



Contents lists available at ScienceDirect

## Current Problems in Cancer

journal homepage: [www.elsevier.com/locate/cpcancer](http://www.elsevier.com/locate/cpcancer)

## Prevalence of bone pain decreases as lymph node stage increases in nonsmall cell lung cancer patients



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### ARTICLE INFO

#### Keywords:

Bone metastasis

Bone pain

Clinical N0

Fluorodeoxyglucose-positron emission tomography/CT

Non-small cell lung cancer

### ABSTRACT

According to lung cancer guidelines, positron emission tomography scan is recommended for initial evaluation of bone metastasis. However, guidelines differ in their recommendations for when it should be used. We investigated the appropriate use of bone imaging in nonsmall cell lung cancer (NSCLC) patients.

One hundred seventy-seven consecutive NSCLC patients who had distant metastases at presentation and were admitted between January 2012 and April 2016 were retrospectively reviewed. Among patients with bone metastases, we explored bone pain, number of bone metastases, location of bone metastases, and clinical tumor (T) and lymph node (N) classification.

Sixty-three patients had bone metastases. There was a trend toward an increase in prevalence of bone metastases as lymph node stage increased. The prevalence of bone pain

\* Formatting of funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The authors have no conflicts of interest to declare.

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significantly decreased as N stage increased ( $p=0.017$ ). N0 and N2-3 patients were more likely to have multiple bone metastases ( $p=0.038$ ). Compared with patients who had a single bone metastasis, patients with multiple metastases had a significantly higher probability of having at least 1 bone metastasis located in the thorax or upper abdomen. All N0 patients have at least 1 bone metastasis in the thorax or upper abdomen.

Clinical N0 NSCLC patients with bone metastasis are likely to have bone pain and have multiple bone metastases. N2-3 patients are more likely to have bone metastases but less likely to have bone pain. If NSCLC patients do not have bone pain, and CT of the chest and upper abdomen does not reveal any lymph node or bone metastasis, further survey for bone metastases may be omitted; bone imaging should be performed in N2 and N3 patients regardless of symptoms.

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## Introduction

Approximately 40% of patients with nonsmall cell lung cancer (NSCLC) develop bone metastases.<sup>1</sup> In lung cancer, it is known that adenocarcinoma and squamous cell carcinoma is associated with higher and lower risks of developing bone metastases.<sup>1</sup> Bone metastases frequently lead to skeletal morbidity that can negatively impact both quality of life and survival.<sup>2</sup> For NSCLC patients with bone metastases, systemic treatment is firstly recommended, but skeletal-related events including bone pain, symptomatic pathologic fracture, and spinal cord compression often require surgery and/or radiation therapy immediately.

Guidelines differ in their recommendations for initial evaluation of NSCLC.<sup>3–6</sup> The European Society for Medical Oncology guideline states that bone imaging is required when bone metastasis is clinically suspected. The American College of Chest Physicians guideline states that positron emission tomography (PET) scan is not required in patients with “peripheral stage clinical IA.” On the other hand, the Japan Lung Cancer Society and National Comprehensive Cancer Network (NCCN) guidelines state that fluorodeoxyglucose (FDG)-PET/CT is recommended for initial systemic screening of metastasis regardless of symptom or stage. We therefore analyzed NSCLC patients with bone metastases to determine the appropriate use of bone imaging.

## Methods

### *Patients*

This study was approved by the Institutional Review Board at The University of Tokyo Hospital. One hundred twenty-four consecutive NSCLC patients with distant metastasis were admitted to the University of Tokyo Hospital between January 2012 and April 2016, and data from 177 patients with distant metastases at presentation were retrospectively reviewed. To evaluate clinical characteristics of metastatic NSCLC with hematogenous spread, we excluded 46 cases with pleural dissemination, 3 cases with distant lymph node metastases, and 1 case with both and finally compared clinical characteristics between 63 patients with bone metastases and 61 patients with distant metastases other than bone. Among patients with bone metastases, we explored bone pain, number of bone metastases, location of bone metastases, and clinical tumor (T) and lymph node (N) classification. We assessed bone pain caused by bone metastases at the discretion of the treating physician.

**Table 1**

Clinical characteristics of patients with bone metastases and metastases excluding bone metastases.

