

## Technetium-99m Sestamibi in Multiple Myeloma

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### ABSTRACT

**Purpose:** Technetium-99m 2-methoxy - isobutyl - isonitrile ( $^{99m}\text{Tc}$ -MIBI) has been reported to be useful in evaluating patients with multiple myeloma. The aim of this study is to evaluate the role of technetium-99m sestamibi ( $^{99m}\text{Tc}$ -MIBI) scintigraphy in the diagnosis, staging and follow-up of patients with multiple myeloma.

**Methods and Materials:** twenty-five consecutive patients with multiple myeloma were studied using  $^{99m}\text{Tc}$ -MIBI. Of the 25 patients included in this study, 6 were in stage I, 11 in stage II and 8 in stage III. Anterior and posterior whole-body imaging were obtained 20 min after I.V. injection of 740 MBq of  $^{99m}\text{Tc}$ -MIBI. Four different MIBI patterns could be described in our patients: physiological (P), diffuse (D), focal (F) and combined diffuse and focal (D+F). All patients in stages II and III as well as 3 patients in stage I were treated with chemotherapy (cyclophosphamide and prednisone) then  $^{99m}\text{Tc}$ -MIBI scans were repeated after 6 courses.

**Results:** in comparison to conventional X-ray skeletal survey,  $^{99m}\text{Tc}$ -MIBI scans showed a higher number of myeloma bone disease at diagnosis. All patients with stage II and III multiple myeloma were positive with  $^{99m}\text{Tc}$ -MIBI scans at diagnosis. The pattern of positive MIBI accumulation was diffuse in 13 (52%) patients, focal in 4 (16%) and combined focal and diffuse in 6 (24%) patients. The intensity of  $^{99m}\text{Tc}$ -MIBI correlated with disease activity as determined by lactate dehydrogenase (LDH), number of plasma cells in bone marrow and serum electrophoresis. There was a direct correlation between  $^{99m}\text{Tc}$ -MIBI scan result and clinical outcome of patients following 6 courses of chemotherapy. Sensitivity and specificity of  $^{99m}\text{Tc}$ -MIBI scintigraphy in detecting myeloma bone lesions were 92% and 90% respectively.

**Conclusion:**  $^{99m}\text{Tc}$ -MIBI scintigraphy is a reliable method to evaluate bone marrow activity in patients with multiple myeloma and follow-up of myeloma bone lesions.

**Key Words:** Multiple myeloma -  $^{99m}\text{Tc}$  MIBI scan.

### INTRODUCTION

Bone destruction is a hallmark of myeloma, with 70% to 80% of patients manifesting with

bone involvement. Destruction is mediated through normal osteoclasts, which respond to local osteoclast-activating microenvironment [7]. Technetium-99m - 2- methoxyisobutylisonitrile (TC-99m MIBI) is a lipophilic agent that accumulates within living malignant cells due to the higher transmembrane electrical potential as a consequence of the higher metabolic rate than in the surrounding normal cells [2]. It has been reported to be useful in detecting disease lesions in multiple myeloma [1,10,17,19,27]. In comparative studies, Tc-99m MIBI scintigraphy proved to be superior to skeletal X-ray survey in detecting bone and bone marrow involvement [8,9]. In myeloma, the isotope bone scan may be falsely negative because of purely osteolytic lesions, but may not be completely normal if there is some osteoblastic activity, particularly in relation to pathological fracture. Other radiopharmaceuticals which have shown promise in the investigation of myeloma include gallium-67, Tc-99m tetrofosmin and thallium-201 [10,29]. Tc-99m-MIBI has been reported to be distributed as a diffuse and/or focal uptake in bone marrow of patients with active myeloma disease. Furthermore, a semiquantitative score based on the extension and intensity of the diffuse uptake on whole-body scan showed a direct correlation with plasma cell infiltration, clinical status and stage of the disease [19]. In patients undergoing chemotherapy, the findings of baseline Tc-99m MIBI scintigraphy are strongly correlated with the clinical outcome at follow-up. These results suggested a potential role of Tc-99m-MIBI in the follow-up of patients with multiple myeloma [22].

The aim of this study was to evaluate the role of Tc-99m-MIBI in the diagnosis, staging and follow-up of patients with multiple myeloma.

