



Rural patients are at risk for increased stage at presentation and diminished overall survival in osteosarcoma

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ABSTRACT

Background: There is an undefined relationship between access to regional referral centers and whether the eventual oncologic outcomes are influenced by distance, travel time, or residence in a rural community.

Methods: We used the Surveillance, Epidemiology and End Results (SEER) Program Database to capture all cases of high-grade osteosarcoma from 1990 to 2014 in Iowa, Utah, and New Mexico. Using univariate, Kaplan Meier survival analysis, and multivariate Cox proportional hazards modeling we analyzed patient and tumor characteristics.

Results: A total of 476 patients met the study criteria. There was an increased incidence of metastases for patients residing in a county with a greater than 2-h drive to the nearest comprehensive cancer center ($p = 0.021$). Individuals residing in “rural” counties and “very rural” counties showed decreased 5-year survival ($p = 0.007$ and 0.003 , respectively) when compared to those living in areas of higher population density. A multivariate regression analysis showed that the presence of metastasis (HR = 2.78 [95% CI: 1.88–4.10], $p < 0.0001$) and rural status (HR = 1.58 [95% CI: 1.03–2.43], $p = 0.037$) were risk factors for mortality when controlling for size of the tumor.

Conclusion: The travel time to the nearest comprehensive center was associated with an increased incidence of metastasis on presentation in patients with osteosarcoma. Metastasis and rural status were independent risk factors for mortality. This investigation suggests that individuals living in rural counties may experience barriers to presentation, treatment, or surveillance that are not present in areas with a higher population density.

1. Introduction

Osteosarcoma is the most common primary sarcoma of bone and affects patients of all ages [1]. The standard of care for high-grade non-metastatic osteosarcoma requires a multidisciplinary approach by specialized medical and orthopaedic oncologists, and consists of treatment with neoadjuvant and adjuvant chemotherapy and complete surgical resection of the primary tumor, either by limb salvage or amputation [2,3]. The 5-year survival rate approaches 70% in patients with localized disease and 20% in patients with metastasis [4,5]. This number has not improved within the last 20 years [5,6].

Sarcoma is a rare form of malignancy, accounting for 1% of all cancer diagnoses, and there are issues of patient access and facility volume that may be important. Patients in rural areas may live at great distances from specialty referral centers with experience managing the multidisciplinary aspects of sarcoma care. These patients may be at risk for adverse outcomes because of logistic challenges causing diagnostic delays, missed appointments, fragmented systemic treatment, and

delayed recognition of complications, or by receiving treatment at a facility that has limited experience and may result in suboptimal outcomes. Higher volume centers have been shown to have improved outcomes for rare cancers requiring specialized surgical treatment [7–12].

Currently, there is an undefined relationship between access to regional referral centers and whether the eventual oncologic outcomes are influenced by distance, travel time, or residing in a rural community. Prior work established that patients with osteosarcoma who live in counties with lower socioeconomic status are more likely to present with metastatic disease [13]. In other forms of cancer there are conflicting results regarding rural versus urban populations and their survival outcomes, but many studies found that increased distance from specialty care results in worse patient outcomes [14–18]. Patients who travel more than 50 miles to a hospital have a more advanced stage at diagnosis, lower adherence to treatments, and worse prognosis [15,15,16,17,18]. These studies have looked at cancers with relatively high incidence. There is currently a lack in analysis of distance to

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specialty care for rarer forms of cancer like osteosarcoma.

This study investigated if patients with osteosarcoma who reside in rural counties or at greater distances removed from comprehensive cancer centers experience higher stage at presentation, larger tumors at presentation, or diminished overall survival.

2. Methods

2.1. Data source

We used the Surveillance, Epidemiology and End Results (SEER) Program Database as our primary data source. This commonly used tool for rare cancer analysis collects data from seventeen geographically variable United States populations. These registries represent approximately 26% of the U.S. population. Selection criteria for this study included patients of all ages, race, and sex with high-grade osteosarcoma diagnosed from 1990 to 2014 residing in states with low population densities (bottom 50% based on 2010 US Census data). In the SEER program database, this included the states of New Mexico, Utah, and Iowa [19]. The histologic subtypes considered high-grade osteosarcoma included: 9180/3 osteosarcoma nos, 9181/3 chondroblastic osteosarcoma, 9182/3 fibroblastic osteosarcoma, 9183/3 telangiectatic osteosarcoma, 9184/3 osteosarcoma in Paget disease of bone, 9185/3 small cell osteosarcoma, 9186/3 central osteosarcoma, 9194/3 high grade surface osteosarcoma. Patients with multiple primary tumors were excluded which left only those with the single cancer diagnosis of osteosarcoma. The time period of 1990–2014 was chosen because it reflected a period of time in which survival outcomes have remained relatively unchanged in the treatment of metastatic osteosarcoma and the standard of care consisted of MRI imaging, neoadjuvant and adjuvant Adriamycin-based chemotherapy, and limb-sparing surgical resection [20].

