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Original article

How does iliac crest bone marrow biopsy compare with imaging in the detection of bone metastases in small cell lung cancer?

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Abstract. Iliac crest bone marrow biopsy (BMB) has often been used as the gold standard for the detection of bone marrow metastases in small cell lung cancer (SCLC). However, it is likely to lead to numerous false-negative results. For this reason, we compared the results of bone scintigraphy (BS), magnetic resonance imaging (MRI), and BMB in 48 sequential patients affected with pathologically confirmed SCLC (47 were evaluable; mean age, 58.4 years). The three procedures were carried out within 1 week, no treatment being performed during this period. Whole-body scans and spot views were obtained in the anterior and posterior projections. For MRI, only the thoracolumbar spine, the sternum and the pelvis were scanned, using spin-echo T1-weighted sequences, resulting in an acquisition time of less than 45 min. Only five BMBs were rated as positive. In these cases, both BS and MRI were also positive. The other 42 biopsies were negative. Among them, in ten cases both BS and MRI were positive. In 21 cases, both BS and MRI were negative. In five cases MRI was positive while BS was negative. Finally, in six cases MRI was negative whilst BS was positive. In most cases in which either BS or MRI was positive, follow-up scans confirmed the initial findings. This study suggests that BMB is more invasive and less sensitive than BS or MRI in detecting bone metastases. MRI seems to be more sensitive than BS in detecting small spinal or pelvic metastases. Whole-body bone scintigraphy is more sensitive in detecting skull, costal or peripheral metastases. BS and MRI should be used in combination and may replace BMB in the detection of bone metastases in SCLC.

Key words: Iliac crest bone marrow biopsy – Bone metastases – Bone scintigram – Magnetic resonance imaging – Small cell lung cancer

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Introduction

Four main histological types of bronchopulmonary cancer are known: squamous cell, small cell, large cell and adenocarcinoma. Small cell lung cancer (SCLC) represents about one-fifth of all bronchopulmonary cancers.

When SCLC has been histologically confirmed, an additional diagnostic step for staging (i.e. assessing the extent of the disease) must be performed [1]. This step is essential for the treatment.

Staging permits a simple two-stage classification: limited and extensive disease. Limited disease is defined as a tumoural process involving only one hemithorax and its regional lymph nodes, including the ipsilateral mediastinal, the ipsilateral supraclavicular and the contralateral hilar nodes (all of which should allow one to perform radiotherapy within the same field). In all other cases (bilateral pulmonary involvement, extrathoracic metastases), disease is classified as extensive. In such cases, the only treatment is chemotherapy and the prognosis is very poor.

The most frequent locations of metastases of bronchopulmonary cancers, especially for SCLC, are liver and skeleton [2]. The most frequent locations of bone metastases of SCLC are spine, pelvis, sternum, ribs and skull [3, 4]. It is very important to assess bone metastases to prevent, as far as possible, fractures and /or spinal compressions.

For 20 years, systematic unilateral or bilateral iliac crest bone marrow biopsy (BMB) has been proposed to demonstrate bone marrow metastatic involvement. Currently, some authors still consider BMB to be the gold standard for staging SCLC patients. Consequently it is still in use in most European cancer centres. Some authors routinely perform a bilateral biopsy [5, 6]. However, it is an invasive and painful procedure and some recent papers have raised the question of its reliability and legitimacy [7, 8].

Bone scintigraphy (BS) is well known to be sensitive

in the detection of bone metastases. To date magnetic resonance imaging (MRI) has not been fully evaluated for the demonstration of bone involvement [9].

This study has been performed to evaluate and compare the sensitivity of BS, MRI and BMB in the diagnosis of bone metastases of SCLC. It is worth noting that bone marrow scintigraphy was not considered despite its reported usefulness in the detection of bone marrow metastases [10] because it is not yet routinely in use in our institution.

Materials and methods

Patients. This work is based on a prospective study, carried out from 1 January 1989 to 31 July 1991, concerning all patients hospitalized in the oncological division of the Department of Pneumology. The diagnosis of SCLC was histologically confirmed in all cases. Details of the patients are given in Table 1.

