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Detection of focal myeloma lesions by technetium-99m-sestaMIBI scintigraphy

LUCIO CATALANO,* LEONARDO PACE,°# CATELLO CALIFANO,* ANNA MARIA PINTO,° AMALIA DE RENZO,* FRANCESCA DI GENNARO,° SILVANA DEL VECCHIO,°# ROSA FONTI,° MARCO SALVATORE,°# BRUNO ROTOLI*

**Cattedra di Ematologia, Dipartimento di Medicina Clinica e Sperimentale; °Cattedra di Medicina Nucleare, Dipartimento di Scienze Biomorfologiche e Funzionali, Facoltà di Medicina e Chirurgia, Università Federico II; #Centro C.N.R. per la Medicina Nucleare, Napoli, Italy*

ABSTRACT

Background and Objective. The tracer technetium-99m-2-methoxy-isobutyl-isonitrile (Tc99m-sestaMIBI) has recently been shown to concentrate in some neoplastic tissues, including myeloma. We investigated the diagnostic capacity and limits of this procedure in tracing focal myeloma lesions, and compared them with those of conventional radiological procedures (Xr).

Design and Methods. We studied 55 patients suffering from multiple myeloma (MM) or solitary plasmacytoma in different stages and clinical conditions, or from monoclonal gammopathy of undefined significance (MGUS), by whole body scans obtained 10 minutes after injection of 555 MBq of Tc99m-sestaMIBI. Scans were defined as *normal* (physiological uptake only), *diffuse* (presence of bone marrow uptake), or *focal* (localized areas of uptake), and were compared to conventional skeletal Xr.

Results. Thirty patients showed no focal areas of Tc99m-sestaMIBI uptake; this group consisted of 5 patients with MGUS, 6 with MM in stage IA and 2 in stage IIA, 11 patients studied after effective chemotherapy and 6 in early relapse. Twenty-five patients showed one or more spots of focal uptake: all of them had active disease (untreated, resistant or relapsing MM).
In the setting of tracing focal lesions, Tc99m-sestaMIBI scans were concordant with the radiological examination in 38 patients and discordant in 17. Among the latter, in 4 cases Tc99m-sestaMIBI revealed focal lesions not detected by Xr, and in 13 cases lytic areas detected by Xr did not show Tc99m-sestaMIBI uptake.

Interpretation and Conclusions. In untreated patients, the number of lesions revealed by Tc99m-sestaMIBI was comparable to that shown by Xr, while in pretreated patients Tc99m-sestaMIBI traced a number of lesions lower than that detected by Xr. The reason for this discrepancy is that Tc99m-sestaMIBI traces only active lesions. Tc99m-sestaMIBI limitations in identifying focal lesions may derive from the dimension of the smallest traceable lesion (about one centimeter), and from the possibility that focal plasma cell localizations in collapsed bone may not be visualized due to inadequate vascularization. Tc99m-sestaMIBI scintigraphy is an interesting tool for diagnosing, staging and following up focal myeloma lesions, in the bone as well as in soft tissues. It is more specific than conventional Xr in identifying sites of active disease.

Correspondence: Lucio Catalano, M.D., Cattedra di Ematologia, Università Federico II, via Pansini 5, 80131 Naples, Italy.
Fax: international +39-081-7462165.

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The search for osteolytic lesions is pivotal for diagnosing and staging plasma-cell dyscrasias. At present, conventional skeletal X ray (Xr) is the only method used for detecting focal bone lesions due to multiple myeloma (MM), since 99Tc-MDP scintigraphy does not trace lesions lacking inflammatory or osteoblastic activity,[1] and CT or MRI skeletal scans are too expensive for routine use. Technetium-99m-2-methoxy-isobutyl-isonitrile (Tc99m-sestaMIBI) scintigraphy is commonly used in heart imaging and has also been shown to concentrate in some tumors, such as breast and lung cancer.[2,3] Recently, a few preliminary reports have shown that Tc99m-sestaMIBI is also taken up by myeloma tissue.[4-8] We tried to define possible advantages and limitations of Tc99m-sestaMIBI bone scintigraphy in tracing focal myeloma lesions compared to those of conventional radiography in a group of patients suffering from plasma cell dyscrasias.

