osteosarcoma in the upper extremities, characteristics are not well described. This study identified the demographics, tumor characteristics, and survival of patients with osteosarcoma of the upper extremities, and determined the difference between osteosarcomas located in the hand and wrist compared to those located in the forearm, arm, and shoulder.

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Key Words: Osteosarcoma, upper extremity, characteristics, NCDB.

Materials and Methods

A retrospective cohort study was conducted by querying the National Cancer Database (NCDB) (8) hospital registry for cases of osteosarcoma in the upper extremities between January 1st 2004 and December 31th 2015.

Inclusion and exclusion criteria. We excluded patients with non-osteosarcoma bone cancers and those with osteosarcomas located outside of the upper extremities from all bone cancer patients diagnosed during the study period. At the end, 991 patients diagnosed with osteosarcoma in the upper extremities were included in the study.

Statistical analysis. A descriptive analysis of the demographics of patients with osteosarcoma of the upper extremities was performed. A multivariate logistic regression was performed to analyze the factors associated with osteosarcoma of the hand and wrist compared with those located in the forearm, arm, shoulder and joints. All unknown values were excluded from the analysis.

Table I. *Demographics*.

Patient characteristics	Total N=991 No.	%
Age group		
<21 years old	455	45.9
21-40 years old	261	26.3
41-60 years old	150	15.1
>61 years old	125	12.6
Sex		
Male	563	56.8
Female	428	43.2
Race		
White	758	76.5
Black	161	16.2
Native American	14	1.4
Asian	33	3.3
Others	13	1.3
Unknown	12	1.2
Comorbidities		
No	896	90.4
Yes	93	9.4
Unknown	2	0.2
Facility type		
Community Cancer Program	10	1.0
Comprehensive Community Cancer Program	64	6.5
Academic/Research Program	175	17.7
Integrated Network Cancer Program	35	3.5
Unknown	707	71.3

Kaplan–Meier survival curves were used to compare 10-year overall survival (OS) between these two groups including only patients diagnosed between January 1st, 2004 and December 31th, 2005 who had follow-up information for ten years. Log-rank test was utilized to determine any significant statistical difference between the survival curves. All the data were analyzed using SPSS, version 25 software (SPSS, Inc, an IBM Company, Chicago, IL, USA). A *p*-value less than 0.05 and a CI of 95% were considered significant for all the analyses.

Results

Osteosarcoma of the upper extremities corresponded to approximately 3.7% of all bone cancers and 12% of osteosarcomas diagnosed in the US population during the study period. While osteosarcomas of the hand and wrist conformed the 0.3% of all bone cancers and 0.9% of all patients with osteosarcomas overall.

Most patients diagnosed with osteosarcoma of the upper extremities were younger than 21 years old (45.9%), white (76.5%), male (56.8%), and without comorbidity (90.4%). Regarding facility characteristics, Academic/Research program presented a higher percentage of diagnosed cases (17.7%), whereas a lower percentage of cases was found in Community Cancer programs (1%) (Table I).

Table II. *Tumor characteristics*.

	Total N=991 No.	%
Histology		
Osteosarcoma NOS*	662	66.8
Chondroblastic osteosarcoma	116	11.7
Fibroblastic osteosarcoma	56	5.7
Telangiectatic osteosarcoma	35	3.5
Osteosarcoma in Paget disease of bone	9	0.9
Small cell osteosarcoma	7	0.7
Central osteosarcoma	39	3.9
Intraosseous well differentiated osteosarcoma	5	0.5
Paraosteal osteosarcoma	48	4.8
Periosteal osteosarcoma	8	0.8
High grade surface osteosarcoma	6	0.6
Location		
Forearm, arm and shoulder	916	92.4
Hand and wrist	75	7.6
Tumor size		
≤8 cm	331	33.4
>8 cm	475	47.9
Unknown	185	18.7
Grade		
Low	100	10.1
High	637	64.3
Cell type not determined, not stated, not applicable	254	25.6
Stage		
Stage I	174	17.6
Stage II	399	40.3
Stage III	27	2.7
Stage IV	164	16.5
Unknown	227	22.9
Lymph nodes		
Negative	78	7.9
Positive	12	1.2
Not assessed	842	84.9
Unknown	59	6.0
Metastasis to lungs		
No	386	39.0
Yes	77	7.8
Unknown	528	53.3
Type of surgery		
None, autopsy only	205	20.7
Local tumor excision	64	6.5
Partial resection	45	4.5
Complete excision of the tumor with limb salvage	543	54.8
Amputation of limb	125	12.6
Unknown	9	0.9
Radiation		
No	918	92.6
Yes	58	5.9
Unknown	15	1.5
Chemotherapy		
No	200	20.2
Yes	772	77.9
Unknown	19	1.9

NOS: Not otherwise specified. *Included Osteogenic Sarcoma and Osteoblastic Sarcoma.

