Tc $^{99m}$ Sestamibi Scanning in Multiple Myeloma – a New look with SPECT-CT

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Abstract

A variety of diagnostic tools including biochemistry, radiological imaging bone marrow studies and recently metabolic imaging with FDG PET are used for assessment of disease extent in myeloma.

Aim: To evaluate the role of metabolic imaging with Tc$^{99m}$ Sestamibi (Mibi) SPECT-CT in Multiple myeloma.

Materials and Methods: Patients in various stages of Myeloma were scanned after 20mCi Tc99mSestamibi was injected i/v. Whole body planar scans were obtained with a dual head gamma camera and SPECT-CT imaging was done. Images were analyzed for degree and extent of abnormal Mibi uptake, extent of lesions seen on low-dose CT and fusion of these images.

Results: 112 Whole body Sestamibi Scans were performed in 84 patients (46 Males; 38 Females). Out of these 24 (28.5%) were recently diagnosed cases (Pre-therapy); 35 (41.7%) were follow-up cases who had received Chemotherapy in the past (Post-therapy), there were 2 cases (2.3%) of Smouldering Myeloma, 4 cases (4.7%) of Plasmacytoma, 13 cases (15.5%) of MGUS (Monoclonal gammopathy of Unknown Significance) and 3 cases (3.6%) of suspected Myeloma (not biopsy confirmed). Myeloma lesions showed good concentration of Mibi. Additionally, the CT scan component of SPECT-CT allowed visualization of osteolytic lesions of myeloma. Mibi uptake becomes positive on scan earlier than radiological changes and in follow-up cases, the presence or absence of Mibi uptake could differentiate active from old burnt-out lesions. Whole body scan could detect additional lesions in Plasmacytoma patients. Patients of MGUS showed poor concentration of Sestamibi.

Conclusion: Whole body Sestamibi Imaging (WBSI) is very useful for evaluating the extent of disease in multiple myeloma. Being a metabolic imaging modality it is superior to radiological (X-ray or CT) assessment alone, and where FDG PET scan is not available, it is a valuable tool for myeloma assessment at a much lower cost.

Introduction

Multiple Myeloma is a neoplastic disorder of plasma cells and primarily involves the bone marrow.¹ It is an incurable, relapsing disease and needs constant monitoring. It accounts for approximately 1% of all malignant diseases and represents about 10% of hematologic malignancies. The median age at diagnosis is 65 years, and about 3% of patients are younger than 40 years.² Haematological parameters like serum globulin level, serum protein electrophoresis, Free light chains with ratio, Beta 2 Microglobin level; Urine for Bence Jones protein and Bone marrow aspiration and biopsy with cytogenetics and FISH (Fluorescent In Situ Hybridisation) for chromosomal defects are routinely used for diagnosis and follow-up of patients.³ Osteolytic bone lesions are seen in up to 90% of patients⁴ which can be detected on plain X-rays and Whole body skeletograms⁵ and have been conventionally used for assessing the extent of bone lesions, but unfortunately these have limited sensitivity.⁶ CT scans have better sensitivity for detection of lytic lesions⁷ than plain X-rays. MRI is very useful for detection of marrow disease and assess sites for biopsy for a better diagnosis, but does have some inherent limitations in follow-up evaluations.⁸ Nuclear Bone scanning with bone agents (Tc99m-
Diphosphonate Bone Scans) have poor sensitivity for detection of osteolytic myeloma bone disease since these lesions do not produce a significant concomitant osteoblastic reaction and may not concentrate the bone tracer. Hence this modality in not recommended in myeloma assessment. PET-CT scanning with FDG (Fluoro-deoxy glucose) has emerged as an excellent technique for imaging myeloma lesions, but still has limited availability in our country and is expensive. We explored the use of another tracer – Tc99m Sestamibi for imaging myeloma. This tracer is easily available in all Nuclear-medicine departments, is cheaper than F18-FDG and can be used without any additional cost of equipment or personnel.

Tc99m Sestamibi

Tc-Sestamibi (Methoxyisobutyl Isonitrile) is a radiotracer which concentrates in mitochondria of cells. Tracer uptake in cells is linked to the mitochondrial transmembrane electric potentials – which is a function of the metabolic activity of cells. It is routinely used for Myocardial Perfusion Imaging (earlier called “Stress Thallium”). Physiological uptake of Sestamibi is seen in salivary glands, thyroid, myocardium, liver, spleen, gall bladder and intestines (through gall bladder excretion), kidneys and urinary tract (through urinary excretion).