Design and Methods

Fifty-five consecutive patients (34 males, 21 females, mean age 61.6 years, range 30-87) suffering from an immune proliferative disorder (MM in various disease status, 46; solitary plasmacytoma, 3; MGUS, 6) were studied between April and December 1997. Tc99m-sestaMIBI at the dose of 555 Mbq was administered in an antecubital vein; anterior and posterior whole body scans were obtained after 10 minutes, 1, 2 and 4 hours, using a large field of view camera (Elscint Apex SP6). For the purpose of this

paper, only the scans performed at 10 minutes were evaluated, to avoid vertebral and pelvic shielding caused by biliary excretion and over time decrease of tracer bone uptake, which occurred in about half of the patients, probably influenced by mechanisms of active extrusion. Scans were classified into four classes: normal (only physiological uptake), diffuse (presence of bone marrow uptake), focal uptake, focal plus diffuse uptake. For each patient a recent skeletal Xr study was available, the results of which were compared with those of the Tc99m-sestaMIBI scans. The diffuse pattern was graded from 0 to 3 for extension, ranging from no uptake to uptake of spine, pelvis and distal epiphyses of long bones, and for intensity, ranging from no uptake to uptake higher than myocardium. For MM patients, disease status was defined at the time of Tc99m-sestaMIBI scintigraphy as follows: i) untreated active disease (n=23) ii) relapsed or refractory disease (n=15) iii) remission (monoclonal component -MC- reduction ≥ 75%) (n= 9) iv) partial remission (MC reduction >50% <75%) (n= 8). In treated patients, Tc99m-sestaMIBI scans were performed at least two months after chemo- or radiotherapy. A detailed semiquantitative study of diffuse bone marrow uptake has been reported elsewhere.[9]

Results

Of the 55 patients studied, six had a normal Tc99m-sestaMIBI scan: they were a patient with MGUS and 5 patients studied after effective chemotherapy. Twenty-four patients showed a diffuse pattern of bone marrow uptake: 4 with MGUS, 10 with MM in stage IA and 2 in stage IIA, 6 patients studied after effective chemotherapy and 2 in relapse. Focal areas of uptake were found as the only pathologic finding in 11 cases, and in combination with diffuse bone marrow uptake in 14 patients. All these 25

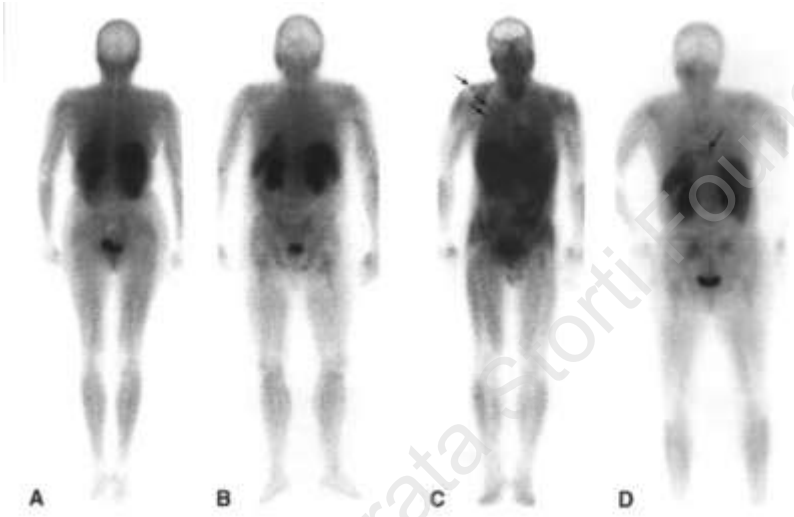

Figure 1. A: normal Tc99m-sestaMIBI scan in a patient with MGUS and minimal bone marrow plasmacytosis (posterior scan). B: diffuse bone marrow uptake in a patient with stage I MM (posterior scan). Spine and pelvis are evident, as well as the proximal segments of long bones. C and D: focal and diffuse Tc99m-sestaMIBI uptake in advanced stage MM. Three focal lesions (C, arrows, anterior scan). Diffuse uptake in spine and pelvis with focal uptake of T9 (D, arrow, posterior scan).