Table III. *Multivariate analysis of tumor factors associated with the hand and wrist osteosarcomas compared to osteosarcomas in the forearm, arm and shoulder.*

	OR	Confidence interval		*p*-Value
		Lower	Upper	
Age group				
<21 years old	1.00*	-	-	-
21-40 years old	1.02	0.26	4.04	0.97
41-60 years old	2.66	0.61	11.55	0.19
>61 years old	1.59	0.30	8.39	0.59
Gender				
Male	1.00*	-	-	-
Female	1.51	0.53	4.29	0.44
Histology				
Osteosarcoma NOS	1.00*	-	-	-
Chondroblastic osteosarcoma	3.03	0.80	11.55	0.10
Paraosteal osteosarcoma	0.22	0.02	2.88	0.25
Other types	0.21	0.02	1.76	0.15
Tumor size				
≤8 cm	1.00*	-	-	-
>8 cm	0.33	0.11	1.04	0.06
Grade				
Low	1.00*	-	-	-
High	0.13	0.02	0.84	0.03
Metastasis to lungs				
No	1.00*	-	-	-
Yes	0.39	0.05	3.35	0.39
Type of surgery				
Tumor excision with limb salvage (local, partial and complete tumor excision)	1.00*	-	-	-
Amputation of limb	1.39	0.26	7.32	0.70
Chemotherapy				
No	1.00*	-	-	-
Yes	3.17	0.53	18.81	0.20

OR: Odds Ratio; NOS: not otherwise specified. *Reference value.

The histology type of osteosarcoma most frequently diagnosed was osteosarcoma not otherwise specified (NOS), which included osteogenic and osteoblastic types (66.8%), followed by chondroblastic osteosarcoma (11.7%). Osteosarcomas were more commonly found in the forearm, arm, and shoulder (92.4 %), with high-grade (64.3%), stage II (40.3%), lymph node-negative (7.9%), and as tumors larger than 8 cm (47.9%) without metastasis to lungs (39.0%). Most patients with osteosarcomas of the upper extremities underwent surgery with complete excision of the tumor and limb salvage (54.8%), chemotherapy (77.0%), and without radiotherapy (92.6%) (Table II).

After analyzing the tumor characteristics of patients with osteosarcoma in the upper extremities according to their location, we found that osteosarcomas in the hand and wrist had a lower risk of being high grade compared with osteosarcomas in the forearm, arm, and shoulder (OR, 0.06; 95% CI=0.001-0.33; p=0.01). No significant differences were found in age, sex, histology, tumor size, metastasis to lungs, type of surgery, and chemotherapy between these two groups (Table III).

This study identified a 10-year OS of 51% in patients with osteosarcoma of the upper extremities. After comparing the survival curves by location in the upper extremities, we found a 10-year OS of 63% in patients with osteosarcomas of the hand and wrist and 50% in patients with osteosarcomas located in the forearm, arm, and shoulder (p=0.33) (Figure 1).

Discussion

To our knowledge, this is the largest study to determine the incidence of osteosarcomas of the upper extremities in the US population. Osteosarcoma of the hand and wrist is very rare; however, we found a higher incidence (0.9%) than previous studies. Okada *et al*. (4) reported an incidence of 0.18% for osteosarcoma of the hand from 1,681 patients with skeletal osteosarcomas, while Anninga *et al*. (5) found an

incidence of 0.5% out of 2,488 osteosarcoma cases. The higher incidence of osteosarcoma of the hand and wrist in our study may be due to the larger sample size.

Regarding patient characteristics in those with osteosarcoma of the upper extremities, we did not find the typical bimodal distribution according to age. Mirabello *et al*. (3) found a peak in the incidence of patients between 0 and 24 years, and a second peak in patients aged 60 years or older. Moreover, our study found that osteosarcomas of the upper extremities tended to appear more often in white men. Previous studies have described that osteosarcomas appear more frequently in white men when they are older, in contrast to osteosarcomas diagnosed at younger ages that are more often in black men (3, 9).

In addition, our study found that patients in Academic/ Research programs were more frequently diagnosed with osteosarcoma of the upper extremities compared to other programs. We believe that this finding may correspond to a higher suspicion for the disease and ability to perform laboratory and imaging tests for diagnosis in academic programs (10). Another explanation may be due to the symptoms that may overlap with other conditions. Osteosarcoma presents with variable dull pain and tenderness that may last several months and suddenly becomes more severe, but as the presentation usually is after a recent history of trauma, its diagnosis may be delayed (11).

Osteosarcomas follow different histologic patterns. According to the predominant type of matrix (osteoid, cartilage, or collagen), they are classified into osteoblastic, chondroblastic and fibroblastic (12). In long bone osteosarcomas, the osteoblastic type predominates and has the worse prognosis (13). In our study, we found that the most common histology type in the upper extremities was osteosarcoma NOS, which included osteogenic and osteoblastic types. Although we could not distinguish the most frequent between these two types of osteosarcoma, we were able to determine that histology type does not differ according to location of osteosarcoma.

