Cancer Epidemiology 54 (2018) 7–11

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Patterns of pathologically confirmed metastasis to bone in Near East population

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ARTICLE INFO

Keywords:
Pattern of metastasis
Bone
Skeletal

ABSTRACT

Background: Metastatic tumors to bone constitute the majority of bone malignancies. The site of metastasis to bone and the prognosis depend chiefly on the primary tumor. Despite all the advances in diagnostic techniques, identifying the primary tumor has not improved significantly.
Methods: A total of 576 cases (Lebanon; n = 306, Pakistan; n = 270) presenting with microscopic evidence of metastasis to bone were reviewed between 1996 and 2016. Clinical and radiologic data were recorded.
Results: Out of 20 types of primary tumors, unknown primary (38.2%), followed by breast (23.8%), lung (10.4%) and thyroid (4.9%) tumors were the most commonly presenting with bone metastasis. The primary source of the tumor showed significant correlation with the site of metastasis, time lag to metastasis and radiologic presentation ($p < 0.001$). Interestingly, a significant variation was noted between the 2 observed populations.
Conclusion: The patterns of pathologically confirmed metastasis to skeletal sites in Near East population showed a special distribution, and variation was even observed between the 2 studied centers. Understanding the biologic variations of the primary tumors in our population may further explain the variation in patterns of metastasis.

1. Introduction

The skeletal system is one of the most common sites of cancer metastasis [1,2].

The incidence of metastasis affecting the skeletal system is significantly higher than that of primary bone cancer [1]. Breast, lung and prostate cancers are among the most common tumors that metastasize to bone [3]. Patients who develop metastatic bone disease are at risk of developing serious complications leading to poor life quality and increased mortality [4].

Metastasis to skeletal system can have characteristic clinical, radiological and prognostic features. Common skeletal sites involved by metastatic cancer include vertebrae, pelvis, femur, skull, and ribs [1,3]. One of the main factors affecting the site of metastasis is the primary tumor. For example, breast cancer shows a predilection for metastasis to the spine and ribs [5]. Often times, metastatic skeletal lesions are the first presenting sign of cancer [6], and finding the primary tumor can be challenging. In fact, 10–15% of cases of metastasis to bone remain of unknown origin, despite recent advances in imaging, histopathological and molecular diagnostic techniques [6,7]. Radiologically, most metastatic bone lesions can be classified by plain radiography as osteoblastic, osteoclastic, or mixed [8], and each primary cancer type has a characteristic radiologic presentation. In terms of presentation and progression, the time between primary cancer diagnosis and the presentation of metastasis, the “time lag”, is variable among the different types of cancer. Lung cancer is known to have a very short time lag, while prostate cancer takes a longer time to metastasize to bone [9].

This study highlights the origins and patterns of metastasis to the skeletal system in a Near East population by examining data from two centers, the American University of Beirut Medical Center (AUBMC), and Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH), and compares these findings to other populations. In addition, the patterns of skeletal metastasis will be correlated with multiple variables related to the primary tumor of origin.

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https://doi.org/10.1016/j.canep.2018.03.002
Received 5 October 2017; Received in revised form 1 March 2018; Accepted 3 March 2018

2. Methods

2.1. Case selection

The archives of the Pathology Department at the American University of Beirut Medical Center (AUBMC), Lebanon, and the Pathology Department at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH), Lahore, Pakistan between the years 1996 and 2016 were reviewed. Cases presenting with microscopic evidence of metastasis to bone were included. Cases with bone marrow involvement only, without bone matrix involvement, or primary hematological malignancy were excluded.

2.2. Clinicopathologic and radiologic data

Multiple clinical and radiologic findings were retrieved from review of clinical charts and radiologic records when available. These included demographics (age, sex), anatomical site of bone metastasis, type of primary malignancy, and time lag between diagnosis and metastasis. Anatomical sites of metastasis were categorized as involving "axial" or "appendicular" locations. Axial sites consisted of the cranium, face, vertebrae, ribs or sternum, while appendicular sites included upper and lower extremities and pelvis. Available radiologic findings describing the type of bone lesion as osteolytic, osteoblastic or mixed were noted. In cases where radiographic data was not available the site of metastasis was documented based on pathology sample site only.

