

When Should ^{99m}Tc Bone Scintigraphy Be Performed in cT1N0 Non-Small Cell Lung Cancer Patients?

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Abstract: The aim of this retrospective study was to investigate the risk factors for bone metastases (BM) in clinical T1N0 non-small cell lung cancer (NSCLC) patients.

From January 2010 to June 2012, 739 patients with primary diagnosed cT1N0 NSCLC were eligible for this study. Clinical variables, including sex, smoking history, age at diagnosis, tumor size, pathologic subtype, preoperative serum Carcino embryonic antigen (CEA) level, lesion imaging performance, and skeletal system symptom, were collected.

BM were found in 7 patients (0.95%), in whom 6 patients had skeletal system symptom and 1 had silent metastasis. The frequency of BM was significantly high in younger patients ($P=0.007$) and in patients with higher preoperative serum CEA level ($P=0.05$). In multivariate analysis, age less than 50 years old (OR=2.23, 95% CI: 1.56–4.21, $P=0.02$), presence of clinical symptom (OR=3.15, 95% CI: 1.98–6.42, $P=0.008$), and CEA level over $5\mu\text{g/mL}$ (OR Presence of skeletal system symptom is not the unique criteria

for performing BS. Younger age at diagnosis and higher preoperative serum CEA level are also risk factors for BM in cT1N0 NSCLC patients. Therefore, the selection of early-stage NSCLC patients being performed BS should be more precise in the future.

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Abbreviations: AIS = adenocarcinoma in situ, BM = bone metastases, BS = bone scintigraphy, CEA = carcino embryonic antigen, CI = confidence interval, CT = computed tomography, GGO = ground-glass opacity, MIA = minimally invasive adenocarcinoma, MRI = magnetic resonance imaging, NSCLC = non-small cell lung cancer, OR = odds ratio.

INTRODUCTION

Bone is a very common site of metastases for cancers in prostate, breast, kidney, and lung. Bone metastases (BM) can cause skeletal pain, hypercalcemia, pathologic fracture, spinal cord, or nerve root compression and significantly worsen the prognosis.¹ Although PET-CT is widely applied for the diagnosis of distant metastases,^{2–5} ^{99m}Tc bone scintigraphy (BS) is still recognized as the most sensitive modality, which also costs less than PET-CT, for the detection and follow-up of BM in various malignancies.^{6–9} Considering the advantages in sensitivity and cost, BS is the most common tool for detecting BM in the preoperative staging procedure in China.

In non-small cell lung cancer (NSCLC), bone metastases were found in approximately 20 to 30% of patients at primary diagnosis.¹⁰ In patients with advanced NSCLC, the incidence of BM was estimated to range from 30 to 40%.^{11–13} In our hospital, as in many other institutes in China, a full-series staging procedure was used for all NSCLC cases, including chest contrast-enhanced computed tomography (CT), ^{99m}Tc BS, enhanced magnetic resonance imaging (MRI) or CT of the brain, and abdominal ultrasonography or contrast-enhanced CT. In our clinical practice, few bone metastases were found in apparently early-stage NSCLC cases in the preoperative staging process. The issue of whether to perform BS routinely in all NSCLC patients is controversial.^{14–17} Therefore, we performed this retrospective study to optimize the selection of patients to receive BS in cT1N0 NSCLC cases.

METHODS

Patients

Patients with primary diagnosed NSCLC between January 2010 and June 2012 in Shanghai Cancer Center were retrospectively collected. Patients, who underwent surgery, had a rereview of pathological diagnosis using postoperative tumor tissue, and patients, who did not receive surgery, had a diagnosis with CT-guide percutaneous lung fine needle biopsy tissue. Contrast-enhanced chest computed tomography, enhanced

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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brain MRI, ^{99m}Tc BS, and abdominal ultrasound were performed for preoperative staging. Clinical and pathologic characteristics, including sex, smoking history, age at diagnosis, tumor size, pathologic subtype, preoperative serum Carcino embryonic antigen (CEA) level, and the lesion imaging performance, were collected from our medical history system. Pure ground-glass opacity (GGO) was defined as a hazy increase in lung attenuation without obscuring underlying vascular markings in the lung window on CT. The including criteria were the following: the diameter of the nodules must be not more than 3 cm; neither mediastinal nor hilar lymph node with a diameter greater than 1.0 cm was found in contrast-enhanced chest CT; all the bone metastases detected by the diagnostic imaging methods were confirmed as true positive by clinical course in the follow-up period; patients should be followed up for at least 18 months. Patients were contacted every 3 months after the date of diagnosis in clinic or by telephone. Written informed consent was received from all enrolled patients. The clinical and follow-up information was collected from the medical history system in our institute. This study was approved by the ethics committee in Fudan University Shanghai Cancer Center.

