

Clinical features and prognostic factors in patients with bone metastases from non-small cell lung cancer

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Xiao-Tian Wu^{1,*} , Jian-Wei Zhou^{2,*},
Long-Ci Pan²  and Ting Ge²

Abstract

Objective: To investigate the clinical features and evaluate the prognostic factors in patients with bone metastases from non-small cell lung cancer (NSCLC).

Methods: We retrospectively investigated 356 patients with NSCLC with bone metastases from January 2012 to December 2017. The overall survival (OS) and 1-year survival rate were calculated by Kaplan–Meier analysis and compared by univariate analysis using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model.

Results: A total of 694 sites of bone metastases were determined among the 356 patients. The most common site of bone metastases was the ribs. The median OS was 12.5 months and the 1-year survival was 50.8% in the overall population. Univariate analysis revealed that histological type, number of bone metastases, Eastern Cooperative Oncology Group performance status (ECOG PS), bisphosphonate therapy, and serum calcium, lactate dehydrogenase, and alkaline phosphatase were significantly correlated with prognosis. Multivariate analysis identified multiple bone metastases, ECOG PS ≥ 2 , lactate dehydrogenase ≥ 225 U/L, and alkaline phosphatase ≥ 140 U/L as independent negative prognostic factors.

Conclusion: Multiple bone metastases, high ECOG PS, and high serum alkaline phosphatase and lactate dehydrogenase are independent negative prognostic factors for bone metastases from NSCLC.

*These authors contributed equally to this work.

Corresponding author:

Long-Ci Pan, Department of Oncology, Qingpu Branch of Zhongshan Hospital, Fudan University, No. 1158 Gongyuan Road, Shanghai 201700, China.
Email: panda0925@sina.com

¹Department of Orthopedics, Qingpu Branch of Zhongshan Hospital, Fudan University, Shanghai, China

²Department of Oncology, Qingpu Branch of Zhongshan Hospital, Fudan University, Shanghai, China



Keywords

Bone metastasis, non-small cell lung cancer, prognostic factor, alkaline phosphatase, lactate dehydrogenase, Eastern Cooperative Oncology Group performance status

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Introduction

Bone metastasis is defined as a primary malignant non-hematopoietic cancer transmitted to the skeletal system via the blood or lymph. Cytokines and chemical mediators released from cancer cells stimulate the periosteum, increase mechanical pressure on the bone, and generate osteolytic lesions, leading to serious bone pain. Bone metastases may be associated with various skeletal-related events (SREs), including pathological fractures, spinal cord compression, and hypercalcemia of malignancy, requiring surgical intervention and/or palliative radiotherapy.¹ The occurrence of SREs significantly decreases the patient's quality of life and increases the risks of morbidity and mortality.² Bone metastases are the most common distant metastases, occurring in about 15% to 40% of patients with lung cancer, and are associated with shorter survival compared with metastases to other systems.^{3,4} Moreover, improvements in the treatment of lung cancer have prolonged the median survival time, thus increasing the risk of bone metastases during the patient's remaining lifetime.

Non-small cell lung cancer (NSCLC) accounts for about 85% to 90% of all lung cancers.⁵ The early diagnosis and prevention of bone metastases are therefore important and can increase the survival rate of patients with NSCLC. An evaluation of the relevant prognostic factors is necessary to ensure the optimal prevention of and precise therapy for bone metastases from NSCLC.⁶ However, the independent prognostic factors for bone metastases

from NSCLC remain unclear, and relevant studies are scarce and controversial.²⁻⁷ In this retrospective study, we investigated the clinical features and evaluated the prognostic factors in patients with bone metastases from NSCLC.

Patients and methods

Patients

We retrospectively investigated patients with NSCLC with bone metastases treated at Qingpu Branch of Zhongshan Hospital from January 2012 to December 2017. All patients had a histological or cytological diagnosis of NSCLC. The diagnosis of bone metastasis was confirmed by positive results of more than two examinations, including X-ray, computed tomography, magnetic resonance imaging, radionuclide bone scan, and positron emission tomography.

