Original articles

Initial staging of non-small cell lung cancer: value of routine radioisotope bone scanning

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Abstract
The exclusion of bone metastases is important in the initial staging of non-small cell lung cancer, though there is debate about whether bone scans should be performed routinely or restricted to patients who present with clinical or laboratory indicators suggesting skeletal metastases. In a prospective study of 110 consecutive patients referred for initial staging of non-small cell lung cancer, we assessed the sensitivity of a group of clinical indicators (chest pain, skeletal pain, bone tenderness on physical examination, serum alkaline phosphatase, and serum calcium) for the presence of skeletal metastases as determined by bone scanning. The final staging result was validated with follow up data over at least three years. At the initial staging 37 of 110 bone scans (34%) showed areas of increased uptake, of which only nine were confirmed to be metastases (by tomography, computed tomography, or biopsy). Half the patients (55) had at least one clinical indicator suggesting skeletal metastases, including all patients with proved skeletal metastases. Thus the sensitivity of these clinical indicators was 100% and the specificity 54%. Within one year three of 27 patients with non-confirmed positive bone scans had skeletal metastases, one of which was in the area that had shown increased uptake initially. All these patients had clinical indicators for skeletal metastases and all had inoperable advanced tumours. Four of 69 patients with an initially negative bone scan developed skeletal metastases within one year. It is concluded that in non-small cell lung cancer bone scanning can be restricted to patients with clinical indicators for skeletal metastases. This approach reduces the number of bone scans and consecutive investigations without loss of sensitivity in the detection of skeletal metastases.

Therapeutic options and prognosis in non-small cell lung cancer depend on the extent of local tumour and the presence or absence of distant metastases. Thorough staging of the tumour is therefore mandatory. Locoregional intrathoracic extension of tumour is usually assessed by bronchoscopy, radiography, computed tomography, and direct mediastinal exploration. The value of these procedures in the staging of non-small cell lung cancer is well documented.[1-8] The search for distant metastases, however, is less satisfactory and the procedures to be used are more controversial. Frequent sites for distant metastases include the brain, liver, and adrenals. The value of computed tomography and radionuclide scans of the brain in non-small cell lung cancer has been clearly defined,[9-11] and abdominal computed tomography and ultrasonography have widely replaced liver radionuclide scans for the detection of abdominal metastases.[12-15]

In addition, bronchogenic carcinoma spreads to the skeletal system.[16] Radioisotope bone scanning has been reported to be a very sensitive method for the detection of such tumour deposits[17 18] and is widely used in the staging of non-small cell lung cancer. Early studies by Hooper et al,[19] Ramsdell et al[20] and White[21] suggested that in the initial staging of non-small cell lung cancer skeletal radionuclide scans could be restricted to patients with clinical signs or symptoms of skeletal disease. This approach was questioned, however, by several authors[22-24] and a recent study by Quinn et al[25] gave inconclusive results on the value of routine bone scans in clinically symptom free patients, the group in which a reliable preoperative assessment of distant metastases is most important.

Our aim therefore was to compare the value of a series of clinical indicators in predicting skeletal metastases in patients with non-small cell lung cancer referred for initial preoperative staging with the value of a skeletal radioisotope scan. The patients were followed for at least three years to validate our clinical staging.

Methods
PATIENTS
We carried out a prospective study of 110 consecutive patients referred to our department for initial staging of non-small cell lung cancer from January 1983 to December 1985. There were 98 men (mean age 62, range 34–79 years) and 12 women (mean age 51, range 41–69 years). Patients known to have had a previous tumour were excluded. Of the 110 patients, 67

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(61%) had a squamous cell carcinoma, 25 an adenocarcinoma, 13 a large cell carcinoma, and five an undifferentiated carcinoma.

STAGING PROCEDURES

A medical history was obtained and physical examination performed · by an internal medicine house staff physician and by a pneumologist. Routine laboratory tests included a full blood count and biochemical screen (including serum alkaline phosphatase, serum aspartate aminotransferase, and serum calcium concentration). This information was fully documented at presentation, independently of subsequent staging investigations. We looked for indicators suggesting metastatic disease, a subset of which was regarded as specific for skeletal metastases (see table 1, modified from Hooper et al[19] and Quinn et al.[25]

Intrathoracic staging included bronchoscopy, posterioanterior and lateral chest radiography, and computed tomography of the thorax. If lymph nodes on the computed tomogram were more than 10 mm in diameter mediastinoscopy was performed to obtain tissue for histological examination. Lymph nodes with a diameter of less than 10 mm were considered to be normal, in accordance with our previous study.[26] Routine extrathoracic staging included computed tomography of the upper abdomen, to include liver, adrenal glands, and kidneys, and a radioisotope bone scan. Computed tomography of the brain was performed only if clinically indicated.

