Technetium-99m-sestaMIBI scintigraphy in multiple myeloma and related gammopathies: a useful tool for the identification and follow-up of myeloma bone disease

ENRICO BALLEARI,* GIUSEPPE VILLA,° SIMONA GARRÈ,* PAMELA GHIRLANDA,* GIUSEPPE AGNESE,° MARCO CARLETTO,° MARINO CLAVIO,# FABIO FERRANDO,@ MARCO GOBBI,# GIULIANO MARIANI,° RICCARDO GHIO*

*Semeiotica e Metodologia Medica I; °Medicina Nucleare; #Ematologia; @Clinica Medica I; Dipartimento di Medicina Interna e Specialità Mediche, Università di Genova, Italy

Background and Objectives. Technetium-99m 2-methoxy-isobutyl-isonitrile (^{99m}Tc-sestamibi) has recently been proposed as a potential tracer in patients with multiple myeloma (MM), as its increased uptake in the bone marrow has been reported as indicator of myeloma activity. We evaluated the role of ^{99m}Tc-sestamibi scintigraphy in the detection of myeloma bone disease in MM and related gammopathies, and also assessed its relationship with clinical status and stage of the disease, focusing in particular on the early follow-up of a small series of MM patients treated with high-dose therapy.

Design and Methods. Forty-six consecutive patients affected by MM or monoclonal gammopathy of undefined significance (MGUS) were studied by whole body scans obtained 20 minutes after administration of 740 MBq of ^{99m}Tc-sestamibi. A semiquantitative uptake score was used and scintigraphic findings were correlated with clinical and laboratory data.

Results. All the MGUS patients showed a negative ^{99m}Tc-sestamibi scan. Among the 32 MM patients (25 with active disease and 7 in clinical remission) 24 showed a positive scan, while 8 presented only a physiologic uptake of the tracer. The uptake score correlated significantly with all the most relevant clinical variables. In the follow-up of 8 MM patients treated with high-dose chemotherapy ^{99m}Tc-sestamibi closely paralleled the activity of myeloma bone disease. Comparison with X-ray skeletal survey showed discordant results in 14 out of the overall 56 scans obtained (27%), with 10 cases of negative ^{99m}Tc-sestamibi scans but lytic bone lesions revealed by X-ray (7 of them were in clinical remission), and 4 negative X-ray surveys in patients with positive ^{99m}Tc-sestamibi scans. Overall sensitivity and specificity of ^{99m}Tc-sestamibi scintigraphy in detecting myeloma bone disease were 90% and 88%, respectively.

Interpretation and Conclusions. This study provides additional evidence indicating that ^{99m}Tc-sestamibi scintigraphy closely reflects myeloma disease activity in bone marrow, with very high sensitivity and specificity. ^{99m}Tc-sestamibi scintigraphy is therefore suggested as a reliable new tool for the staging and follow-up of myeloma bone disease.

Key words: technetium-99m-sestamibi; multiple myeloma; MGUS; scintigraphy; myeloma bone disease

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Correspondence: Enrico Balleari, M.D., Dipartimento di Medicina Interna e Specialità Mediche, Università di Genova, viale Benedetto XV 6, 16132 Genoa, Italy. Phone: international +39.010.3538964 – Fax: international +39.010.3538649 – E-mail: balleari@unige.it

Technetium-99-m-labeled hexakis-2-methoxy-isobutyl-isonitrile (^{99m}Tc-sestamibi), a lipophilic cationic γ-emitting radiopharmaceutical, was originally introduced into clinical use as a myocardial perfusion imaging agent. Because of its biochemical characteristics which favor accumulation in tissues with high cell density and mitochondrial activation, ^{99m}Tc-sestamibi is also actively concentrated in a variety of malignant tumors, including sarcomas, brain, lung, breast and thyroid cancer,[1] so much so that its clinical use has also been approved for breast cancer imaging.