Methodology of acquisition

Except for the very first cases, for which investigations were performed over a slightly longer period (although not longer than 3 weeks), BS, MRI and BMB were carried out within 1 week. The procedures commenced before chemotherapy and as soon as the diagnosis of SCLC was histologically confirmed.

Bone scintigraphy. Technetium-99m labelled methylene diphosphonate (^{99m}Tc-MDP) was used. 11.1 MBq/kg ^{99m}Tc-MDP was injected intravenously. Scans were acquired 3–4 h after injection using a dual-head gamma camera (Rotacamera, Siemens), equipped with a LEAP collimator. A 20% energy window was set at about the 140-keV photopeak.

The patient was asked to drink about 1.5 l water between injection and acquisition, in order to reduce circulating activity. The bladder was emptied just before acquisition.

The procedure was as follows: anterior and posterior whole-body scans were acquired at the speed of 22–24 cm/min (about one million counts per view). Views centered on regions considered as suspect on whole-body scans by the nuclear medicine physician in charge (Y.B. or I.P.-R.) were then acquired with the following settings: 800 kc for the pelvis; 600 kc for the thorax; 300 kc for the skull. Images were displayed on radiological films using a semi-automatic tuning, allowing optimization of film contrast. The average duration of bone scintigram acquisition was about 40 min.

Table 1. Patient data

No. of patients	48
No. of evaluable cases	47[a]
Mean age (±SD)	58.4 (±10.3) years
Minimum age at time of diagnosis	30 years
Maximum age at time of diagnosis	78 years
Sex ratio	5.7:1
No. of male patients[b]	40
No. of female patients[c]	7

[a] In one case, BMB was uninterpretable
[b] Mean age: 59.0 (±11.0) years; range: 30–78
[c] Mean age: 55.1 (±5.0) years; range: 47–61

Magnetic resonance imaging. MRI scans were performed with a 1.5-T device (Magnetom Siemens). T1-weighted images were acquired using a spin-echo sequence with a short repetition time (TR < 0.7 s), a short echo time (TE < 30 ms) and a number of repetition (NR) varying from 1 to 4.

Presaturation bands were used to avoid vascular artefacts (especially for slices at the level of T8–9). Acquisitions were synchronized to cardiac pulses (ECG gating). Respiratory movements were not corrected for and induced image artefacts, especially in the sternum.

Slice thickness and orientation were different for the various studied regions: 4-mm sagittal slices for the spine, 8-mm frontal slices for the pelvis, and 4-mm parafrontal slices for the sternum. Duration of MRI acquisition was about 1 h.

The presence of metallic foreign bodies, especially neurosurgical clips installed before 1986 (from this date they have no longer been ferromagnetic in our institution), intraocular foreign bodies, insulin pumps or cardiac pacers was considered a contraindication to MRI acquisition. Moreover, patients had to accept the following acquisition constraints: (a) confinement inside the device, which may induce claustrophobic reactions (about 0.5% of cases), (b) a high noise level and (c) the need to remain still, which may induce pain at the supporting points (as BS does).

Iliac crest bone marrow biopsy. In all cases a non-selective, unguided unilateral biopsy was performed at the level of the postero-internal part of the iliac crest. This remains an invasive and painful procedure, poorly tolerated by patients despite premedication and local anaesthesia.

Methodology of interpretation

Bone scintigraphy. All scans were separately read and interpreted at the end of the study by two experienced nuclear medicine physicians (Y.B. and I.P.-R.), who compared their interpretations later.

To permit the analysis of results, findings were rated as follows:
1. Positive: lesions strongly suggestive of metastases
2. Negative: non-specific lesions or findings considered normal

Magnetic resonance imaging. On T1-weighted images, bone marrow appears with increased signal while a non-lipidic space-occupying lesion such as a metastasis appears with reduced signal. Contrast resolution between a (black) metastatic hypointense signal and the (white) bone marrow hyperintense signal is excellent.

Lesions smaller than 4 mm are difficult to detect. False-negatives can occur when the fat content of bone marrow is low (such as in the case of hematopoietic regeneration), causing poor image contrast. Conversely, reduced signal in the spine may be present in cases of arthrosis, vertebral crush fractures of osteoporotic origin, intraspongious herniation, benign condensed osteoma and spondylitis.