Whole body radioisotope bone scanning was performed with a Philips Gamma Diagnost A Camera with a single sweep, high resolution collimator. The scans were full length images recorded with a moving table, three hours after administration of 20 mCi technetium-99m labelled DPD. For additional spot scans a Picker DYNA camera was used. Bone scans were interpreted routinely by the nuclear medicine house staff and a respiratory physician. Any localised increase in radionuclide uptake was considered initially as indicating skeletal metastases; if no increased uptake was seen the scan was negative. All positive scans were assessed further by additional radiographs, conventional tomography, com-

*Table 1   Clinical indicators used for trying to identify metastatic disease**

History
  weight loss > 3 kg/3 months
  chest pain
  skeletal pain
  neurological symptoms: headaches, nausea, seizures,
    pronounced personality changes, paralysis

Physical examination
  enlarged lymph nodes (> 1 cm)
  hepatomegaly (> 1 cm)
  bone tenderness or pain with motion or palpation
  central nervous system abnormalities found by
    neurological examination

Labortory investigations: any rise in serum
  alkaline phosphatase
  serum aspartate aminotransferase
  calcium

*Indicators considered as organ specific for skeletal metastases are italicised.

puted tomography, or biopsy, except when the increased uptake was recognised as being due to a benign condition by the nuclear medicine staff (in accordance with a corresponding history and physical findings of degenerative, osteoarthritic, or traumatic changes). Because the decision on how to treat and whether to operate or not depends on this skeletal staging, we defined a true positive bone scan as a scan with typical, multiple areas of increased uptake or a single area of increased uptake considered by the physician in charge to be of tumour origin, and a false positive scan was defined as one in which the increased uptake was not proved to be tumour. The validity of this clinical judgement was then assessed by follow up.

The final T and N stage was determined according to the recommendations of the American Joint Committee for Cancer Staging and End-results Reporting (1979) and the 1981 American Thoracic Society recommendations.[27 28] Thus it was based on the pathological and anatomical findings in patients who underwent resection, and on the results of computed tomography and mediastinoscopy in patients not undergoing surgical treatment. Of the 110 patients, 31 were in stage I, 26 in stage II, 34 in stage III without distant metastases, and 19 in stage III with distant metastases.

FOLLOW UP

The follow up period for this study was at least three years. Five of the 110 patients were lost to follow up (all had moved out of Switzerland). Sixty two patients underwent resection of the tumour and were followed regularly every three months for up to two years and every six months for up to five years postoperatively. Routine visits included history taking, physical examination, and chest radiography. If there was any suspicion of local recurrence or of metastatic spread further investigations were performed as necessary.

Of the 43 patients not undergoing surgical treatment, 20 were seen regularly by the oncology house staff while receiving chemotherapy, five were seen regularly by the radio-oncology house staff while they received radiotherapy, and eight by both the oncology and the radiotherapy staff because they received both chemotherapy and radiotherapy. These patients continued to be seen regularly after completion of these treatments. Ten of the patients who received no treatment after initial staging were followed by their general practitioner, from whom we obtained complete follow up information until they died. Sixty five of the 105 patients died during the follow up period until December 1988; necropsy was performed in 21.

ANALYSIS

The sensitivity and specificity of the clinical indicators for metastatic disease in general and for skeletal metastases in particular were calculated according to the following formulae:
sensitivity = number of patients with both positive clinical indicators and true positive results in the tests for metastases divided by the

Table 2 Details of further investigation and final interpretation of bone scans in the 37 out of 110 patients with increased radionuclide uptake

Further investigation	False positive	True positive
None	7	—
Radiography or tomography	20	5
Computed tomography	—	4
Biopsy	1	—
	28	9

total number of patients with true positive results;

specificity = number of patients without clinical indicators and without true positive results in the tests for metastases divided by the total number of patients with negative or false positive results.

Results

BONE SCANS

Thirty seven of 110 radioisotope bone scans (34%) showed one or more areas of increased uptake (table 2). In seven of these 37 patients no further examinations were done, because the area of increased uptake corresponded with the site of degenerative arthritic disease, osteoarthritis, or an obvious traumatic lesion. None of these seven patients developed skeletal metastases during follow up. In 25 patients additional radiography or conventional tomography (or both) was performed. In five of these patients multiple skeletal metastases were confirmed but in the remaining 20 the increased uptake was interpreted as being of degenerative or traumatic origin. In a further four patients regional computed tomography confirmed multiple skeletal metastases. The last patient had a rib lesion on a conventional tomogram but needle biopsy failed to show malignancy. Thus 28 of the 37 bone scans showing increased uptake were considered to represent false positives. Nine of the original 110 patients were found to have multiple skeletal metastases (table 2).