Recently, some reports have described the uptake of ^{99m}Tc-sestamibi by myeloma tissue, thus outlining the potential of this tracer for detecting myeloma bone disease in patients with multiple myeloma (MM).[2-7]

The assessment of bone involvement is of pivotal importance for diagnosing and staging patients with MM and related plasma cells disorders. At present the standard whole body imaging technique to evaluate bone lesions due to MM is plain skeletal radiography (X-ray), which is more sensitive than conventional bone scintigraphy[8,9] and less expensive as well as more readily available than other sophisticated imaging techniques such as magnetic resonance (MR). X-ray may, however, yield confounding patterns, in particular when patients with previously documented bone lesions must be re-evaluated after therapy.

The aims of this study were to validate the reliability of ^{99m}Tc-sestamibi scintigraphy for detecting bone marrow involvement in patients with MM or with related gammopathies and to assess its clinical usefulness in the follow-up of MM patients with bone lesions after potentially eradicating treatment, focusing in particular on its relationship with clinical status and stage of the disease.

Design and Methods

Patients

Between September 1998 and December 1999, 46 consecutive patients (24 men and 22 women, mean age 60 years, range 28-88 years) affected by either MM

(32/46, 69%) or monoclonal gammopathy of undefined significance (MGUS) (14/46, 31%) were enrolled in the study. The main clinical characteristics of the patients evaluated are summarized in Table 1.

Diagnosis of the disease was made according to standard criteria.[10,11] The clinical status of patients at the time of the ^{99m}Tc-sestamibi scan was assessed by complete clinical and biochemical evaluations including full blood counts, renal and liver function tests, protein electrophoresis and evaluation of monoclonal component (MC), serum immunoglobulin concentration, C-reactive protein (CRP), β_2-microglobulin, urinary light chain excretion, 24-hour proteinuria and bone marrow biopsy. According to the results of the staging procedure, patients were classified into three groups: a) 25 MM patients with active disease (patients with untreated, refractory or relapsed disease or patients achieving only a partial remission, i.e., 25-75% reduction of MC after appropriate treatment); b) 7 MM patients in complete clinical remission (patients with MC reduction > 75% and bone marrow plasma cells < 5% after appropriate treatment); c) 14 patients with MGUS.

Eight patients with active MM underwent at least one course of high-dose alkylating agent chemotherapy (HDT) supported by peripheral blood stem cells (PBSC); they were re-evaluated scintigraphically within two months after the end of the procedure and at least six months after the first ^{99m}Tc-sestamibi scan in order to ascertain the reliability of this imaging procedure in the follow-up of this subset of patients. Scintigraphic follow-up was performed once in 6 patients and twice in 2 patients.

Each patient had a whole body X-ray study within one month of ^{99m}Tc-sestamibi scintigraphy, in order to compare the two imaging techniques.

^{99m}Tc-sestamibi scan and interpretation

A total of 56 ^{99m}Tc-sestamibi scans were performed, as follows: anterior and posterior whole-body scans (5 minutes for each static acquisition) were obtained 20 minutes after the i.v. injection of 740 MBq of ^{99m}Tc-sestamibi, employing a large-field-of-view gamma-camera (Elscint APEX SP6 HR) equipped with a low-energy high-resolution microcast collimator. Scans recorded at later times (1, 2 and 4 hours after the tracer injection) were found not to be useful for staging purposes, because of vertebral and pelvic shielding due to hepato-biliary and renal excretion, and because of possible release of the agent from the uptake sites over time.

Basically, as previously reported,[7] four patterns of ^{99m}Tc-sestamibi distribution could be observed:

- normal (N), with only physiologic uptake of ^{99m}Tc-sestamibi;
- diffuse (D), with diffuse bone marrow uptake of the radiotracer;
- focal (F), with obvious areas of focal uptake;
- diffuse and Focal (D + F), when both diffuse and focal uptakes were observed.

