

# Analyses of the clinical characteristics of 49 cases of malignancy with multiple bone lesions as the first manifestation

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## Abstract

**Objective** To investigate the clinical features of several cases of malignancy with multiple bone lesions as the first manifestation.

**Methods** Forty-nine cases of malignancy with multiple bone lesions as the first manifestation were retrospectively analyzed from May 2018 to July 2019. All patients complained of “pain at the site of bone lesion” upon admission. Baseline patient information, such as age, gender, location of bone lesions, etiology, diagnosis method, time of onset was collected.

**Results** The median age of the patients was 56 years old, of which 83.7% (41/49) were aged  $\geq 50$  years. The median time of onset was 2 months. Among the cases, 40 were confirmed as solid tumor bone metastasis, whereas the remaining 9 cases as hematological system tumor. Lung cancer and multiple myeloma were the main tumor types, accounting for 40.8% (20/49) and 16.3% (8/49), respectively. Other common causes were seven cases of cancer affecting the digestive system (three cases of liver cancer, three cases of gastric cancer, and one case of esophageal cancer), as well as seven cases of unknown primary cancer. Half of the solid tumors had only multiple bone metastases but no other distant metastasis.

**Conclusion** Multiple bone lesions accompanied by pain may be the first clinical manifestation in various malignant tumors. The common tumor types were lung cancer, multiple myeloma, and digestive system tumor. It is more common in people aged 50 years and older. Multiple bone lesions might be the only metastasis site of some solid tumors, and its mechanism needs further investigation.

**Key words:** Bone lesions, malignancy, bone metastasis, clinical characteristics

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The incidence of malignant tumors has been increasing annually, and advanced malignant tumors are one of the most common causes of deaths<sup>[1]</sup>. Bones are one of the most common metastatic sites of malignant tumors<sup>[2]</sup>. The onset of some malignant tumors is occult, and patients may not show the symptoms of primary lesions. Multiple bone metastases or multiple bone diseases may only be detected when the tumor affects the bone and causes bone pain. Hence, bone pain may be the only or the first manifestation of the tumor, and it can often be misdiagnosed and mistreated.

With the continuous development of tumor treatment, the survival time of advanced malignant tumor is prolonged. Early detection and intervention of advanced

malignant tumor will help to improve the overall survival of patients. At the same time, bone metastasis may lead to bone related events, multiple bone destruction is more prone to bone related events, and seriously affect the quality of life of patients. Early detection and intervention will significantly improve the quality of life of patients. Many types of malignant tumors have multiple bone destruction as the initial manifestation, but no systematic clinical report has been published on the clinical characteristics and diagnosis of this kind of disease.

In this study, 49 cases with multiple bone destruction as the first manifestation were treated and analyzed in our oncology department. The clinical characteristics of

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these diseases were preliminarily discussed. We hope to provide a new direction for the diagnosis and treatment of such diseases.

## Materials and methods

A retrospective analysis was made on 49 cases with multiple bone destruction as the first manifestation in the oncology department of Tongji Hospital from May 2018 to July 2019.

All cases met the following criteria: (1) The chief complaint was “pain at the bone destruction site”, and multiple bone destruction was the first manifestation of the patient. (2) The patients had at least three bone destruction sites that have not been directly invaded by the same mass. (3) Malignant tumor was confirmed by pathology or cytology. (4) The patients had no history of tumor.

The patients were examined via positron emission computed tomography (PET-CT) or conventional imaging examination methods, such as CT, MRI, and radionuclide bone scan (ECT). One or more examinations, such as biopsy of bone lesions, biopsy of primary focus, puncture cytology, or bone marrow biopsy, were performed to confirm the diagnosis.

Baseline patient information, such as age, gender, bone lesion location, etiology, diagnosis method, onset time, imaging examination methods used, and other information, was collected. The onset time of the patient was defined as the time from the onset of pain symptoms to the examination of multiple bone destruction.