2.3. Statistical methods

Data analysis was performed using the statistical program SPSS version 20 (IBM Corp. in Armonk, NY). Descriptive analysis and measures of frequencies were conducted; and measures of association were performed when possible. Chi square test, *t*-test, ANOVA and linear regression were used when appropriate with $p < 0.05$ as a cutoff for statistical significance.

2.4. Institutional approval

The Institutional Review Boards at AUBMC and SKMCH approved this study. All cases were de-identified before data entry.

2.5. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

3. Results

3.1. Demographics and clinical parameters (Table 1)

The data included 576 patients with metastasis to bone; 310 males and 266 females, with 306 patients coming from AUBMC and 270 patients from SKMCH. Patients' ages ranged between 2 and 91 years (mean = 57 ± 14), with 86% of patients above the age of 40. Metastasis to appendicular sites was more prevalent compared to axial sites (53.6% and 43.3% respectively). The most common known primary cancers to metastasize to bone were breast (23.8%), followed by lung (10.4%) and thyroid (4.9%) tumors.

3.2. Distribution of metastasis to skeletal sites (Fig. 1)

A statistically significant relationship was observed between the tumors of origin and their respective sites of metastasis ($p < 0.001$). For example, breast cancer had predilection to metastasize to the spine (34.8%), pelvis (23.5%) and femur (24.2%). Interestingly only 4.5% of breast cancer cases metastasized to the ribs. Lung cancer had also a similar pattern of metastasis with 28.8% metastasis to spine and 20.3% were to pelvis and femur.

Table 1
Demographics and Clinical Parameters.

		Number (%)
Gender	Male	310 (53.8)
	Female	266 (46.2)
Age	< 20	5 (0.9)
	21–40	72 (12.5)
	41–60	255 (44.2)
	> 60	244 (42.4)
Site of Metastasis	Axial	251 (43.6)
	Appendicular	309 (53.6)
	Unknown Site	16 (2.8)
Tumor of Origin		
Unknown		220 (38.2)
Breast		137 (23.8)
Lung		60 (10.4)
Thyroid		28 (4.9)
Kidney		27 (4.7)
Prostate		24 (4.2)
Liver		20 (3.5)
Colon		16 (2.8)
Other tumor*		44 (7.6)

*Other tumors include (n): urinary bladder (10), soft tissue (6), Pancreaticobiliary (5), stomach (5), bone (4), upper respiratory (3), tongue (2), skin (2), esophagus (2), uterine cervix (2), uterus (1), central nervous system (1), salivary gland (1).

3.3. Comparison between AUBMC and SKMCH (Table 2)

Patients at AUBMC had a similar distribution of bone metastasis lesions to axial and appendicular sites (47.9% and 48.9% respectively), while cases at SKMCH presented more at appendicular than axial locations (58.9% and 38.5% respectively). Of the available cases presenting with bone metastasis, the most common known primary tumors at AUBMC were breast cancer (36.5%) followed by lung cancer (15%), whereas at SKMCH the most common were breast (9.3%) and thyroid (8.5%). Despite the use of comprehensive immunohistochemical and molecular test in attempting to diagnose the tumor of origin, lesions of unknown primary tumor represented 36.5% of cases at AUBMC and 55.9% of cases at SKMCH. There is also a variation in the type of tumor and the pattern of metastasis to appendicular or axial site between AUBMC and SKMCH. This difference was significant for breast and thyroid tumors ($p < 0.05$).1

3.4. Time lag (Table 3)

Data for time lag analysis was only available for 63% of cases retrieved from AUBMC. The leading predictor for time lag was the primary source of the tumor ($p < 0.001$), i.e. in lung cancer the cases predominantly presented with metastasis before or at diagnosis (41.5%), whereas in breast cancer, patients presented with bone metastasis within or after 5 years (77.8%).Another predictor for time lag was "patient's gender" ($p < 0.001$); were the mean time lag is significantly different between the two genders (39 months for females versus 23 months for males). Other variables showed no predictive value for the time lag.

3.5. Radiologic findings (Table 4)

Radiologic data was only available for 75% of AUBMC patients. Different primary tumors showed variable patterns of radiologic presentations including osteolytic, osteoblastic and mixed. As per imaging, the majority of the patients (74.2%) had at least 2 sites of bone metastasis with axial-appendicular combination being the most common (51.9%)