As suggested by Pace *et al.*[6] the scans were scored according to the extension (E) and the intensity (I) of the radiotracer uptake. With slight modifications of Pace's score system, extension of ^{99m}Tc-sestamibi uptake was scored as follows: E0 = no evidence of marrow uptake; E1 = uptake in the spine and/or pelvis; E2 = uptake in the spine, pelvis and ribs or proximal humeral and femoral epiphyses; E3 = uptake in the spine, pelvis, ribs and distal humeral and femoral epiphyses. Intensity was scored as follows: I0 = no evidence of bone marrow uptake; I1 = bone marrow uptake of the same intensity as in the muscle; I2 = bone marrow uptake higher than in the muscle but less than in the myocardium; I3= bone marrow uptake of the same intensity as in the myocardium; I4 = bone marrow uptake higher than in the myocardium. A summed score of E and I, ranging from 0 to 7, was thereafter computed for each patient.

Ten patients undergoing routine ^{99m}Tc-sestamibi myocardial perfusion scintigraphy were considered as controls for the physiologic tracer distribution in the bone marrow.

Figures 1 to 3 show various examples of scintigraphic patterns observed in different patients.

Statistical analysis

Sensitivity and specificity of ^{99m}Tc-sestamibi scintigraphy were calculated as follows:

- sensitivity = true positives x 100/(true positives + false negatives);
- specificity = true negatives x 100/(true negatives + false positives).

Chi-squared analysis and analysis of variance were

Table 1. Clinical characteristics of 46 consecutive patients with either multiple myeloma (MM) or monoclonal gammopathy of undefined significance (MGUS) at the time of baseline study.

	All (n.46)	*MM (n.32)*	*MGUS (n.14)*
Males/females	27/19	20/12	7/7
Age (years) mean (range)	60 (28-88)	60 (28-83)	61 (45-88)
Treated/untreated	19/27	19/13	0/14
Disease stage			
IA		3 (9%)	N.A.
IIA		13 (41%)	N.A.
IIIA		4 (12%)	N.A.
IIIB		5 (16%)	N.A.
clinical remission		7 (22%)	N.A.
MC type			
Ig G	31	22	9
Ig A	11	6	5
Ig D	1	1	-
Bence Jones	3	3	-
Hb (g/dL) mean (range)	11.6 (7-14.7)	10.8 (7-14.4)	13.3 (11-14.7)
CRP (mg/L) mean (range)	12.6 (0.5-136)	17.8 (0.6-136)	1.9 (0.5-3)
Marrow plasmacells (%) mean (range)	31 (1-95)	40 (1-95)	7 (4-12)

employed for multiple comparisons, as appropriate. The two-tailed Mann-Whitney non-parametric test was used to evaluate differences of ^{99m}Tc-sestamibi uptake score between groups. Spearman's correlation was used to assess the relationship between the summed score of ^{99m}Tc-sestamibi uptake and other clinical variables;

p values < 0.05 were considered as statistically significant.

Results

Baseline study

At baseline examination, 24 out of the 46 patients (52%) showed an increased uptake of ^{99m}Tc-sestamibi ("positive scans"), while the remaining 22 (48%) showed only a physiologic uptake of the tracer ("negative scans").

All these 24 positive scans were observed in patients with MM, while none of the 14 MGUS patients exhibited a positive ^{99m}Tc-sestamibi scan. Among the 24 patients with a positive scan, 13 were untreated, *de novo* diagnosed MM patients, 9 had either refractory or relapsed MM, and 2 were patients in complete clinical remission after PBSC-supported HDT; thus, there were 22 true-positive and 2 false-positive ^{99m}Tc-sestamibi scans.

On the other hand, the 22 patients with a negative ^{99m}Tc-sestamibi scan included all the 14 MGUS patients, 5 MM patients in complete clinical remission after effective chemo-radiotherapy, and 3 with active MM; thus, there were 19 true-negative and 3 false-negative ^{99m}Tc-sestamibi scans.

Follow-up study

Among the 8 patients included in the follow-up study, the ^{99m}Tc-sestamibi scan converted from positive to negative in 2 out of the 3 patients who actually achieved a complete clinical remission; a third ^{99m}Tc-sestamibi scintigraphy repeated in these two patients 6 months after the first follow-up evaluation remained negative in the patient maintaining the status of complete clinical remission, while it converted to positive in the other patient who in fact had a relapse. On the other hand, ^{99m}Tc-sestamibi scintigraphy showed a single focal uptake area in one patient in complete clinical remission (plasmacell bone marrow infiltration < 5%), after two courses of PBSC-supported HDT (false-positive). In the other 5 MM patients with partially responding or refractory MM, the ^{99m}Tc-sestamibi scan remained positive, even if in most of them the summed score of uptake was reduced (see Table 2).