## PATIENTS AND METHODS

This study included 25 patients with multiple myeloma (14 males and 11 females, mean age  $66\pm 9$  years). Diagnosis and staging were determined by X-ray skeletal survey, haematological and biochemical examination including full blood count, liver and renal function tests, serum calcium, bone marrow aspiration and/or biopsy and protein electrophoresis. All patients were studied using Tc-99m-MIBI. Anterior and posterior whole body imaging were obtained 20 min after intravenous injection of 740 MBq of Tc-99m MIBI using a large field of view gamma camera equipped with a low energy parallel-hole collimator. Four different Tc-99m MIBI patterns could be described in our patients: physiological (P), diffuse (D), focal (F) and combined diffuse and focal (D+F). Diffuse bone marrow uptake was graded according to the extension and the intensity of radioactivity accumulation. Extension was grade I when uptake was noticed in axial skeleton, grade II in axial skeleton and ribs or proximal appendicular skeleton uptake and grade III in axial skeleton, ribs, proximal and distal appendicular skeleton uptake. Intensity of radiotracer accumulation was scored into 3 scores according to whether it was lower, equivalent or higher than myocardial uptake. All patients in stage II and III as well as 3 patients in stage I (due to disease progression) received chemotherapy in the form of cyclophosphamide 800 mg/m<sup>2</sup> I.V. day 1 and prednisone 40 mg/m<sup>2</sup> orally for 5 days every 3 weeks. In addition, 5 patients in stage II and III received local radiotherapy to deal with severe local problems. Also, 5 patients received bisphosphonate 90 mg in combination with chemotherapy. All the previously described radiological, haematological and biochemical studies as well as whole body scan with Tc-99m MIBI were repeated after 6 courses of chemotherapy to evaluate the effect of treatment.

## RESULTS

Of 25 patients included in this study, 6 patients had stage I disease, 11 had stage II and 8 had stage III disease. Nineteen myeloma patients in the our study (76%) presented with pain of varying intensity especially in lower back and ribs. Ten patients (40%) had anaemia (haemoglobin value below 10gm%). Spinal cord compression was evident in two patients

(8%). Hypercalcaemia was detected in 6/25 (24%) myeloma patients [2 in stage II (8%) and 4 in stage III (16%)] whereas all patients in stage I disease had normal calcium value (Table 1). Conventional X-ray skeletal surveys showed lytic bone lesions in 21/25 (84%) patients [3 out of 6 (50%) patients in stage I, 10/11 (91%) in stage II and 8/8 (100%) in stage III]. In comparison to skeletal radiographs, Tc-99m MIBI scans recognized abnormal bone lesions in 23 of 25 (92%) patients at diagnosis while 2 patients (8%) in stage I disease presented with a physiologic uptake (P) of radiotracer. Results between Tc-99m-MIBI scans and X-ray survey did not coincide in 4 patients with positive lesions, where as 3 patients with positive Tc-99m-MIBI were negative by X-ray and the fourth patient although negative by Tc-99m-MIBI showed lytic lesion in X-rays. However, there was one stage I myeloma disease with patient with negative both Tc-99m MIBI scan and X-ray survey (Table 2).

The pattern of positive Tc-99m-MIBI accumulation were diffuse (D) in 13 (52%) patients, focal (F) in 4 (16%) and combined diffuse and focal (D+F) in 6 (24%) patients (Table 3 and Figs. 1,3,5). The extension of diffuse radiotracer accumulation was classified into 3 grades. Out of 13 patients with diffuse bone marrow uptake, 6 patients (46%) had grade I radiotracer extension (axial skeletal uptake), 3 patients (23%) had grade II uptake (axial skeletal and ribs uptake) whereas, 4 patients (31%) had grade III uptake (whole skeletal uptake). In 6 patients with combined radiotracer uptake (D+F), 4 (67%) had grade II and 2 (33%) had grade III radiotracer extension. The intensity of diffuse radioactivity accumulation was related to the stage of myeloma disease. In stage I, 2/6 cases (33%) showed no bone marrow uptake of radiotracer whereas, the other 4 cases (67%) showed score I radiotracer accumulation (lower than myocardial uptake). On the other hand, in 11 patients with stage II disease, 4 cases had focal radioactivity accumulation whereas in 7 cases with diffuse radiotracer uptake, 4 patients (57%) had radiotracer concentration of score II (equal to myocardial uptake), 2 patients (29%) had score III uptake (higher than myocardial uptake) and only one case (14%) had score I uptake. However, all Tc-99m MIBI scans (100%) of patients in stage III showed score III of bone marrow uptake (Table 4).