The most common location of osteosarcomas in the upper extremities was the forearm, arm, and shoulder. The humerus accounts for 10% to 15% of all the cases of osteosarcoma, and it is considered the third most common location of primary osteosarcoma, (7) after the distal femur and proximal tibia (14). The proximal humerus is the most common location of osteosarcoma in the upper extremities, followed by the radius, ulna, metacarpals, and phalanges (15).

Negative prognostic factors for osteosarcoma survival include high grade, large tumor size, location in limbs, and presence of metastasis at time of presentation (16). Our study described the frequency of the prognostic factors in patients with osteosarcomas of the upper extremities. Most patients presented with high-grade tumors larger than 8 cm and without metastasis to lymph nodes or lungs.

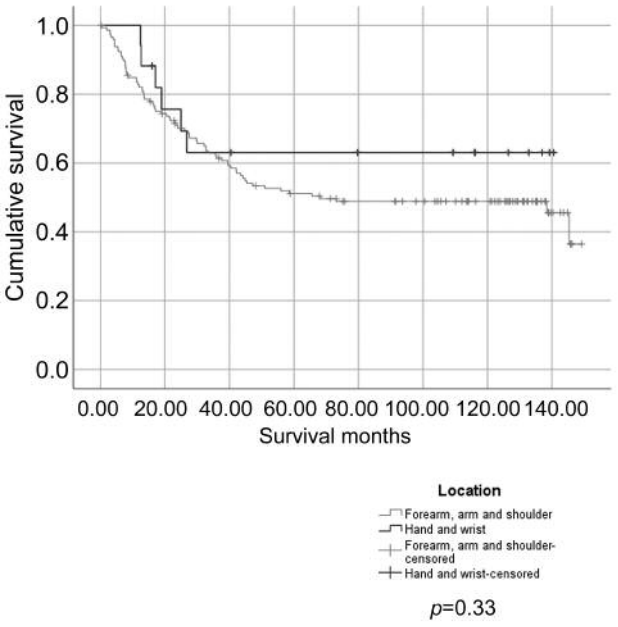

Figure 1. *Ten-year overall survival according to location in the upper extremities.*

Conventional treatment for osteosarcomas consists of a combination of surgery and chemotherapy (17). Surgical options include limb salvage and amputation. Although, there is controversy regarding the use of these procedures, both treatments are still being performed as the objective of both is complete resection of the tumor (18). Our study found that most of the patients with osteosarcomas of the upper extremities underwent complete excision of the tumor with limb salvage and chemotherapy. Limb salvage surgeries include resection and reconstruction of the limb, providing a safe treatment for patients with high-grade osteosarcoma (19). Development of new schemes of chemotherapy has prevented distant metastasis, controlling invasion, reducing the size of primary tumors and improving survival (2). Regarding other types of treatment, we found that a lower number of patients underwent radiotherapy. This could be due to the late disease stage found in some of these patients. Radiotherapy is recommended for patients with osteosarcoma that presents with inaccessible lesions, for those refusing surgery, or for whom surgical resection is not possible, and represents an alternative therapy to control the local tumor in the extremities (20).

When tumor characteristics were compared, we only found statistical difference in the grade of tumor. The lower risk of high-grade tumors in the hand and wrist suggests better prognosis and less aggressiveness compared to osteosarcomas of the forearm, arm, and shoulder. However, 10-year OS demonstrated no statistical difference between these two locations, possibly due to a similar proportion of patients with the same prognostic factors in both locations. The 10-year OS

of osteosarcoma of the upper extremities in the US population has not been described before. Colding-Rasmussen *et al*. (21) identified a 46% 10-year OS in patients with appendicular osteosarcomas in Denmark. This result is close to the 10-year OS of 51% in patients with osteosarcoma of the upper extremities in the US found in our study.

As a retrospective study, a few limitations of this NCDB study should be noted. In particular, our results were dependent on the information compiled in the NCDB, which was not always complete. In an effort to obtain the most accurate results possible, we excluded missing information that would have affected the models. Furthermore, the histology classification was also database-dependent, and the category 'osteosarcoma NOS' included different histology types. However, we were still able to determine the most frequent histology types. Despite these limitations, we believe this study reports a valuable analysis of the demographics and tumor characteristics of patients with osteosarcoma of the upper extremities. These findings determine the character of the disease and underscore the importance of prompt diagnosis.

In conclusion, this study identified that osteosarcomas of the upper extremities were more commonly located in the forearm, arm, and shoulder, with high-grade tumors larger than 8 cm and absence of metastasis. Most patients underwent surgery with limb reconstruction and chemotherapy. In addition, although osteosarcomas in the hand and wrist were less likely to be high grade compared with osteosarcomas located in the forearm, arm, and shoulder, we found no difference in the 10-year OS between the two locations. This study highlights the importance of the characteristics of osteosarcoma in the upper extremities that would help to better approach the disease.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

MTH, DJR and AJF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: MTH, AJF, ACS. Acquisition, analysis, or interpretation of data: MTH, ASP, AJF. Drafting of the manuscript: MTH, DJR, DB, AS. Critical revision of the manuscript for important intellectual content: RSE, HGC, SLM, MTH, ACS and AJF. Study supervision: AJF.

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