



Research Paper

The need for bone biopsies in the diagnosis of new bone lesions in patients with a known primary malignancy: A comparative review of 117 biopsy cases



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ABSTRACT

Objective: This study used a clinical dataset to investigate the proportion of the newly found bone lesions in malignant patients diagnosed by biopsy as being benign, malignant but unrelated to the primary malignancy, or bone metastases of the primary malignancy. The clinical factors that might affect the correlation between bone lesions and the primary malignancy were also analyzed. It is expected to obtain some information contributing to the clinical decision-making regarding the need for biopsy of these lesions from the research results.

Methods: Data from patients with a single known malignant tumor who had undergone biopsy of newly found bone lesions at our research institution between January 2012 and December 2017 were reviewed. Based on the pathology results, included cases were divided into a bone-metastasis-of-primary-tumor group (Group 1) and a non-bone-metastasis-of-primary-tumor group (Group 2). The sex, age, diagnostic interval time between the primary malignancy and bone lesions, clinical symptoms, number of involved bones, sites of bone biopsy, and ¹⁸F-FDG PET/CT results were compared between groups.

Results: A total of 117 patients (92 in Group 1 and 25 in Group 2) were included in the study. There was no significant difference in the sex, age or diagnostic interval time between patient groups. Of all the cases, 17.9% (21/117) were identified to be benign lesions such as fibrous dysplasia ($n = 2$), bone tuberculosis ($n = 1$), simple bone cyst ($n = 1$), aneurysmal bone cyst ($n = 1$), or solitary fibrous tumor ($n = 1$). Meanwhile, 3.4% (4/117) were new malignancies including chondrosarcoma ($n = 1$), plasmacytoma ($n = 1$) and bone metastases unrelated to the primary malignancy ($n = 2$). Bone metastases pertinent to the primary tumor accounted for 78.6% (92/117) of cases. Liver ($n = 18$), kidney ($n = 14$), breast ($n = 13$) and lung ($n = 12$) were the most common cancers among cases. Cases with clinical symptoms exhibited a higher likelihood of their bone lesions being diagnosed as bone metastases of their primary malignancy than those without clinical symptoms (81.3% (87/107) vs. 50.0% (5/10)) ($P = 0.021$). Neither the number of bone lesions nor the biopsy sites appeared to influence whether the bone lesions were metastases of the primary malignancy or not. In PET/CT examination, the mean maximum standardized uptake values of the two groups were similar.

Conclusions: This study indicated that more than 1/5 of newly identified bone lesions in patients with a single known malignancy were not clinically associated with their primary tumors. Furthermore, 3.4% of these were newly discovered malignant bone tumors. The presence of clinical symptoms may be a significant factor affecting whether a new bone lesion is clinically linked to a patient's primary malignancy. Based on the experience from these patients, as for the newly found bone lesions, it is worthy to perform an active biopsy on those asymptomatic ones to avoid misdiagnosis and less biopsy on symptomatic ones for the sake of less cost and risks.

Abbreviations: MDT, multidisciplinary team; PET, positron emission tomography; CT, computed tomography; FDG, fluorodeoxyglucose; ECT, emission computed tomography; SUV, standardized uptake value; SREs, skeletal-related events

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1. Introduction

Almost all malignant tumors can metastasize to the skeletal system. Estimates suggest that bone metastases could occur in 70–80% of breast and prostate cancer patients before their death [1]. Although new bone lesions are often detected in malignant patients, not all of them are bone metastases of the primary malignancies. According to the previous reports, about 16.7% (0–34.3%) and 3.2% (0–18%) of all bone lesions were identified to be benign and malignant but unrelated to the primary malignancy, respectively [2–7]. If such lesions are misdiagnosed as bone metastases of the primary malignancy and inappropriate surgery or radiotherapy treatments are administered, this could result in considerable damage to patients [5].

