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BONE MARROW IMMUNOSCINTIGRAPHY COMPARED WITH CONVENTIONAL BONE SCINTIGRAPHY FOR THE DETECTION OF BONE METASTASES

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Immunoscintigraphy of haematopoetic bone marrow was compared to conventional bone scanning in 141 patients with malignant disease. Forty patients had breast cancer, 25 prostatic carcinoma, 14 kidney or bladder cancer, 13 bronchial carcinoma, 39 malignant lymphoma and 10 multiple myeloma. A total of 18 800 skeletal regions were evaluated. Marrow scans showed more metastatic lesions than bone scanning in all patient subgroups. Computerized tomography was concordant with bone marrow scintigraphy in 83.3% of 323 skeletal sites. Bone marrow scans in 30 control patients with fever of unknown origin were abnormal only in 3 patients and in only 7 out of 2 135 skeletal regions examined. In patients with malignant lymphoma, bone marrow histology or aspiration cytology was concordantly positive in 14 and concordantly negative in 17 patients. We conclude that immunoscintigraphy of haematopoetic bone marrow provides a reliable, sensitive and safe novel approach for non-invasive detection of metastatic spread to the skeleton.

The skeletal system is a common site of metastases (1). Bone metastases have been found on autopsy in 50–85% of patients with breast or prostate carcinoma, malignant lymphoma, bronchial carcinoma or renal cell carcinoma (1–3). The tumour cells are, however, primarily localized in haematopoetic bone marrow, and osteolytic destruction and/or osteoblastic skeletal reactions develop at a later stage (2, 4–8). Reactions in the bone are mediated via specific stimulation of osteoclasts and/or osteoblasts by mediator substances, secreted by tumour cells or mononuclear cells in the metastatic microenvironment (2, 9).

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Although skeletal metastases can be reliably detected by several imaging modalities, such as plane radiographs, conventional tomography, computerized tomography (CT) or more recently magnetic resonance (MR) bone scanning is most commonly used for skeletal surveys because of its sensitivity in detecting new bone formation in response to metastatic lesions, and the convenience of whole body imaging (10, 11).

We have recently used a monoclonal antibody that binds to granulopoetic cells in bone marrow (12, 13) and to granulocytes in peripheral blood (14, 15) for the immunoscintigraphic examination of haematopoetic bone marrow in humans (12, 13). High-quality scans showing the distribution of haematopoetic bone marrow were consistently obtained (12, 13). Since the demonstration of bone marrow involvement is not dependent on secondary bony reaction, bone marrow scanning promises to be a more sensitive method of detection of bone metastases. We therefore compared the sensitivity of this novel approach to that of conventional bone scanning. The two imaging modalities were compared in groups of patients with primary solid malignant tumours, such as carcinoma of the breast, prostate, kidneys, bladder or the bronchial system as well as malignancies originating from haematopoetic

or lymphatic tissue, i.e. multiple myeloma or malignant lymphoma.

Material and Methods

Antibody. A ^{99m}Tc-labelled murine, monoclonal isotype IgG_1 antibody BW 250/183 (Szintimmun Granulozyt), Hoechst AG, Frankfurt, FRG) was used for bone marrow imaging. The antibody had excellent in vivo stability, sustained immunoreactivity above 80% of the unlabelled material, and an affinity constant of 2×10^9 l/mole (15).

Principle of immunoscintigraphy of granulopoetic bone marrow. Non specific cross-reacting antigen-antibody (TcNCAA) binds to granulopoetic bone marrow cells and granulocytes in peripheral blood via interaction with non-specific cross-reacting antigen 95 (NCA-95) (14). NCA-95 is expressed in the cytoplasm and at the cell membrane of granulocytes as well as on mature granulopoetic bone marrow cells (16–21). Erythropoetic, thrombopoetic and lymphatic cells did not express NCA-95 (18, 20). Since granulopoetic bone marrow cells are 50 to 100 tines more frequent than granulocytes in peripheral blood (22), TcNCAA distributes primarily to the bone marrow after i.v. injection (12, 13). Immunohistology and flow cytometry of human bone marrow showed selective TcNCAA-binding to granulopoetic cells both after in vitro incubation with TcNCAA and after TcNCAA injection i.v. (23).