In eight of the nine patients with skeletal metastases there were no other extrathoracic metastases but the remaining patient had additional brain metastases. All nine patients with bone metastases had locally advanced tumours (ipsilateral mediastinal lymph node tumour in two, chest wall infiltration in two, malignant pleural effusion in two, metastases of mediastinal structures in three). Three patients had a squamous cell carcinoma, three an

adenocarcinoma, and three a large cell or undifferentiated carcinoma.

Eleven patients without skeletal metastases had metastatic spread elsewhere (multiple brain metastases in one, liver in five, lung and liver in two, contralateral lung in five, adrenal gland (proved by biopsy) in one).

CLINICAL INDICATORS OF METASTATIC DISEASE

Eighty of the 110 patients (73%) had at least one clinical indicator suggesting metastatic disease. The sensitivity of the non-organ specific indicators for detecting metastases (of any type) was 95% (19 of 20 patients with distant metastases, including those with skeletal metastases), with a low specificity of only 32%.

Half of the patients (55) had one or more organ specific indicators suggesting skeletal metastases, including all nine patients with proved skeletal metastases. Seven of these nine patients had two or more signs suggesting bone metastases. Thus the sensitivity of the organ specific clinical indicators for detecting skeletal metastases was 100% and the specificity 54%. The frequency of positive clinical indicators of skeletal metastases and the relation to a positive bone scan are shown in table 3. Eight of the nine patients had raised serum alkaline phosphatase activity and seven had localised skeletal pain, either spontaneously or with palpation.

FOLLOW UP

All nine patients with proved skeletal metastases at the initial staging died within four to 10 months of diagnosis as a result of progression of the tumour.

For the remaining 96 patients the appearance of new skeletal metastases during the follow up period is shown in table 4. Three of the 27 patients with a false positive bone scan at the initial staging (one patient was lost to follow up) developed skeletal metastases within one year. In all three patients additional radiography and conventional tomography had been performed at the initial staging to clarify the cause of the increased uptake; this had been interpreted as of benign origin or irrelevant to the further management of the patient. Only one of the new skeletal metastases appeared in the area of increased uptake on the initial bone scan. Skeletal metastases had not been excluded with certainty in this patient by the additional radiography and conventional tomography, but biopsy was not attempted because the

Table 3 Sensitivity and specificity of clinical indicators specific for skeletal metastases in relation to localised increases in radionuclide uptake on bone scans (positive scans)

	Bone scans		
Clinical indicators for skeletal metastases	*Total positive*	*False positive*	*True positive*
All patients (n = 110)	37	28	9
Without (n = 55)	16	16	—
With (n = 55)	21	12	9
Sensitivity	100%		
Specificity	54%		

Table 4 New skeletal metastases during follow up in 96 patients without skeletal metastases

Time of detection (months after staging)	*<6*	*6–<12*	*12–24*
Initial bone scan* (n = 96)			
False positive (n = 27)	3	0	1
Negative (n = 69)	3	2	4
Surgery† (n = 96)			
Curative resection (n = 62)	1	1	3
No surgery (n = 34)†	5	1	2

*Depending on the initial bone scan result.
†Depending on surgical treatment (33 patients without surgery, one patient with non-curative resection).

carcinoma was non-resectable. The second patient was the only one to have a non-curative surgical resection and the third patient was not operated on because of contralateral mediastinal lymph node tumour. All three patients had clinical indicators suggesting skeletal metastases at the time of the initial staging. The sensitivity of the clinical indicators for skeletal metastases was not altered therefore by using the follow up data.

In five of the 69 patients with a negative bone scan at the initial staging new skeletal metastases appeared within one year of the initial staging. Of the three patients who had not had surgery, this was due to direct local tumour invasion in two and preceded by liver metastases in one. In two patients with T2 N2 disease who had undergone curative resection the skeletal metastases were preceded by local tumour recurrence.