2.2. Measures

Patient demographic variables included age, sex, and race. Patient outcome variables of interest included metastatic disease at presentation, tumor size, and patient survival. Patients classified as having “distant” disease were considered metastatic while “localized” or “regional” were considered non-metastatic. Those missing data for distant, localized, or regional disease were excluded. Tumor size was categorized as < 8 cm or ≥ 8 cm. Survival was measured in months after diagnosis.

We recorded the distance and time required to travel from a patient’s residence to the nearest comprehensive cancer center, as a measure of proximity to a sarcoma center. SEER provides county-level data, and we calculated the centroid distances from the county of a patient’s residence to the nearest comprehensive cancer center, as defined by the National Cancer Institute. We used the designation of a “comprehensive cancer center,” of which there are 70 in the United States, as a surrogate marker for a facility with a multidisciplinary sarcoma clinical service line. The cases were analyzed by the time required to travel and distance to travel to the nearest comprehensive cancer center. The distances and times to travel were calculated using county centroid coordinates and Google maps. Wednesday at 9:00 am was chosen as a standard time for calculating drive times. SEER does not provide patient treating centers, and our analysis was focused on proximity to the nearest comprehensive cancer center. The specific facility in which they received care was not known.

The cases were also grouped based on designation of counties using a Rural-Urban continuum code (RUCC) found within SEER*stat (version 8.3.4). Patients were compared by two means. One form of comparison was by grouping patients as “urban” or “rural”. In the other, the comparison was made by grouping patients as “very rural” or “not very rural”. We considered a patient to be “very rural” if they resided in a rural county, and if their county of residence was not adjacent to an

urban county. The remaining patients (those who qualified as “urban” or “rural” but their county of residence was adjacent to an urban county) were grouped together as “not very rural”.

2.3. Data analysis

We performed a univariate analysis to determine if the distance or time to a comprehensive cancer center affected the rate of presentation with metastatic disease or tumor size greater than 8 cm, both of which have been shown to be strong predictors of survival in osteosarcoma [4]. This analysis was done using mile groupings of 50, 100, and 200 miles from a comprehensive cancer center, and 1 and 2 h travel time from a comprehensive cancer center. We then analyzed five-year survival rates via Kaplan-Meier survival curves based on a patient’s rural status for both “rural” versus “urban” patients and “very rural” versus “not very rural” patients. Lastly, a multivariate analysis was done utilizing two cox regressions to control for a patient’s rural status, the presence of metastatic disease, and tumors ≥ 8 cm. In one analysis, we used “rural” versus “urban” and in the other we used “very rural” versus “not very rural.” To ensure that additional known risk factors were not over represented in our rural patients, we compared the proportion of patients in our study groups based on gender, age, and location of tumor with a chi-squared analysis.

3. Results

There was a total of 511 patients who met the inclusion criteria. Of those patients, 35 (6.8%) were excluded due to missing data for distant, localized, or regional disease leaving a cohort of 476. Of those remaining patients, 131 (27.5%) were missing the size of tumor data. Those missing size of tumor data were excluded from the tumor size univariate analysis and the multivariate analyses.

3.1. Univariate analysis

For the univariate analysis, there was variation in the rate of metastatic presentation for both those who lived over 200 miles versus less than 200 miles (28.0 and 20.2%, $p = 0.200$) and over 2 h versus less than 2 h (28.1 and 18.4%, $p = 0.021$) to the nearest comprehensive cancer center (Table 1). There was a trend toward increased rates of presentation with a tumor greater than 8 cm for patients who had further time to travel, but no clear relationship between distance and tumor size (Table 2).

Table 1
Univariate Analysis for the Presence of Metastatic Disease at Presentation.

