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What Factors Define Limb Salvage or Amputation Surgery in Osteosarcoma of the Upper Extremities?

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Abstract. *Background/Aim: Controversy exists between performing limb salvage or amputation to treat osteosarcoma of the upper extremities. Our aim was to review the characteristics associated with limb amputation due to osteosarcoma of the upper extremities. Patients and Methods: A descriptive study was performed by querying the National Cancer Database from January 1, 2004 to December 31, 2015. Statistical analysis was performed using chi-squared test and a multivariate logistic regression model. Results: A total of 777 patients diagnosed with osteosarcoma of the upper extremities who underwent surgery met the inclusion criteria. Patients between 61 and 80 years were less likely to undergo limb amputation. Moreover, facilities located in the South Atlantic region, and stage IV of the disease were factors independently positively associated with amputation. Conclusion: Patients in facilities located in the South Atlantic region and those with stage IV disease were more likely to undergo amputation.*

Osteosarcoma is the most common bone tumor, with a global incidence of three cases per million per year (1). Osteosarcomas in the upper extremities are rare, occupying the third most common location of primary osteosarcoma after the distal femur and the proximal tibia (2).

Due to the aggressive pattern of this tumor, the standard treatment has historically been amputation; however, the effectiveness of chemotherapy has resulted in improvement of survival rates and has allowed limb-salvage resection (3). Different factors decide the type of surgery to be performed. A limb-salvage surgery is preferred when it is possible to obtain negative margins through a wide-margin resection (4). Relative and absolute contraindications to limb-salvage surgery, such as neurovascular compromise, pathological fracture with hematoma extended beyond compartment boundaries, errant biopsy placement, tissue coverage problems, or severe infections in the surgical site, direct the decision to performing an amputational surgery (5). To date, as far as we are aware, no study has described other characteristics that may influence the type of surgery chosen for treatment of osteosarcomas of the upper extremities. This study describes and identifies patient, facility, and tumor characteristics that determine the type of surgical treatment of patients with osteosarcoma of the upper extremities in the United States.

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Patients and Methods

A retrospective cohort study was conducted by querying the National Cancer Database (NCDB) (6) for cases of osteosarcoma in the upper extremities diagnosed and treated between January 1, 2004, and December 31, 2015.

Inclusion and exclusion criteria. We excluded patients with diagnoses other than osteosarcoma, as well as those with osteosarcoma in locations other than the upper extremities. Additionally, patients who did not undergo surgery, or had missing data related to the type of surgery performed were excluded. Finally, 777 patients diagnosed with osteosarcoma in the upper extremities were considered for the study.

Variables. Independent variables included patient characteristics (age, sex, race, comorbidities, Hispanic origin, insurance, income, and education), facility characteristics (facility type, facility location, and setting), and tumor characteristics [tumor site, size, and American Joint Committee on Cancer (AJCC) 7th edition stage

(7)]. The dependent variable was type of surgery, including local resection with limb salvage or amputation of the limb. All missing values were excluded for the analysis.

Statistical analysis. A chi-squared analysis was performed to compare characteristics between patients who underwent tumor resection with limb salvage with those who underwent amputation of the limb. A multivariate logistic regression was performed to analyze the factors associated with amputation of the limb as surgical management. A value of $p<0.05$ was considered significant for the analysis. All data were analyzed using SPSS, version 25 (IBM, Armonk, NY, USA) software.

Results

A total of 125 (16.1%) patients with osteosarcoma of the upper extremity had an amputation of the limb and 652 (83.9%) patients underwent a local resection with limb salvage (Table I). Most of the patients with osteosarcoma of the upper extremity who underwent an amputation lived in areas where a high rate of people did not graduate from high school (38.4%), were White (71.2%) men (68%) younger than 21 years old (41.6%) with government insurance (48.8%) and an income between $38,000 and $47,999. Regarding facility characteristics, most were treated in Academic/Research programs (20.0%) and belonged to metropolitan areas (85.6%). Most tumors were located in the hand (92%), larger than 8 cm (66.4%), and in stage II of disease (45.6%).

Patients diagnosed between 61 and 80 years of age were less likely to undergo amputation of the limb [odds ratio (OR)=0.04; 95% CI=0.01-0.42; $p=0.01$] when compared to patients between 21 and 40 years old. On the other hand, patients with stage IV of the disease (OR=7.45; 95% CI=1.22-45.54; $p=0.03$) and treated in facilities located in the South Atlantic (OR=8.51; 95% CI=1.10-65.86; $p=0.04$) were more likely to have undergone an amputational surgery when compared to patients who underwent local resection with limb salvage (Table II). No statistical differences in sex, race, comorbidities, Hispanic origin, insurance, income, education, facility type, setting, tumor site, and tumor size were found.

