Which Factors Affect Survival in Patients With Upper Limb Osteosarcoma?

DAVID J. RESTREPO¹, MARIA T. HUAYLLANI¹, DANIEL BOCZAR¹, ANDREA SISTI¹,
AARON C. SPAULDING², RICKEY E. CARTER², STEVEN L. MORAN³,
ALEXANDER S. PARKER⁴, GALEN PERDIKIS⁵ and ANTONIO J. FORTE¹

¹*Division of Plastic Surgery and Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Jacksonville, FL, U.S.A.;*

²*Department of Health Science Research, Mayo Clinic, Jacksonville, FL, U.S.A.;*

³*Division of Plastic Surgery, Mayo Clinic, Rochester, MN, U.S.A.;*

⁴*Office of Research Affairs, University of Florida, College of Medicine, Jacksonville, FL, U.S.A.;*

⁵*Department of Plastic Surgery, Vanderbilt University Medical Center, Nashville, TN, U.S.A.*

Abstract. *Aim: The purpose of this study was to identify patient-, facility-, disease-, and treatment-specific characteristics that increase mortality in patients with upper limb osteosarcoma. Patients and Methods: The National Cancer Data Base (NCDB) was queried for bone cancer. With Cox regression, the demographic, facility, tumor-specific and treatment characteristics were analyzed to identify factors that increased mortality. Results: Cox regression model showed that patients older than 40 years had a significantly higher likelihood of dying from upper limb osteosarcoma than those aged 0-14 years [hazard ratio (HR)=4.12, 95% confidence interval (CI)=2.261-7.508]. Patients with an income of \$38,000-47,999 (HR=3.335, 95%CI=1.694-6.57) or less than \$38,000 (HR=2.41, 95%CI=1.098-5.288) were also at greater risk of dying from their tumor. Patients who received radiation therapy (HR=2.457, 95%CI=1.056-5.717) had a higher likelihood of dying than patients who did not undergo this therapy. Conclusion: Age, gender, income, education, stage at diagnosis, radiation therapy and type of surgery seem to increase mortality from upper limb osteosarcoma.*

Considered the most frequent primary malignant bone tumor type, osteosarcoma is an aggressive malignancy that mostly metastasizes to the lung (1). It is an uncommon pathology with a yearly incidence of 1.5 to 4 cases per million people (2).

Correspondence to: Antonio Jorge Forte, MD, Ph.D., Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, Florida 32224, U.S.A. Tel: +1 9049532073, e-mail: ajvforte@yahoo.com.br

Key Words: Osteosarcoma, upper limb, survival, survivors, treatment.

Before the introduction of chemotherapy treatment, osteosarcoma was considered incurable because, even when a surgical resection was thought to have successfully removed the tumor, metastasis appeared in 80-90% of patients (3). A systematic literature review showed that 5-year survival without chemotherapy was 16% [95% confidence interval (CI)=9-23%], increasing to 70% when treated with three or more chemotherapeutic agents. Current treatment for osteosarcoma has not changed much in the past 30 years, and survival rates have plateaued. New chemotherapeutic agents have not proven to be substantially better than the current treatment (4). Since no new therapy has emerged, we wondered if, from a public health standpoint, mortality for this devastating disease can be reduced. The purpose of our study was to identify patient, facility, disease, and treatment characteristics that increase mortality in patients with upper limb osteosarcoma.

Patients and Methods

The National Cancer Database (NCDB), jointly sponsored by the American College of Surgeons and the American Cancer Society, collects data from approximately 70% of patients who were newly diagnosed with cancer in the United States (5). Certified Tumor Registrars are trained to submit information from patient records to the database. Information is then revised for accuracy (5). Our retrospective cohort analysis was exempt from Institutional Review Board evaluation due to the unidentified population-based nature of the NCDB.