		Bone metastases (N = 63)	Metastases other than bone (N = 61)	P
Age, median ± SD		66 ± 10	67 ± 9	
Gender, N (%)	Male	35 (56)	39 (64)	0.37
	Female	28 (44)	22 (36)	
Smoking history, N (%)	Smoker	40 (63)	39 (64)	1.0
	Non-smoker	23 (37)	22 (36)	
Pathology, N (%)	Ad	43 (68)	47 (78)	0.28
	Sq	6 (10)	7 (11)	
	NSCLC	14 (22)	7 (11)	
Mutation, N (%)	EGFR	23 (53)	18 (38)	0.12
	ALK	0 (0)	3 (6)	
	none	20 (47)	26 (55)	

Ad, adenocarcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; N, number of patients; NSCLC, nonsmall cell lung cancer; SD, standard deviation; Sq, squamous cell carcinoma.

### Staging

CT of the chest and upper abdomen was defined as scans between the first thoracic vertebra and the second lumbar vertebra and/or inferior margin of liver. Staging was determined according to the seventh edition of the Union of International Cancer Control (UICC) TNM classification. Lymph node metastasis was diagnosed by FDG-PET/CT and/or contrast-enhanced CT. Diagnosis of bone metastases were made by FDG-PET/CT in 70% of cases, by bone scintigraphy in 20% of cases, by contrast-enhanced CT in 10% of cases, and by MRI in 8% of cases, with some overlap.

### Statistical analysis

To compare 2 groups, contingency tables were prepared. Fisher's exact test was performed for 2 × 2 comparisons, and Chi-square test was performed for all other comparisons. Statistical analysis was performed using SigmaPlot (Systat) version 12.3.

### Results

Clinical characteristics of patients with bone metastases and patients with metastases excluding bone metastases are shown in Table 1. The 2 groups were similar in age, sex, smoking status, pathologic diagnosis, and frequency of gene mutations. Among the 63 patients with bone metastases, 35 (56%) had metastases to other organs.

Table 2 shows the ratio of patients with bone metastases according to clinical TN classification. Tumor factor did not associate with the presence of bone metastases, while prevalence of bone metastases tended to increase as lymph node stage increased. However, relying only on N factor to determine the necessity of bone imaging would lead to many missed bone metastases. We next analyzed whether bone pain would be a predictor of metastases. The prevalence of bone pain significantly decreased as N stage increased, and all clinical N0 patients had bone pain (Table 3).

We analyzed whether prevalence of bone pain was higher among lower N stage patients because they were more likely to have multiple bone metastases. We found that multiple bone metastases occur more frequently in clinical N0 and N2-3 patients but less in N1 patients (Table 4). We next determined whether bone pain was present more frequently in patients with multiple metastasis, and found that having a single or multiple bone metastases did not associate with presence of bone pain (Table 4).

**Table 2**

Number of patients with bone metastases according to clinical tumor (T) and lymph node (N) classification.

	Bone metastases (N = 63)	All metastases (N = 124)	Patients with bone metastases (%)
T1	12	23	52
T2	24	45	53
T3	10	16	63
T4	17	40	43
N0	7	22	32
N1	10	20	50
N2	23	44	52
N3	23	38	61

**Table 3**

Association between clinical lymph node (N) stage and bone pain in patients with bone metastasis.

	Bone pain		<i>P</i>
	Positive (N = 36)	Negative (N = 27)	
N0	7	0	0.002
N1	7	3	
N2	15	8	
N3	6	17	

**Table 4**

Association between number of bone metastases and lymph node (N) stage, bone pain, and location of bone metastases.

		Number of bone metastases		<i>P</i>
		Single (N = 20)	Multiple (N = 43)	
N stage	N0	1	6	0.038
	N1	7	3	
	N2	6	17	
	N3	6	17	
Bone pain	Positive	11	25	1.0
	Negative	9	18	
Location of bone metastases	At least 1 in thorax or upper abdomen	10	40	<0.001
	None in thorax or upper abdomen	10	3	

We next analyzed the association between the number and location of bone metastases to determine whether patients with multiple bone metastasis are likely to have at least 1 bone metastasis located in the thorax or upper abdomen (Table 4). Compared with patients who had a single bone metastasis, patients with multiple metastases had a significantly higher probability of having at least 1 bone metastasis located in the thorax or upper abdomen. Notably, all 7 N0 patients had bone metastases located in the thorax or upper abdomen.