## Results

### Patients' characteristics

The clinical data of 49 patients were analyzed. All patients complained of “pain”, and the first manifestation was multiple bone destruction. Among them, 27 were males and 22 were females, and the male-to-female ratio was 1.23. The median age of the patients was 56 years (34–79 years), and 41 patients (83.7%) were over 50 years old. The median onset time was 2 months (ranging from 10 days to 1 year);  $\leq 2$  months for 28 cases, 2–6 months for 18 cases, and 7 months up to 1 year for 3 cases. Laboratory examination revealed that 29 cases (59.1%) had elevated alkaline phosphatase, and 19 cases (38.8%) had anemia, including 17 cases of mild anemia (hemoglobin 90 g/L to lower limit of normal value) and 2 cases of moderate anemia (hemoglobin 60–90 g/L). The common bone-related events were spinal cord compression in 3 cases, pathological fracture in 11 cases, hypercalcemia in 2 cases, bone metastasis radiotherapy in 10 cases, and spinal surgery in 2 cases (Table 1).

Twenty cases of solid tumor had only multiple bone

**Table 1** Clinical characteristics of 49 patients

Variables	No. of patients ( <i>n</i> = 49)
Gender	
Male	27
Female	22
Age (years)	
< 40	3
40–49	5
50–59	20
$\geq 60$	21
Onset times (months)	
$\leq 2$	28
$>2$ and $\leq 6$	18
$> 6$	3
ALP	
$> \text{ULN}$	29
Anemia	
Mild	17
Middle	2
Skeletal related events	
Spinal cord compression	3
Pathologic fractures	11
Hypercalcemia	2
Radiation to bone	10
Surgery to bone	2
Metastasis to other organ	
Regional lymph node	16
Distant metastasis	20

ALP: Alkaline phosphatase; ULN: Upper limit of normal value

metastases and no other distant metastasis (accounting for 50% of solid tumors). Sixteen cases of solid tumor had regional lymph node metastasis.

Given that the biopsy tissue was small, only 12 cases of solid tumor were classified by analyzing pathologic differentiation degree. Among them, 11 cases were poorly differentiated carcinoma, and 1 case was highly differentiated carcinoma.

### Etiology of bone destruction

The diagnosis of primary tumor was confirmed via imaging examination, cytology, and pathology. The diagnosis of multiple myeloma also required routine laboratory examination. A total of 25 patients were examined via PET. The final diagnosis of 19 patients was largely consistent with the judgment of the primary disease via PET, and the coincidence rate was 76%.

Forty cases of solid tumors, including 20 cases of lung origin (13 cases of adenocarcinoma, 3 cases of squamous cell carcinoma, 1 case of small cell, and 3 cases of undetermined pathological classification), 7 cases of digestive tract origin (3 cases of liver cancer, 3 cases of gastric cancer, and 1 case of esophageal cancer), and 7 cases of unknown primary tumor metastasis (4 cases of

adenocarcinoma, 2 cases of undetermined pathological type, and 1 case of neuroendocrine carcinoma). The other types of tumors were 4 cases of prostate cancer, 1 case of nasopharyngeal carcinoma, and 1 case of mediastinal neuroendocrine carcinoma. There were 9 cases of hematological tumors: 8 cases of multiple myeloma, and 1 case of lymphoma bone marrow infiltration (Table 2).

### Bone metastasis pattern

PET/CT, SPECT, CT, and MRI are all effective detection methods for malignant bone lesions. In this study, four patients were assessed via CT scan only, whereas the rest were examined via two or more of the aforementioned methods. Malignant bone lesions involved multiple skeletons in the whole body, including spine, pelvis, sternum, ribs, femur, humerus, scapula, skull, and clavicle. The most common sites of bone destruction were thoracic vertebrae (73.5%), lumbar vertebrae (71.4%), ribs (65.3%), and pelvis (69.4%). Twenty-three cases (46.9%) had five or more bone metastasis sites (Table 3).

**Table 2** Etiology of the patients

Primary tumors	No. of patients (%) (n = 49)
Lung cancer	20 (40.8%)
Adenocarcinoma	13
Small cell lung cancer	1
Squamous cell carcinoma	3
Others	3
Digestive system cancer	7 (14.3%)
Liver cancer	3
Gastric cancer	3
Esophageal cancer	1
Other solid tumor	13 (26.5%)
Prostatic cancer	4
Nasopharyngeal carcinoma	1
Mediastinal tumor	1
Unknown primary origin	7
Hematological tumors	9 (18.4%)
Multiple myeloma	8
Lymphoma	1

