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Prevalence of metastasis at diagnosis of osteosarcoma: an international comparison

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Abstract

Background—Osteosarcoma is the most common primary malignant bone tumor in many countries, with metastatic disease responsible for most patient deaths. This study compares the prevalence of metastatic osteosarcoma at diagnosis across countries to inform the critical question of whether diagnostic delay or tumor biology drives metastases development prior to diagnosis.

Procedure—A literature search of the PubMed database was conducted to compare the prevalence of metastatic disease at the time of OS diagnosis between countries. A pooled prevalence with 95% confidence intervals was calculated for each study meeting inclusion criteria. Studies were grouped for analysis based on human development index (HDI) scores.

Results—Our analysis found an 18% (95% CI: 15%, 20%) average global pooled proportion of metastasis at osteosarcoma diagnosis. The average prevalence of metastasis at diagnosis increased as HDI groupings decreased, with very high HDI, high HDI, and medium/ low HDI groups found to be 15% (95% CI: 13%, 17%), 20% (95% CI: 14%, 28%), and 31% (95% CI: 15%, 52%), respectively.

Conclusions—Our evidence suggests there is a biological baseline for metastatic OS at diagnosis, which is observed in countries with very high HDI. In countries with medium/ low HDI, where there are more barriers to accessing healthcare, the higher prevalence of metastasis may result from treatment delay or an artificial prevalence inflation due to patients with less severe symptoms not presenting to clinic. Additional research in countries with medium/ low HDI may reveal that earlier detection and treatment could improve patient outcomes in those countries.

Keywords

osteosarcoma; metastasis; bone cancer; epidemiology; human development index

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Introduction

Osteosarcoma (OS) is the most common primary malignant bone tumor in many countries, [1–3] with a peak in adolescence and often a second smaller peak starting in the sixth decade of life. [3–6] Despite combined therapies, treatment failure is experienced within 5 years of diagnosis by over 40% of patients, generally due to metastatic disease developed before or after diagnosis. [7] Survival has not improved substantially over the past 30 years, [5] and metastatic OS is usually incurable and requires palliation. Older age, [6, 8, 9] axial tumor location, [6, 8–15] and tumor size [1, 9, 14] have been reported by a number of research groups to increase risk of metastatic disease and worsen survival outcomes. The incidence of OS is fairly constant worldwide, particularly among individuals ≤24 years, [4] but an international comparison of the prevalence of metastasis at diagnosis has not been compiled. The purpose of this study is to compare prevalence of metastatic OS at diagnosis across countries to inform the critical question of whether diagnostic delay or tumor biology drives metastases development prior to diagnosis.

Methods

International Literature Search

A literature search of the PubMed database was conducted to compare the prevalence of metastatic disease at the time of OS diagnosis between countries. All fields were searched for the terms osteosarcoma/ osteogenic sarcoma/ bone sarcoma AND metastases/ metastasis/ metastatic, yielding 9595 papers (last search conducted on May 19, 2015). Titles were screened and abstracts reviewed for single-institutional, multi-institutional, and population-based studies within a single continent that reported the prevalence of metastatic disease at diagnosis of high-grade, skeletal OS in a minimum of 20 patients. Papers were only included if information was available for all OS patients treated at a clinic(s) over the given period of data collection. Key phrases indicating a study fell into this search criteria were “all patients” and “consecutive patients.” Exceptions were made for publications reporting on patients of a specific age at diagnosis. Only those studies with a publication date of 1980 or later were considered. When studies with significantly overlapping datasets were encountered, to the best we could discern, the study covering the largest data collection period was included for analysis.

Effort was made to include papers written in any language. Seven papers were not available in English that were identified as possible candidates for our study. Three could not be readily translated and were excluded from analysis because data could not be extracted.

Several studies reported the prevalence of metastasis at OS diagnosis from single institutions in the United States. However, since Duong and Richardson provided a large, nationwide report using the Surveillance, Epidemiology, and End Results Program database in conjunction with the National Program of Cancer Registries’ central cancer registries, [16]this study was used to evaluate United States data.