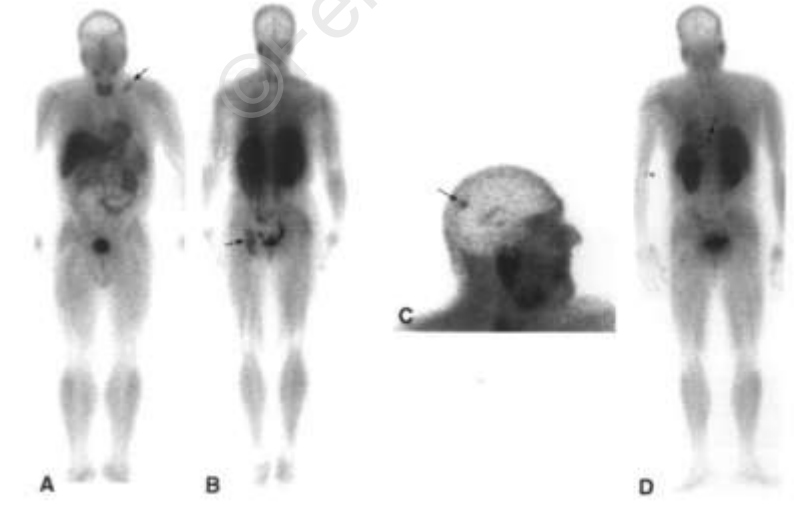

Figure 2. Tc99m-sestaMIBI scans in four MM patients with focal bone localizations (arrows). A: left clavicular uptake (anterior scan). B: left ischiatic uptake (posterior scan). C: parietal uptake. D: vertebral uptake (posterior scan).