Patients. In all, 141 patients with malignant disease, referred for initial staging or restaging during follow-up between March 1988 and January 1990, were enrolled in the study. Forty patients had carcinoma of the breast, 25 carcinoma of the prostate, 14 kidney or bladder cancer, 13 bronchial carcinoma, 10 multiple myeloma and 39 malignant lymphoma (Table 1). The diagnosis was confirmed in all patients by histology. Thirty patients without any suspicion of malignant disease, examined for fever of unknown origin (FUO), served as controls. Since no imflammatory lesions were found in the skeleton of these patients, this population was regarded as normal with respect to haematopoetic bone marrow. In these patients, only bone marrow scans were available. Patient characteristics are summarized in Table 1. The stage of patients with malignant disease was determined according to the UICC (24).

Scintigraphy. Immunoscintigraphy of haematopoetic bone marrow studies were done as previously described (12, 13). Briefly, patients were injected with 300 ± 15 MBq/0.25 mg protein TcNCAA. Bone marrow imaging was done 3–4 h later using a LFOV gamma camera. Overlapping spot views of the axial and the proximal appendicular skeleton were routinely done in anterior and posterior views. Five hundred to 1 000 kcounts were acquired per view in the axial and 250 kcounts in the peripheral skeleton. The radiation exposure caused by 300 MBq ^{99m}Tc-labelled antibody amounts was calculated as 6.5 mGy in the liver, 8.7 mGy in the spleen, 5.7 mGy in the kidneys, 8.8 mGy in bone marrow and 1.5 mGy in the whole body (25).

Bone scans including the peripheral skeleton were obtained within 14 days of immunoscintigraphy after i.v. injection of 600 ± 45 MBq ^{99m}Tc DPD (Hoechst AG, Frankfurt, Germany) using standard techniques and identical gamma cameras. The scan results were recorded on x-ray film and read by two experienced observers not aware of the clinical data, results of other imaging methods or bone marrow histology. The criterion for a metastatic lesion at immunoscintigraphy was a clearly-defined focus of deficient antibody uptake in haematopoetic bone marrow. Since previous studies in our laboratory have shown a variable and unhomogenous distribution of haematopoetic bone marrow in the proximal parts of both femur and humerus, especially in elderly patients, only multiple and extensive defects were judged indicative of metastatic involvement in these locations. Since occasionally metastatic lesions can present on microcolloid scans as hot spots (26), special attention was given to the occurrence of hot spots on immunoscans of bone marrow.

Table 1

Some characteristics of patients with malignancies studied with bone marrow and bone scanning

Diagnosis	Mean age (years)	Stage					Time since diagnosis (years)	Sex	
		I	II	III	IV	N.A.		M	F
Breast ca.	54	4	22	8	2	4	4.8	0	40
Prostate ca.	75	3	6	5	9	2	1.5	25	0
Kidney ca. Bladder ca.	65	0	1	2	9	2	0.6	3	11
Bronchial ca.	58	0	1	5	2	5	0.4	12	1
Lymphoma	54	7	11	2	13	6	1.8	13	26
Myeloma	66	2	1	4	–	3	1.9	4	4
Controls	58	–	–	–	–	–	–	10	20

Bone scans were interpreted according to published guidelines (11). Seventy-five skeletal regions were evaluated in each patient by both procedures. The results from each of the 75 skeletal regions were analysed with a statistical data analysis computer package (27). The number of lesions was determined and compared with a dedicated computer program. Since some bone regions were not adequately imaged due, for example, to disabling disease or were classified as other than normal or metastatic, 9 400 skeletal regions were available for comparison of the two scintigraphy methods. To compare imaging results in the different patient subgroups, the ratio of metastatic lesions to all skeletal regions was determined and taken as an index of the extent of skeletal involvement.

Comparison with CT. For 323 skeletal regions, the results of CT examinations done for clinical indications were available. Normal or metastatic lesions, demonstrated by CT, were compared with the findings at bone marrow scanning for the respective sites. A time gap of 4 weeks between bone marrow scanning and CT was allowed. The findings were compared with those of CT examinations to corroborate the results of bone marrow scanning with a high resolution imaging method. We are aware that CT is not the ideal method for verifying bone metastases, as it has small margin of error (28). Magnetic resonance imaging (MRI) is probably the best non-invasive imaging method but it was not generally available for the study population.