According to the overall results obtained, global sensitivity and specificity of ^{99m}Tc-sestamibi scintigraphy were 90% and 88%, respectively. Consequently, the overall positive predictive value of ^{99m}Tc-sestamibi scanning was 90.3% and its diagnostic accuracy was 83%.

Comparison with conventional X-ray survey

The conventional X-ray skeletal survey was concordant with the results of ^{99m}Tc-sestamibi scintigraphy in 42 out of the 56 cases evaluated (73%): 27 patients presented a positive scan and at least one osteolytic area, while 15 patients (all the MGUS cases and one MM case) had a negative scan associated with a negative X-ray skeletal survey. On the other hand, results were discordant in 14 cases, all MM patients. Ten of them had a negative ^{99m}Tc-sestamibi scan associated with bone lesions as revealed by X-ray, while 3 patients had a negative X-ray survey (in one case both before and after chemotherapy), associated with a positive ^{99m}Tc-sestamibi scan.

Among the 10 patients with negative ^{99m}Tc-sestamibi scan and positive X-ray survey, 7 were actually in complete clinical remission after effective chemotherapy, and their osteolytic lesions had already been detected before chemotherapy; the remaining 3 patients were those considered as false-negative ^{99m}Tc-sestamibi cases.

Relationship between ^{99m}Tc-sestamibi uptake and clinical status

When the ^{99m}Tc-sestamibi bone marrow uptake scores obtained in the patients with MM were correlated to the most relevant clinical and hematologic variables in the patients with MM, a highly significant positive correlation was found between the scores and both the percent

Table 2. Relationship between clinical status and ^{99m}Tc-sestamibi scintigraphy in the follow up of 8 MM patients before and after PBSC-supported high dose chemotherapy.

	Before therapy				*After therapy*				*Last follow-up*			
Pt.	*Stage*	*% marrow plasma cells*	*MIBI score*	*Uptake pattern*	*Stage*	*% marrow plasma cells*	*MIBI score*	*Uptake pattern*	*Stage*	*% marrow plasma cells*	*MIBI score*	*Uptake pattern*
2	IIA	65	3	D	CR	1	0	-	CR	3	0	-
3	IIIA	55	7	D+F	CR	2	0	-	IIA	25	2	D
4	IIA	35	2	F	IIA	35	3	F				
18	IIIA	95	6	D+F	IIA	35	3	F				
19	IIIB	90	6	D+F	IIB	50	3	D+F				
21	IIA	55	4	D	IIA	40	1	D				
23	IIIA	30	2	D	IIA	15	1	D				
28	IA	30	3	D	CR	2	2	D				

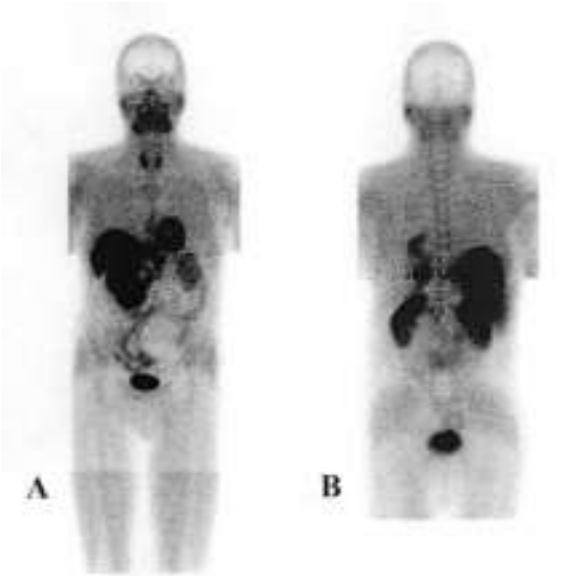

Figure 1. Anterior (A) and posterior (B) scans obtained 20 min after ^{99m}Tc-sestamibi injection in a MGUS patient showing a negative pattern. A physiologic uptake in the thyroid, salivary glands, heart, liver and gastrointestinal tract is visible, with absence of uptake in the spine and other bone marrow sites.