Nineteen patients in stage II and III myeloma disease started chemotherapy (cyclophosphamide and prednisone) after diagnosis. Of these 19 patients, 5 patients received local radiotherapy for spinal cord compression in 2 patients and to palliate pain in 3 patients. Also, 3 patients in stage II and 2 patients in stage III received bisphosphonate, 90 mg concomitant with chemotherapy. Three patients in stage I were treated due to disease progression (increase in M-component in one case; progressive anaemia and elevated serum calcium in the other two patients). After 6 courses of chemotherapy, all initial investigations were repeated. Five patients (23%) showed complete remission (one in stage I and 4 in stage II disease); 8 patients (36%) showed partial remission (2 in stage I, 3 in stage II and 3 in stage III); 5 patients (23%) showed stable disease (all in stage III) and 4 patients (18%) showed progressive disease (all in stage II) (Table 6 and Figs. 2,4,6). At the same time, the 3 patients in stage I who did not receive treatment between the two Tc-99m MIBI scans, showed stable disease. All 5 patients with CR had diffuse radiotracer uptake (pattern D) in the initial Tc-99m MIBI scans. From 8 patients with PR, 6 had pattern D and 2 had combined diffuse and focal uptake (pattern D+F). As regard stable myeloma disease, one patient had pattern D and 4 had pattern D+F uptake. However, all 4 patients with disease progression showed focal radionuclide concentration (pattern F) (Table 6).

The intensity of Tc-99m MIBI concentration (4 scores) correlated with disease activity and patterns of clinical status evaluated after treatment in 20/22 patients (91%). All 5 patients with CR had physiological radiotracer uptake in the second scans. However, from 8 patients with PR, one had physiological radioactivity ac-

cumulation and the other 7 patients showed partial improvement in the second Tc-99m MIBI scans. Four out of 5 patients with stable disease showed no change in the second scan whereas one patient had progressive bone disease. On the other hand, all 4 patients with progressive disease showed more bony lesions in the second scan.

The overall sensitivity and specificity of Tc-99m scintigraphy in detecting bone disease were 92% and 90% respectively.

Table (1): Clinical presentation of 25 patients with multiple myeloma.

Symptoms	Number (%)
Bone pain	19 (76%)
Anaemia	10 (40%)
Cord compression	2 (8%)
Hypercalcaemia	6 (24%)

Table (2): Comparison between Tc-99m MIBI and conventional X-ray survey for diagnosis of multiple diagnosis.

Radiological diagnosis	Number (%)
+ve X-ray survey	21/25 (84%)
+ve Tc-99m MIBI scan	23/25 (92%)
+ve X-ray & -ve scan	1/25 (4%)
-ve X-ray & +ve scan	3/25 (12%)
-ve X-ray & -ve scan	1/25 (4%)

Table (3): Pattern of bone marrow uptake of radiotracer for multiple myeloma disease.

Uptake pattern	Number (%)
Physiological (P)	2/25 (8%)
Diffuse (D)	13/25 (52%)
Focal (F)	4/25 (16%)
Combined (D+F)	6/25 (24%)

Table (4): Intensity of radiotracer uptake in Tc-99m MIBI scans for patients with multiple myeloma.