In this study, we included male and female patients, aged 2 years or older, diagnosed with osteosarcoma of the upper extremities at any stage of disease between January 31st, 2004 and December 31st, 2015. We excluded patients with non-osteosarcoma bone tumors and those with osteosarcomas located in sites other than the upper extremities. We also excluded patients who were diagnosed between 2011 and 2015 because they lack a complete a 5-year

follow-up because the NCDB data ended on December 31, 2015. Inclusion and exclusion criteria are illustrated in Figure 1. Our primary outcome was patient survival, which the NCDB defines as the number of months from the date of diagnosis to the time of death, when patients were lost to follow-up, or the last date of our study. It is important to note that the NCDB does not collect specific cancer survival information.

Our primary independent variables included the following demographic covariates: Age (categorized by group), race, sex, insurance status [private, government (Medicare and Medicaid) or uninsured], income (estimated by average income in the zip code of residence), education level (estimated by percentage of patients with no high school diploma in the zip code of residence), and population density. Age was categorized from 0-14 years (pediatric), 15-39 (adolescent and young adult) and 40 years or older (adult) based on a previous study that categorized age groups in this manner (6). We also included disease characteristics [namely, tumor site, stage of disease and Charlson–Deyo score (comorbidity index)], and treatment characteristics (namely, chemotherapy, radiation surgery, and type of surgery if not radiation). These covariates were selected because they characterize the patient, facility, disease, and treatment variables that might have an impact on patient mortality.

We did not include facility characteristics such as type and location because more than 70% of patients were lacking such information. This is because the NCDB does not include facility type and facility location information for patients who are 39 years or less in order to protect their identity. Because osteosarcoma is a disease most frequent in young patients, more than 70% of the population fell in that age group, forcing us to exclude these variables.

We examined the survival differences among patients diagnosed with upper extremity osteosarcoma. A multivariate Cox regression model was used to analyze the impact of patient, disease, and treatment characteristics on the odds of mortality after adjusting for the mentioned covariates. Facility characteristics were not included in our multivariate analysis due to the large percentage of missing information for both covariates. Whether the patient underwent surgery or not was also excluded from the multivariate model due to an insufficient number of patients in the no-surgery group. Patients with missing data were excluded from regression models. Significance was set at $p < 0.05$. Statistical analysis was performed using SPSS 25.0 statistical software (IBM, Armonk, NY, USA).

Results

A total of 26,722 patients diagnosed with bone cancer were identified in the NCDB during the study period, and 591 met inclusion criteria for our study. Mean age ($\pm$ SD) was 30.74 ± 21.18 years; 444 (76.5%) patients were White and 123 (19.3%) were non-white (Black, Asian, or Native American). Demographic, facility, and disease characteristics are further described in Table I.

In the adjusted Cox regression model (see Table II), we found significant differences in patient-specific characteristics. Our results show that adult patients had significantly higher a higher likelihood of dying from upper limb osteosarcoma than pediatric patients [hazard ratio (HR)=4.12, 95% CI=2.261-7.508]. Female patients (HR=0.608, 95% CI=0.408-0.905)

Figure 1. Patient selection criteria.

presented a lower likelihood of death than male patients. When adjusted for confounders, income level showed a significantly higher likelihood of dying for patients with income between \$38,000-\$47,999 (HR=3.335, 95%CI=1.694-657) or less than \$38,000 (HR=2.41, 95%CI=1.098-5.288). Our results also showed that patients that lived in a zip code in which 13-20.9% (HR=0.459, 95%CI=0.221-0.953) or more than 21% (HR=0.304, 95%CI=0.126-0.731) of the population did not graduate high school, had a lower likelihood of dying when compared to patients that lived in a zip code in which under 7% of the population did not graduate high school. No statistically significant differences were found by insurance and population density.

Tumor-specific characteristics were also shown to affect the survival of patients independently. When compared to those with stage 1 disease, those with stage 2 (HR=4.362, 95%CI=1.8-10.569), stage 3 (HR=8.669, 95%CI=2.612-28.764) and stage 4 (HR=14.39, 95%CI=5.567-37.192) disease had a higher likelihood of dying of upper limb osteosarcoma. Interestingly, comorbidities (assessed with the Charlson–Deyo score) had no statistically significant impact on mortality.