Image were read twice by the same radiologist (T.B.) using the following rating:
1. Positive: lesions strongly suggestive of metastases
2. Negative: non-specific or dubious lesions or findings considered normal

Iliac crest bone marrow biopsy. The BMB samples were histologically analysed by one pathologist (M.F.) and rated positive when metastatic cells were seen and negative when they were absent.

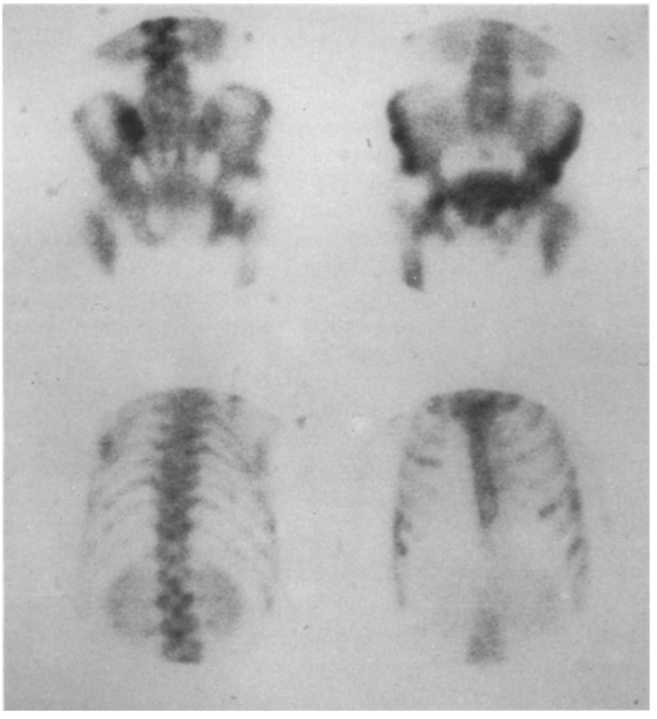

Fig. 1. BS showing multiple bone metastases (ribs, spine, pelvis)

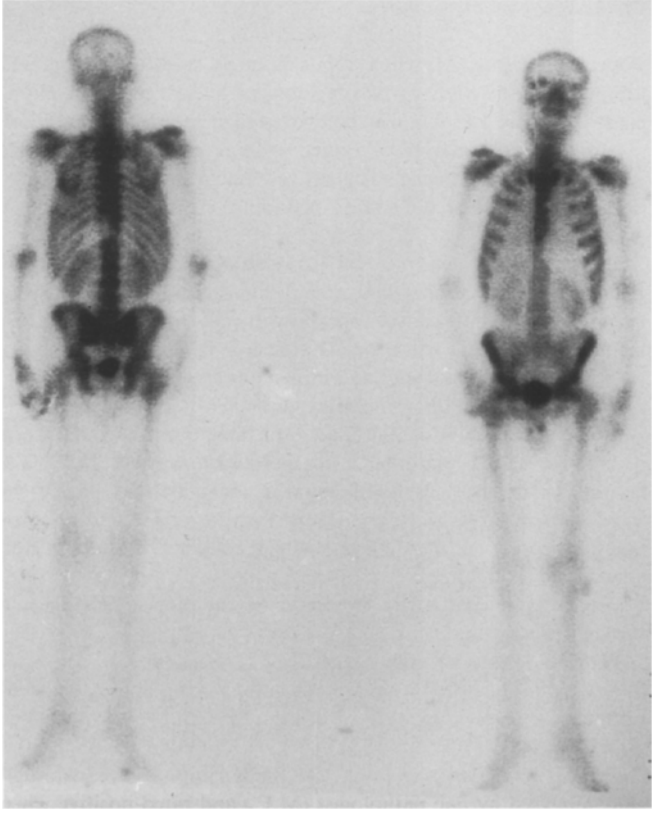

Fig. 2. BS showing osteolytic metastasis (thoracic vertebra)

Methodology of comparison

ROC analysis was not carried out. No normal subject was investigated, and the total number of patients studied is still small. BS, MRI and BMB were compared qualitatively as regards their ability to differentiate metastatic disease from SCLC.

Results

BS was positive in 21 patients (i.e. 44.7% of cases) (Figs. 1–3). In all cases but one, both readers agreed. In one case, heterogeneous spinal uptake was considered suggestive of metastasis by one reader but not by the other. Images were re-interpreted by both readers at the same time and a consensus was achieved.