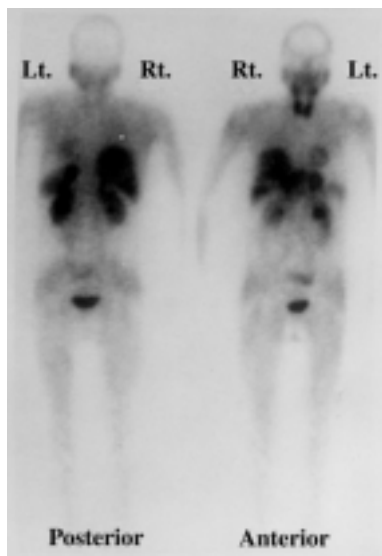
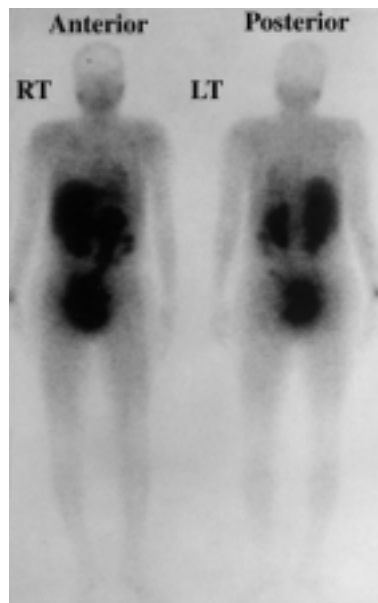
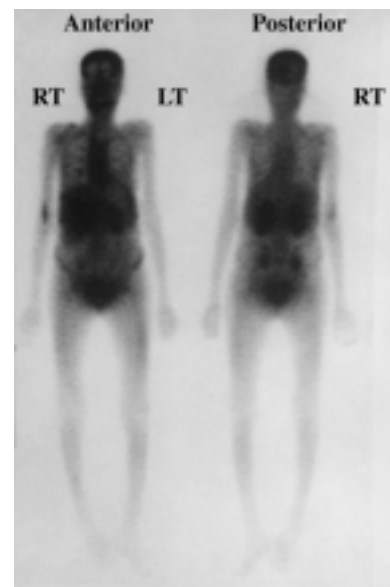
Uptake concentration	Stage I (6)	Stage II (11)	Stage III (8)
No uptake	2/6 (33%)	—	—
Focal uptake	—	4/11(36%)	—
Diffuse uptake score I	4/6 (67%)	1/7 (14%)	—
Diffuse uptake score II	—	4/7 (57%)	—
Diffuse uptake score III	—	2/7 (29%)	8/8 (100%)

Table (5): Treatment protocols for patients with multiple myeloma.

Treatment protocols	Stage I	Stage II	Stage III
No treatment	3/6 (50%)	–	–
Chemotherapy alone	3/6 (50%)	6/11 (55%)	3/8 (37.5%)
Chemotherapy+Radiotherapy	–	2/11 (18%)	3/8 (37.5%)
Chemotherapy+bisphosphonate	–	3/11 (27%)	2/8 (25%)

Table (6): Results of treatment after 6 courses of chemotherapy in 22 patients with multiple myeloma.

Result of treatment	No.	%	Initial scan	No.	Second scan	No.
Complete remission (CR)	5	23	Diffuse (D)	5	Negative	5
Partial remission (PR)	8	36	Diffuse (D)	6	Negative	1
			Combined (D+F)	2	Improvement	7
Stable Disease (SD)	5	23	Diffuse (D)	1	No change	4
			Combined (D+F)	4	More lesions	1
Progressive Disease (PD)	4	18	Focal (F)	4	More lesions	4

Fig. (1): Baseline whole body  $^{99m}\text{Tc}$ -MIBI scan for a patient with multiple myeloma showed diffuse (D) radiotracer uptake.Fig. (2): The second  $^{99m}\text{Tc}$ -MIBI for the same patient in figure (1) after treatment showed physiological radiotracer uptake.Fig. (3): Baseline  $^{99m}\text{Tc}$ -MIBI scan for a patient with multiple myeloma showed combined diffuse and focal (D+F) uptake.

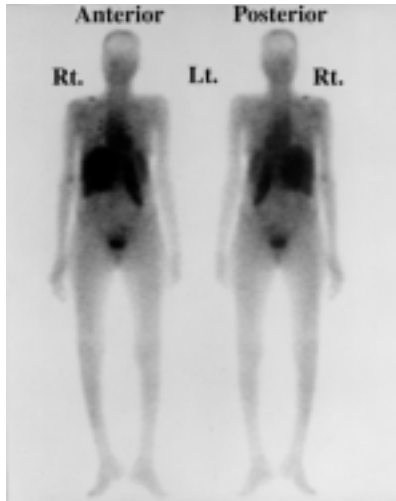


Fig. (4): The second scan for the same patient in figure (3) showed partial improvement after 6 courses of chemotherapy.