Bone biopsy plays an important role in the definitive diagnosis. However, it is also at the risk of resulting in such complications as infection, hematoma and organ damage, and of increasing the economic and mental burden of the patients [8]. Therefore, it is necessary to balance the benefits and risks of the procedure before performing biopsy. Creek et al. [9] recommended that several clinical factors should be considered preoperatively, such as clinical symptoms, diagnostic interval time between the primary malignancy and bone lesions, and the number and specific sites of the bone lesions. Decision-making may depend on an assessment of the likely correlation between bone lesions and the primary malignancy.

This study aims to investigate the nature of the newly detected bone lesions diagnosed by bone biopsy. The clinical factors that might affect the correlation between bone lesions and primary malignancy were also analyzed. These results might inform the clinical decision-making concerning the need for biopsy of such lesions in patients with a single known malignancy.

2. Patients and methods

2.1. Patients

Data for our study were reviewed from electronic medical records in Zhongshan Hospital, Fudan University. This retrospective study was approved by hospital ethics committee. Inclusion criteria consisted of hospitalized patients with bone lesion biopsies performed between January 2012 and December 2017; patients with a single known malignant tumor (e.g. malignant epithelial tumors, melanoma and soft tissue sarcoma); and patients with a definite pathological diagnosis of the primary malignancy and bone lesions. Exclusion criteria included: primary malignancies diagnosed as primary malignant bone tumors and blood tumors; patients with multiple primary malignancies concomitantly; more than one biopsy site in a one-stage operation; and a history of previous bone lesions.

2.2. Treatment

The appropriate biopsy modality and biopsy location of the included patients had been decided by the multidisciplinary team (MDT) of orthopedic oncology on the basis of the patient's clinical manifestations, the state of their primary malignancy and the preoperative imaging findings. We orthopedic surgeons did the core needle and open biopsies which were performed on only one suspected bone lesion per patient. Anesthesia methods were selected based on the specific circumstances of patients and the chosen biopsy modality. Core needle biopsies were performed by inserting an 11-gauge bone biopsy needle into the bone lesion percutaneously and obtaining 3 to 5 strips of tissue, sampled from different directions with the guidance of an image-intensifier. In open biopsies, a small incision was made followed by a unicortical drill hole by high-speed burr under the guidance of an image-intensifier. An adequate amount of lesion tissue was then acquired with a curette.

All of the tissue samples were embedded in paraffin and evaluated by a senior pathologist. According to the pathological results, cases

were divided into bone-metastasis-of-primary-tumor group (Group 1) and non-bone-metastasis-of-primary-tumor group (Group 2). The clinical and diagnostic characteristics of patients were reviewed and compared across the two groups.

2.3. Statistical analysis

Analysis was performed using SPSS software (IBM, Armonk, NY, USA). Differences between patient groups were identified using Fisher's exact test for qualitative variables and the Student *t*-test for quantitative variables. The critical *P* value for statistical significance was set at *P* < 0.05.

3. Results

3.1. Demographic characteristics

A total of 117 patients (92 in Group 1 and 25 in Group 2) were included in the study, with an average age of 57.9 ± 13.2 years. There was no significant difference in gender or age between the two groups. The mean diagnostic interval time between the primary malignancy and bone lesions was 43.2 ± 47.2 months in Group 1 and 71.6 ± 96.1 months in Group 2, but did not differ significantly.

3.2. Outcome

According to the results of pathological examination of the bone lesion biopsies, 17.9% (21/117) of all the cases were identified as benign lesions and 3.4% (4/117) were malignant lesions unrelated to the primary tumor, as showed in Table 1. Bone metastasis of the primary malignancy accounted for 78.6% (92/117). Liver (*n* = 18), kidney (*n* = 14), breast (*n* = 13) and lung (*n* = 12) were the most common cancers in our study (Table 2).