Discussion

Osteosarcoma treatment consists of a combination of surgery and chemotherapy (8). A study by Simon *et al*. suggested the safety of performing a conservative surgery with limb salvage rather than amputation in patients with high-grade osteosarcoma (9). However, there are still controversies in the long-term outcomes regarding the type of surgery that should be performed (10). For instance, Rougraff *et al*. (11) reported a higher rate of local recurrence in patients with limb salvage even when they noticed that survival of patients treated with limb salvage or amputation was not different. On the other hand, Yin *et al*. (12) and Li *et al*. (13) found no significant difference in risk of local recurrence and 5-year overall survival between these types of surgery. Chemotherapy has helped to increase the survival of patients with these types of bone tumor (14), and as a result, limb salvage surgeries are commonly preferred thanks to the advantages after tumor resection in preserving functionality of the limb. To our knowledge, the factors associated with the decision between limb amputation and limb salvage in osteosarcoma of the upper extremities have not been analyzed. Our study found a greater likelihood for limb salvage surgery in patients between 61 and 80 years compared to younger patients. The type of treatment for elderly patients requires special evaluation because of existing comorbidities that may influence the clinical course and prognosis (15). Additionally, as metastasis is more common in this age group, most surgeons try to preserve the limb, reserving amputation for curative intent or palliative reasons. The surgeons' decision in this patient group was probably based on careful risk–benefit evaluation and evidence of studies supporting the use of limb-salvage surgery (16).

Our study also found that stage was the only tumor factor that influenced the type of surgery. We found that patients with osteosarcomas of AJCC disease stage IV had a higher likelihood of amputation over limb salvage. This is most likely related to the presence of metastasis at late stages of the disease. However, in the meta-analysis conducted by Xiaojuan Li *et al*. of patients with osteosarcomas in Enneking stage IIA and IIB, no significant difference between the two surgery methods was found; however, they found a high rate of local recurrence in five of 17 studies and a lower rate of metastatic occurrence in four of 17 studies in patients who underwent limb salvage surgery compared to amputation (13). Enneking staging system for malignant mesenchymal tumors considers surgical grade (G1, G2, G3), local extent (T, T1, T2), and presence or absence of metastasis (M0, M1) (17). Stage IIA and IIB include high-grade tumors without metastasis which are more likely to invade surrounding host tissue. We believe that other factors related to the biology of the disease, such as genomic complexity and instability and intra- and intertumoral heterogeneity, may influence the discrepancies in the outcomes between studies (18). For that reason, we suggest that further studies comparing the recurrence and survival between types of surgeries for osteosarcoma patients should be conducted. In addition, since the benefits of performing limb-salvage surgeries are unclear, the decision on the type of surgery in osteosarcoma of the upper extremities should be guided based on the patient response to chemotherapy, although the benefit from performing a limb-salvage surgery in patients with AJCC disease stage IV seems to be secure.

We did not find any association with sex, race, Hispanic origin, insurance, income, education, facility type, setting,

Table I. *Patient demographics and tumor characteristics*.

		Surgical treatment				
		Local resection with limb salvage		Amputation of limb		*p*-Value
		n	%	n	%	
Total		652	830.9	125	160.1	
Age	<21 Years	311	470.7	52	410.6	0.03
	21-40 Years	172	260.4	42	330.6	
	41-60 Years	101	150.5	13	100.4	
	61-80 Years	61	90.4	13	100.4	
	≥81 Years	7	10.1	5	40.0	
Sex	Male	359	550.1	85	680.0	0.01
	Female	293	440.9	40	320.0	
Race	Race	507	770.8	89	710.2	
	White	115	170.6	33	260.4	0.03
	Others	30	40.6	3	20.4	
	Missing data					
Comorbidities	No	590	900.5	114	910.2	0.80
	Yes	62	90.5	11	80.8	
Origin	Non-Spanish, non-Hispanic	540	820.8	102	810.6	0.32
	Hispanic, Spanish origin	81	120.4	20	16	
	Missing data	31	40.8	3	20.4	
Insurance	Not insured	24	30.7	8	60.4	<0.001
	Private	400	610.3	54	430.2	
	Government	207	310.7	61	480.8	
	Missing data	21	30.2	2	10.6	
Income	≥$63,000	204	310.3	27	210.6	0.08
	$48,000-$62,999	163	250.0	31	240.8	
	$38,000-$47,999	137	210.0	37	290.6	
	<$38,000	142	210.8	28	220.4	
	Missing data	6	0.9	2	10.6	
Education‡	<7%	154	230.6	25	20	0.01
	7-12.9%	192	290.4	26	200.8	
	13-20.9%	155	230.8	48	380.4	
	≥21%	145	220.2	24	190.2	
	Missing data	6	00.9	2	10.6	
Facility type	Community Cancer Programs	39	60.0	8	60.4	0.44
	Academic/Research Program	110	160.9	25	20	
	Integrated Network Cancer Program	23	30.5	2	10.6	
	Missing data	480	730.6	90	72	
Facility location	New England and Middle Atlantic	28	40.3	6	40.8	0.81
	South Atlantic	33	50.1	10	8	
	East Central (North and South)	50	70.7	8	60.4	
	West Central (North and South)	26	40.0	6	40.8	
	Mountain	15	20.3	2	10.6	
	Pacific	20	30.1	3	20.4	
	Missing data	480	730.6	90	72	
Setting	Metropolitan	523	800.2	107	850.6	0.15
	Urban	95	140.6	10	8	
	Rural	18	20.8	4	30.2	
	Missing data	16	20.5	4	30.2	
Tumor site	Hand	610	930.6	115	92	0.52
	Forearm, arm and shoulder	42	60.4	10	8	
Tumor size	≤8 cm	249	380.2	25	20	<0.001
	>8 cm	321	490.2	83	660.4	
	Missing data	82	120.6	17	130.6	
Stage[a]	I	133	200.4	15	12	0.01
	II	305	460.8	57	450.6	
	III	20	30.1	5	4	
	IV	74	110.3	29	230.2	
	Missing data	120	180.4	19	150.2	