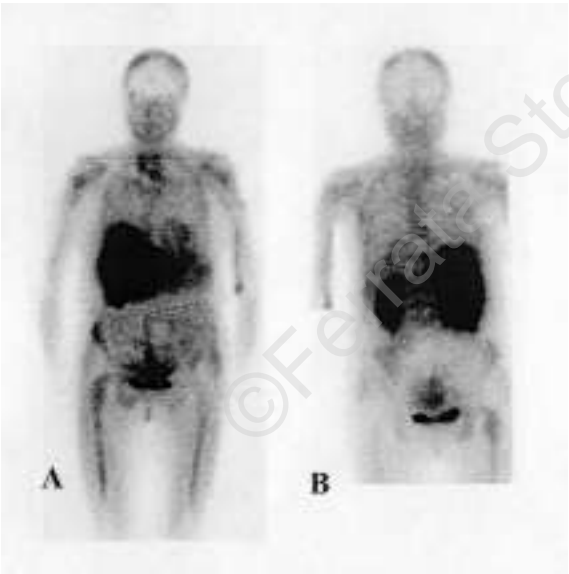

Figure 2. Anterior (A) and posterior (B) scans obtained 20 min after ^{99m}Tc-sestamibi injection in a MM patient showing a diffuse pattern of tracer uptake. A diffuse uptake of the tracer is visible in the spine, ribs and femora.

fraction of bone marrow plasmacells and MC concentration (Spearman's r correlation coefficient 0.65 and 0.40, respectively, $p < 0.0001$ and $= 0.009$). A significant correlation was also observed between the scintigraphic score and the concentration of a marker of disease activity such as CRP (Spearman's r correlation coefficient = 0.61, $p = 0.003$) while a significant negative correlation was observed between uptake score and hemoglobin (Spearman's r correlation coefficient -0.56 $p < 0.001$) (see Figure 4).

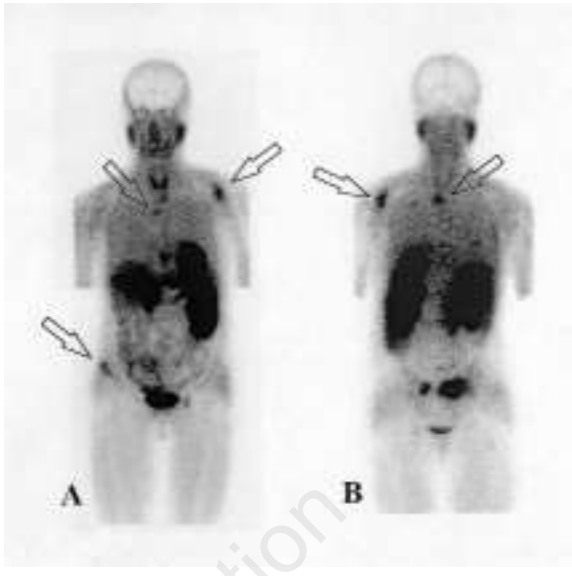

Figure 3. Anterior (A) and posterior (B) scans obtained 20 min after ^{99m}Tc-sestamibi injection in a MM patient showing a focal pattern of tracer uptake. Multiple areas of focal uptake (arrows) are present.

Among the 42 ^{99m}Tc-sestamibi scans obtained in the patients with MM, 4 (9%) were performed in stage I patients, 16 (39%) in stage II patients, 12 (28%) in stage III patients, while 10 (24%) were performed in patients in complete clinical remission. In this group of patients, chi-squared analysis showed a significant difference ($p < 0.001$) in the pattern of ^{99m}Tc-sestamibi uptake between patients in remission and those with active disease (Figure 5). In particular only 3 cases of patients in complete clinical remission showed a positive ^{99m}Tc-sestamibi scan, with an uptake score always lower than 3. In the 32 scans obtained from MM patients with active disease, the same analysis showed a significantly different distribution of ^{99m}Tc-sestamibi uptake pattern between patients in different stages of disease (Figure 6).