Clinical features

Multiple clinical variables were evaluated as potential prognostic factors, including age, sex, number of primary lesions, histological type, number of bone metastases, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), surgery for primary lesions, chemotherapy, radiotherapy, and bisphosphonate therapy. We also assessed serum concentrations of biochemical and biological markers, including calcium, sodium, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), neuron-specific

enolase (NSE), carbohydrate antigen 125 (CA125), and carbohydrate antigen 199 (CA199). According to standard laboratory values, hyponatremia was defined as a serum sodium level <135 mmol/L and hypercalcemia as a serum calcium level ≥ 2.4 mmol/L. The following upper cut-off values were applied: LDH 225 U/L, ALP 140 U/L, CEA 5 ng/mL, CYFRA21-1 3 ng/mL, NSE 20 ng/mL, CA125 35 U/mL, and CA199 27 U/mL.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). The overall survival (OS) and 1-year survival rate were calculated using the Kaplan–Meier method. OS was defined as the time from diagnosis of bone metastasis to the date of death or the last follow-up.⁶ Survival differences were compared by univariate analysis using the log-rank test. Independent prognostic factors were identified by multivariate analysis using the Cox proportional hazards model. Odds ratios and 95% confidence intervals were

calculated. A P value < 0.05 was considered to be statistically significant.

This study was approved by Zhongshan Hospital Ethics Committee and all procedures were conducted in accordance with the Declaration of Helsinki. All participants signed written informed consent.

Results

A total of 356 patients with NSCLC with bone metastases were included in the study, including 213 men and 143 women. Their median age was 53 years (range 23–89 years) and 252 patients were aged 50 years or older. Based on the histological classification, 203 patients were identified as having adenocarcinoma, 98 squamous cell carcinoma, and 55 not otherwise specified (NOS). A total of 694 sites of bone metastases were determined, including 401 in patients with adenocarcinoma, 234 for squamous cell carcinoma, and 59 for NOS. The most common site of bone metastases was the ribs ($n = 186$), followed by the thoracic ($n = 147$) and lumbar spine ($n = 116$). The least affected site was the tibia/fibula (Table 1).

Table 1. Sites of bone metastases for different histological types of non-small cell lung cancer.

Histology	Adenocarcinoma	Squamous	NOS	
Skull	12	7	4	23
Scapula	15	11	2	28
Clavicle	9	4	2	15
Rib	109	60	17	186
Humerus	11	8	0	19
Cervical spine	29	11	5	45
Thoracic spine	86	50	11	147
Lumbar spine	58	45	13	116
Pelvis	45	29	5	79
Femur	23	8	0	31
Tibia and fibula	4	1	0	5
Total	401	234	59	694

NOS: not otherwise specified.

A total of 187 patients were former or current smokers. Most patients ($n=267$) had an ECOG PS >2 . At the time of diagnosis, 225 patients had bone metastases at more than two sites and 131 patients had single bone lesions. The median OS was 12.5 months and the 1-year survival rate was 50.8%. The correlations between clinical factors and OS are summarized in Table 2. Univariate analysis identified histological type ($P=0.019$), number of bone metastases ($P=0.005$), ECOG PS ($P<0.001$), bisphosphonate therapy ($P=0.041$), serum calcium ($P=0.037$), LDH ($P=0.009$), and ALP ($P=0.009$) as factors significantly correlated with prognosis (Table 2). Multivariate analysis confirmed that multiple bone metastases, ECOG PS ≥ 2 , LDH ≥ 225 U/L, and ALP ≥ 140 U/L were independent negative prognostic factors. The risks of multiple bone metastases and ECOG PS ≥ 2 were 2.169 times ($P=0.009$) and 1.967 times ($P=0.006$) greater than the risks of single bone metastasis and ECOG PS <2 , respectively. Patients with high serum LDH levels and ALP levels had 1.194-fold ($P=0.025$) and 1.383-fold ($P=0.013$) increased risks of shorter OS, respectively. Despite the positive findings in univariate analysis, histological type was not a significant independent prognostic factor in multivariate analysis (Table 3).