‡Percentage of people without a high school diploma within the patient's zip code. [a]According to the American Joint Committee on Cancer 7th edition (7).

Table II. *Multivariable logistic regression model for amputation of the limb.*

	OR	CI	*p*-Value
Age			
21-40 Years	1.00*		
41-60 Years	0.15	0.01-5.44	0.30
61-80 Years	0.04	0.01-0.42	0.01
≥81 Years	0.10	0.01-1.07	0.06
Gender			
Male	1.00*		
Female	0.55	0.15-1.97	0.36
Race			
White	1.00*		
Other	1.70	0.28-10.17	0.56
No	1.00*		
Comorbidities			
Yes	0.57	0.11-2.88	0.49
Origin			
Non-Spanish, non-Hispanic	1.00*		
Hispanic, Spanish origin	0.25	0.02-3.92	0.32
Insurance			
Not insured	1.00*		
Private	0.89	0.05-15.57	0.94
Government	0.51	0.02-10.70	0.67
Income			
≥$63,000	1.00*		
$48,000-$62,999	0.94	0.16-5.65	0.94
$38,000-$47,999	1.00	0.13-7.89	>0.99
<$38,000	0.35	0.03-4.38	0.42
Education‡			
<7%	1.00*		
7-12.9%	1.37	0.19-9.68	0.75
13-20.9%	5.47	0.60-50.08	0.13
≥21%	1.54	0.08-31.06	0.78
Facility type			
Community Cancer Programs	1.00*		
Academic/Research Program	2.75	0.53-14.15	0.23
Integrated Network Cancer Program	0.22	0.01-6.11	0.37
Facility location			
South Atlantic	8.51	1.10-65.86	0.04
East Central (North and South)	2.40	0.33-17.42	0.39
West Central (North and South)	2.83	0.32-24.93	0.35
Mountain	6.89	0.56-84.49	0.13
Pacific	8.14	0.81-81.88	0.08
Setting			
Metropolitan	1.00*		
Urban	1.24	0.27-5.74	0.78
Rural	1.91	0.05-73.69	0.73
Tumor site			
Hand	1.00*		
Forearm, arm and shoulder	2.35	0.25-22.19	0.46
Tumor size			
≤8 cm	1.00*		
>8 cm	2.79	0.79-9.89	0.11
Stage[a]			
I	1.00*		
II	0.78	0.16-3.68	0.75
III	0.81	0.04-16.69	0.89
IV	7.45	1.22-45.54	0.03

OR: Odds ratio; CI: confidence interval. *Reference value. ‡Percentage of people without a high school diploma within the patient's zip code. [a]According to the American Joint Committee on Cancer 7th edition (7).

tumor site, and tumor size in performing either type of surgery, perhaps due to the low frequency of patients with osteosarcomas of the upper extremities.

A few limitations of this retrospective database 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 those with missing information; although the sample size decreased, this study evaluated the highest number of patients with osteosarcoma of the upper extremities to date. Despite these limitations, we believe this study reports a valuable analysis of the factors associated with type of surgery performed.

In conclusion, our study found that osteosarcomas of the upper extremities are more likely to be surgically treated by amputation of the limb rather than limb-salvage surgery when they have AJCC disease stage IV. This study highlights the importance of disease stage in the surgical treatment of osteosarcoma of the upper extremities.

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 article: MTH, DJR, DB, AS. Critical revision of the article for important intellectual content: BR, SLM, MTH, ACS and AJF. Study supervision: AJF.

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