Analysis of variance showed a significant difference in the bone marrow ^{99m}Tc-sestamibi uptake score among MM patients according to their clinical status, with significantly higher scores observed in patients with active (untreated, refractory or relapsed) MM than in those with MM in clinical complete remission (Figure 7). Similarly, when MM patients were divided according to their clinical stage, significantly different ^{99m}Tc-sestamibi uptake scores were observed in patients with advanced stages of the disease, the summed uptake score being particularly higher in patients with stage III disease (Figure 8).

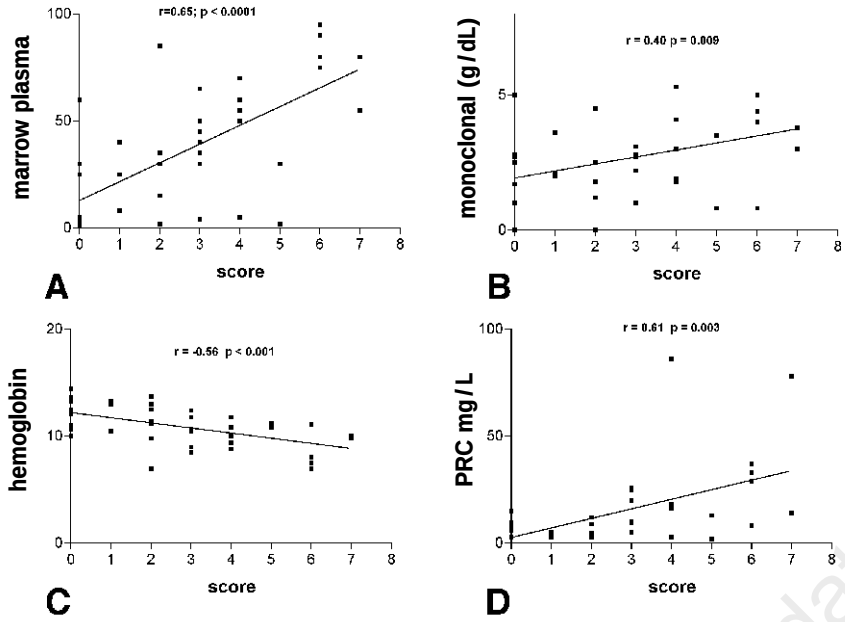

Figure 4. Relationship between bone marrow plasmacells (A), monoclonal component (B), hemoglobin (C) and CRP concentrations (D) with the summed score of ^{99m}Tc-sestamibi uptake in 36 patients with multiple myeloma.

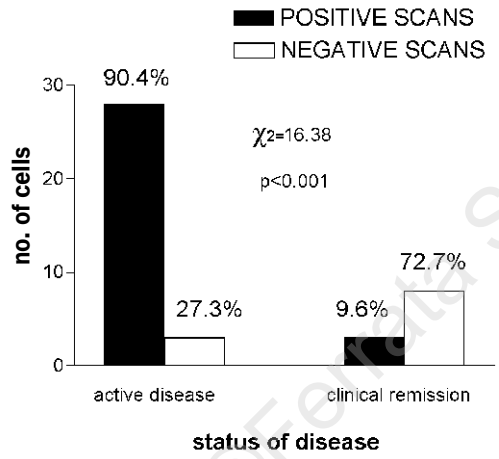

Figure 5. Distribution of ^{99m}Tc-sestamibi uptake pattern in patients with MM in clinical remission and with active disease.

Discussion

In the present study, the ^{99m}Tc-sestamibi scintigraphic evaluation of patients affected by MM and related gammopathies showed high sensitivity and specificity in detecting patients with or without active myeloma bone disease. Specificity rose to 100% in patients with MGUS.