This tracer is also known to concentrate in certain solid tumors. First reports of Sestamibi uptake in benign and malignant lung tumors was in 1989. Now it is quite extensively used for the imaging of Parathyroid adenomas and tumors in Brain and Breast (Scintimammography) in all Nuclear Medicine departments. It was first used for Myeloma imaging in 1996. There have been few reports of its use in imaging multiple myeloma, but it never became popular in clinical practice. All previous reports have discussed planar imaging with Tc Sestamibi (Mibi) and few used SPECT or SPECT-CT. Apart from detection of active disease, uptake patterns of Mibi in myeloma are known to have significant prognostic value. Sestamibi, being a substrate for p-Glycoprotein in cells, is a unique tracer which can help predict resistance of tumor cells to chemotherapy. With all these aspects in mind we decided to study a series of patients with multiple myeloma with Tc99m- Sestamibi with planar and SPECT-CT scanning.

Materials and Methods

Whole-body planar and SPECT-CT Tc99m-Sestamibi scans were performed on known cases of Myeloma in various stages of the disease – from recently diagnosed to post chemotherapy and long term relapse. Where required, patients had follow-up scans to assess the progress of disease and change in scan pattern. The haematological parameters studied were CBC (Complete blood count) by automated 5 part cell counter, serum protein electrophoresis and serum B2 microglobulin and serum free light chains with kappa:lambda light chain ratio. Other biochemical tests like Liver function tests, Serum creatinine, Calcium were done. Additionally urine for Bence Jones Proteins was done in all patients.

Procedure

Whole body Tc99m Sestamibi Imaging (WBSI) : 20 mCi of Tc99m Sestamibi was injected intravenously in a peripheral vein and whole-body scan was acquired after 5 minutes (Early WB scan) on a dual head Gamma camera using LEHR collimators. This was followed by SPECT-CT on a GE Hawkeye system, imaging in two bed positions covering the body area from mid-skull to base of thigh level. SPECT was acquired at 20 sec per step at 6 degree step-and-shoot method.

CT scanning with low dose (2mA) helical CT is an integral part of the SPECT-CT scan and was acquired with the patient lying in the same position, immediately after the SPECT acquisition. This allows perfect superimposition of the SPECT and CT data to produce Fused images (Figure 1). Whole body planar scan was repeated at 2 – 3 hours after injection (Delayed scan).

The scans were interpreted on high resolution colour monitors. Xeleris software was used for processing and display of SPECT-CT images, which allows simultaneous viewing of attenuation-corrected...
SPECT images, the corresponding CT scan slice and Fused images where the tracer uptake in superimposed on the CT (anatomical) images (Figure 1).

Reporting of the scans included description of the areas of abnormal tracer uptake and correlation with the CT images to exactly localize the sites of uptake. Additionally, the low dose CT scan images were also evaluated in the bone and soft tissue window settings to look for osteolytic bone lesions or other abnormalities. The results of scanning were compared with the clinical condition of the patient, haematological parameters, other radiological reports (where available) and any previous Sestamibi scan if available.

**Results**

From 2009 till May 2012, a total of 112 Whole body Sestamibi Scans were performed in 84 patients (46 Males; 38 Females). Out of these 24 (28.5%) were recently diagnosed cases (Pretherapy); 35 (41.7 %) were follow-up cases who had received Chemotherapy in the past (Post-therapy), there were 2 cases (2.3%) of Smouldering Myeloma, 4 cases (4.7 %) of Plasmacytoma, 13 cases (15.5 %) of MGUS and 3 cases (3.6%) were referred for a clinical suspicion of Myeloma (not biopsy confirmed).

WBSI showed abnormal concentration of tracer in the bone marrow of patients of myeloma. The degree of uptake varied, from mild to moderate to intense and there were different patterns of tracer distribution seen (as discussed below). In addition, the low dose CT scan images of SPECT-CT showed changes ranging from the typical osteolytic lesions of myeloma, or sclerotic lesions or vertebral fractures in the bones in many patients. In effect this modality allowed two whole different types of ‘skeletal survey” of the patient. The Radionuclide distribution reflected the areas of abnormal increased metabolic activity (active disease) and the low dose CT images from base of skull to mid-thigh level provided an equivalent of a radiological skeletogram. The fusion of both this data provided an effective differentiation of the extent of myeloma bone disease.

Certain Key Findings that were noted during this study are highlighted below

1. SPECT-CT images showed the areas of tracer uptake more prominently than the planar images. In most Sestamibi scans there is very prominent physiological uptake of tracer in hepatobiliary system and intestines, which causes relative reduction in contrast in marrow lesions in planar gamma camera images. In these cases particularly, the SPECT-CT images showed the abnormal areas of uptake more clearly (Figures 2a and b).