Category	No.	Metastatic Disease at Presentation (No. [%])	P value
Distance to Nearest Center (Miles)			
≤ 50	168	33 (19.6)	0.589
> 50	308	67 (21.8)	
≤ 100	311	61 (19.6)	0.305
> 100	165	39 (23.6)	
≤ 200	426	86 (20.2)	0.2
> 200	50	14 (28.0)	
Time to Nearest Center (Hours)			
≤ 1	130	25 (19.2)	0.56
> 1	346	75 (21.7)	
≤ 2	348	64 (18.4)	0.021
> 2	128	36 (28.1)	

Table 2
Univariate Analysis for the Presence of Tumors ≥ 8 cm at Presentation.

Category	No.	≥ 8 cm Tumor at Presentation (No. [%])	P value
Distance to Nearest Center (Miles)			
≤ 50	119	59 (49.6)	0.184
> 50	226	129 (57.1)	
≤ 100	224	119 (53.1)	0.488
> 100	121	69 (57.0)	
≤ 200	314	170 (54.1)	0.676
> 200	31	18 (58.1)	
Time to Nearest Center (Hours)			
≤ 1	93	45 (48.4)	0.167
> 1	252	143 (56.8)	
≤ 2	255	132 (51.8)	0.087
> 2	90	56 (62.2)	

3.2. Survival analysis

A Kaplan Meier survival analysis for 5 years was utilized to find if there was a difference in survival for patients based on their rural status (Fig. 1). When comparing “rural” versus “urban” patients, we found that patients residing in rural counties had a decreased five-year survival (50.3% [95% CI = 41.9–58.7%]) versus urban counties (62.3% [95% CI = 56.5–67.9], $p = 0.007$). Also, patients that were considered “very rural” had a decreased survival rate (42.2% [95% CI = 30.4–54.4%]) when compared to “not very rural” patients (61.5% [95% CI = 56.4–66.6%], $p = 0.003$).

3.3. Multivariate analysis

In both models, metastasis was a risk factor for mortality when controlling for rural status and size of tumor comparing “rural” to “urban” (HR = 2.78 [95% CI: 1.88–4.10], $p < 0.0001$) (Table 3) and “very rural” and “not very rural” (2.91 [95% CI: 1.98–4.27], $p < 0.0001$) (Table 4). Patients considered “very rural” demonstrated increased mortality when controlling for metastases and tumor size (HR = 1.58 [95% CI: 1.03–2.43], $p = 0.037$).

When comparing “rural” vs “urban” patients we found no difference in the gender distribution or in the location of their tumors. We did find that our “rural” patients had a higher proportion of patients greater than 40 years old, $p = 0.01$ (Table 5). In our “very rural” vs “not very rural” patients we also saw no difference in gender distribution or in the location of their tumors. While the “very rural” patients did have a

Table 3
Multivariate Analysis of Risk Factors for Osteosarcoma Mortality (Rural vs Urban).

Variable	Hazard Ratio (95% Confidence Interval)	P-Value
Metastatic		
Yes	2.91 (1.98–4.27)	< 0.0001
No	Ref	
Rural Status		
Rural	1.34 (0.934–1.91)	0.112
Not Rural	Ref	
Size		
> 8 cm	1.08 (0.762–1.54)	0.654
< 8 cm	Ref	

Table 4
Multivariate Analysis of Risk Factors for Osteosarcoma Mortality (Very Rural vs Not Very Rural Patients).

Variable	Hazard Ratio (95% Confidence Interval)	P-Value
Metastatic		
Yes	2.78 (1.88–4.10)	< 0.0001
No	Ref	
Rural Status		
Very Rural	1.58 (1.03–2.43)	0.037
Not Very Rural	Ref	
Size		
> 8 cm	1.11 (0.784–1.58)	0.549
< 8 cm	Ref	

higher proportion of patients greater than 40 years old it failed to reach statistical significance (Table 5).

