Is there a role of whole body bone scan in early stages of non small cell lung cancer patients?

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Summary

Purpose: The aim of our study was to re-evaluate the role of whole-body bone scanning (WBBS) in detecting bone metastases in apparently operable stages of non small cell lung cancer (NSCLC) patients.

Patients and methods: We made a retrospective analysis of 60 patients (53 males, 7 females, aged 47-87 years, mean 68±4) between 2004-2006. All patients had a full series of imaging staging procedures including WBBS. Their medical records were reviewed with respect to how often bone metastases were detected and whether or not the patients showed any symptoms or laboratory abnormalities indicating bone involvement.

Results: Skeletal metastases (confirmed afterwards by x-ray, computed tomography or biopsy) were found in 11 (18.3%) patients. All of them had normal serum alkaline phosphatase and calcium concentrations. Eleven patients had symptoms suggesting bone metastases and 49 were asymptomatic. Bone metastases were detected in 3 (27.2%) of 11 clinically symptom-positive patients and in 8 (16.3%) of 49 clinically symptom-negative patients.

Conclusion: The present study indicates that if bone scans were done only in patients reporting skeletal symptoms an important number of patients (16.3%) would have been misstaged due to asymptomatic bone metastases. We conclude that in patients with apparently operable NSCLC preoperative staging using WBBS is useful to avoid understaging and futile surgery.

Key words: bone metastases, bone scan, early stage, non small cell lung cancer

Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide both in men and women [1]. Surgical resection of the lung tumor with mediastinal node dissection is the best treatment modality for NSCLC in patients without preoperative evidence of mediastinal invasion or distant metastasis.

Despite surgical curative resection recurrence rates are very high [2,3]. Early postoperative disease recurrence in the skeleton suggests that undetected metastases are present prior to surgical treatment.

The optimal approach to the investigation of possible distant metastases in patients with early, apparently operable stages of NSCLC patients who do not have symptoms suggesting metastatic disease is controversial. According to the American College of Chest Physicians (ACCP) evidence-based guidelines [4,5] patients with clinical stage I and II lung cancer and normal results of a clinical evaluation require no further imaging for detection of extrathoracic disease. However, patients with stage IIIA and IIIB disease should undergo routine imaging studies. Some authors [6-8] advocate proceeding immediately to thoracotomy, while suggest a more aggressive approach to rule out clinically occult but detectable metastases. These groups suggest that imaging of the adrenal glands [9],
head [10], bones [11], liver [12], or some combination of these [13-16] should be included in the investigation before thoracotomy in all patients with lung cancer.

To help answer this controversy with regard to bone metastases, we offered imaging procedures including WBBS and in selected cases SPECT bone scan in all patients who had histologically or cytologically proven NSCLC with clinical stages I and II, irrespective of the presence or absence of clinical or laboratory indicators suggesting skeletal metastases, and in selected IIIA (apparently operable) stage patients with negative initial clinical and laboratory screening. They were then retrospectively subjected to evaluation for bone metastases.

The aim of this investigational approach was to detect those patients with occult metastatic disease at the time of presentation and spare them an unnecessary thoracotomy.

Patients and methods

Between January 2004 and May 2006, and in collaboration with the Department of Thoracic Surgery of our hospital we studied 60 patients (53 men, 7 women) who had histologically or cytologically proven NSCLC. The mean age (± SD) was 68 ±4 years (range 47-87). Histologic subtypes of NSCLC were as follows: squamous cell carcinoma 21 (35%); undifferentiated carcinoma 19 (32%); adenocarcinoma 18 (30%); large-cell/anaplastic carcinoma 2 (3%) (Figure 1).

All patients included in the study had undergone a CT scan of the thorax and upper abdomen (liver and the adrenal glands). T and N evaluation was performed by CT and fiberoptic bronchoscopy according to the International System for Staging Lung Cancer adopted by the American Joint Committee on Cancer and the International Union Against Cancer in 1997. The potentially operable clinical stages of disease based on CT of the thorax were as follows: IA/B, n = 33 patients (55%); IIA/B, n = 13 (21.7%); and selected IIIA (only tumors involving the ipsilateral mediastinal lymph nodes (T1N2M0 or T2N2M0) n = 14 (23.3%) (Figure 2).

Patients with inoperable stages at the initial screening or if the nodal stage was not described were excluded from the study. If neither tissue pathologic confirmation nor clinical outcome was available, patients were excluded from further analysis.

We performed bone scans blinded to the history and findings of the physical examination. Then the patients were classified into 2 main groups. The first group (n=11) included patients with clinical or laboratory indicators suggesting skeletal metastases (chest pain, skeletal pain, bone tenderness on physical examination, increased serum alkaline phosphatase and serum calcium) and the second group (n=49) included patients without findings on history, physical examination and laboratory investigations suggestive of skeletal metastases. At initial evaluation the first group included 20 and the second group 40 patients. Nine patients were excluded from the first group due to symmetric location and the osteoarthritic origin of the skeletal lesions as confirmed with plain radiography and they were placed in the second group.