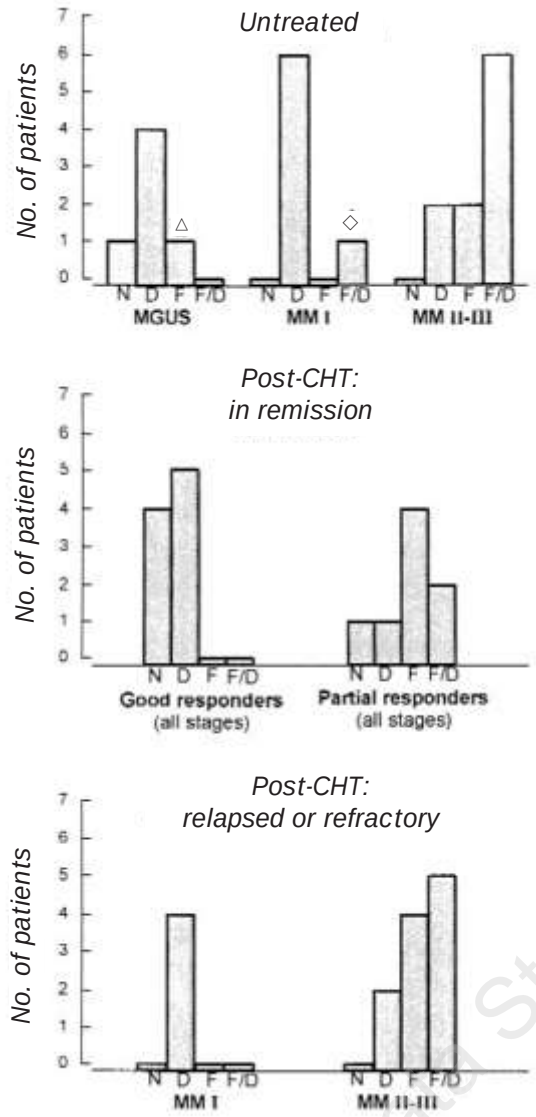

Figure 3. Patterns of Tc99m-sestaMIBI scans in 55 patients affected by plasma cell dyscrasia.
△ Lymph node metastasis of bladder tumor.
◇ Patient in disease progression, who required treatment soon after scintigraphy (Table 3, #4)
Pattern of uptake: N = normal, D = diffuse, F = focal, F/D = focal and diffuse.

patients had active disease (untreated, resistant or relapsing MM). Examples of the different patterns (normal, diffuse, focal, and diffuse+focal) are shown in Figures 1 and 2. The results from our cohort of patients are summarized in Figure 3.

In untreated patients, the number of focal lesions detected by Tc99m-sestaMIBI was comparable to that detected by Xr (mean number of lesions by Xr: 1.4±2.7; mean number of lesions by Tc99m-sestaMIBI: 1.1±1.6, ; p=0.58; n=23), while in pre-treated patients the number of lesions detected by Tc99m-sestaMIBI was significantly lower than that detected by Xr (mean number of lesions by Xr: 5.3±7.3; mean number of lesions by Tc99m-sestaMIBI: 2.3±4.8; p= 0.005; n=32). In three cases Tc99m-sestaMIBI scans revealed soft tissue involvement adjacent to bone lesions (arms, chest) that could not be revealed by Xr.

Table 1. Results of Tc99m-sestaMIBI scans in comparison with conventional radiography (Xr) in bone lesion identification. While the 4 MIBI+/Xr– cases suggest a higher sensitivity of Tc99m-sestaMIBI, the discrepancy MIBI–/Xr+ is only apparent, since in the majority of cases it refers to inactive bone lesions in patients in remission after chemotherapy.

	Xr +	*Xr –*
MIBI +	21	4
MIBI –	13	17

As far as focal lesions are concerned in the whole series of patients, Tc99m-sestaMIBI scans were concordant with the radiological examination in 38 patients: 17 had no focal uptake and no osteolysis (MIBI–/Xr–), 21 had focal areas of uptake in the bone and osteolyses (MIBI+/Xr+), with or without diffuse pattern of bone marrow uptake. In 17 patients the results were not concordant: 4 had focal uptake with normal X ray survey (MIBI+/Xr–), and 13 had no focal uptake but radiographic evidence of lytic areas (MIBI-/Xr+) (Table 1). Of the 13 MIBI–/Xr+ patients, 10 had received effective chemotherapy (Table 2); one of these patients is a very long surviver (more than twenty years) after conventional chemotherapy, off treatment since 1978, still bearing multiple Tc99m-sestaMIBI negative lytic areas in the skull (Figure 4). Three relapsed patients showed vertebral fractures at Xr, which had been detected even before chemotherapy. Three patients had not received any treatment before scintigraphy: one had a collapsed T7, which could be due either to osteoporosis or to myeloma lesions, and two had small areas (< 1 cm) of uncertain significance in the skull or in forearm bones. In one of these patients we performed a fine needle biopsy on the cranial osteolysis: no plasma cells were found.

The four MIBI+/Xr– patients are listed in Table 3. Two untreated patients with costal or vertebral focal uptake required treatment for MC progression soon after scintigraphy. One patient, showing costal focal uptake, was in relapse (BM plasma cells: 46%, MC: 8.1g/dL) after chemotherapy. In the fourth case (MGUS with focal inguinal uptake), histologic examination of the inguinal node showed metastatic adenocarcinoma.

Table 2. Clinical status and sites of X ray alteration in 13 patients with absence of focal Tc99m-sestaMIBI uptake and abnormal radiographic survey (MIBI-/Xr+).