4. Discussion

Osteosarcoma has a dismal prognosis when presenting with an advanced stage of disease. Despite advances in care, survival rate has remained unchanged since the 1990s [20]. While ultimately the discovery of novel systemic therapeutics will change the treatment of distant metastatic disease and improve survival, there may be other mitigatable risk factors that could be addressed to minimize the number of patients presenting with metastasis and large tumors, two of the most important risk factors to prolonged survival in osteosarcoma. This study was conducted to find if there is a relationship amongst proximity to a comprehensive cancer center, rurality, and adverse oncologic outcomes. Overall, the distance and the time to travel to the nearest comprehensive cancer center showed a moderate effect on the size of the tumor or the presence of metastasis at presentation for

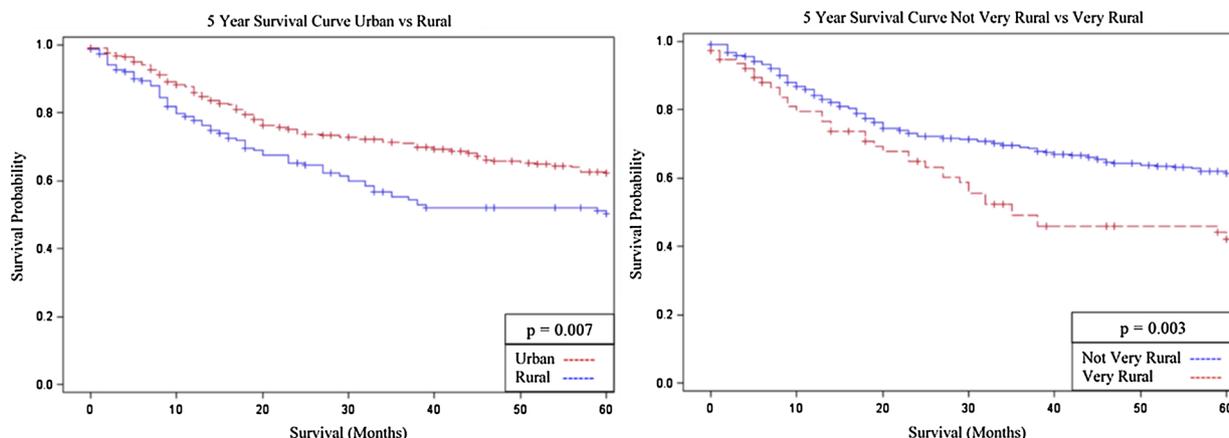


Fig. 1. Kaplan Meier survival curves for patient’s rural status based on country of residence’s rural status.

Table 5
Chi-squared Analysis of Additional Risk Factors for Mortality in Osteosarcoma.

	Rural	Urban	P-value	Very Rural	Not Very Rural	P-value
Gender			0.546			0.648
Female	67 (43.8)	132 (40.9)		34 (44.2)	165 (41.4)	
Male	86 (56.2)	191 (59.1)		43 (55.8)	234 (58.6)	
Tumor Location			0.278			0.804
Distal Extremity	115 (75.2)	257 (79.6)		61 (79.2)	311 (77.9)	
Axial/Proximal Extremity	38 (24.8)	66 (20.4)		16 (20.8)	88 (22.1)	
Age			0.01			0.059
40 +	50 (32.7)	70 (21.7)		26 (33.8)	94 (23.6)	
< 40	103 (67.3)	253 (78.3)		51 (66.2)	305 (76.4)	

osteosarcoma patients. However, a patient's rural status was shown to be a risk factor for mortality even when controlling for metastasis and tumor size. Several the findings warrant further discussion.

We found a general trend towards the presence of metastasis and large tumors in patients at a greater distance or travel time to the nearest comprehensive treatment center, but the effect appeared moderate. The most compelling association was patients living greater than 2 h from any comprehensive cancer center demonstrating a higher rate of metastasis at presentation. The current literature on distance to treating centers and outcomes for cancer patients is sparse and conflicting. A review by Meilleur et al found that studies looking at breast cancer and multiple cancers found no association with travel distance and stage of diagnosis, while a study on melanoma found an association between distance and outcomes [21]. Conversely, Scoggins et al found that breast cancer patients that had increased travel distances were diagnosed at later stages [18]. Our findings confirm that this association is possibly present, but not substantial and unlikely to impact survival meaningfully.

Despite only moderate association between patients' travel distance and presentation with metastasis or increased tumor size, rural patients experienced decreased survival, as seen in the five-year survival analysis. This difference in survival was most pronounced between the "very rural" (42.2%) and the "not very rural" (61.5%). When assessing mortality through multivariate analysis the presence of metastasis had the greatest increased risk of mortality with a hazard ratio of almost three, consistent with many prior reports [4,22,23]. "Rural" patients were not at a significantly higher risk of mortality compared to "urban" patients when controlling for the presence of metastasis and tumor size. However, "very rural" patients were found to have an increase in mortality compared to "not very rural" patients even when controlling for metastasis. Similar results were seen in rural patients with colon cancer [24]. Other studies have shown no association between rural status and survival in patients with intrahepatic cholangiocarcinoma, gastroesophageal cancer, and lung cancer [14,25,26].