Table 3 showed that there were 24 single lesion cases (16 in Group 1 and 8 in Group 2) and 59 multiple lesions cases (47 in Group 1 and 12

Table 1
Pathological types of bone lesions unrelated to the primary malignancy (*n* = 25).

Bone lesions	Primary malignancy
Benign	
Aneurysmal bone cyst	Breast
Bone marrow adipogenesis	Liver
Bone necrosis	Breast
Bone tuberculosis	Pancreas
Fibrogenesis	Ovary
Fibrous dysplasia	Breast
Fibrous dysplasia	Thyroid
Inflammation	Glioma
Normal bone and bone marrow	Breast
Normal bone and bone marrow	Breast
Normal bone and bone marrow	Cervix
Normal bone and bone marrow	Colon
Normal bone and bone marrow	Kidney
Normal bone and bone marrow	Lung
Normal bone and bone marrow	Lung
Normal bone and bone marrow	Lung
Normal bone and bone marrow	Lung
Normal bone and bone marrow	Nasopharynx
Osteoid osteoma	Thyroid
Simple bone cyst	Ovary
Solitary fibrous tumor	Rectum
Malignant	
Bone metastasis of lung cancer	Gastrointestinal interstitialoma
Bone metastasis of lung cancer	Rectum
Chondrosarcoma	Lung
Plasmacytoma	Prostate

Table 2
Pathological types of the primary malignancy with bone metastases ($n = 92$).

Type	<i>n</i>
Liver	18
Kidney	14
Breast	13
Lung	12
Stomach	4
Thyroid	4
Colon	3
Esophagus	3
Liposarcoma	3
Rectum	3
Malignant solitary fibrous tumor	2
Nasopharynx	2
Rhabdomyosarcoma	2
Bladder	1
Cholangiocarcinoma	1
Hemangiosarcoma	1
Larynx	1
Melanoma	1
Meningioma	1
Paget's disease of scrotum	1
Prostate	1
Synovial sarcoma	1

Table 3
Comparison of clinical and diagnostic characteristics of the patients between two groups ($n = 117$).

	Group 1	Group 2	<i>P</i>	
Sex	M	51	10	0.171
	F	41	15	
Age (y)		58.0 ± 12.9	57.9 ± 14.7	0.962
Diagnostic interval time (m)		43.2 ± 47.2	71.6 ± 96.1	0.192
Clinical symptoms	Yes	87	20	0.021*
	No	5	5	
Number of bones involved	Single	16	8	0.209
	Multiple	47	12	
Sites of bone biopsy	Axial	43	11	0.808
	Appendicular	49	14	
SUV _{max} (¹⁸ F-FDG PET/CT)		9.7 ± 7.4	9.0 ± 6.2	0.818

* $P < 0.05$.

Table 4
The previous reports of the biopsy results of new bone lesions in the patients with a known malignancy.

Author	Year	Patients with definitive diagnosis	Benign	Malignant unrelated to the primary malignancy	Bone metastases of the primary malignancy	Whether to advocate the bone biopsy
Aoki et al. [6]	2005	35	34.3% (12/35)	0	65.7% (23/35)	Yes
Clayer and Duncan [5]	2006	50	4% (2/50)	18% (9/50)	78% (39/50)	Yes
Toomayan et al. [4]	2011	93	4.3% (4/93)	7.5% (7/93)	88.2% (82/93)	Yes
Raphael et al. [3]	2013	434	23.7% (103/434)	3.5% (15/434)	72.8% (316/434)	Yes
Monfardini et al. [7]	2014	290	15.5% (45/290)	0	84.5% (245/290)	Yes
Cronin et al. [2]	2009	43	0	2.3% (1/43)	97.7 (42/43)	No