## Discussion

We found that the prevalence of bone metastases tended to increase as N stage increased, and clinical N0 patients with bone metastases were more likely to have bone pain, have multiple bone metastases, and have at least 1 bone metastasis in the chest or upper abdomen, while N2 and N3 patients are more likely to have bone metastases but less likely to have bone pain.

Previous analysis of clinical T1-2N0 cases has shown that extrathoracic imaging may not be necessary in asymptomatic patients, because silent metastasis was detected only in 0.5% of T1N0 cases and 0.9% of T2N0 cases.<sup>7</sup> Based on this report, American College of Chest Physicians cur-

rently recommends against routine bone scan for patients with clinical stage IA NSCLC.<sup>4</sup> In addition, Li et al reported that bone imaging is not required for cT1N0 NSCLC patients who are older than 50 years old, with no skeletal symptoms, and serum CEA level less than 5 µg/mL.<sup>8</sup> The European Society for Medical Oncology guideline states that bone imaging is required if bone metastases are clinically suspected.<sup>3</sup> On the other hand, Schirrmeyer et al reported that 14%–22% of patients with bone metastases would be overlooked if bone scans were performed only when patients had symptoms.<sup>9</sup> The first 2 conclusions are based on findings that the prevalence of asymptomatic bone metastases in early-stage NSCLC patients is very small. By analyzing patients with bone metastases, we conclude that clinical N0 NSCLC patients without bone metastases on the chest and upper abdomen CT and without symptoms suggestive of bone pain may not need bone imaging, while N2 and N3 NSCLC patients need bone imaging regardless of symptoms.

Our results show that N0 patients without symptoms suggestive of bone metastases do not need bone imaging. This does not mean these patients can omit PET scans altogether, as guidelines recommend PET scans to detect lymph node metastasis and distant metastasis. On the other hand, guidelines differ on whether patients who are considered stage IA by chest and abdominal CT need PET scans. Therefore, whether PET scans may be omitted in stage IA patients without bone pain requires further validation. In addition, in clinical practice, patients sometimes do not undergo PET scans due to cost, availability, or high blood glucose. Our results are likely helpful in this population of patients.

NSCLC without lymph node metastasis were less likely to metastasize to the bone (Table 2); however, when they did, they were likely to produce bone pain (Table 3), have multiple metastasis (Table 4), and have at least 1 bone metastasis in the thorax or upper abdomen. Conversely, N2–3 NSCLC were more likely to metastasize to the bone, less likely to produce bone pain, and have multiple metastasis. These findings suggest that N0 NSCLC that metastasize to the bone have high affinity toward bone, although it is not clear why N0 patients with bone metastases are likely to have bone pain. Bone pain has long been considered to be caused by stimulation of sensory fibers distributed in periosteum. It is now known that bone pain is also associated with factors such as prostaglandins, endothelin, nerve growth factor, or ATP produced by cancer cells or inflammatory cells.<sup>10</sup> Bone pain may also be caused by activation of several acid sensing receptors by local tissue acidosis.<sup>11</sup>

This study has several limitations. First, the number of cases was small and data were analyzed retrospectively. Second, lymph node metastases were diagnosed mostly by FDG-PET/CT and some by contrast-enhanced CT, and not by pathologic testing such as EBUS-TBNA. Third, diagnosis of bone pain was made at the discretion of the treating physician. Fourth, lung cancer spreads to distal extremities more often than other cancers<sup>12</sup>; however, because bone metastases were detected mostly by FDG-PET/CT, some bone metastases may have been overlooked.

## Conclusions

In summary, patients without lymph node metastasis but with bone metastasis were more likely to have bone pain, have multiple bone metastases, and have at least 1 bone metastasis between the chest and upper abdomen. If NSCLC patients are clinical N0, do not have bone pain, and CT of the chest and upper abdomen does not reveal any bone metastasis, further survey for bone metastases may be omitted; if they are N2–3, bone imaging should be performed regardless of symptoms.

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