2. Anatomical localization of the areas of abnormal
of myeloma in many cases. However very often, though there was abnormal increased MIBI concentration in the bone, the CT images showed no obvious lytic or sclerotic changes (Figure 3). This is because metabolic changes on radionuclide scanning become apparent much earlier than radiological changes.

3. Conversely, in many patients the CT images showed widespread osteolytic areas in bones but no abnormal tracer concentration in these lesions (arrow marked areas in Figure 4). These were all in post-treatment patients where radiological changes persisted even though lesions had become metabolically negative.

4. Sometimes areas of apparently abnormal tracer uptake noted on the planar Sestamibi images, on correlation with the anatomical image on fused tracer uptake on the corresponding CT image showed typical punched-out osteolytic changes.
SPECT-CT images, were found to be areas of physiological uptake – most often physiological muscle uptake (Figure 5), a thyroid lobe, or gut activity. Hence addition of correlative CT scan helped reduce false positives.

5. In addition to abnormal Sestamibi distribution in bone marrow, the low-dose scan helped identify other associated skeletal changes such as vertebral fractures or abnormal associated soft tissue lesions (Figure 6).

6. The planar WBSI occasionally detected disease in soft tissue such as lymph nodes, in addition to bone disease. Occasionally active disease was seen in the peripheries, in clinically unsuspected sites, and in those areas not routinely covered in radiological assessments (Figure 7).

7. In cases where FDG PET scan was also done, there was good correlation with findings on both scans. The lesions were definitely more intense and well defined on the FDG PET scan (Figure 8a) in most cases, but on careful inspection most of the areas of abnormal uptake could be also visualized on Mibi SPECT-CT (Figure 8b). This is due to the

![Fig. 7](image1.png)

![Fig. 8](image2.png)
intrinsic higher resolution ability of PET imaging and the better resolution of the CT on the PET-CT scanner, as compared to the low dose CT scanner of SPECT-CT.

8. There was also good correlation between WBSI and MRI of patients with newly diagnosed myeloma (Figure 9).

An exception to note

In an isolated case (Figure 10) where we found diffusely increased abnormal concentration of MIBI in a newly diagnosed case of Myeloma (Biopsy proven), the FDG PET-CT scan done elsewhere had been (falsely) reported as Normal. On retrospective evaluation of the PET images it was noticed that there was in fact, diffuse uptake of FDG in the marrow. This is just to highlight that occasionally a very diffuse, homogenous uptake of FDG in marrow could be difficult to differentiate from the normal pattern of physiological FDG uptake. FDG uptake in lesions is also significantly linked to blood glucose profile, and this could have been one of the contributory factors for relatively low uptake in lesions.

Analysis of Pre-therapy Patients

All (100%) newly diagnosed myeloma patients, scanned prior to the commencement of chemotherapy showed abnormal concentration of Tc Sestamibi in the bones/marrow. Three basic scan patterns (Figure 11) were observed.

1. Diffusely increased tracer uptake in skeleton
(59% of patients) - uniformly increased uptake especially in all vertebrae, bilateral pelvic bones, bilateral ribs and chest bones and prominent uptake in upper ends of femurs and humerii. Occasionally diffuse increased uptake in skull bones was seen.

2. Multiple discrete focal areas of increased tracer uptake (33% cases)

3. Mixed pattern of diffuse and additional focal areas of uptake (8% of cases) - in addition to the diffuse uptake in marrow, there were some areas showing markedly increased focal uptake, more intense than other areas.

Chart 1 below demonstrates the relative occurrence of these 3 patterns

Analysis of the low-dose CT scan images of these pre-therapy patients revealed three main categories of findings (Chart 2) 71% (46% +25%) cases showed presence of osteolytic bone lesions (often lesser than the extent of Mibi uptake) and 29% showed no osteolytic changes in spite of the abnormal Mibi uptake.

**Analysis of Post Therapy Patients**

35 Follow-up cases of myeloma, who had received chemotherapy with or without bone marrow transplant in the past (ranging from 3 months to 7 years post therapy) were scanned. Of these, 18 patients (51.4%) were clinically stable (in Remission) with plasma...
protein levels and B2 Microglobin levels in the acceptable range; 17 (48.6%) presented with clinical Recurrence with abnormal biochemical markers, with or without symptoms. The aim of the scans was to detect presence, and assess the extent of recurrent disease.