All patients were questioned regarding skeletal system complaint, including the localization, type, intensity, and duration of pain or discomfort. Physical examination, including percussion, compression, flexion, extension and rotation of the vertebral column and extremities, and evaluations of the neurological status were performed in all patients. All the procedures of question and examination were accomplished by 2 experienced specialists.

The patients, with or without the findings of history and physical examination, all received ^{99m}Tc BS. Two experienced nuclear medicine physicians made the interpretations. They decided whether a bone scan was positive or negative and whether further radiographs should be performed blindly to each other. If the 2 doctors did not agree on the result, a senior physician would discuss with them about their differences and reached a consensus interpretation. When a positive result was made, MRI of the lesion would be done to validate the result.

Statistical Analyses

Pearson χ^2 test or Fisher exact tests were adopted to assess the correlations between clinicopathologic variables and the frequency of BM. For the characteristics, which were proved to be significantly associated with BM in univariate analysis, the binary logistic regression model was used to test their odds ratios (ORs). The statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

A total of 739 patients were eligible for the retrospective analysis and 7 of them had BM (0.94%). Of the 373 clinical T1a patients, 2 BM cases were found. Of the 366 clinical T1b cases, 5 patients were found to have BM. After surgery, 137 patients were found to have lymph node metastasis (80 N1+N2– cases, 46 N1+N2+ cases, and 11 N1–N2+ cases). The frequency of BM had no association with sex, tumor size, smoking history, and pathologic subtype (Table 1).

In the patients with positive imaging findings, pelvis, rib, and vertebral body metastases were found in 1, 2, and 4 patients, respectively. Six of the 7 patients with bone metastasis had skeletal or neurologic system symptom, 4 had pain, and 2 had numbness. Only 1 silent metastasis occurred in a patient

with a 2.8-cm adenocarcinoma in the right upper lobe ($P=0.001$, Table 1).

Through investigation of the relationship between BM and clinical variables, we found that the frequency of BM was significantly higher in patients with age at diagnosis less than 50 years old ($P=0.007$, Table 1). Serum CEA level was also related to BM, remarkably more BM cases were found in patients with CEA level over 5 $\mu\text{g/mL}$ ($P=0.05$, Table 1).

Correlations between BM and clinical variables, including age at diagnosis, clinical symptom, and CEA level, were further evaluated by logistic regression analysis. Age less than 50 years old (OR = 2.23, 95% CI: 1.56–4.21, $P=0.02$), presence of clinical symptom (OR = 3.15, 95% CI: 1.98–6.42, $P=0.008$), and CEA level over 5 $\mu\text{g/mL}$ (OR = 2.14, 95% CI: 1.37–3.53, $P=0.03$) were independently associated with BM in clinical T1N0 NSCLC patients.

DISCUSSION

Bone metastases in NSCLC patients with early clinical stage are not a common event. This retrospective study determined the frequency of BM in NSCLC patients with clinical stage T1N0, and the clinical characteristics associated with BM. To the best of our knowledge, there is no similar study revealing the risk factors of BM in early-stage NSCLC.

According to the clinical practice guidelines of the European Society for Medical Oncology on pretreatment evaluation of NSCLC, preoperative imaging of bone metastases in patients who had no symptom was not recommended.¹⁸ However, this series indicated the frequency of BM in asymptomatic cT1N0 NSCLC patients was 0.18% (1 out of 567). Although it is an acceptable low frequency, omission of BS might lead to inappropriate surgery in these patients. Therefore, only according to the presence of symptom to decide the necessity of BS in cT1N0 NSCLC patients was unreliable.