**Table 3** Location of bone lesions

Metastatic site	No. of patients (%) (n = 49)
Cervical vertebra	19 (38.8)
Thoracic vertebra	36 (73.5)
Lumbar vertebra	35 (71.4)
Sacral vertebrae	22 (44.9)
Ribs	32 (65.3)
Pelvis	34 (69.4)
Humerus	17 (34.7)
Femur	18 (36.7)
Sternum	15 (30.6)
Scapula	10 (20.4)
More than 5 metastatic sites	23 (46.9)

## Discussion

Bones are often invaded by malignant solid tumors and multiple myeloma. Bone destruction due to bone metastasis or bone involvement can cause pain and other bone-related events that seriously affect the quality of life of patients [3-4]. Some of the patients who were recently diagnosed with bone metastases had bone metastasis after the primary malignant tumor was confirmed, but they did not have symptoms of bone metastasis. In the other part patients, bone pain due to bone metastasis is the first manifestation. In these patients, bone pain was often not accompanied by primary tumor symptoms. The diagnosis of multiple bone metastases is often delayed. Timely detection of multiple bone destruction lesions and identification of the primary cause may avoid misdiagnosis and mistreatment of such diseases. Doing so will help in improving the quality of life of patients and in increasing their survival rate.

All the patients in this study were diagnosed with bone destruction due to bone pain, and multiple bone destruction was found at the initial diagnosis. The median time from bone pain to the diagnosis of multiple bone destruction was 2 months (ranging from 10 days to 1 year). Among the patients, 83.7% were over 50 years old. According to previous studies, the incidence of bone metastasis in advanced malignant tumors is 65%–75% in breast cancer, 65%–75% in prostate cancer, 67%–75% in nasopharyngeal carcinoma, 30%–40% in lung cancer, 14%–45% in melanoma, 13%–41% in liver cancer, 1%–7% in colorectal cancer, and 13% in gastric cancer [4]. In this study, we found that the solid tumors with multiple bone destruction as the first manifestation were lung cancer and gastrointestinal tumor. Prostate cancer was observed in four cases, and nasopharyngeal carcinoma was noted in one case. No one among the patients had breast cancer. This result was not consistent with the reported incidence of bone metastasis of advanced tumors. We analyzed two possible reasons that explain this discrepancy. First, breast cancer, prostate cancer, and nasopharyngeal carcinoma are more likely to have primary lesion symptoms, and thus the primary tumors are easily confirmed. Second, the previous reports included not only newly diagnosed bone metastases but also diagnosed bone metastases after disease progression. In this study, patients with bone metastasis or osteopathy as the first manifestation were included. The clinical characteristics and pathogenesis between early multiple bone metastases and late bone metastases (after disease progression) must be further studied. Kim et al reported that the overall survival after the diagnosis of metastatic or recurrent gastric cancer (MRGC) is substantially shorter in the initial BM group ((BM present at initial diagnosis of MRGC) than in the late bone metastasis group [5]. Therefore, malignant tumors

with multiple bone metastases as the first manifestation may have different biological behaviors. The study of these phenomena will provide a new direction for the treatment of these diseases. At the same time, 12 cases of the above carcinoma were classified by pathologic degree. We found that 11 cases (91.7%) were poorly differentiated and only 1 case was well differentiated. This suggests that poorly differentiated cancer is more likely to have distant bone metastasis.

In this study, the most common primary tumor with multiple bone destruction was lung cancer, accounting for 40.8% of all cases and 50% of solid tumors. Lung adenocarcinoma was the most important pathological type. In China, the incidence of lung cancer in men and women is increasing every year. In the whole population, lung cancer is the most common malignant tumor in the country and also the main cause of cancer-related deaths [6]. Bone metastasis is one of the most common metastatic sites of lung cancer. Some studies reported that the bone is the most common distant metastatic site in newly diagnosed stage IV NSCLC [7]. He *et al* [8] found that lung adenocarcinoma is the most important pathological type in patients with lung cancer with initial bone metastasis, and the prognosis of patients with bone metastasis from lung adenocarcinoma is better than that of patients with squamous cell carcinoma. With the continuous improvement of lung cancer treatment methods and technologies, the expected survival rate of patients with advanced lung cancer can be prolonged. The detection of patients with lung cancer with bone metastasis should be timely to improve the quality of life and prolong the survival of patients. Therefore, patients with unexplained bone and joint pain or bone destruction, especially those over 50 years old, should be considered for routine lung CT screening. Nevertheless, this proposal must be explored further.