Of the 18 patients in Clinical Remission (Chart 3a)

a. 11 (61%) showed no abnormal concentration of Sestamibi. Considering that all these patients had active bone disease in the past, CT images showed persistent osteolytic lesions in a large proportion of these patients. However these osteolytic bone lesions were negative for Mibi uptake (metabolically inactive). 3 patients showed neither abnormal MIBI uptake nor any osteolytic bone lesions

b. 7 patients (39%) showed osteolytic areas with some areas of minimally increased tracer uptake.

Of the 17 Clinically Recurrent patients (Chart 3b)

All (100%) showed abnormal tracer concentration. However there were various combinations of scan findings in these patients as demonstrated in the chart 3b. 9 patients (53%) showed multiple osteolytic areas - some showing areas of abnormal uptake and some showing no uptake and in addition some areas of abnormal uptake where no lytic lesions were seen (Mixed pattern). 7 patients showed multiple abnormal areas of uptake, many of which revealed no corresponding lytic areas and some showed osteolytic lesions (ie Areas of Uptake > osteolytic areas). In 1 patient, all the areas of tracer uptake correlated to lytic lesions.

In 2 cases where CT scan findings of osteolysis seemed clinically very suspicious, the lesions were actually biopsied and revealed absence of active disease (fibrosis) in osteolytic areas showing no tracer uptake (Figure 12).

**Plasmacytoma Patients**

4 patients diagnosed as Plasmacytoma clinically and by radiology, were referred for scan. The aim was to assess the metabolic activity of the lesion and rule out possibility of multiple / metastatic lesions. The site of the plasmacytoma was in the Sternum in 3 cases and in the vertebra in one. All the patients...
demonstrated intense uptake of Tc Sestamibi in the primary lesion with associated osteolytic changes seen on CT images (Figure 13).

In one of the 3 cases, additional smaller areas of abnormal tracer uptake were detected on scan. (Figure 14). This patient was given radiotherapy to the sternal lesion and after 3 months referred for scan again to assess the response to treatment. The follow-up scan showed reduction in the intensity of the sternal lesion; however multiple other marrow lesions had developed elsewhere in the body.

MGUS Patients

13 patients of Monoclonal gammopathy with no identifiable radiological lesions and biopsy negative for myeloma were studied. Of these 9(69.2%) showed no abnormal uptake of Tc Sestamibi in the skeleton. 2 patients (15.3%) showed very mild diffusely increased tracer uptake in bones with no osteolytic areas seen and 2 (15.3%) showed prominent diffusely increased tracer uptake in the marrow but no osteolytic areas (Chart 4). One of the patients with prominent diffuse marrow uptake was re-biopsied but no active myeloma disease was seen and histopathology showed reactive marrow only.

Patients with Follow-up Scans

Of our total series of 84 patients, 23 patients had follow-up scans. Nineteen patients had a single follow up, 3 had two follow-up scans and 1 patient had three follow up scans. At each point of time there was found to be good correlation between the
Fig 15: (a) In a case of myeloma post chemotherapy and clinically and biochemically in remission in Feb 2010, the whole body scan showed no abnormal tracer uptake. (b): In 2012 patient had body ache and anaemia. WBSI showed diffusely increased tracer uptake in vertebrae, sternum, scapulae, ribs, bilateral pelvic bones, upper ends of humerii and femurs and left upper tibia. She was found to have abnormal rise in plasma protein and B2 Microglobin levels and biopsy confirmed recurrent disease.

Biochemical parameters of the patient and the scan findings and Tc Sestamibi scan was able to provide indication about the extent of disease. Figure 15 gives an illustrative example of detection of recurrent disease by WBSI.

Discussion

The physiological uptake of Tc-Sestamibi by multiple organs causes significant background activity of tracer and on planar Gamma camera scanning this makes it difficult to detect lesions. This is probably the main reason Tc Sestamibi never became popular as a whole body tumor-imaging agent. However in our study we found several factors that have emerged from the development of technology, that make WBSI a viable option. The intrinsically higher resolution of newer gamma cameras, addition of SPECT and now the incorporation of inbuilt CT scanner in SPECT-CT imaging adds two major benefits – (a) use of attenuation correction in SPECT-CT dramatically increases sensitivity (Figure 2) (b) Radiological image corregistration increases Specificity by distinguishing abnormal vs. physiological uptake and allows further characterization of the lesions (Figure 5).