N	*Diagnosis*	*Stage*	*Status at MIBI scan*	*Radiography*	*Interpretation*
1	MM IgGλ	IIA	remission	Collapsed L5	Inactive lesion
2	MM IgGk	IIA	remission	Multiple osteolyses since 1978	Inactive lesions
3	MM IgGk	IA	remission	Skull, radius	Inactive lesions
4	MM IgAλ	IIIA	remission	Skull, ribs	Inactive lesions
5	MM IgGk	IIIA	remission	Multiple vertebral collapse	Inactive lesions
6	MM IgAλ	IIA	remission	Small cranial osteolysis	Inactive lesion
7	MM IgAk	IIA	partial remission	Suspect ischiatic osteolysis	Inactive lesion
8	MM IgAk	IIA	relapse	Collapsed L3	Residual fracture (since 1995)
9	MM IgGk	IB	relapse	Collapsed T7,T8,T9	Residual fractures (since 1993)
10	MM λ	IIIA	relapse	Collapsed T12	Residual fractures
11	MGUS IgGk		untreated	Small cranial osteolysis	Clinically stable. No treatment
12	MM IgGk	IIB	untreated	Small radial and ulnar osteolyses	Clinically stable. No treatment
13	MM λ	IIIB	untreated	Collapsed T7	Not traced due to impaired vascularization

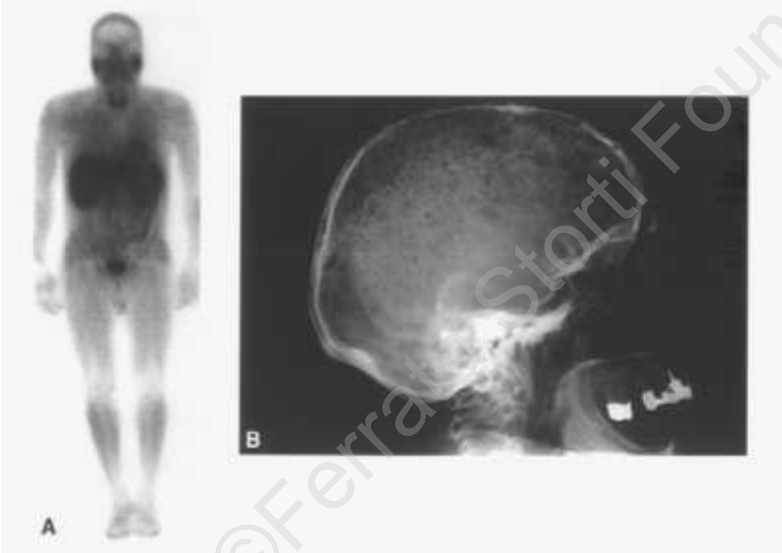

Figure 4. A: normal Tc99m-sestaMIBI scan in a patient in continuous remission (twenty years) after chemotherapy for stage III plasmacytoma. B: same case. Persistence of multiple inactive skull lesions at Xr.

Table 3. Clinical status and sites of Tc99m-sestaMIBI focal accumulation in 4 patients with negative radiological survey (MIBI+/Xr–). Fo = focal pattern of bone uptake. Fe = focal pattern of uptake in soft tissues. D = diffuse pattern of uptake.

No.	*Dx*	*Stage/status*	*MC g/dL*	*% BM plasma cell*	*MIBI*	*Focal sites*
1	MM IgGl	IA/relapse	8.0	46	Fo, D	4th left rib
2	MGUS IgGk	–/untreated	2.1	26	Fe	inguinal node (adeno K metastasis)
3	MM IgAl	IIA/untreated	3.9	30	Fo, D	r. acromion, r. ribs
4	MM IgGk	IA/untreated	3.4	52	Fo, D	T9