The second most common bone destruction tumor found in this study was multiple myeloma. This tumor is closely related to the clinical characteristics of mm. About 70%–90% of patients with multiple myeloma may have bone damage accompanied with bone pain and other bone-related events, and about two-thirds may suffer from bone pain. Multiple myeloma is often complicated with hypercalcemia, renal insufficiency, anemia, and other symptoms. Routine blood biochemical examination of patients with multiple myeloma shows elevated globulin levels. PET/CT has a high value in the differential diagnosis of solid tumor bone metastasis and MM [9]. Nevertheless, the final diagnosis should be combined with blood tests, urine tests, bone marrow tests, and imaging examination. The risk of multiple myeloma is much higher in older age groups. The relative 5-year survival rate was about 45% in the period 2019–2020 [10]. Bone pain is a common symptom in elderly patients.

Multiple myeloma may be one of the causes of occult disease. Therefore, timely examination and diagnosis can help to improve the diagnosis rate of this kind of disease and improve the overall survival of patients.

Another common tumor type found in this study was digestive system tumors, including liver cancer and gastric cancer. This result suggested that the origin of digestive tract, especially the liver and stomach, for multiple bone metastases of unknown origin should be considered. Bae *et al* reported a rare case of small solitary HCC, presenting multiple bone involvement as a first manifestation of extrahepatic metastasis in patient with no cirrhotic liver [11]. Gastric cancer with initial bone metastasis has been reported in some studies, and the prognosis is poor. Gomi *et al* also suggest that gastric cancer should be considered in the differential diagnosis in patients initially presenting with single or multiple bone metastases [12].

Moreover, this study found seven cases of patients with unknown primary metastatic carcinoma, of which the most common pathological type was adenocarcinoma, which was consistent with the study of unknown primary metastatic carcinoma. Previous studies established that adenocarcinoma is the most common pathological type of unknown primary metastatic carcinoma [13].

Malignant bone lesions often involve the spine, pelvis, ribs, skull, and femur [4]. Our study revealed that in patients with multiple bone destruction as the first manifestation, the spine, ribs, and pelvis were the most common metastatic sites. Furthermore, about half of the patients with solid tumors only had multiple bone metastases and no other distant metastases. Therefore, further study on the clinical characteristics and pathogenesis of malignant tumors with multiple bone metastases as the first manifestation will help to improve our understanding of this disease. Multiple bone metastases are more prone to bone-related events [14–15]. This study had 11 cases of pathological fracture, 2 cases of hypercalcemia, 10 cases of bone metastasis radiotherapy, and 2 cases of spinal surgery. Therefore, patients with newly diagnosed multiple bone destruction diseases should be given active treatment as soon as possible and educated on the prevention of bone-related events. Bone destruction can be examined via ECT or PET-CT, CT or MRI, And X-ray examination [16–17]. The patients in our group were mostly examined via PET/CT, ECT, and CT/MRI. These methods can detect bone destruction earlier than X-ray examination, Moreover, through these methods, multiple bone destruction lesions can be easily spotted. PET/CT is one of the most important methods for examining unknown primary metastatic carcinoma [18]. In this study, the coincidence rate of PET in the diagnosis of primary disease was 76%.

## Conclusion

Multiple bone destruction with bone pain is one of the first manifestations of various malignant tumors. Diagnosis of this condition is often delayed. Imaging examination should be promptly conducted. The most common tumors associated with this disease are lung cancer, multiple myeloma, and digestive system tumors. It can occur at different ages, but it is more common in people aged 50 years and older. Targeted examination should be performed to determine the cause in time. Routine lung CT examination will be helpful to the screening of lung cancer in patients with bone pain as the first manifestation. Multiple bone destructions are more likely to be associated with bone-related events. Thus, patients should be educated on pathological fractures. This study was retrospective in nature, and the sample size was small. Solid tumors with multiple bone destruction as the initial manifestation may have unique biological behaviors that should be explored in prospective studies and related basic research.

## Conflicts of interest

The authors indicated no potential conflicts of interest.

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