The type of treatment that a patient received was also found to affect mortality in patients with upper limb osteosarcoma. Patients treated with chemotherapy (HR=0.891, 95%CI=0.476-1.667) had no significant difference in survival when compared

Table I. Demographic characteristics of patients (n=591).

Characteristic	Subgroup	N	%
Age	0-14 Years	141	23.9
	15-39 Years	279	47.2
	≥40 Years	171	28.9
	Missing data	0	0
Race	White	444	75.1
	Other*	123	20.8
	Missing data	24	4.1
Gender	Male	334	56.5
	Female	257	43.5
	Missing data	0	0
Insurance	Private	32	5.4
	Government	334	56.5
	Not insured	192	32.5
	Missing data	33	5.6
Average income in zip code	>\$63,000	170	28.8
	\$48,000-62,999	140	23.7
	\$38,000-47,999	131	22.2
	<\$38,000	138	23.4
	Missing data	12	2
% Without HSD in zip code	<7.0%	138	23.4
	7.0-12.9%	160	27.1
	13.0-20.9%	153	25.9
	>21.0%	128	21.7
	Missing data	12	2
Population density	Metropolitan	473	80
	Urban	82	13.9
	Rural	18	3
	Missing data	18	3
Tumor site	Forearm, arm, shoulder and joints	541	91.5
	Hand, wrist and joints	50	8.5
	Missing data	0	0
	Missing data	0	0
AJCC stage	I	73	12.4
	II	233	39.4
	III	21	3.6
	IV	86	14.6
	Missing data	178	30.1
Charlson–Deyo score	0	535	90.5
	≥1	55	9.3
	Missing data	1	0.2
Chemotherapy	No	115	19.5
	Yes	465	78.7
	Missing data	11	1.9
Radiation	No	542	91.7
	Yes	36	6.1
	Missing data	13	2.2
Surgery	No	105	17.8
	Yes	460	77.8
	Missing data	31	3.1
Type of surgery	Local excision with limb salvage	369	62.4
	Amputation of limb	86	14.6
	Missing data	136	23

HSD: High school diploma; AJCC: American Joint Committee on Cancer. *Black, Asian and Native American.

Table II. Hazard ratios of dying from upper limb osteosarcoma.

Factor	HR	95% CI	p-Value
Age	1		
	0-14 years	1.319	0.732-2.376
	15-39 years	4.12	2.261-7.508
	≥40 years		<0.001
Race	1		
	White	0.742	0.445-1.238
	Others*		0.253
Sex	1		
	Male	0.608	0.408-0.905
	Female		0.014
Insurance	1		
	Private	1.278	0.527-3.101
	Government	1.988	0.785-5.036
	Not insured		0.147
Average income in zip code	1		
	≥\$63,000	1.565	0.796-3.075
	\$48,000-62,999	3.335	1.694-6.567
	\$38,000-47,999	2.41	1.098-5.288
Without HSD in zip code	1		
	<7.0%	0.6	0.314-1.146
	7.0-12.9%	0.459	0.221-0.953
	13.0-20.9%	0.304	0.126-0.731
	≥21.0%		0.008
Population density	1		
	Metropolitan	0.834	0.471-1.476
	Urban	0.792	0.208-3.018
Tumor site	1		
	Forearm, arm, shoulder and joints	0.437	0.132-1.446
	Hand, wrist and joints		0.175
AJCC stage	1		
	I	4.362	1.8-10.569
	II	8.669	2.612-28.764
	III	14.39	5.567-37.192
Charlson–Deyo score	1		
	0	1.431	0.766-2.672
	≥1		0.261
Chemotherapy	1		
	No	0.891	0.476-1.667
	Yes		0.718
Radiation	1		
	No	2.457	1.056-5.717
	Yes		0.037
Type of surgery	1		
	Local excision with limb salvage	1.902	1.18-3.064
	Amputation of limb		0.008