Statistical Analysis

The summary statistic for each study is a prevalence proportion, calculated as the ratio of the number of individuals presenting with metastasis to the sample size of the study. A random-effects model with inverse-variance weighting was used to calculate a pooled prevalence and 95% confidence intervals (CI). [17] Statistical heterogeneity was evaluated with the Cochran's Q statistic[18] and quantified using an I^2 statistic.[19]The United Nations' human development index (HDI) value for each country, which is based on the population's average life expectancy, years of schooling, and gross national income, was used to group studies. Studies were categorized into groupings defined by the United Nations as very high HDI, high HDI, and medium/ low HDI. For multi-institutional studies that included countries from multiple HDI groups, the HDI group from which the majority of patients were seen was chosen.

Subgroup analysis was performed to account for heterogeneity. Subgroups were categorized from very high HDI studies into general age groupings: pediatric (upper age no greater than 18 years), adult (no pediatric cases), and mixed ages (all patients seen at a clinic that included pediatric and adult populations). A subgroup analysis was not performed from high HDI and medium/ low HDI studies because each had an insufficient number of studies restricted to either pediatric or adult populations for a pooled subgroup analysis. All meta-analysis was performed using R version 3.2.1. [20]

Results

Thirty-five studies met the inclusion criteria (Table I): very high HDI (n=23), [1, 6, 8, 10, 13–16, 21–35] high HDI (n=7),[3, 11, 12, 36–39]and medium/ low HDI (n=5). [2, 40–43] Figure 1 depicts the prevalence of metastatic OS at diagnosis stratified by HDI group. The pooled proportion of patients presenting with metastatic OS at diagnosis in very high HDI, high HDI, and medium/ low HDI groups were found to be 15% (95% CI: 13%, 17%), 20% (95% CI: 14%, 28%), and 31% (95% CI: 15%, 52%), respectively. All 35 studies pooled together gave a global proportion of 18% (95% CI: 15%, 20%).

Figure 2 details information on the subgroup analysis of the 23 studies from very high HDI countries. The pooled prevalence for adult patients presenting with metastatic OS in very high HDI countries was found to be 18% (95% CI: 11%, 27%). Among pediatric patients presenting with metastatic OS in very high HDI countries, the pooled prevalence was 14% (95%CI: 10%, 20%). Studies that included a mixed age grouping from countries with a very high HDI had a pooled prevalence of metastatic OS at diagnosis of 15% (95%CI: 13%, 18%).

Heterogeneity within HDI groups as measured by Cochran's Q were all significant ($p < 0.05$), and remained statistically significant from the subgroup analysis of age groupings (pediatric, adult, and mixed age) (Figure 2). An apparent reduction in heterogeneity was noticed between studies restricted to either pediatric (I-squared = 60%) or adult cases (I-squared= 72.1%), but not between studies that included both pediatric and adult cases (I-squared = 86.2%). The lower heterogeneity from the pediatric and adult subgroups compared to the mixed age subgroup could reflect a difference in the prevalence of

metastatic OS between pediatric and adult populations, and the heterogeneity between the studies from the same HDI group may be partially explained by differing age ranges.

Discussion

Prior to the introduction of high-dose chemotherapy to osteosarcoma (OS) treatment regiments in the United States, the 5- year survival rate of patients with localized disease was around 20% following amputation. [44] The improved survival with systemic chemotherapy likely results from the eradication of micrometastases not detected by current imaging techniques. The presence of detectable metastatic OS at diagnosis may be driven by two broad factors. If diagnosis is delayed, micrometastases may be allowed more time to leave dormancy and develop into macrometastases, increasing the observed prevalence of metastases at diagnosis. Alternatively, the biology of OS may drive the rate of metastasis, with a subset of OS having an intrinsically poor biology leading to macrometastases development.