Histology and cytology. In 36 patients with malignant lymphoma, the results of bone marrow biopsy or bone marrow aspiration cytology were available for comparison with the findings of bone marrow scanning.

Statistics. The frequencies of normal and metastatic lesions found by bone and bone marrow scanning were compared in the subgroups of patients with malignant disease by the χ^2-test (27). A p-value < 0.05 was regarded as significant.

Results

In control patients antibody uptake was homogenous in the axial and in the proximal third of the appendicular skeleton (Fig. 1). In addition, faint antibody uptake in the liver and moderate uptake in the spleen were observed which only mildly obscured overlying structures, such as the spine or the ribs. The image quality of the antibody scan was comparable to that of a bone scan and clearly superior to bone marrow radiocolloid scans.

Mixed osteoblastic/osteolytic metastases were concordantly detected by both scintigraphic methods, as shown in Fig. 2. However, in most patients bone marrow scanning detected additional metastatic foci. Surprisingly, not only small but sometimes rather large lesions (Fig. 3) were detected only by marrow scanning, and appeared normal in the bone scan. Occasionally, generalized skeletal metastatic spread was easily demonstrated by bone marrow scanning, whereas bone scans depicted only a few or no metastatic foci (Fig. 4). Bone scans were clearly superior in demonstrating metastases to the femoral neck and the long bones, as the occurrence of haematopoetic bone marrow in these locations is highly variable or virtually deficient in elderly patients. Advanced multiple myeloma was characterized by multiple bone marrow defects. In these patients scans demonstrated the larger osteolytic foci, but the detection of increased tracer due to osteoporotic microfractures or bone marrow infiltration was difficult or impossible. Similarly, bone marrow involvement was easily detected in malignant lymphomas (Fig. 5), whereas bone scans in these patients showed rather unspecific changes in tracer uptake. In accordance with our previous studies (12, 13), hot spots were not observed in any of the bone marrow scans.

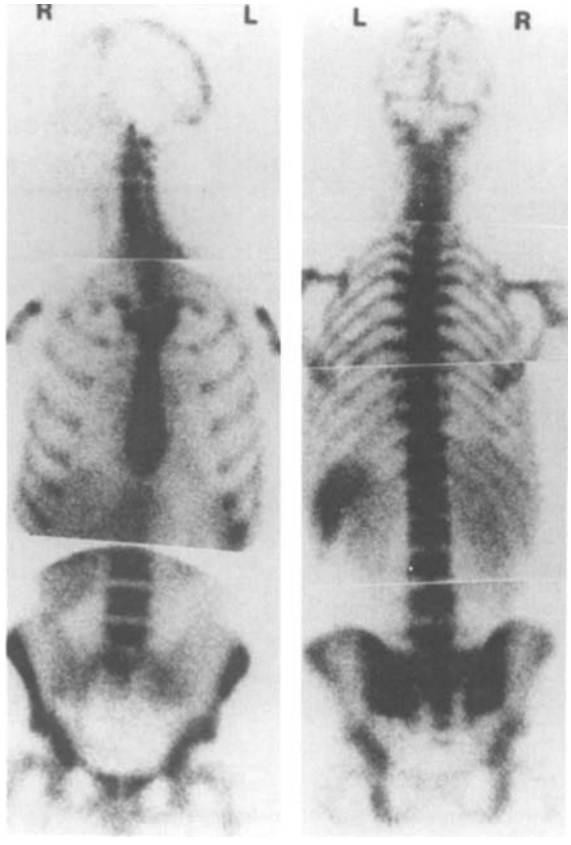


Fig. 1. Normal bone marrow scan. Left: anterior; right: posterior view.