WBBS was performed in both groups and was obtained with a dual-headed whole-body scanner.

**Figure 1.** Histological subtypes of NSCLC in 60 patients.

<table>
<thead>
<tr>
<th>Stage</th>
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<tbody>
<tr>
<td>IA/B</td>
<td>33</td>
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<td>IIA/B</td>
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**Figure 2.** CT-based clinical TNM stages.
(Phillips Forte - Adac Laboratories) equipped with a parallel-hole collimator for each detector head. Approximately 3 h after intravenous administration of approximately 20 mCi technetium 99m methylene diphosphonate, whole-body images were obtained with the patient in the supine position. A 20% energy window centered over the 140 keV photopeak was used. Anterior and posterior images were acquired at a speed of 10 cm/min and were formatted with a dual-intensity display on 11 × 14-inch film. Additional SPECT scan was obtained for the assessment of a solitary or few bone lesions in bone scan.

MRI or CT scans were performed when clinical factors did not correlate with WBBS findings. If the abnormal findings were multiple and asymmetric, they were considered positive for metastatic disease. Study findings were classified as normal if there was no scintigraphic abnormality or if there was a definite benign explanation for the scintigraphic findings (osteoarthritis, osteomalacia, trauma, surgery, or other benign bone diseases). The remaining study findings were classified as “probable” for metastatic disease and they were further investigated with plain radiography, CT scan, MRI and, in selected patients, needle aspiration biopsy was obtained for histological diagnosis of suspected metastasis.

Results

Skeletal metastases were detected by clinical indicators and bone scan (confirmed by x-ray, CT, MRI or biopsy) in 11 of 60 (18.3%) patients. All of them had normal serum alkaline phosphatase and calcium concentrations. For the first group of patients (n=11) bone metastases were detected in 3 of 11 (27.2%) clinical symptoms-positive patients (Figure 3) and for the second group (n=49) in 8 of 49 (16.3%) clinical symptoms-negative patients (Figure 4, 5). One of the 9 patients with lesions of osteoarthritic origin at initial screening showed skeletal metastases on WBBS (Figure 6). The existence of clinical symptoms as indicators of metastasis presented 27.2% sensitivity, 83.6% specificity and 73.3% accuracy.

Abnormal bone scan results positive for metastatic disease were obtained in all patients with bone metastases. An abnormal bone scan as an indication of metastasis presented 100% sensitivity and specificity. Abnormal bone scan and clinical symptoms were in agreement in 3 of 11 (27.2%) patients.

According to TNM stage, we found bone metastases in one patient with T1N0M0, and in 3 patients with T2N0M0. Only 2 of the 4 patients had clinical symptoms suspicious for metastases. Four of 7 patients in T2N1M0 (stage IIB) had bone metastases but only one had symptoms. Stage IIB was the most common stage (36.4%) found in patients with bone metastases (Figure 7).

The tumor stages in both groups and the number of patients with bone metastases per tumor stage are shown in Table 1.

The histological analysis revealed bone metastases in 6 patients with adenocarcinoma, in 3 with...
Figure 5. Asymptomatic stage II B patient. A 74-year-old male diagnosed with NSCLC and no clinical indicators suggesting skeletal metastases. Whole body bone scan identified an asymptomatic metastasis localised in the 5th lumbar vertebra confirmed with additional SPECT bone scan and a plain radiograph in the lumbar spine showing a compressive fracture of metastatic origin. Histology: moderately differentiated adenocarcinoma.

Figure 6. Discordance of skeletal symptoms with the location of metastasis. A 69-year-old male in good general condition with preoperative CT stage IA. He reported pain in his back and a x-ray in lower thoracic and lumbar spine showed degenerative changes and his complaints were correctly interpreted as being arthritic in origin. Despite the x-ray interpretation a bone scan was performed and revealed foci of increased uptake in the right shoulder and focal areas of mildly increased tracer uptake in the lower thoracic and lumbar spine, compatible with degenerative changes. Additional x-ray of the right shoulder showed a micronodular morphology lesion in the head and in the upper one third of the right humerus, compatible with metastasis. If skeletal scintigraphy was not done, the patient would undergo a futile surgery. Histology: poorly differentiated adenocarcinoma.
squamous cell carcinoma and in 2 with undifferentiated carcinoma. Among the 11 patients with bone metastases more than half (6 of 11; 54.5%) had adenocarcinoma (Figure 8).