CI: Confidence interval; HR: hazard ratio; HSD: high school diploma; AJCC: American Joint Committee on Cancer. *Black, Asian and Native American.

to patients who did not receive chemotherapy. However, for patients who received radiation therapy (HR=2.457, 95%CI=1.056-5.717) the likelihood of dying was significantly increased when compared to patients who did not receive

radiation therapy. For patients who underwent a limb amputation (HR=1.902, 95% CI=1.18-3.064), the likelihood of dying was also increased when adjusted for confounders.

Discussion

Osteosarcoma of the upper extremities is an uncommon type of cancer that has a bimodal peak incidence, presenting more commonly in adolescents and patients older than 60 years. Its 5-year survival rate has increased significantly with the introduction of chemotherapeutic agents into the treatment. However, for the past 30 years, survival has not improved, and new drugs have failed to reduce the mortality of osteosarcoma. The importance of this study relies on its public health approach instead of a pharmacological or surgical approach. It was our intent to identify factors that affect mortality and which can be modified from a public health point of view.

The results of this study showed that osteosarcoma of the upper extremities led to significantly higher mortality in adult patients, even when adjusted for factors such as comorbidities and stage. The results of this study are congruent with a previous study that showed poor prognosis in elderly patients (7). The second peak of incidence of osteosarcoma occurs after 60 years of age and is more commonly a secondary malignancy, usually associated with Paget disease or previous radiation (8). Osteosarcoma in elderly patients is known to present more commonly on the axial skeleton (6), which has been demonstrated to have a higher incidence of metastasis at diagnosis (9). This tumor site location has been proposed as one of the explanations for worst prognosis; however, our study excluded patients with axial skeleton osteosarcoma. Another possible reason for increased mortality in elderly patients with osteosarcoma is a lower response to chemotherapy, which is known to be one of the major predictive factors of survival (10). It has been stated that 90% or more tumor necrosis with chemotherapy treatment is a sign of good prognosis (10). There is no established standard treatment for this population and administering chemotherapy is still controversial (7). Furthermore, older patients have a lower renal clearance than children and therefore might present a lower tolerance to methotrexate treatment (11).

Our results also showed that the estimated average household income of patients had a statistically significant effect on survival. This was particularly true for the groups with a lower income (\$38,000-47,999 and <\$38,000). Several studies have previously demonstrated for other types of cancer that socioeconomic status can be deleterious to survival, particularly if the patient belongs to the lower income groups (12). Although the causality of these findings is hard to assess, it is likely that lower income, education, awareness, access to specialty care, adherence to treatment,

time to diagnosis and compliance with long-term surveillance are factors that contribute to the lower survival of these patients (13). A previous study of NCDB data showed that patients with high-grade osteosarcoma with a low socioeconomic status had diminished overall survival (14).

Regarding patient race, our results showed no significant difference in survival when adjusting for confounders. This is not congruent with a previous study on Ewing sarcoma that showed that factors such as ethnicity to have a significant impact on overall survival (63 months for White non-Hispanic, and 23 months for Hispanic) (15). When studying breast cancer survival, race has also been shown to be a significant prognostic factor that negatively affects survival for minorities (16). Correlations between racial minorities with lower income and education average have shown that poorer outcomes in racial minorities can be due to socioeconomic disparities rather than true biological disparities (16). Considering that previous studies have found racial disparities in patients with Ewing sarcoma and breast cancer, it is possible that no disparities were found in our study due to a substantial number of patients with missing information, thereby reducing the power of the study.

Not surprisingly, we found that patients diagnosed with higher stage disease had higher mortality. This is true for most cancer types and stage is commonly used as a predictor of prognosis. The significance of this finding relies on the fact that if early detection, patient awareness, and education can be improved, we a significant decrease in mortality in patients with upper limb osteosarcoma could potentially be achieved.