In 52 previously irradiated patients, the radiation ports were clearly visualized in the bone marrow scans as sharply delimited areas with highly reduced antibody uptake in the bone marrow. Of 30 control patients with FUO, bone marrow scans were abnormal in 3; only 7 of the 2 135 skeletal regions showed borderline defects in the bone marrow scans. The two observers who independently examined the bone marrow scans agreed in their judge-

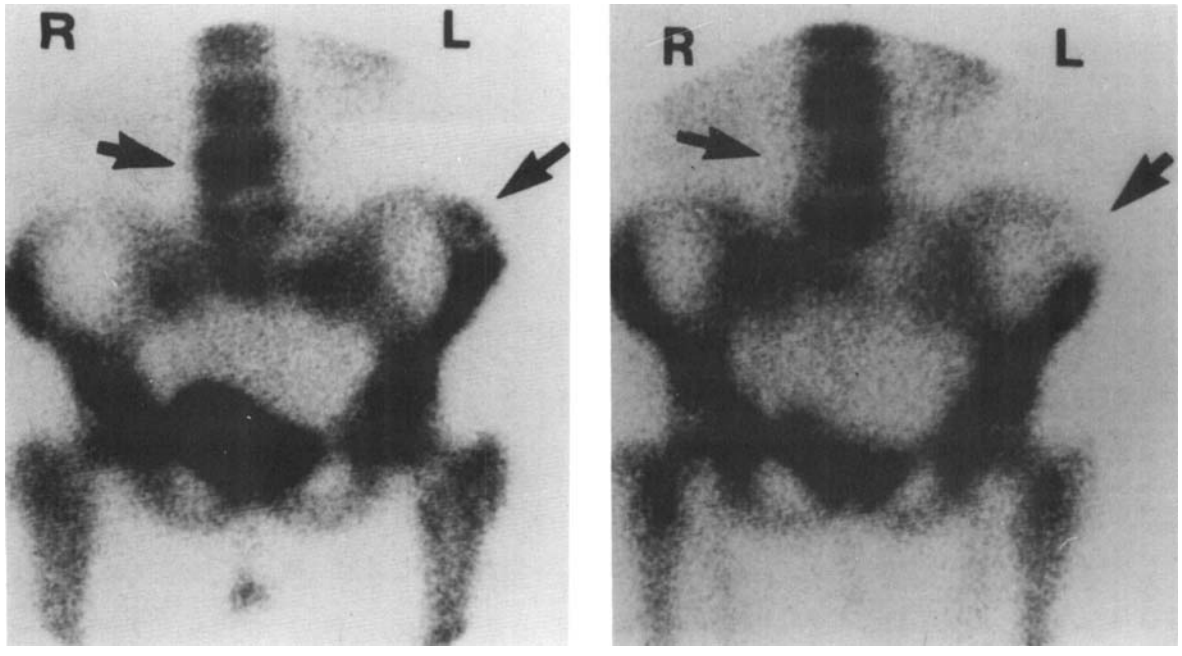


Fig. 2. Concordant visualization of mixed osteolytic/osteoblastic metastases by bone scanning (left) and bone marrow scanning (right) in a patient with renal adenocarcinoma.

ment concerning 97.2% of all metastatic lesions. For the remaining lesions, agreement was obtained by consensus.

Conventional bone scans showed fewer metastatic sites than bone marrow scans in all patient subgroups (Table 2). These differences were highly significant ($p < 0.001$ to $p = 0.0175$). The extent of skeletal involvement, as assessed by the two scintigraphic methods is summarized in Table 3. Bone marrow scans demonstrated significantly more widespread involvement of the skeletal system than conventional bone scans.

CT examinations were available for 226 skeletal regions in patients with solid tumours and for 97 regions in patients with malignant lymphoma or multiple myeloma. Findings concordant with the bone-marrow scans were observed in 84.5% of the sites in the subgroup with solid primary tumours, and in 80.4% of patient with malignant lymphoma or multiple myeloma (Table 4).

Table 2

Extent of skeletal involvement according to bone marrow scanning (IBM) and bone scanning (BS)

Diagnosis	No of patients	Percentages of skeletal regions with metastatic lesions		
		IBM	BS	p-value
Breast ca.	40	32.2	10.6	<0.001
Prostate ca.	25	17.7	11.9	=0.175
Kidney/bladder ca.	14	3.6	1.5	=0.002
Bronchial ca.	13	10.7	5.1	<0.001
Lymphoma	39	10.6	1.0	<0.001
Myeloma	10	19.7	4.7	<0.001

Table 3

Skeletal regions judged to be normal or to contain metastatic lesions by bone scanning and bone marrow scanning