Discussion

Surgical resection offers the highest probability of a favorable outcome in patients with NSCLC. However, the survival of patients who undergo surgery remains low, probably because of presurgical understaging [17]. Bone metastases are diagnosed at initial presentation in 3.4-60% of patients with NSCLC. A bone scan may help to accurately stage patients with lung cancer, even in those individuals who are not considered "suspicious" of having bone metastases. Bone pain is usually considered an indicator of skeletal metastases, but only up to 40% of lung cancer patients with proven bone metastases are symptomatic [18-22].

99mTc-methylene diphosphonate (99mTc-MDP) is the most commonly used tracer for skeletal imaging in nuclear medicine. In contrast with x-rays, as little as a 5-10% change in the ratio of a lesion to normal bone is required to detect an abnormality on bone scan [23,24]. It has been estimated that bone scan can detect malignant bone lesions 2-18 months earlier than x-rays [23]. Being widely available it provides an entire skeletal visualization within a reasonable amount of time and cost [24-26].

Published sensitivity rates of bone scan in detecting bone metastases vary between 62 and 100%, with a specificity of 78-100% [25]. The detection of a solitary or few bone lesions on bone scan often indicates the need for further assessment of the lesions. Correlation with CT or MRI is commonly performed to overcome the limited specificity of bone scan [25-27].

SPECT is more sensitive in detecting bone lesions than planar scintigraphy. The better accurate localization of a scintigraphic lesion within the vertebrae by SPECT has been reported to improve the specificity of 99mTc-MDP bone scan, differentiating between benign and malignant sites of uptake [28,29].

Our study showed 3 important differences in comparison with previous studies aimed at assessing the benefit of bone scan in the preoperative screening of NSCLC patients for occult skeletal metastases.

First, the patient population consisted only of patients with histologically or cytologically proven NSCLC with apparently operable stages according to CT scan of the thorax; second, SPECT bone scan was performed in cases of solitary or few bone lesions, aimed to increase the specificity of the method; and
third, there was an evaluation of benign bone lesions according to history, clinical examination and plain radiographs.

In previous similar studies [30-33] there was not discrimination in skeletal symptoms between patients with arthritic complaints and those suspicious for skeletal metastases. In most cases a bone scan was considered false-positive if a x-ray in the location of the scintigraphic lesion was normal without performing additional SPECT bone scan or MRI (especially if the bone lesion was located in a vertebra).

The studies of Hetzel et al. [34] and Erturan et al. [35] represent an exception from preceding studies. Erturan et al. found bone metastases in 53% (n=21) of 39 clinical factor-positive patients, 5.8% (n=5) of 86 clinical factor-negative patients, and 20.8% of the total number of patients. The existence of bone-specific clinical factors as indicators of metastasis and an abnormal WBBS presented 81.6% and 91.2% accuracy as compared with 73.3% and 100% in our study. However, in the Erturan’s et al. study only 25.6% (n=32) of 125 patients had operable stages, a case that justifies the high incidence of patients with bone specific clinical factors (53% vs. 18.3%) in our study. Similarly, Hetzel et al. investigated 153 patients with lung cancer. They found that clinical symptoms as indicators of metastases presented 53% sensitivity vs. 73% for routine bone scan. They also found that if bone scans were done selectively to those 23 patients with suspicious complaints they would have resulted in a further reduction in sensitivity to 20% (8 patients). This comes in agreement with the low sensitivity (27.2%) of clinical symptoms as indicators for bone metastases found in our study.

The tumor cell type seems to play a role in the development of distant metastases. According to our results adenocarcinoma was the main cell type in patients with bone metastases and this is in agreement with the results of other studies [31,35,36].

As mentioned above, there is a controversy whether or not to investigate for metastatic disease in patients with operable, early-stage lung cancer according to CT of the thorax. According to our results if bone scans were done in only the 11 patients reporting skeletal complaints suspicious for metastases, 8 of the 49 (16.3%) patients without clinical symptoms should undergo a futile thoracotomy. Sider and Horejs [37] investigated 95 patients who had NSCLC without evidence of endotheorac or extrathoracic involvement. Bone metastases were detected in 8 (8.4%) patients.

Earnest et al. [27] in a study of 27 patients with NSCLC and a lung mass > 3 cm, with no clinical evidence of metastases and with no evidence of mediastinal disease or abdominal metastases, found 5 of 27 (18.5%) patients with bone metastases. The relatively recent study by the Canadian Lung Oncology Group [38] showed the staging strategy of searching for occult metastases in every patient before surgical intervention to be cost-effective.

Kelly et al. [16] also suggested that bone scans seem to be the most cost-effective means of examination.

In summary, this study provides support for extensive investigation with bone scanning in patients with apparently operable early stages NSCLC without clinical or laboratory findings suggesting skeletal metastases. The benefit of such an approach is to spare patients a thoracotomy without a chance for cure that would otherwise had been undertaken.

References

The role of whole-body bone scanning and clinical factors