Discussion

Originally developed as a myocardial perfusion agent, Tc99m-sestaMIBI has also been proposed as a tracer in several neoplasias, such as breast and lung cancer.[2,3] Recently, preliminary reports pointed to Tc99m-sestaMIBI scintigraphy as a tracer of myeloma lesions.[4-8] Basically, three patterns may be observed by whole body Tc99m-sestaMIBI scintigraphy in plasma cell proliferations: (i) normal, with physiologic uptake in salivary glands, thyroid, heart, liver, spleen, small intestine, bladder; (ii) diffuse bone uptake, designing bone profiles with variable extension and intensity; (iii) focal, in bones or in soft tissues. A mixed diffuse+focal pattern can also be seen. The diffuse pattern has been analytically described elsewhere.[9] Its extension and intensity correlated directly with bone marrow plasma cell infiltration and with the amount of monoclonal component (r 0.71, $p < 0.005$ and r 0.56, $p < 0.05$, respectively; n= 18).

In this study we analyzed patients affected by plasma cell proliferations in different stages and at different follow-up times, comparing the detection of focal lesions by conventional Xr and by Tc99m-sestaMIBI scintigraphy.

Xr and Tc99m-sestaMIBI were concordant in 69% of the cases: both surveys were negative in 17 patients (MIBI–/Xr–), and both detected focal lesions in 21 patients (MIBI+/Xr+). As expected, MGUS and MM in stage I or in clinical remission prevailed in the first group of patients, while the majority of the 21 MIBI+/Xr+ patients (focal or focal+diffuse Tc99m-sestaMIBI pattern) had active disease, either untreated or relapsing.

In untreated patients, the number of focal lesions detected by Xr and by Tc99m-sestaMIBI was equivalent; in addition, Tc99m-sestaMIBI detected soft tissue localizations in three cases. By contrast, in treated MM patients a higher number of focal bone lesions was detected by Xr; from a clinical point of view, these are false positives, since they relate to areas of osteolysis in which plasma cell proliferation is no longer present, due to effective chemo- or radiotherapy.

If we take into consideration only untreated patients (n= 23), concordance between Xr and Tc99m-sestaMIBI was present in 17 cases (74%) (MIBI–/Xr–: 10; MIBI+/Xr+: 7), while 3 cases were MIBI+/Xr- and 3 MIBI–/Xr+. All three MIBI+/Xr– patients (Table 3, patients #2,3,4) required therapeutic intervention (for CM progression in two MM patients and for metastatic adenocarcinoma in a patient with MGUS), while only one (Table 2, patient #13) of the three MIBI–/Xr+ patients (Table 2, patients #11,12,13) required treatment, indicating that the abnormal X ray finding was clinically irrelevant in the other two patients. Indeed, the cytologic examination of a MIBI–/Xr+ lesion did not show plasma cell infiltration.

In summary, focal or focal+diffuse Tc99m-sestaMIBI patterns were always found in patients with active disease, while a normal pattern was found in patients in remission or with low disease activity. The clinical relevance of diffuse bone marrow uptake relies on the extent and the intensity of the uptake.[9]

The mechanism of Tc99m-sestaMIBI uptake by malignant tissues is still unclear.[10] It is conceivable that abnormal plasma cells may have metabolic and membrane peculiarities able to influence Tc99m-sestaMIBI accumulation inside the cells.[11] It has been found that the retention of Tc99m-sestaMIBI in tumor cells may be governed by the MDR-1 system.[7] Since we had not assessed the PGP status in the cohort of patients studied, in order to avoid the bias of a possible active extrusion of the radiotracer in MDR+ cells, we used only the 10 minute scan for the analysis of our data. Additional studies are needed to verify the connection between Tc99m-sestaMIBI and PGP in MM patients.