Diagnostic delay may occur at the level of the patient (education, resources, socio-economic status), provider (referral centers, specialized oncology clinics, imaging facilities), and country (health care system organization, access to health care, social security). [2] If metastasis were attributable to diagnostic delay, one would expect longer duration of symptoms among these patients. One European group reported an association between increased time to diagnosis and metastasis at presentation. The German-Austrian-Swiss Osteosarcoma Study Group [8] observed an association of axial primary tumors ($p<.001$, X^2), metastases at diagnosis ($p<.007$, X^2), and increasing age ($P<.001$, t-test) with prolonged history of symptoms before diagnosis. However, given that axial tumors and older age are known to increase metastasis, [6, 9, 11–15] history of symptoms should be evaluated with multivariable analysis to determine if a correlation with metastases at presentation exists within their population.

Several research groups from single institutions in countries with high and very high HDI have also evaluated the effect of diagnosis delay on the prevalence of metastasis at OS diagnosis. No difference was observed in symptom duration to OS diagnosis between patients with or without metastasis at presentation by groups from Indianapolis, [45] Hong Kong, [46] and Taiwan. [47] Patients seen at the Italian Rizzoli Institute with extremity tumors had a shorter interval between onset of symptoms to time of diagnosis if metastases were found at presentation (2.17 months vs. 2.54 months; $P<0.0002$). [48] Although not statistically significant in all reports, there appears to be a trend that patients with metastases actually present *earlier* to clinic from symptom onset, likely due to the disease severity. These reports provide evidence that diagnosis delay does not increase the risk of developing detectable metastasis before OS diagnosis. Rather, they suggest that tumor biology is the driver of malignant tumor character.

Studies reporting the highest prevalence of metastasis at OS diagnosis were from countries with medium/ low HDI. [2, 41] Socio-economic status, educational levels, and healthcare systems and resources can negatively effect patient outcomes. [2] Within the United States' healthcare system, counties with the lowest composite socioeconomic status scores had a

higher proportion of patients with metastasis at diagnosis. [9] Socioeconomic status combines individual elements, social factors, and local infrastructure, and may identify communities with less access to medical care. Comparatively, Central American and African countries have a higher proportion of the population in underdeveloped communities with limited access to medical care. Barriers to accessing medical care may discourage individuals from seeking medical attention unless symptoms are severe. Similar to the observation of patients with metastatic disease presenting earlier to clinic in very high HDI countries, if individuals with severe symptoms are more likely present to clinic in medium/ low countries, the prevalence of metastatic disease at diagnosis will be artificially inflated in these countries.

Alternatively, the delay in diagnosis may be longer and driving a higher prevalence of metastasis at diagnosis in countries with medium/ low HDI as compared to countries with very high/ high HDI. Three of the four research groups evaluating the effect of diagnosis delay on the prevalence of metastasis at OS diagnosis had an upper range of 1–2 years from onset of symptoms to diagnosis. One group had a range of 10 years. [45] When comparing the lower and upper quartile of symptom length, a difference in diagnostic delay on metastatic development prior to diagnosis was still not observed. While this suggests that diagnosis delay does not have an effect up to a decade, the results cannot be extrapolated to countries with medium/ low HDI, where diagnostic delay may be even longer. The improved prognosis with addition of chemotherapy to OS treatments demonstrates that intervention is needed to prevent development of metastatic disease. It is unclear how well individuals in countries with medium/ low HDI are being diagnosed and treated compared to those in countries with very high/ high HDI. Research must be conducted in medium/ low HDI countries to determine if diagnosis delay is affecting patient outcomes.

The findings that the prevalence of metastasis is relatively constant and is not affected by diagnosis delay in countries with very high HDI values suggest there is a biological baseline for the presence of metastasis at diagnosis. Given that patients with metastases present earlier to clinic in countries with very high HDI, early detection may not be useful in improving survival rates. In countries with medium/ low HDI, where there are more barriers to accessing healthcare, two phenomenon may occur that give rise to the observed higher prevalence of metastasis at OS diagnosis. First, patients may delay seeking treatment significantly longer than patients in developed countries, allowing micrometastases time to develop into detectable metastasis above the 18% baseline observed in very high HDI countries. Second, patients with less severe symptoms may not present to clinic, artificially inflating the percentage of severe cases with detectable metastasis.