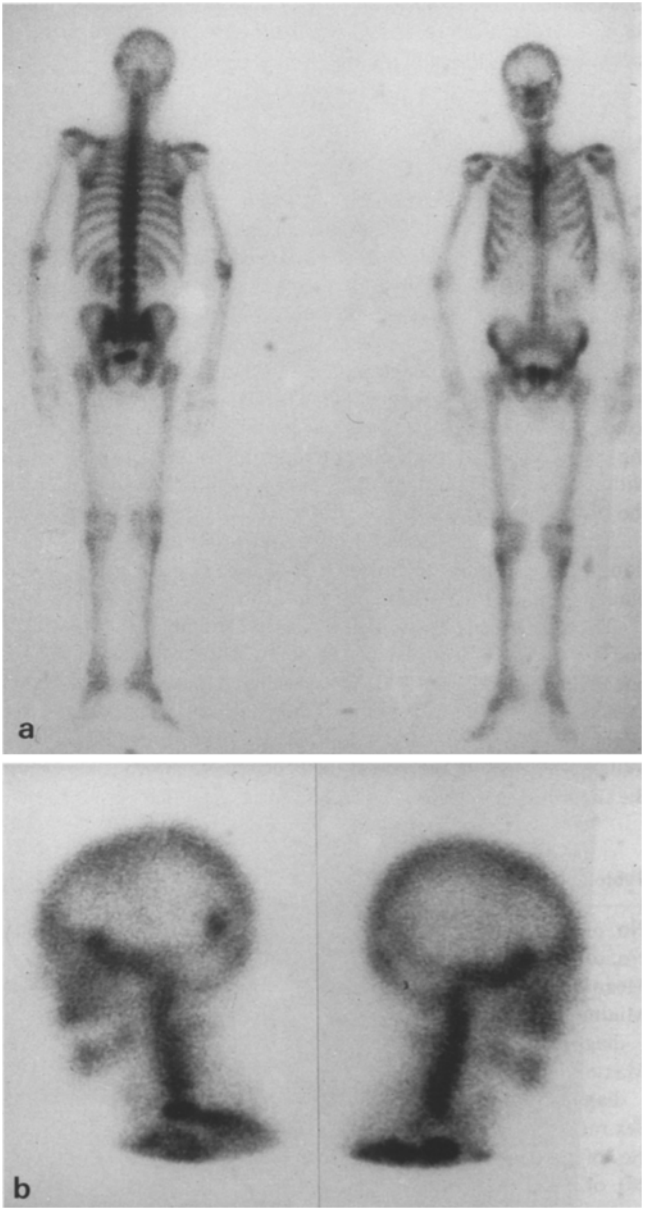

Fig. 3a, b. BS. **a** Whole-body scan showing skull and rib metastases. **b** View centered on skull (in the same patient) exhibiting the metastasis (MRI was negative in this patient)

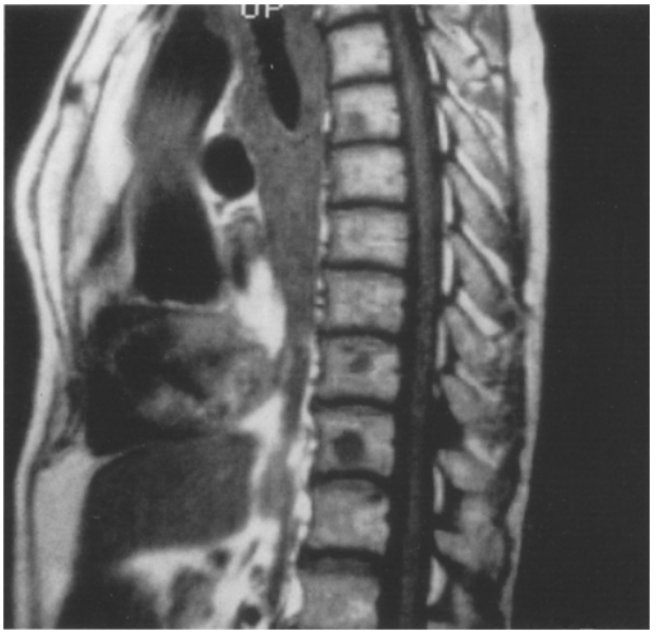

Fig. 4. MRI: low signals suggestive of spinal metastases (BS was negative in this patient)

Table 2. Comparative results

BS	MRI	BMB	Number of cases
+	+	+	5
−	−	−	21
+	+	−	10
+	−	−	6
−	+	−	5

MRI was positive in 20 patients (42.6%) (Figs. 4, 5).