Discussion

This study found that the ribs and thoracolumbar spine, which are relatively close to the lungs, were the most common sites of bone metastases from NSCLC. Cancer cells mainly spread via the blood circulation, and the bones of the trunk are rich in red bone marrow, with abundant capillary vessels. With intercostal and vertebral vein branches, the ribs and thoracolumbar spine provide favorable conditions for the colonization and proliferation of cancer cells,

which express high levels of adhesion molecules. Metastases may thus occur in the bones of the trunk at an early stage, followed by the limb bones at more advanced stages.⁸ In the current study, adenocarcinoma was associated with the highest incidence of bone metastases, possibly because it often occurs in the margins of the lung, making it easy for the cancer cells to invade the blood system at an early stage.

The relationship between lung cancer histology and the risk of bone metastasis is controversial. Different histological types have shown distinct prevalence and heterogeneity in relation to bone metastases. Oliveira et al.⁹ revealed that adenocarcinoma was associated with a higher risk and squamous cell carcinoma with a lower risk of bone metastases, while Zhang et al.¹⁰ also suggested that adenocarcinoma had a poorer prognosis than other histological types. However, squamous cell carcinoma has also been associated with a bad prognosis,¹¹ and patients with non-adenocarcinoma were documented as being more likely to have SRE throughout the course of NSCLC.¹² Wang et al.¹³ reported that patients with adenocarcinoma were prone to bone metastases and that squamous cell carcinoma had a poor prognosis. However, the current results indicated that histological type was not an independent prognostic factor for OS in multivariate analysis. This may be because recent epidermal growth factor receptor mutation-targeted therapies have prolonged the survival time, especially in patients with adenocarcinoma, who tend to have a higher incidence of this mutation.^{7,14}

The results of the current study were consistent with previous studies, revealing that the number of bone metastases and ECOG PS have significant impacts on survival time in patients with NSCLC.^{15,16} Multiple bone metastases often indicate high activity and malignancy of cancer cells, while the ECOG PS is the standard

Table 2. Characteristics of patients with bone metastases from non-small cell lung cancer and univariate analysis of prognostic factors.

Clinical factor	Number of patients	Median OS (months)	1-year survival rate (%)	P value
Total	356	12.5	50.8	
Sex				
Male	213	13.6	48.5	0.692
Female	143	11.9	52.9	
Age (years)				
<50	104	13.8	55.9	0.782
≥50	252	11.2	49.9	
Number of primary lesions				
Single	276	13.2	56.3	0.753
Multiple	80	5.3	30.1	
Histology				
Adenocarcinoma	203	8.4	34.2	0.019
Squamous	98	13.5	56.1	
NOS	55	11.6	48.3	
Number of bone metastases				
Single	131	14.2	70.1	0.005
Multiple	225	7.2	45.2	
Smoking history				
Yes	187	11.2	46.7	0.573
No	169	13.9	55.3	
ECOG PS				
<2	89	13.4	63.2	<0.001
≥2	267	4.3	25.4	
Surgery for primary lesion				
Yes	210	13.1	57.5	0.289
No	146	8.2	45.2	
Chemotherapy				
Yes	264	14.9	53.2	0.365
No	92	9.4	46.5	
Radiotherapy				
Yes	229	14.2	55.9	0.226
No	127	10.5	48.6	
Bisphosphonate therapy				
Yes	275	14.5	65.6	0.041
No	81	8.1	45.1	
Calcium (mmol/L)				
<2.4	78	14.8	59.5	0.037
≥2.4	278	8.2	31.8	
Sodium (mmol/L)				
<135	201	11.3	50.4	0.85
≥135	155	14.8	46.2	
LDH (U/L)				
<225	112	15.7	57.7	0.009
≥225	244	8.8	35.3	

(continued)

Table 2. Continued.