A limitation of this study is the lack of research that has been conducted in countries with medium/ low HDI. Research must be performed to address the question of whether delay in diagnosis increases the prevalence of detectable metastatic disease at the time of OS diagnosis in these countries. This knowledge will direct the treatment course if it can be determined whether earlier detection and treatment could improve patient outcomes in countries with medium/ low HDI.

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Abbreviations

OS	Osteosarcoma
CI	Confidence Interval
HDI	Human Development Index

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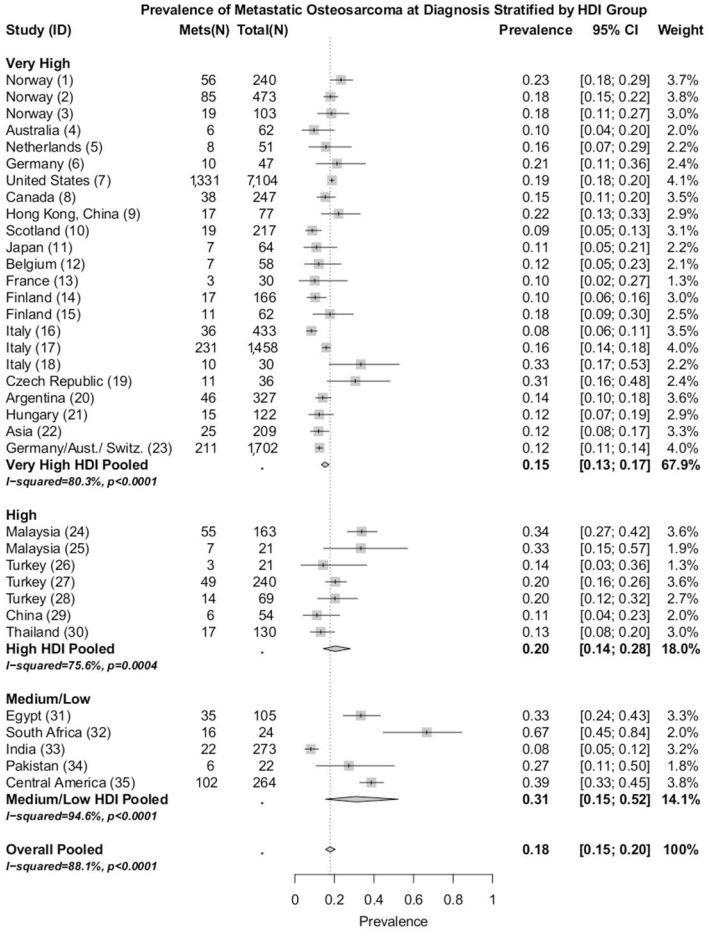

Figure 1.

Prevalence (boxes), 95% confidence intervals (lines), and pooled prevalence (diamonds). 'Overall Pooled is the pooled prevalence of all 35 studies. 'ID' refers to table I ID.