Sixty two of the 96 patients without skeletal metastases underwent curative resection of the tumour (27 in stage I, 21 in stage II, 14 in stage III). Thirty three patients were not operated on (11 with distant metastases, 15 who had stage III disease with non-resectable tumours, and seven because of poor lung function) and in one patient a locally incomplete resection was performed. New skeletal metastases in patients with and without curative resection are shown in table 4. Two of the 62 patients with resected tumours developed skeletal metastases within one year, preceded in both by reappearance of tumour elsewhere. Six of 34 patients with non-resectable tumours but with no skeletal metastases initially developed skeletal metastases within 12 months.

The appearance of skeletal metastases more than 12 months after the initial staging in five additional patients was always associated with previous local tumour recurrence or distance metastases other than in the skeletal system (table 4).

Discussion

In this prospective clinical study in 110 consecutive patients with non-small cell lung cancer we found good sensitivity for a few readily available clinical indicators in suggesting the presence of possible skeletal metastases, a result that is confirmed by complete follow up data. On the basis of these findings we suggest that bone scanning in the initial staging of non-small cell lung cancer can be restricted to patients with clinical indicators that suggest skeletal metastases. This will reduce the number of bone scans by half and reduce unnecessary further examinations prompted by false positive results.

Our study confirms previous reports by Hooper et al [19] and Ramsdell et al,[20] who have already underlined the usefulness of clinical indicators for skeletal metastases, but the present study is the first to validate the final clinical staging by follow up data for a minimum of three years. Our findings are at variance, however, with the conclusion of the recent study of Quinn et al,[25] who found a 15% yield for discovery of occult bone metastases by bone scanning in a group of 53 patients with non-small cell lung cancer. This study population differed from ours in that the percentage of patients with adenocarcinoma was higher (38%, compared with 23% in our study). Patients with adenocarcinoma have a higher incidence of skeletal metastases in the early stages of the disease.[29] Sixty one per cent of our patients had squamous cell carcinoma, typically with a low incidence of metastatic spread in early stages of the disease.[30-33] In Quinn's study, however, as in other studies,[20 24] the follow up data, the ultimately most important means of validating the staging procedure, were incomplete.

The value of bone scans in the preoperative staging of non-small cell lung cancer in patients with locally resectable tumours cannot be definitely answered from our data alone. Seven of the nine patients with skeletal metastases at the initial staging had locally advanced inoperable tumours, on the basis of the radiographic findings and computed tomograms. This underlines the importance of the local investigations in preoperative staging of bronchial carcinoma. The other two patients with ipsilateral lymph node tumour did not undergo surgery, however, because distant metastases were detected on the bone scan. We would not, therefore, advocate an even more restrictive use of bone scanning—for example, only in patients with locally advanced tumours.

In comparison with other studies,[16 22 34] the incidence of metastatic disease in non-small cell lung cancer in our study population (17%) and of bone metastases (8%) was rather low. Our follow up data confirm that this is not due to an incomplete or insensitive search for metastases. Twelve months after the initial staging only eight patients initially free of skeletal metastases had evidence of new metastases and in only one was the metastasis in the same location as the increased uptake in the original bone scan. Of the five patients with a negative bone scan initially, three had a non-resectable tumour and the other two had an advanced but resectable tumour. Furthermore, all the patients who later developed skeletal metastases had local tumour recurrence before the appearance of bone disease, which indicates that in most cases skeletal spread occurs at an advanced intrathoracic tumour stage. Our study group represents a preselected population in that mainly patients with potentially resectable tumours were referred by their practitioners. More than half of our study population were in stages I or II. This fact reinforces our statement about the high sensitivity of the clinical indicators used in this study to predict bone metastases, because this is the group of patients with non-small cell lung cancer where we need to know whether routine bone scans will reveal clinically occult metastases.

The correct assessment of areas with increased radionuclide uptake in inconclusive bone scans is an important step in preoperative staging of bronchial carcinoma, and has to be performed in an individualised fashion for every patient. There is no doubt that the radionuclide scan is the most sensitive clini-

cally available method to detect and localise skeletal metastases.[17][18] This is confirmed by our follow up data. The procedures used in our patients varied according to the specific circumstances, but our follow up results document that the initial skeletal staging was adequate, even though it was rarely based on histological or cytological verification.

The high rate of false positive bone scans reduces the usefulness of this examination if performed as a routine procedure and increases not only the cost but also the potential risk for the patient because of further unnecessary examinations. To minimise the number of tests with false positive results bone scans should be performed only if suspicion of bone metastases arises from a careful clinical assessment. This strategy is safe, as we showed, because we would not have missed any patient with skeletal metastases at the initial staging in the present study had we followed this recommendation. We conclude that routine bone scanning is not justified in the initial staging of non-small cell lung cancer in patients without clinical suspicion of skeletal metastases.

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