Clinical factor	Number of patients	Median OS (months)	1-year survival rate (%)	P value
ALP (U/L)				
<140	111	15.6	59.2	0.008
≥140	245	8.2	24.3	
CEA (ng/ml)				
<5	104	13.8	55.2	0.242
≥5	252	11.7	49.4	
CYFRA21-1 (ng/mL)				
<3	95	14.4	53.6	0.176
≥3	261	10.6	50.2	
NSE (ng/mL)				
<20	188	12.2	54.3	0.454
≥20	168	11.4	47.6	
CA125 (U/mL)				
<35	99	14.9	53.5	0.259
≥35	257	11.4	42.6	
CA199 (U/mL)				
<37	137	14.3	53.2	0.672
≥37	219	11.7	47.3	

OS, overall survival; NOS, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; CYFRA, cytokeratin 19 fragment; NSE, non-specific enolase; CA, carbohydrate antigen.

Table 3. Multivariate analysis of potential prognostic factors in patients with bone metastases from non-small cell lung cancer.

Clinical factor	OR	95% CI	P value
Histological type			
Adenocarcinoma vs squamous	1.629	1.216–1.975	0.238
Squamous vs NOS	0.752	0.534–0.891	0.375
Adenocarcinoma vs NOS	1.376	1.021–1.774	0.417
Multiple bone metastases	2.169	1.217–3.985	0.009
ECOG PS ≥2	1.967	1.126–2.493	0.006
Bisphosphonate therapy	0.908	0.560–1.236	0.273
Calcium ≥2.4 mmol/L	0.872	0.327–1.149	0.169
LDH ≥225 U/L	1.194	0.515–1.533	0.025
ALP ≥140 U/L	1.383	0.932–1.951	0.013

OR, odds ratio; CI: confidence interval; NOS, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase.

criterion for measuring the impact of cancer on the patient's daily activity and physical ability. Patients with a high ECOG PS have generally poor health and are intolerant to

high-intensity radiotherapy and chemotherapy.¹⁰ Multiple bone metastases and a high ECOG PS are therefore associated with a poor prognosis.

The bone structure is maintained by the dynamic balance between bone resorption and formation. Bone metastases disrupt this balance and stimulate bone formation. ALP, as an indicator of osteoblastic activity, is produced by the bone and liver, and serum ALP levels indicating bone formation are elevated in lung cancer patients with osteolytic metastases, providing a potentially useful predictor of bone metastases.¹⁷ LDH is an important enzyme associated with glycolysis, which is increased by bone metastases. Previous studies revealed that high serum levels of ALP and LDH were negative prognostic factors for bone metastases in patients with small cell lung cancer,^{18,19} and the current study demonstrated similar results for NSCLC.

Biphosphonate therapy has been strongly recommended to prevent or delay the development of SREs in patients with NSCLC with bone metastasis.²⁰ Izumi et al.²¹ indicated that zoledronate-related fever was associated with improved OS. Hypercalcemia is usually accompanied by SREs at an advanced stage of lung cancer, and is a predictive factor for the occurrence of SREs.²² In the current study, biphosphonate therapy and hypercalcemia were both significant factors affecting OS according to univariate analysis; however, their significance was not retained in multivariate analysis, and they may thus be regarded as potential prognostic factors.

This study was limited by being a retrospective, single-center, observational study with a short follow-up interval, which was therefore susceptible to bias in terms of data collection and analysis. Further, large-scale prospective multi-center studies are therefore warranted to confirm the current findings.

Conclusion

According to the current study, the ribs and thoracolumbar spine are the preferred sites

of bone metastases from NSCLC, while multiple bone metastases, high ECOG PS, and high serum ALP and LDH levels are independent negative prognostic factors for bone metastases from NSCLC. Further studies are needed to verify the current findings, with the aim of establishing a predictive model for bone metastases from NSCLC.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iDs

Xiao-Tian Wu  <https://orcid.org/0000-0001-7141-1550>

Long-Ci Pan  <https://orcid.org/0000-0001-8645-0835>

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