Apart from a whole body MIBI distribution, the WBSI also incorporates a whole-body low-dose CT scan. Low-dose CT scans are better than plain X-rays for detection of osteolytic myeloma bone lesions (23) and there are recent reports regarding use of whole body low dose CT scans for assessment of myeloma extent. (24) However, metabolic imaging becomes positive earlier than X-ray changes, and as seen in our series, in many newly diagnosed patients, many areas of early active disease which showed abnormal MIBI uptake were not apparent on X-ray / CT due to absence of lytic / sclerotic changes (Figure 3 and Table 2). Therefore, the use of only X-rays or low-dose CT scan for initial staging assessment may be questionable.

Moreover in post-therapy follow-up patients, WBSI can differentiate old burnt-out osteolytic lesions (which may persist for years despite therapy25 and are inactive) from those that are active (Figure 12).

FDG PET-CT which combines metabolic imaging with high resolution CT scanning is emerging as the ideal modality for imaging myeloma. Its advantages over MRI are better body coverage, and more specificity in post treatment evaluation. Multiple studies have now proven the benefit of FDG PET-CT scanning for assessment of myeloma extent. (26-29) Where not available, we found that MIBI imaging to be a useful surrogate since patterns of disease extent were similar on both these scans.

MRI is excellent for detection of areas of altered marrow signal and is a very useful tool at initial diagnosis of disease. A comparative study by Fonti et al (26) showed good correlation between detection of myeloma lesions in spine and pelvis by both MRI and Sestamibi scan. In the recently diagnosed cases in our series, where available, WBSI compared very well with MRI findings (Figure 9). MRI has the distinct advantage of better anatomical detailing of bone and soft tissue lesions and can define bone masses causing pressure effects and identify any neurologically critical lesions. The only major advantage of WBSI at diagnosis over MRI would be the wider whole-body coverage of WBSI as compared to regional MRI, with the occasional chance of missing out on peripheral lesions (Figure 7).
However in the post treatment scenario, the specificity of MRI marrow changes is somewhat reduced since it may not be able to differentiate active disease from reparative marrow changes.\textsuperscript{25} WB SI in this setting was found to be useful to pick out only the areas of active disease (Table 3).

The Durie Salmon PLUS staging system for myeloma integrates the more sensitive techniques like MRI, CT and PET-CT into its classification system.\textsuperscript{30} However, the current IMWG (International Myeloma Working Group) and NCCN guidelines do not recommend the routine use of radiological imaging other than X-Ray skeletal survey, except in certain situations. However, the issue whether the emphasis on X-ray skeletal survey for detection of bone disease in myeloma is appropriate, as it can miss lesions till 30\% of the bone mass is destroyed and its high false negative rate of 30-70\%.\textsuperscript{23,24,31} Moreover for follow-up of patients, X-ray cannot be reliable for assessment of response to therapy as the lytic bone lesions seldom show evidence of healing.\textsuperscript{25} Also, skeletal survey finds no place in the ISS score which looks at the extent of the disease biochemically. If the Durie –Salmon scoring were to be considered, IMWG mentions that ‘bone lesions need to be treated even if the patient is asymptomatic’, which means that a sizeable patients (with false negative X-ray survey) will not be treated due to the inherent deficiency of this modality.

In clinical practice, biochemical markers are usually used as follow-up indicators for disease recurrence. In our study we found that all (100\%) follow-up patients with clinical suspicion of relapse showed positive WB SI scan (Table 3). In this category of patients mixed pattern of disease is commonly seen with active lesions with or without osteolytic changes interspersed with old non-osteolytic lesions. A typical bone marrow examination from the posterior superior iliac spine may be negative due to patchy marrow involvement of myeloma. WB SI may be useful to detect and guide the exact areas of active disease to decide biopsy site.

WB SI is particularly useful in cases which present as plasmacytomas. It is known that after local radiotherapy many of ‘plasmacytoma’ patients return with multiple myeloma since the smaller lesions were missed by conventional radiology at initial screening.\textsuperscript{32,33} Detection of additional areas of active disease at the time of diagnosis would help restage the disease and prompt initiation of systemic therapy early along with locoregional therapy of the plasmacytoma mass (Figure 12).

**Conclusion**

WB SI with SPECT-CT is a very useful and easily available technique for imaging of Myeloma. It has good sensitivity in detection of diffuse and focal disease - with SPECT – CT remarkably improving the sensitivity. At any given clinical point, it demonstrates the extent of disease and distinguishes Active vs. Inactive lesions. Most importantly it is a cost-effective study, with distinct advantages over conventional radiology. In the absence of a PET-CT, it is an effective tool for assessing myeloma disease extent at diagnosis and follow-up.

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