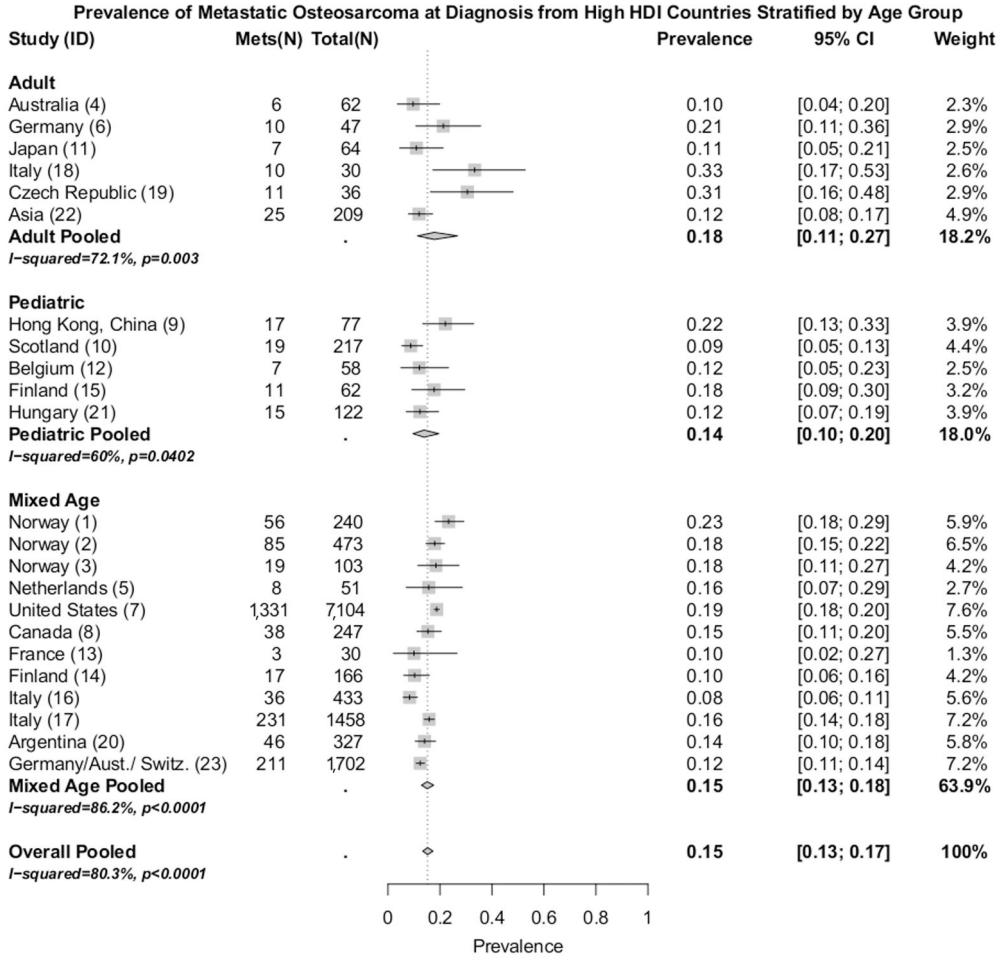

Figure 2.

Prevalence (boxes), 95% confidence intervals (lines), and pooled prevalence (diamonds). Study classifications: adult (no pediatric cases), pediatric (upper age no greater than 18 years), and mixed ages (all patients seen at a clinic that included pediatric and adult populations). ‘Overall Pooled’ is pooled prevalence of the 23 studies from very high HDI countries. ‘ID’ refers to table I ID.

Table I

Prevalence of Metastatic Osteosarcoma at Diagnosis Stratified by HDI Group

ID	Country	HDI Value	HDI Group	Centers/Registries	Collection Period	Total Patients	Age Group
1	Norway	0.944	Very High	Norwegian Cancer Registry	1953–1977	240	Mixed Age
2	Norway	0.944	Very High	Norwegian Cancer Registry	1975–2009	473	Mixed Age
3	Norway	0.944	Very High	Norwegian Radium Hospital, Oslo	1981–1995	103	Mixed Age
4	Australia	0.935	Very High	Royal Prince Alfred Hospital, Camperdown	1979–1994	62	Adult
5	Netherlands	0.922	Very High	Nijmegen University Hospital, Nijmegen	1974–1996	51	Mixed Age
6	Germany	0.916	Very High	Hannover University Medical School, Hannover	1980–1991	47	Adult
7	United States	0.915	Very High	Surveillance, Epidemiology, and End Results Program (NCI); National Program of Cancer Registries (CDC)	1999–2008	7104	Mixed Age
8	Canada	0.913	Very High	Mount Sinai Hospital, Toronto	1986–2003	247	Mixed Age
9	Hong Kong, China	0.910	Very High	Chinese University of Hong Kong, Prince of Whales Hospital, Hong Kong	1993–2008	77	Pediatric
10	Scotland	0.907	Very High	University of Glosgow, Glosgow	1933–2004	217	Pediatric
11	Japan	0.891	Very High	Tohoku Musculoskeletal Tumor Society and the National Cancer Center, Tokyo	1972–2002	64	Adult
12	Belgium	0.890	Very High	University Hospital Leuven, Pellenberg	1962–1987	58	Pediatric
13	France	0.888	Very High	Hospital of Hautepierre, Strasbourg	1983–1994	30	Mixed Age
14	Finland	0.883	Very High	Finnish Cancer Registry	1971–1990	166	Mixed Age
15	Finland	0.883	Very High	Finnish Cancer Registry	1991–2005	62	Pediatric
16	Italy	0.873	Very High	Rizzoli Orthopedic Institute, Bologna	1959–1979	433	Mixed Age
17	Italy	0.873	Very High	Rizzoli Orthopedic Institute, Bologna	1982–2002	1,458	Mixed Age
18	Italy	0.873	Very High	Rizzoli Orthopedic Institute, Bologna	1961–2006	30	Adult
19	Czech Republic	0.870	Very High	Masaryk Memorial Cancer Institute, Brno	1999–2010	36	Adult
20	Argentina	0.836	Very high	Italian Hospital of Buenos Aires, Buenos Aires	1980–2004	327	Mixed Age
21	Hungary	0.828	Very High	Second Department of Pediatrics, Budapest	1988–2006	122	Pediatric
22	Asia	N/A	Very High	*	N/A-2001	209	Adult
23	Germany, Austria, Switzerland	N/A	Very High	German-Austrian-Swiss Osteosarcoma Study Group	1980–1998	1,702	Mixed Age
24	Malaysia	0.779	High	Hospital Universiti Sains Malaysia, Kelantan	2005–2010	163	Mixed Age
25	Malaysia	0.779	High	Hospital of Kuala Lumpur, Kuala Lumpur	1995–1999	21	Mixed Age