Unlike Ewing sarcoma, conventional osteosarcoma (except the rare small-cell variant) is believed to be relatively resistant to radiotherapy (17). Radiotherapy is not recommended as adjuvant therapy or as replacement for surgery (18). It can be considered in patients who refuse or are not candidates for surgery due to comorbidities or anatomical location of the tumor (18). The results of this study show that patients with upper extremity osteosarcoma who received radiation therapy were more likely to die than patients that did not. As mentioned previously, this treatment is only used in patients who, for whatever reason, are not candidates for complete surgical excision of the tumor. This concords with our findings for our cohort, which had a higher proportion of patients with stage 3 and stage 4 disease in the group that received radiotherapy when compared to the group without radiotherapy. When given radiotherapy, it is possible that most of these patients were beyond a curable stage of cancer.

Our study has several limitations. Due to the retrospective nature using a large national database, we were unable to verify the accuracy of the data. A large proportion of patient records were missing information on facility type and location, causing us to remove these variables from multivariate

analysis. Furthermore, education and income levels were based on averages in the zip code of residence rather than those of the actual patient, which leads to assumptions that are not necessarily true. Moreover, the NCDB does not include information on response to chemotherapy, which is an important factor used to determine prognosis in this disease.

Osteosarcoma of the upper extremities is an uncommon disease with a mortality that has not changed significantly in the past 30 years. Our analysis showed that age, gender, income, education, stage at diagnosis, radiation therapy and type of surgery seem to affect the mortality of patients with this condition. From a public health stand point, some of these factors can be addressed and, therefore, efforts should be made to reduce the mortality of upper extremity osteosarcoma.

Conflicts of Interest

No Authors present conflicts of interest in regard to this study.

Authors' Contributions

All Authors contributed to the study design, commented on previous versions of the article, read and approved the final article. Material preparation, data collection and analysis were performed by DJR, ACS and AJF. The first draft of the article was written by DJR and MTH.