in Group 2) confirmed by ¹⁸F-FDG PET/CT or ECT examination; these differences between patient groups were not significant. Biopsy sites of bone lesions included spine, rib, pelvis, proximal femur, proximal humerus and scapula. Fifty-four of the cases involved lesions of the axial skeleton (43 in Group 1 and 11 in Group 2) and sixty-three involved those of the appendicular skeleton (49 in Group 1 and 14 in Group 2); again these were not significantly different. Clinical symptoms reported by patients included pain, movement disorders after pathological fracture and neurologic impairment due to spinal cord or nerve compression. Of the cases with clinical symptoms, 81.3% (87/107) were diagnosed as bone metastases of the primary malignancy. This proportion was significantly higher than that observed in asymptomatic cases (50.0%, 5/10) ($P = 0.021$). In total, 25 patients underwent ¹⁸F-FDG PET/CT examination. The mean maximum standardized uptake values (SUV_{max}) of Group 1 ($n = 18$) and Group 2 ($n = 7$) were similar (9.7 ± 7.4 and 9.0 ± 6.2 , respectively).

4. Discussion

With the increasingly widespread application of ECT and PET/CT in clinical practice, suspicious bone lesions are frequently detected in patients with a known malignant tumor. Patient reported symptoms such as pain, pathological fractures and neurological dysfunction also sometimes leads to the discovery of bone lesions in these patients. Because of the clear history of a primary malignant tumor, the clinicians often take it for granted that these lesions would be the bone metastases of the known malignancy. However, not all new bone lesions are associated with primary tumors [3–7,10].

The performance of an active bone biopsy facilitates a definitive diagnosis of new bone lesions and consequently enables a more targeted treatment to be delivered [7]. However, there is debate over the necessity of performing biopsies for all bone lesions (Table 4). The result of the present study suggested that 17.9% of the biopsied bone lesions were benign and 3.4% were newly discovered malignant bone tumors. These findings are broadly consistent with the review by Raphael et al. [3]. However, it is known that core needle and open biopsy techniques can sometimes result in hematoma, tissue or organ damage, tumor cell dissemination or other complications [8,11]. Therefore unnecessary biopsies should be avoided, especially if a patient has concomitant visceral metastases which lead to an almost definite diagnosis of bone metastasis.

The presence of clinical symptoms is an important factor to consider in deciding whether to perform a bone biopsy. Bone metastases of many malignancies can result in skeletal-related events (SREs) such as bone pain, pathological fractures, spinal cord or nerve compression and hypercalcemia [1]. A retrospective study of 1819 cases by Oster et al. indicated that the incidence of SREs in patients with bone metastases from breast, prostate and lung cancer was up to 22% [12]. When SREs occur, they often compel a patient to visit the hospital, whereupon bone metastasis of a primary malignancy will consequently be diagnosed. The findings of the present study indicated that the presence of clinical symptoms had a significant influence on the strength of the correlation

between bone lesions and primary malignancy. The probability of a diagnosis of bone lesions as being bone metastases of primary malignancy was significantly higher in symptomatic patients compared with asymptomatic ones (81.3% vs. 50.5%, $P = 0.021$). Therefore, it is recommended that the possibility of an asymptomatic bone lesion being benign should be ruled out via meticulous imaging examination and a bone biopsy.

A long diagnostic interval time between a primary malignancy and the new bone lesions may lead to an increasing clinical suspicion of unconfirmed metastatic bone lesions. However, it has been shown that bone metastases from breast cancer, kidney cancer and melanoma can be identified several years after the initial diagnosis of a primary malignancy [2]. In our study, the diagnostic intervals for breast and kidney cancer were 67.8 months (6.1–246.4 months) and 50.1 months (3.4–210.9 months) respectively, while for liver and lung cancer they were only 29.1 months (1.1–159.7 months) and 20.6 months (1.6–51.9 months). On the other hand, new malignant bone tumors are also detected in patients exhibiting a shorter diagnostic interval time [10]. The present study identified a numerically longer average diagnostic interval in Group 2 than Group 1, although the difference was not statistically significant ($P = 0.192$). For the study sample as a whole, the longest diagnostic interval between the primary carcinoma and a metastatic bone lesion was more than 10 years, in a breast cancer patient with bone metastases, while the shortest interval was less than 1 year, for a chondrosarcoma in a lung cancer patient.