It has been shown previously that age, gender, and tumor location are additional risk factors for mortality in osteosarcoma that were not assessed in our multivariate analysis [4]. To ensure that these factors were not over represented in the rural population we compared our study groups using a chi-squared analysis. In both of our comparisons, neither gender nor tumor location were unevenly distributed. However, rural patients did have a higher proportion of patients over the age of 40. This was less pronounced in our "very rural" patient group. If age was the primary driver of mortality in this patient group it would be assumed that our "very rural" patients would have had less of a difference in mortality, but this was the group which showed a larger difference in mortality when compared to their more urban counterparts.

Our analysis suggests that there are intangible drivers to rural patients' decreased survival besides distance to a comprehensive cancer center. The most isolated patients are presenting with higher rates of metastasis and have decreased survival compared to their less rural counterparts. Studies addressing rurality and treatment modalities have

found that more rural patients are less likely to receive chemotherapy in colorectal cancer and they are less likely to receive radiation therapy in breast and endometrial cancer [21,27,28]. Although the barriers that result in diminished survival are not elucidated by these data, it is possible that rural osteosarcoma patients are presenting later, receiving sub-optimal treatment, or experiencing difficulties with protocol adherence.

In the future, areas with poor healthcare access could be improved through initiatives such as telemedicine and outreach clinics in states with larger rural populations, which may provide mechanisms for early identification, expeditious diagnosis, and access to centers specialized in sarcoma management. It is unclear what effect this would have on osteosarcoma patients, but it does appear that residence in a rural country alone is a risk factor for diminished survival. Telemedicine has been demonstrated as an effective intervention for other malignancy. For post-operative colorectal surgery, telemedicine was able to reduce costs to patients while maintaining survival rates [29]. Post-radiotherapy compliance rates were shown to increase as well as disease free survival rate in patients with esophageal SCC utilizing telemedicine [30].

4.1. Limitations

There are several limitations to this study. We relied on county level data to assign a patient's rural-urban status. This does not allow for assessment of individual living situations, but it is a method that has been utilized in similar investigations and generally reflects the area in which an individual resides. In addition, the treating center for each patient was not known, so no facility-level analyses were possible. We find this to be justified because our interest was in access and the proximity to a comprehensive cancer center. This study did not consider a patient's socioeconomic status which has been shown to affect mortality in osteosarcoma patients [4]. This represents a future focus for further research. This study looked at patients of all ages, but because of the small cohort size we did not control for age in our multivariate analysis. It is possible that increased age is contributing to the decreased survival seen in rural patients. We also do not know the chemotherapeutic protocols or patient's response to chemotherapy, which is a significant factor in successful cure of osteosarcoma. It is possible there were specific approaches to chemotherapy that provided survival benefits that we are unable to assess through the SEER database. Due to the nature of database studies, a quarter of our cohort was missing the size of tumor data which we dropped from the multivariate analysis and the size of tumor analysis. By decreasing the number of patients in the cohort we decreased the sensitivity of our analysis. This may mean that distance/time plays a larger role in the size of a tumor at presentation than reported in this study.

5. Conclusions

We found that patients living in rural counties, far removed from larger population centers, are at a higher risk of mortality from

osteosarcoma than those living in more densely populated counties when controlling for tumor size or presence of metastatic disease. A patient's distance from a comprehensive cancer center may be a less important consideration than diminished access to care resulting from living in a rural area. Although the specific causes of the disparities are unclear, efforts to diminish impediments caused by travel distance or county infrastructure may result in improved survival in rural patients with osteosarcoma.

Authorship contribution

Ryan Wendt, BS: (1) Conception and design, acquisition of data, and analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, and (3) final approval of the version to be published.

Yubo Gao, PhD: (1) Acquisition of data, and analysis and interpretation of data, (2) revising it critically for important intellectual content, and (3) final approval of the version to be published. Benjamin J. Miller, MD, MS: (1) Conception and design, acquisition of data, and analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, and (3) final approval of the version to be published.

Conflict of interest

None.

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