So far, the value of ^{99m}Tc-sestamibi scintigraphy in MM has been explored in few studies,[2–7] mostly anecdotal. Only two relatively large studies have been published to date on this topic, using however quite different methodologic approaches.[4,6] In the first study, Tirovola *et al.* evaluated ^{99m}Tc-sestamibi scanning for imaging bone lesions in 21 patients with either MM or MGUS 1 and 4 hours after injection of the radiotracer, reporting a 100% sensitivity in spite of a considerably lower specificity.[4] Higher specificity associated with satisfactory sensitivity of the ^{99m}Tc-sestamibi scan in identifying MM patients with active bone disease has more recently been reported by Pace *et al.*, who performed ^{99m}Tc-sestamibi scintigraphy starting 10 minutes after tracer injection.[6] In our study we performed scintigraphy 20 minutes after the injection of a larger dose of the tracer and confirmed the good results obtained by Pace *et al.*,[6] exploring however its diagnostic accuracy also in individuals affected by MGUS.

Timing of the scan is probably crucial to explaining the discrepancies observed. The mechanism of ^{99m}Tc-sestamibi concentration in abnormal plasmacells seems to be dependent on altered cell metabolism of malignant cells, affecting the membrane potential.[12] P-glycoprotein is associated with multi-drug resistance in MM,[13] and has been shown to be responsible for the active efflux of ^{99m}Tc-sestamibi from malignant cells.[14] The energy-dependent pump activity of P-glycoprotein on the extrusion of ^{99m}Tc-sestamibi might, therefore, have a role in determining the occurrence of false negative ^{99m}Tc-sestamibi scans observed when later (4 hours) acquisitions are obtained. The P-glycoprotein-mediated mechanism of ^{99m}Tc-sestamibi efflux suggests a possible role of ^{99m}Tc-sestamibi scintigraphy for *in vivo* detection of the multidrug resistance phenotype in MM, as already tested in breast cancer patients.[15]

When the results of scintigraphic scans were correlated to the clinical status of the patients studied, a close correlation between high ^{99m}Tc-sestamibi uptake and myeloma bone disease activity was observed, fur-

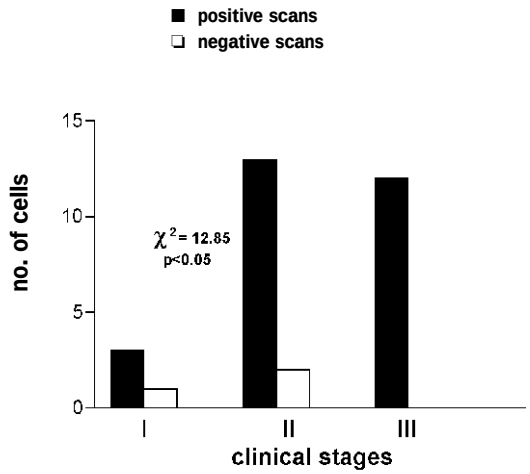

Figure 6. Distribution of 99mTc-sestamibi uptake pattern in patients with MM divided according to the stage of the disease.

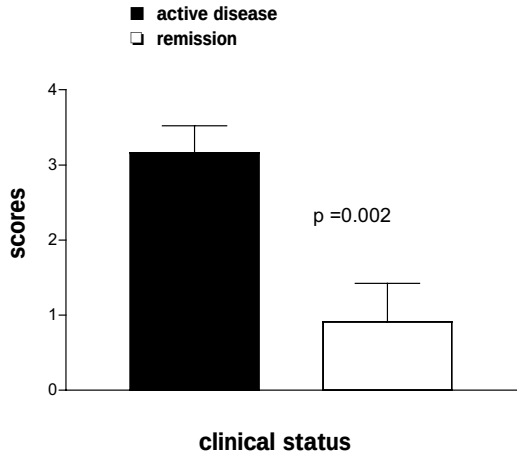

Figure 7. Bone marrow 99mTc-sestamibi uptake scores in MM patients with active disease and in clinical remission after effective chemo-radiotherapy.