ID	Country	HDI Value	HDI Group	Centers/Registries	Collection Period	Total Patients	Age Group
26	Turkey	0.761	High	Ankara Numune Education and Research Hospital, Ankara	2002–2012	21	Adult
27	Turkey	0.761	High	**	1995–2011	240	Mixed Age
28	Turkey	0.761	High	Hacettepe University, Ankara	1985–2004	69	Pediatric
29	China	0.727	High	Peking University People's Hospital, Beijing	1998–2011	54	Adult
30	Thailand	0.726	High	Faculty of Medicine Ramathibodi Hospital Mahidol University, Bangkok	1985–1988	130	Mixed Age
31	Egypt	0.690	Medium/Low	University Hospital, Alexandria	1979–1988	105	Mixed Age
32	South Africa	0.666	Medium/Low	Greys Hospital, University of KwaZulu-Natal, Pietermaritzburg	2009–2011	24	Mixed Age
33	India	0.609	Medium/Low	Tata Memorial Hospital, Bombay	1985–2988	273	Mixed Age
34	Pakistan	0.538	Medium/Low	Aga Khan University Hospital, Kariachi	2004–2008	22	Adult
35	Central America	N/A	Medium/Low	***	2000–2009	264	Pediatric

N/A: Data not available or applicable.

*Countries: S. Korea, Japan, Thailand, China, Philippines. Centers/ Registries: Catholic Center Hospital, Seoul; National Cancer Center Hospital, Tokyo; Seoul National University Hospital, Seoul; Siriraj Hospital, Bangkok; Korea Cancer Center Hospital, Seoul; Kosin University Gospel Hospital, Busan; Jishuitan Hospital, Beiging; Kanazawa University Hospital, Kanazawa; Tata Memorial Hospital, Mumbai; Philippine General Hospital, Manila.

**Country: Turkey. Centers/ Registries: Ankara Oncology Training Center and Research Hospital, Ankara; Dicle University Hospital, Diyarbakir; Ankara Numune Training and Tresearch Hospital, Ankara; Erciyes University Hospital, Kayseri; 9 Eylul University Hospital, Izmir.

***Countries: Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama. Centers/ Registries: National Children's Hospital, San Jose; Benjamin Bloom National Children's Hospital, San Salvedor, National Pediatric Oncology Unit, Guatemala City; Maternity and Children's Hospital, Honduras; "La Mascota" Children's Hospital, Managua; Children's Hospital of Panama, Panama City; Pediatric Specialties Hospital, Panama.

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