Diagnosis	Bone scan		Bone marrow	
	Normal	Metastatic	Normal	Metastatic
Breast ca.	2 421	324	1 591	832
Prostate ca.	1 417	246	1 512	328
Kidney/bladder ca.	994	18	827	37
Bronchial ca.	946	46	703	83
Lymphoma	2 380	31	2 061	264
Myeoloma	403	25	402	127

The findings of bone marrow histology or cytology were available for comparison scans in 36 patients with malignant lymphoma. Concordant negative results were found in 17 patients, whereas 14 patients had concordant positive results indicating bone marrow infiltration. In 5 patients, histology was negative but bone marrow scans showed defects indicating bone marrow involvement. Histological evidence of bone marrow infiltration in combination with normal bone marrow scan was not observed.

Discussion

In the present study, bone marrow scanning detected considerably more metastatic lesions than conventional

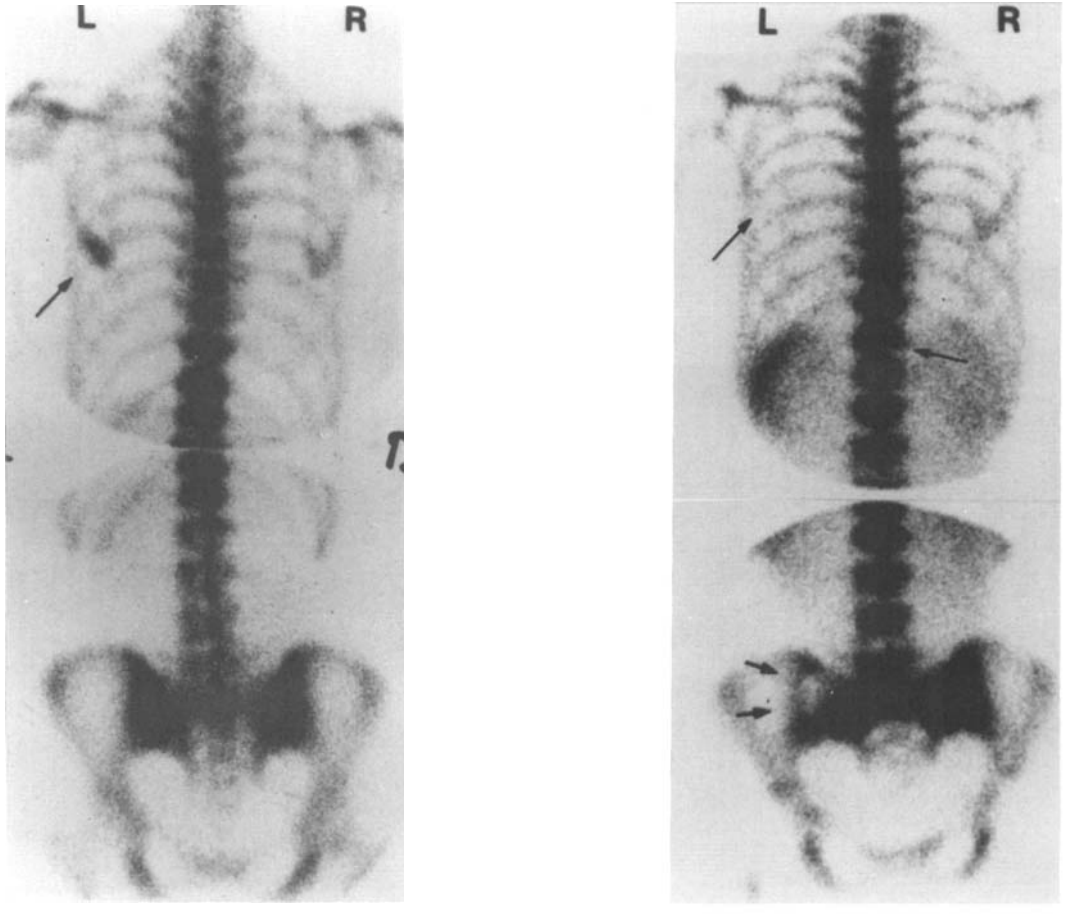


Fig. 3. Large osteolytic metastasis in left pelvis visualized by bone marrow scanning in a patient with breast cancer (right). The bone scan (left) was normal in this region. Additional metastases in Th 12 and left scapula (arrows). Only the latter lesion was detected by bone scanning. The spot view of the bone marrow scan (lower image) shows the lesions more clearly. The importance of high quality bone marrow scans for detecting small lesions is clearly demonstrated.