BMB demonstrated metastatic cells within the iliac bone in only five patients (10.7% of cases). The fact that only blind and only iliac biopsies were performed partially explains such a poor yield.

Results obtained from the three procedures (BS, MRI and BMB) are summarized in Table 2. All three procedures were positive in five patients. In each of the five patients with a positive BMB, metastatic deposits in numerous locations were easily demonstrated. In all these cases, disease progression was quickly lethal (none of the patients survived longer than 5 months). In 21 patients, the three procedures were negative. In ten patients, both BS and MRI showed evidence of bone metastases at the same locations. In six patients, lesions suggestive of bone metastases were detected on BS while MRI was normal. These patients essentially exhibited skull and rib metastases. Finally, in five patients, MRI was positive while BS was negative. These patients had mainly small spinal and/or pelvic lesions.

If the positivity of only one procedure was considered sufficient to make the diagnosis of SCLC bone metastases, 26 out of 47 studied patients (55.3% of cases) had metastases.

Discussion

The above results are in agreement with previously published data. On the basis of standard X-ray procedures and bone scintigrams, Eguchi et al. [4] found that 42 out of their 97 patients affected with SCLC had bone metastases (i.e. 43.3%). Using MRI, Carney et al. [11] demonstrated bone marrow metastases in eight out of their 20 patients (40%). The poor result obtained in our study with BMB is equally consistent with published data [5, 12]. It is likely that BMB underestimates the rate of bone marrow metastases. In a study where bilateral iliac crest biopsy was performed [6], 3 out of 19 cases were positive, i.e. 15.8%, indicating that bilateral iliac crest biopsies do not significantly increase the rate of positivity.

Our data can contribute to the debate on whether or not BMB of the iliac crest should still be used in the evaluation of these patients. The role of BMB in the staging and therapeutic management of SCLC patients appears minor while its drawbacks are important. It follows that BMB should be withdrawn from the diagnostic armamentarium used for the staging of SCLC.

When both BS and MRI are positive (as happened 10 times in our study), it is almost certain (or highly probable) that these cases are true-positive. This assumption was confirmed by follow-up imaging procedures.

In contrast, it is necessary to discuss the six cases in which only BS was positive and the five cases in which only MRI was positive. Some of these 11 cases may represent false-positives.

In the six cases in which only BS was positive, the metastases were located at sites that are poorly or not explored by MRI (such as skull and ribs). In all cases tracer uptake was dramatically increased such that they most probably correspond to true-positives. Follow-up scans confirmed these lesions.

In the five cases in which only MRI was positive, lesions were located in the spine and/or the pelvis, at sites where BS may fail. Lesions were either small or purely medullary, without bone reaction. These characteristics explain why BS might appear as normal. The probability of false-positives on MRI is extremely low, as shown by Fiche et al. [13], who compared MRI data and bone marrow samples from autopsy material.

It seems that both MRI and BS must be performed to detect bone metastases of SCLC. Their positivity is induced by different phenomena: direct visualization of medullary metastasis which replaces fat content on MRI images, and indirect visualization of an osteoblastic reaction around the metastasis or ischaemic necrosis induced by a metastasis on bone scintigrams. Moreover each of