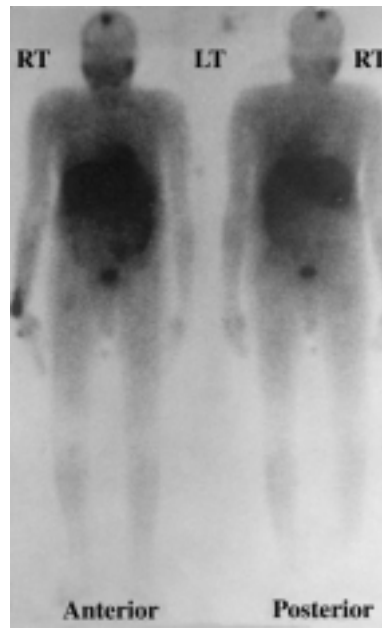


Fig. (5): Initial  $^{99m}\text{Tc}$ -MIBI scan for a patient with multiple myeloma showed focal radiotracer uptake (F) in the skull.

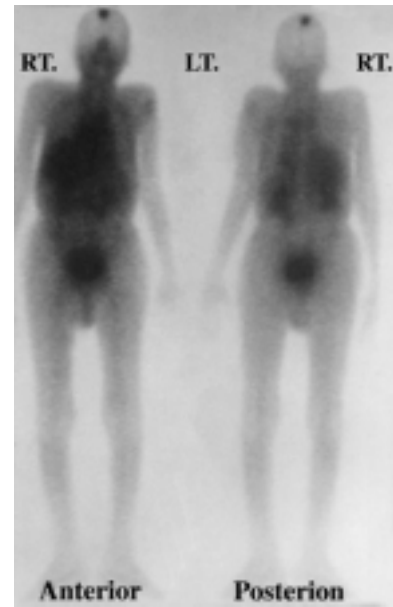


Fig. (6): Follow-up  $^{99m}\text{Tc}$ -MIBI scan for the same patient in figure (5) showed no change in the skull lesion.

## DISCUSSION

Technetium-99m-sestamibi ( $\text{Tc-}^{99m}\text{-MIBI}$ ) is a radionuclide tracer taken up by different malignant tumours including breast [21], lung [6], brain [24], thyroid [11], parathyroid [26], soft tissue sarcomas [23], lymphomas [30] and multiple myeloma [1,8,27]. The exact uptake mechanism of  $\text{Tc-}^{99m}\text{-MIBI}$  in malignant tumours has not been completely discovered. A number of studies have documented passive influx of this lipophilic cation in relation to high negative transmembrane potentials, and a reversible accumulation within mitochondria of both normal and malignant cells [20]. It can be hypothesised that  $\text{Tc-}^{99m}\text{-MIBI}$  uptake could be influenced by P-glycoprotein expression [16].

Multiple myeloma is an immunoproliferative disease characterized by the infiltration of monoclonal plasma cells in bone marrow.  $\text{Tc-}^{99m}\text{-MIBI}$  has been reported as a potential tracer for multiple myeloma imaging [9,15,28]. Different pattern of  $\text{Tc-}^{99m}\text{-MIBI}$  uptake were described in patients with multiple myeloma. A semiquantitative evaluation of these patients showed a correlation with clinical status and stage of the disease [19].

In this study, 76% of our patients had bone pains and hypercalcaemia was detected in 24%

of patients. Berenson [5] showed that the majority of myeloma patients (about 70%) present with pain and hypercalcaemia is present in 30% of the patients at diagnosis. In our study,  $\text{Tc-}^{99m}\text{-MIBI}$  scan detected abnormal bone lesions in 23/25 (92%) patients while conventional X-ray detected lytic bone lesions in 21/25 (84%) patients with multiple myeloma. There was one patient with negative  $\text{Tc-}^{99m}\text{-MIBI}$  scan but positive in conventional X-ray and there were 3 patients with negative X-ray but positive in  $\text{Tc-}^{99m}\text{-MIBI}$  scans. Other studies proved that  $\text{Tc-}^{99m}\text{-MIBI}$  is more sensitive in the detection of multiple myeloma bone disease than plain radiographs or bone scanning with traditional isotopes [13]. Also, in a comparative studies,  $\text{Tc-}^{99m}\text{-MIBI}$  scintigraphy proved to be superior to skeletal X-ray survey in detecting bone marrow involvement [8,9]. These findings were confirmed in the study of Svaldi et al. [25] who found that in comparison to conventional skeletal radiographs, MIBI scans recognized a higher number of myeloma lesions at diagnosis. Moreover, the study of Alexandrakis et al. [2] showed that  $\text{Tc-}^{99m}\text{-MIBI}$  can detect bone marrow lesions in myeloma patients that cannot be detected by other imaging methods and that it can be useful especially in solitary myeloma to exclude other involved sites. In comparison with X-ray skeletal survey, Balleari et al. [4]

showed discordant results in 7/56 cases with 3 cases of negative Tc-99m MIBI scan but lytic bone lesions revealed by X-ray and 4 negative X-ray surveys in patients with positive Tc-99m MIBI scans.