In conclusion, in tracing focal myeloma lesions, Tc99m-sestaMIBI scintigraphy compared to standard Xr is more specific in identifying active bone lesions, may show additional soft tissue tumor localizations and offers the advantage of ignoring inactive bone lesions. Tc99m-sestaMIBI may be taken up by tumor cells other than myeloma. Strictly speaking, this means reduced specificity; however, this may be a further advantage, since the tracer may detect additional neoplastic disorders, which are not rare in patients with plasma cell dyscrasias. One of our patients is an example of such an occurrence (occasional detection of a metastatic carcinoma in a patient with MGUS). As far as the safety of the scintigraphic procedure is concerned, we have calculated that with the administration of 555 MBq of the tracer the thyroid receives a dose of 14.5 mGy, the ovary 2.1, the testicles 0.75 and the bone marrow 1.5, while a conventional skeletal survey exposes the same organs to doses of 9.1, 8.7, 4.8 and 3.9 mGy, respectively.

Future technical improvements are needed to overcome the intense hepatosplenic uptake obscuring possible focal lesions in the surrounding areas, and to increase the sensitivity, in order to detect even lesions smaller than one cm. The correlation found between intensity of the diffuse pattern of bone uptake and bone marrow plasma cell percentage is a further element of interest, as it also qualifies Tc99m-sestaMIBI scintigraphy as an indicator of the extent of the disease.

Contributions and Acknowledgments

LC and LP designed the study. LC wrote the paper. LC, CC, AMP and ADR were involved in clinical assessment of patients and in data recording and analysis. LP, AMP, FDG, SDV and RF performed the scintigraphic procedures and analyzed the results. MS and BR revised the manuscript and gave final approval for publication.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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References

1. Scutellari PN, Spanedda R, Feggi LM, Cervi PM. The value and limitations of total body scan in the diagnosis of multiple myeloma: a comparison with conventional skeletal radiography. Haematologica 1985; 70:136-42.
2. Kao CH, Wang SJ, Liu TJ. The use of technetium-99m-methoxyisobutylisonitrile breast scintigraphy to evaluate palpable breast masses. Eur J Nucl Med 1994; 21:432-6.
3. Hassan I, Sahweil A, Costantinides C, Mahmoud A, Nair M, Abdel-Dayem H. Uptake and kinetics of Tc-99m hexakis 2-methoxy isobutyl-isonitrile in benign and malignant lesions in the lungs. Clin Nucl Med 1989; 14:333-40.
4. Durie BGM, Waxman A, Jochelson M, Giles FJ, Hamburg G, Avedon M. Technetium-99m-MIBI scanning in multiple myeloma (MM) [abstract]. Proc Am Soc Clin Oncol 1994; 13:411.
5. Malpas JS, Tirovola EB, Biassoni L, Kaleva N, Kouykin V, Britton KE. Myeloma imaging with Tc-99m MIBI [abstract]. Proc. 5th International Workshop on Multiple Myeloma, La Baule, France, 10-13 September 1995. p.120.
6. Unlu M, Haznedar R, Atavci S, Inanir S, Targut B. Detection of bone lesion in multiple myeloma using Tc-99m MIBI scintigraphy [abstract]. Eur J Nucl Med 1995; 22 (suppl):739.
7. Tirovola EB, Biassoni L, Britton KE, Kaleva N, Kouykin V, Malpas JS. The use of 99m-Tc-MIBI scanning in multiple myeloma. Br J Cancer 1996; 74:1815-20.
8. Adams BK, Fataar A, Nizami MA. Technetium-99m-sestaMIBI uptake in myeloma. J Nucl Med 1996; 37: 1001-2.
9. Pace L, Catalano L, Pinto AM, et al. Different patterns of technetium-99m-sestaMIBI scintigraphy in multiple myeloma. Eur J Nucl Med 1998; 25:714-20.
10. Ciarmiello A, Del Vecchio S, Silvestro P, et al. Tumor clearance of 99mTc-sestaMIBI as a predictor of response to neoadjuvant chemotherapy for locally advanced breast cancer. J Clin Oncol 1998; 16:1677-83.
11. Chiu ML, Kronauge JF, Piwnica-Worms D. Effect of mitochondrial and plasma membrane potentials on accumulation of hexakis (2-methoxyisobutyl isonitrile) technetium in cultured mouse fibroblasts. J Nucl Med 1990; 31:1646-53.