References

- Wang X, Zheng H, Shou T, Tang C, Miao K and Wang P: Effectiveness of multi-drug regimen chemotherapy treatment in osteosarcoma patients: A network meta-analysis of randomized controlled trials. *J Orthop Surg Res* 12(1): 52, 2017. PMID: 28356114. DOI: 10.1186/s13018-017-0544-9
- Kumar R, Kumar M, Malhotra K and Patel S: Primary osteosarcoma in the elderly revisited: Current concepts in diagnosis and treatment. *Curr Oncol Rep* 20(2): 13, 2018. PMID: 29492676. DOI: 10.1007/s11912-018-0658-1
- Friedman MA and Carter SK: The therapy of osteogenic sarcoma: Current status and thoughts for the future. *J Surg Oncol* 4(5): 482-510, 1972. PMID: 4566220.
- Senerchia AA, Macedo CR, Ferman S, Scopinaro M, Cacciavillano W, Boldrini E, Lins de Moraes VL, Rey G, de Oliveira CT, Castillo L, Almeida MT, Borsato ML, Lima E, Lustosa D, Barreto JH, El-Jaick T, Aguiar S, Brunetto A, Greggiani L, Cogo-Moreira H, Atallah A and Petrilli AS: Results of a randomized, prospective clinical trial evaluating metronomic chemotherapy in nonmetastatic patients with high-grade, operable osteosarcomas of the extremities: A report from the Latin American Group of osteosarcoma treatment. *Cancer* 123(6): 1003-1010, 2017. PMID: 28263383. DOI: 10.1002/cncr.30411
- Bilimoria KY, Stewart AK, Winchester DP and Ko CY: The National Cancer Data Base: A powerful initiative to improve cancer care in the United States. *Ann Surg Oncol* 15(3): 683-690, 2008. PMID: 18183467. DOI: 10.1245/s10434-007-9747-3
- Iwata S, Ishii T, Kawai A, Hiruma T, Yonemoto T, Kamoda H, Asano N and Takeyama M: Prognostic factors in elderly osteosarcoma patients: A multi-institutional retrospective study of 86 cases. *Ann Surg Oncol* 21(1): 263-268, 2014. PMID: 23975321. DOI: 10.1245/s10434-013-3210-4
- Nishida Y, Isu K, Ueda T, Nishimoto Y, Tsuchiya H, Wada T, Sato K, Tsukushi S and Sugiura H: Osteosarcoma in the elderly over 60 years: A multicenter study by the Japanese Musculoskeletal Oncology Group. *J Surg Oncol* 100(1): 48-54, 2009. PMID: 19384906. DOI: 10.1002/jso.21287
- Ottaviani G and Jaffe N: The epidemiology of osteosarcoma. *Cancer Treat Res* 152: 3-13, 2009. PMID: 20213383. DOI: 10.1007/978-1-4419-0284-9_1
- Bielack SS, Wulff B, Delling G, Gobel U, Kotz R, Ritter J and Winkler K: Osteosarcoma of the trunk treated by multimodal therapy: Experience of the Cooperative Osteosarcoma Study Group (COSS). *Med Pediatr Oncol* 24(1): 6-12, 1995. PMID: 7968796.
- Joo MW, Kang YK, Yoo CY, Cha SH and Chung YG: Prognostic significance of chemotherapy-induced necrosis in osteosarcoma patients receiving pasteurized autografts. *PLoS One* 12(2): e0172155, 2017. PMID: 28196121. DOI: 10.1371/journal.pone.0172155
- Yang Y, Wang X, Tian J and Wang Z: Renal function and plasma methotrexate concentrations predict toxicities in adults receiving high-dose methotrexate. *Med Sci Monit* 24: 7719-7726, 2018. PMID: 30369593. DOI: 10.12659/MSM.912999
- Melvan JN, Sancheti MS, Gillespie T, Nickleach DC, Liu Y, Higgins K, Ramalingam S, Lipscomb J and Fernandez FG: Nonclinical factors associated with 30-day mortality after lung cancer resection: An analysis of 215,000 patients using the National Cancer Data Base. *J Am Coll Surg* 221(2): 550-563, 2015. PMID: 26206651. DOI: 10.1016/j.jamcollsurg.2015.03.056
- Crawford SM, Sauerzapf V, Haynes R, Forman D and Jones AP: Social and geographical factors affecting access to treatment of colorectal cancer: A cancer registry study. *BMJ Open* 2(2): e000410, 2012. PMID: 22535788. DOI: 10.1136/bmjopen-2011-000410
- Miller BJ, Gao Y and Duchman KR: Socioeconomic measures influence survival in osteosarcoma: An analysis of the National Cancer Data Base. *Cancer Epidemiol* 49: 112-117, 2017. PMID: 28601784. DOI: 10.1016/j.canep.2017.05.017
- Koohbanani B, Han G, Reed D, Zhao Q, Yi D, Henderson-Jackson E and Bui MM: Ethnicity and age disparities in Ewing sarcoma outcome. *Fetal Pediatr Pathol* 32(4): 246-252, 2013. PMID: 23043418. DOI: 10.3109/15513815.2012.721480
- Newman LA and Kaljee LM: Health disparities and triple-negative breast cancer in African American women: A review. *JAMA Surg* 152(5): 485-493, 2017. PMID: 28355428. DOI: 10.1001/jamasurg.2017.0005
- Stein B, Cavazzana A and Kinsella TJ: Small-cell osteosarcoma: Correlation of *in vitro* and clinical radiation response. *Int J Radiat Oncol Biol Phys* 15(5): 1233-1238, 1988. PMID: 3182355.
- DeLaney TF, Park L, Goldberg SI, Hug EB, Liebsch NJ, Munzenrider JE and Suit HD: Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys* 61(2): 492-498, 2005. PMID: 15667972. DOI: 10.1016/j.ijrobp.2004.05.051

Received July 26, 2019

Revised August 8, 2019

Accepted August 9, 2019