Our results showed that the pattern of positive Tc-99m MIBI uptake were diffuse (D) in 52% of patients, focal (F) in 16% and combined (F+D) in 24% of patients. These results were proved in the study of Pace et al. [19] that 46% of patients showed pattern D, 5% pattern F and 31% pattern D+F. Also, Fonti et al. [12] showed that bone marrow uptake was diffuse in 60% of patients, focal in 5% and combined in 30% of patients. On the other hand, the study of Pace et al. [18] showed that 32% of patients had diffuse uptake, 23% had focal uptake and 13% had combined focal and diffuse radiotracer uptake.

In the present study, there was a correlation between the intensity of radioactivity accumulation and the stage of myeloma disease. It has been reported that sestamibi uptake in bone marrow correlates with the extent of the myeloma bone disease [10]. Also, this finding was in agreement with the data of Pace et al. [19] that a relationship has been demonstrated between scintigraphic patterns of Tc-99m MIBI uptake and both clinical status and stage of myeloma bone disease. Moreover, Pace et al. [18] showed a clear association between Tc-99m MIBI scintigraphic findings and variations in the clinical status of myeloma disease.

Twenty-two patients included in this study were treated. After 6 courses of chemotherapy 23% showed complete response (CR), 36% showed partial response (PR), 23% had stable disease (SD) and 18% showed progressive disease (PD). Alexanian and Dinopoulos [3] showed an objective response rate reflected by a 50% improvement in myeloma patients who had received cytoxan and prednisone. Another study of Ludwig and Fritz [14] showed that myeloma patients who had received induction chemotherapy showed a response rate of 46.7%. On the other hand, a recent study showed that clinical remission (either complete or partial) was detected in 44% of myeloma patients, 23% had stable disease and 33% showed disease progression.

The present study showed that there was a direct correlation between Tc-99m MIBI results and clinical outcome of patients following ac-

tive treatment in 91% of cases. This finding was observed in a study by Look et al. [13] who stated that Tc-99m MIBI has a significant role in the detection of early myeloma disease and in monitoring disease progression during and after therapy. Also, Pace et al. [19] showed a clear correlation between bone marrow uptake of Tc-99m MIBI with the amount of the monoclonal component and the percentage of bone marrow plasma cells. In addition, Alexandrakis et al. [2] proved that the semiquantitative score of Tc-99m MIBI bone marrow uptake correlates with disease activity. A recent study showed that the degree of tracer uptake both in vitro and in vivo is related to the percentage of infiltrating plasma cells which accumulate the tracer in their inner compartments [14]. Moreover Pace et al. [18] showed that the variation in Tc-99m MIBI findings comparing baseline and follow-up evaluation was significantly associated with clinical status in 91% of patients undergoing chemotherapy.

The overall sensitivity and specificity of Tc-99m scintigraphy in detecting myeloma bone disease were 92% and 90% respectively. Previous studies have reported high sensitivity and specificity of Tc-99m MIBI scintigraphy in patients with multiple myeloma [8,19]. Also, the study of Balleari et al. [4] showed that the sensitivity and specificity of Tc-99m MIBI scan in diagnosis of myeloma bone disease were 90% and 88% respectively. On the other hand, the study of Tirovola et al. [27] showed a higher sensitivity (100%) and a lower specificity (88%) of Tc-99m MIBI scan in multiple myeloma disease. Moreover, Svaldi et al. [25] showed that the sensitivity of MIBI scan at diagnosis was 100% whereas the specificity was 93%.

In conclusion, we believe that Tc-99m MIBI scintigraphy is an effective tool in the diagnosis of myeloma bone disease that cannot be detected by other imaging modalities and it is a useful method to evaluate disease activity and staging. In addition, Tc-99m MIBI scan has proved to be a sensitive method in follow-up of myeloma bone disease after treatment.

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