ther confirming the results reported by Pace *et al*.[6] Furthermore, to the best of our knowledge, this is the first study in which the use of 99mTc-sestamibi scintigraphy in the follow-up of MM patients treated with HDT has been assessed. Although obtained in a relatively small cohort of patients, the present data provide evidence of a satisfactory correlation between the results of semi-quantitative 99mTc-sestamibi scintigraphy and bone marrow biopsy. Even if the changes of the M-protein in serum and/or urine are the usual parameters taken into account for following up in patients with monoclonal gammopathies, the invasive biopsy procedure is at present used as standard for assessment of myeloma bone disease when disease progression occurs, and in particular it is necessary to verify the etiology (not necessaryily neoplastic) of any new skeletal event.

The presence and extension of bone disease are very important clinical clues both for staging and for following up patients with MM. Because of the poor osteoblastic response usually produced by myeloma in the bone, conventional radionuclide bone imaging with 99mTc-labeled phosphonates is less sensitive than X-ray at detecting skeletal lesions in MM;[8] conventional X-ray skeletal survey is, therefore, at present the standard imaging technique for identifying and monitoring myeloma bone disease. However, particularly in previously treated patients, conventional X-ray may identify bone lesions corresponding to sites no longer active because of successful therapy. Conventional X-ray is not capable of reliably evaluating bone marrow disease activity in this particular clinical setting, in which it is better evaluated by bone marrow biopsy. Nevertheless, this invasive procedure is susceptible to sampling errors and it may be inaccurate in reproducibly counting plasmacell infiltration in bone marrow. In our study 99mTc-

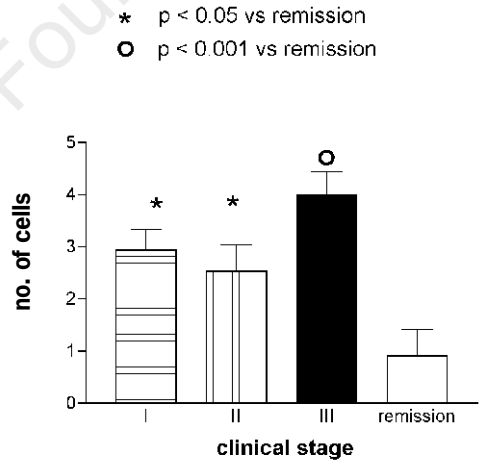

Figure 8. Bone marrow 99mTc-sestamibi uptake scores in MM patients according to their clinical stage.

sestamibi scintigraphy appeared to overcome these limitations, reliably detecting active bone lesions in MM patients. In fact, it showed a good correlation with the degree of bone marrow MM involvement, in particular when used in the follow-up of treated patients with already documented bone lesions. Furthermore, 99mTc-sestamibi scintigraphy has been recently reported as more specific than conventional X-ray in detecting active focal lesions in MM patients.[7]

99mTc-sestamibi scintigraphy has been reported to correlate extremely well with MR imaging studies aimed at detecting intramedullary malignancy,[16] and it might reflect the extent of myeloma bone disease[17] better than

fluorine-18-FDG –PET, although very recently ^{67}Ga scanning has been suggested as a possibly more reliable imaging technique for identifying MM with very aggressive disease.[18]

In conclusion, because of its high accuracy in identifying patients with active bone disease, ^{99m}Tc-sestamibi scintigraphy appears to be a reliable new tool for evaluating bone marrow disease activity in patients with MM or related gammopathies, and it may be particularly useful for monitoring patients' response to treatment during long-term follow-up.

Contributions and Acknowledgments

EB and GV designed the study. EB wrote the paper. EB, SG, PG, MCl and FF were involved in clinical assessment of patients and in data recording and analysis. GV, GA, MCa and GM performed the scintigraphic procedures and analyzed the results. RG, MG and GM revised the manuscript and gave final approval for submission.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Federico Caligaris-Cappio, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Caligaris-Cappio and the Editors. Manuscript received September 5, 2000; accepted November 21, 2000.

Potential implications for clinical practice

Technetium-99m sestamibi scintigraphy could become the standard imaging technique for the assessment and follow-up of MM bone disease.[19,20]

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