bone scanning. This observation was not surprising in haematopoetic or lymphatic malignancies in view of earlier reports (11, 29–37). However, immunoscintigraphy of the bone marrow also detected significantly more lesions than bone scanning in solid tumours, indicating that the bone marrow frequently contains metastases which have not yet induced osteoblastic or osteolytic response detectable by bone scanning.

Several authors have reported that bone scintigraphy is more sensitive than bone marrow scanning with radioactive microcolloids in detecting bone metastases from prostate and breast cancer and other solid tumours (31, 36). Some authors (26, 33, 34) concluded that radiocolloid bone marrow scanning helps to distinguish benign from malignant skeletal lesions, and this method and bone scanning provide complementary information. Others have reported that lumbar spine and pelvic radiocolloid bone marrow scans were highly sensitive in detecting metastatic disease (35). Similarly, Bourgeois et al. (36) found 'an earlier and more precise detection of skeletal invasion' in radiocolloid marrow scans than on bone scans in 10 out of

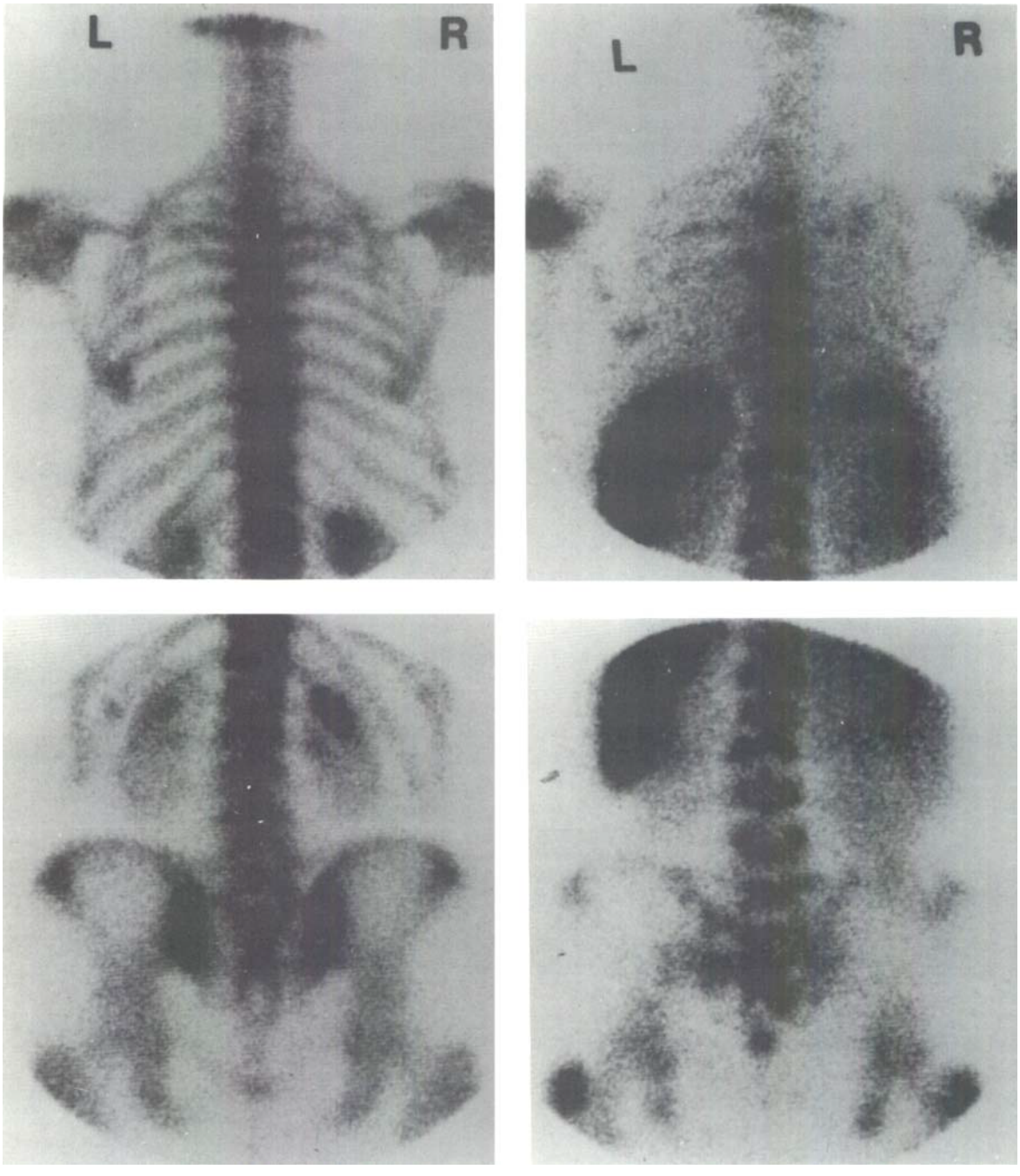
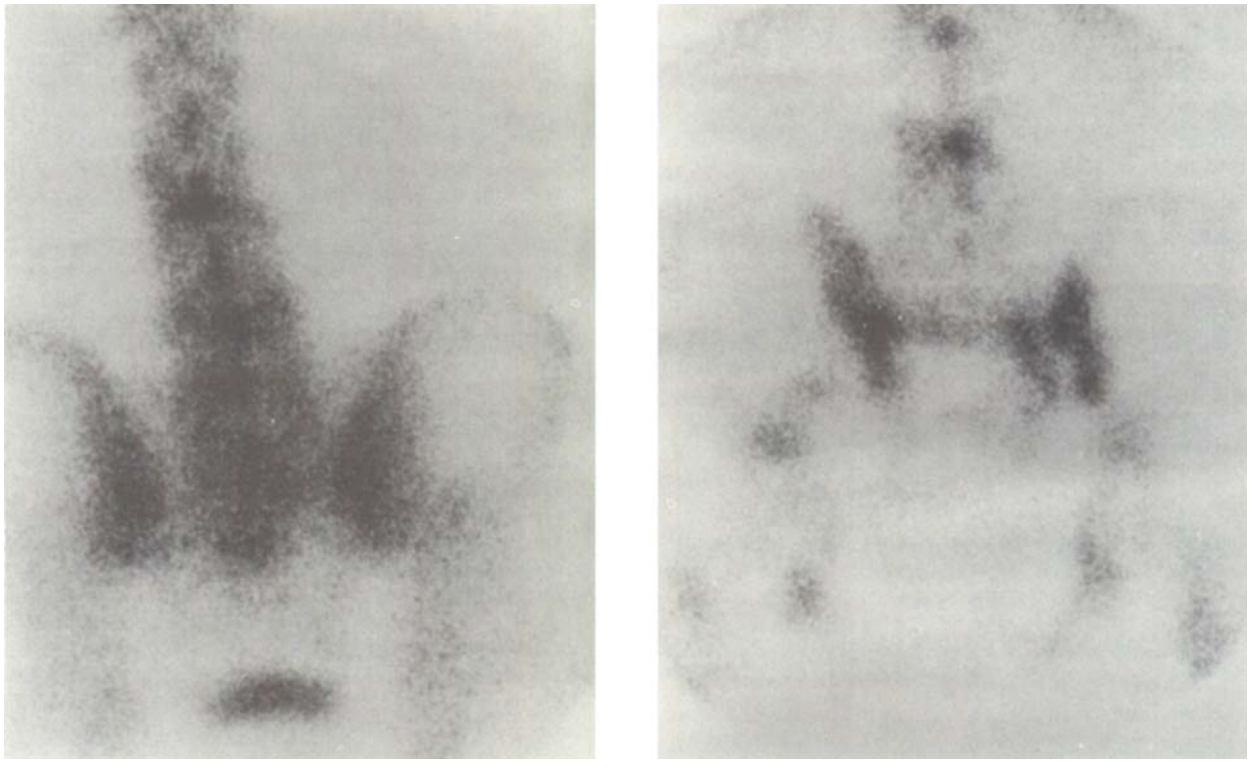


Fig. 4. Generalized bone metastases in a patient with breast cancer. The bone marrow scan shows multiple defects (right images). Increased antibody uptake in the spleen, possibly due to extramedullary haematopoesis. The bone scan shows increased uptake in left upper kidney pole, but was otherwise normal (left images).