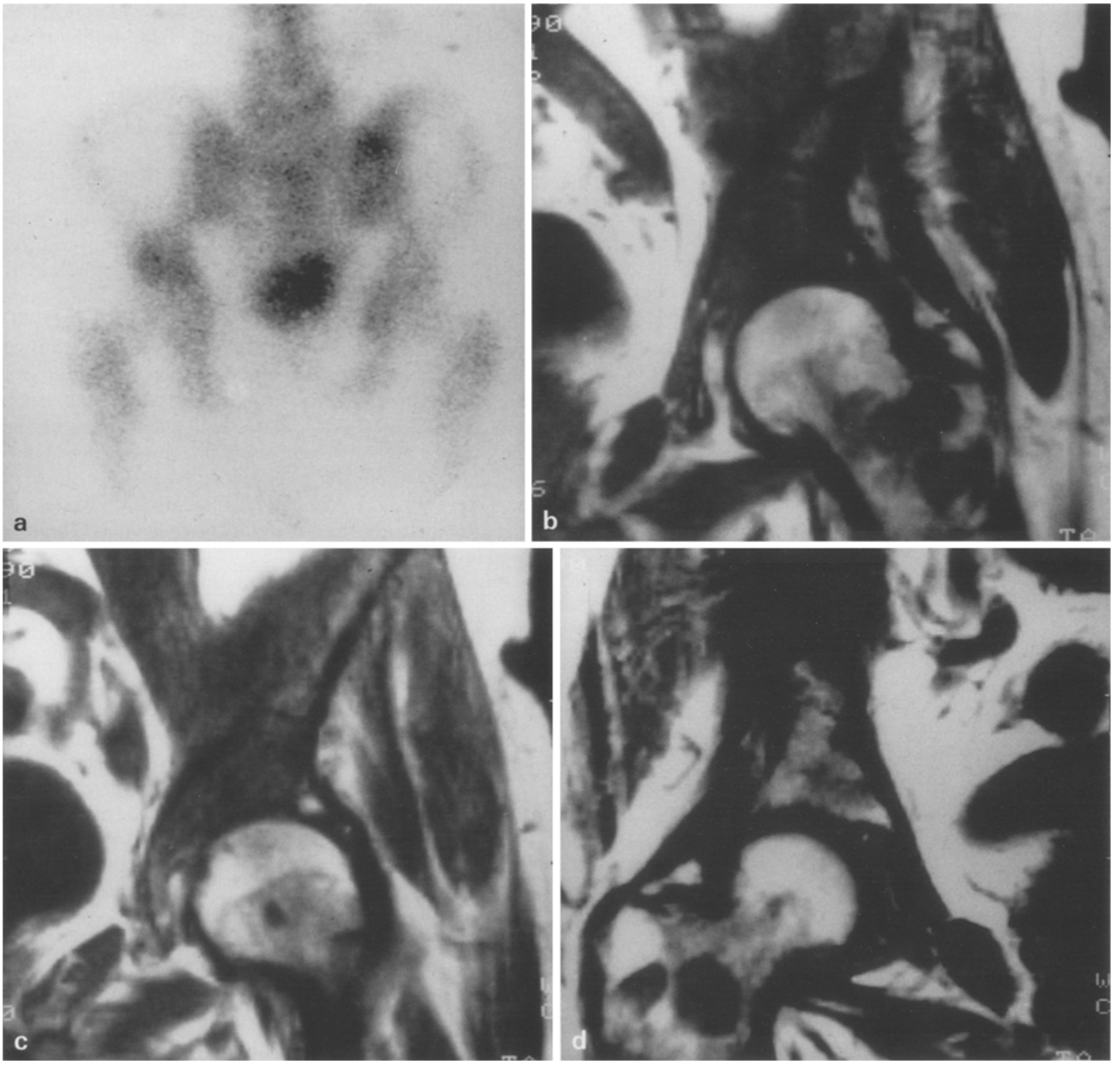

Fig. 5a–d. MRI vs BS. **a** BS centered on pelvis (posterior view) showing metastases of left hip, right part of sacrum and right hip. **b, c** MRI centered on left hip exhibiting metastasis shown by BS and demonstrating additional metastases within upper part of the femur. **d** MRI centered on right hip, yielding the same results

these procedures explores anatomical regions which are poorly imaged by the other.

To summarize, iliac crest BMB, an invasive and painful procedure, is very poor in the detection of bone marrow metastatic spread. MRI is highly sensitive in the detection of spinal, pelvic and sternal metastatic sites; however, it takes time (1 h) and is expensive (costing twice as much as BS). BS is sensitive in detecting skull, rib and limb metastatic sites; however, it may not detect small lesions or those which do not cause a significant osteoblastic response. It thus appears that BS and MRI are complementary procedures for the detection of bone metastases of SCLC and that both need to be performed when staging this cancer.

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