In the previous studies, the affect of age at diagnosis on clinical/pathologic features and prognosis in NSCLC patients was under discussed and the conclusions were inconsistent.^{19–}

²¹ In our series, age at diagnosis was a significant risk factor of BM in cT1N0 NSCLC cases. The frequency of BM in younger patients (age less than 50-years old) was remarkably high ($P=0.007$). This result may consist of the previous study revealing that lung cancer cell in younger patients had more aggressive biologic behavior.²² However, due to the weakness of this retrospective study, more convincing results should be concluded in a perspective cohort study.

Several previous studies had revealed that NSCLC patients with high preoperative serum CEA level had unfavorable prognosis.^{23–26} Therefore, tumors associated with high CEA level were assumed to have aggressive biologic features. Our findings corresponded to this assumption, the results indicated that the high preoperative serum CEA level was a risk factor for BM in cT1N0 NSCLC patients, and all the BM occurred in patients with CEA level over 5 ng/mL . To our knowledge, this is the first study revealing the association between preoperative CEA level and BM in cT1N0 NSCLC patients.

In this series, we also intended to investigate the association between tumor size, tumor imaging performance, pathologic subtype, and the frequency of BM in cT1N0 NSCLC. Unexpectedly, tumor size had no correlation with BM. However, bone was a relatively rare metastatic site in cT1a patients (0.27%). We also thought that pure GGO could be a protective factor for BM, but it did not reach the statistical significance, even there was no BM occurring in patients with pure GGO.

TABLE 1. Clinical Features and Frequency of Bone Metastases

Variables	Total (%)	BM Positive (%)	BM Negative (%)	P
Sex				
Male	214 (28.9)	3 (1.40)	211 (98.60)	0.419
Female	525 (71.1)	4 (0.76)	521 (99.24)	
Age				
≥50	492 (66.6)	1 (0.20)	491 (99.80)	0.007
<50	247 (34.4)	6 (2.43)	241 (97.57)	
Pathology				
Adenocarcinoma	427 (57.8)	5 (1.17)	422 (98.83)	0.705
Squamous cell cancer	168 (22.7)	2 (1.19)	166 (98.81)	0.661
AIS or MIA	144 (19.5)	0 (0)	144 (100)	0.356
Smoking history				
Smoker	282 (38.2)	2 (0.71)	280 (99.29)	0.714
Non-smoker	457 (61.8)	5 (1.09)	452 (98.91)	
T stage				
T1a	373 (50.5)	2 (0.54)	371 (99.46)	0.282
T1b	366 (49.5)	5 (1.37)	361 (98.63)	
Tumor size				
<1 cm	212 (28.7)	1 (0.47)	211 (99.53)	0.68
≥1 cm	527 (71.3)	6 (1.14)	521 (98.86)	
Lesion imaging performance				
Pure GGO	158 (21.4)	0 (0)	158 (100)	0.356
Mixed lesion	581 (78.6)	7 (1.20)	574 (98.80)	
Symptom				
Positive	172 (23.3)	6 (3.49)	166 (96.51)	0.001
Negative	567 (76.7)	1 (0.18)	566 (99.82)	
CEA level				
≥5 ng/mL	463 (62.7)	7 (1.51)	456 (98.49)	0.05
<5 ng/mL	276 (37.3)	0 (0)	276 (100)	
Total	739 (100)	7 (0.95)	732 (99.05)	

AIS = adenocarcinoma in situ; MIA = minimally invasive adenocarcinoma.

Pathologic subtypes did not relate to BM in cT1N0 NSCLC either, despite no BM being found in AIS or MIA cases.

Our work was a retrospective study essentially and the number of patients occurred BM was too small. With continuous collection of patients and their clinical and pathological data, more convincing and precise results could be obtained in the future. We are also planning to validate the findings of our work in larger patients cohorts from other lung cancer centers in China.

Although BM in cT1N0 NSCLC is not a common event, millions of early-stage NSCLC patients in China undergo BS every year. This situation is not only heavy burden to medical insurance system, but also increases the waiting time of patients before surgery. Therefore, we performed this study and found out some risk factors of BM in cT1N0 NSCLC patients. According to our results, presence of skeletal system symptom is not the unique criteria for performing BS. cT1N0 NSCLC patients with younger age at diagnosis or higher serum CEA level should also be considered to give bone-imaging modality. In summary, the selection of patients being performed BS should be more precise in the future.

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