101 patients with carcinoma of the breast. Preliminary results published by Majimiyi & Shepstone (37) are in accord with these observations.

Colloid uptake in the liver and spleen, which overlap large parts of the spine and thorax deteriorates the image quality of radiocolloid marrow scans considerably (11) which prevents an adequate comparison between bone marrow and bone scanning. This disadvantage is largely overcome by bone marrow immunoscintigraphy. Thus, in virtually all subgroups of malignant diseases this method was found to be superior to conventional bone scanning for detecting metastases in the skeletal system. However, to demonstrate metastases in the femoral head and long bones the findings with bone marrow and bone scanning were complementary.

Bone marrow defects may have a variety of causes, the more common being malignant lesions, inflammatory, circulatory or degenerative changes, fibrosis, fatty degenera-



a) b)

Fig. 5. Generalized bone marrow infiltration in Hodgkin's disease, confirmed by bone marrow biopsy. The bone marrow scan shows only spotty residual islands of haematopoetic bone marrow (b) The scan (a) shows a slight diffuse increase in tracer uptake in lumbar vertebrae III–V compatible with osteoarthritis.

Table 4

Comparison between computerized tomography (CT) and bone marrow scanning (BMS) for selected skeletal regions. CT examinations were done to clinical indications. The percentages of concordant and discordant findings are indicated

	Solid tumors n = 226	Lymphomas and myelomas n = 97	Total n = 323
CT + /BMS +	56.6%	6.2%	41.5%
CT − /BMS −	27.8%	74.2%	41.8%
CT + /BMS −	18.6%	2.2%	7.1%
CT − /BMS +	1.0%	13.3%	9.6%
Concordant findings	84.5%	80.4%	83.3%

tion, necrosis, extensive osteoarthritis, and fatty or bony islands (3, 10–12, 26). Thus, the specificity of the frequent bone marrow defects observed in the present patient population with malignant diseases remains to be determined. However, the concordance with histologic and CT findings, when these were available, and the largely negative findings in control patients, strongly support that the defects actually represented malignant bone marrow lesions. The findings in the control patients also gave the impression that active bone marrow is distributed in a remarkably homogeneous manner in the axial skeleton.

Linden et al. (38) recently reported that chemotherapy did not significantly alter the distribution of normal haematopoetic bone marrow imaged by radiocolloids or MRI. Radiotherapy exerted well-known local effects on the bone marrow, which were easily detected by MRI or bone marrow scanning, but did not alter the appearance of the bone marrow scans outside the radiation ports (12, 13, 38); similar observations were obtained in the present study.

It may be difficult or impossible to distinguish between active bone marrow disease and bone marrow fibrosis solely on the basis of a bone marrow defect. In doubtful cases more specific procedures, such as MRI or bone marrow biopsy have been advocated (38, 39). Bone marrow scanning in such cases may help in directing the biopsy or selecting sites for further investigation.

In a patient material as the present one a selection bias in favour of patients with advanced disease has to be taken into account. The important question of early detection of metastatic disease in the skeleton by bone marrow scanning awaits further clarification. However, results recently reported by Duncker et al. (40) indicate that bone marrow immunoscintigraphy holds promise for the 'early detection of bone metastatic involvement in patients with breast cancer'.

Antibody response to the injected murine antibody may have serious implications for repeated immunoscinti-

graphic studies (41). However, in a preliminary study of 86 patients, receiving TcNCAA we found measurable indication of human antimouse antibodies (HAMA) in only 4 patients. Additional 3 patients had borderline titres (42). We thus feel that the HAMA response to 100–250 μg ^{99m}Tc-labeled TcNCAA might be small compared to the response to some other substances used for clinical immunoscinitigraphic procedures (43).

In conclusion, bone marrow immunoscintigraphy had superior sensitivity compared to conventional bone scanning in patients with various solid and haematological malignancies. Further studies are needed to elucidate the potential of this novel approach for the early diagnosis of metastatic spread to the skeleton.

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