As a diagnostic imaging technique, ^{18}F -FDG PET/CT is widely used for screening and diagnosis of metastatic tumors [13]. In clinical practice, SUV_{max} is the usual approach of choice for distinguishing between malignant and benign lesions, and for indicating the degree of malignancy. Nevertheless, sometimes a high uptake of ^{18}F -FDG with an SUV_{max} of more than 10 can occur in certain benign lesions such as tuberculosis or acute inflammation. Conversely, in a malignant tumor with diameter less than 1 cm, low grade malignancies or carcinoid tumors, ^{18}F -FDG uptake is generally low with SUV_{max} of below 2.5 [14]. Moreover, it is not possible to differentiate between primary and secondary malignant bone tumors based on values of SUV_{max} alone. In the present study, there was no significant difference in SUV_{max} between the two patient groups. Hence, this suggested that SUV_{max} was a poor predictor of the correlation between bone lesions and the primary malignancy.

Bone is the third most common organ of distant metastases; bones of the axial skeleton, like spine and rib, are the commonest sites, and those of the appendicular skeleton, like the pelvis and proximal femur, are in the second most common [1,15]. However, in the present study, the results suggested that the site of a bone lesion (axial or appendicular skeleton) was not related to whether the lesion was a metastatic tumor. Although bone lesions of the axial skeleton are more commonly proved metastatic, tuberculosis, osteoporotic pathological fractures and certain hematological malignancies like myeloma and lymphoma also preferentially involve in the axial skeletons. More attention should be paid to the differential diagnosis of spinal lesions.

It has often previously been thought that solitary bone lesions are more likely to be irrelevant to metastases of primary tumors [5,9,16]. Patton et al. reviewed 60 cases of isolated bone lesions unrelated to primary malignant tumors and stressed the need for bone biopsy of a single lesion [10]. However, our findings suggested that the number of bones involved (single or multiple) was not a significant factor influencing the correlation between bone lesions and the primary malignancy. Rather, we consider that these isolated metastatic bone lesions may in fact be an early imaging manifestation of the process of bone metastasis that will evolve into visible multiple bone metastases during the later follow-up. In addition, it is known that other diseases such as tuberculosis, histiocytosis of Langerhans cells, myeloma, and lymphoma can also lead to multiple bone destruction. All of these circumstances increase the complexity of making differential diagnoses.

There are some limitations to our study. Firstly, most of the patients

with bone biopsies were referred by surgery departments of our hospital, which could lead to a selection bias in the composition of the malignant patients. Another limitation is that the decision-making of bone biopsy depended on the experience and judgment of the members of orthopedic oncology MDT in our hospital without standardized criteria. In addition, some benign results, especially when diagnosed as normal bone and bone marrow, might not accord with the true nature of the lesions and would be corrected with the development of the disease [7]. We hadn't yet collected the data about subsequent workup to reassure the initial biopsy results.

5. Conclusions

In summary, the analyses undertaken in the present study suggest that various clinical factors should be taken into account when making clinical judgments on the likely metastatic bone lesions of patients with a known malignant tumor. Based on the above data, we found that, for the patients with preexisted primary malignancy, the emerging of clinical symptoms was a significant factor affecting the clinical link between the new bone lesions and the primary malignancy. Whereas, more than 1/5 of the bone lesions were different from their primary malignancy, especially when there were no symptoms. For the patients with a primary malignancy, prudent discussion and weighing up are necessary and beneficial to them before undergoing the biopsy. As for the newly found bone lesions in these patients, we consider it is worthy to perform active biopsy on those asymptomatic ones to avoid misdiagnosis and less biopsy on symptomatic ones for the sake of less cost and risks.

Conflict of interest

None.

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Supplementary materials

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