

Role of Tc-99m SESTAMIBI in Assessment of Treatment Response to Chemotherapy in Bone Sarcomas

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ABSTRACT

The aim of this prospective study is to test the value of Tc99m MIBI scanning in assessment of response of bone sarcomas to chemotherapy. It included 28 patients with primary bone tumors [18 patients with osteosarcoma, 10 patients with Ewing's sarcoma (ES)]. Their age ranged from 8-19 years, 24 males and 4 females. All patients had pre-chemotherapy assessment with 20 mCi of Tc-99m MDP triple phase bone scan. Early dynamic and blood pool whole body scan (WBS) imaging at 2-5 min post injection and delayed (3 hours) image were acquired to assess the primary lesion and exclude metastatic spread. Both early (20 min) and delayed (2 hrs) WBS images with Tc-99m SestaMIBI were performed before chemotherapy and after 3-4 courses of chemotherapy to assess chemotherapy treatment response. Imaging was done on dual head gamma camera interfaced with a recent version computer system. Images were interpreted both qualitatively and quantitatively. Correlation of Tc99m MIBI scan with tumor percentage necrosis in histo-pathological examination was possible in 19 patients following salvage surgery for the involved limb. The remaining 9 patients were assessed clinically and radiologically in comparison with Tc-99m MIBI WBS.

The results of the current study divided our patients according to response to therapy and scintigraphic data into 3 groups:

Good responders: 12 (43%) patients with marked changes in qualitative images and marked decrease in Tc-99m MIBI ratio in both early and late images. This group showed > 90% tumor necrosis. The second group included partial responders (6 patients) with some changes in the qualitative and quantitative images (mean Tc-99m MIBI uptake ratio). Percentage of tumor necrosis in this group ranged from 50-90%. The third group included patients with no response to chemotherapy with no appreciable change in qualitative images and quantitative ratio before and after treatment. This group had < 50% of tumor necrosis histo-pathologically.

It is concluded that Tc99m MIBI scan is a valuable diagnostic tool in assessment of response to chemotherapy in patients with bone sarcomas, its results are comparable to histopathological data. It can be safely performed dur-

ing therapy to assess success of employed therapeutic strategy and guide its modulation.

Key Words: Bone - Sarcomas - Tc-99m MIBI scan.

INTRODUCTION

Bony sarcomas are aggressive tumors treated by multi-modality approaches. Early detection of residual or recurrent tumor tissue after treatment protocol is very important for further management of these patients. This is currently done by clinical evaluation, diagnostic radiological procedures, radionuclide imaging techniques using tumor imaging agents (TL 201-Tc99m MIBI) and histological examinations [1,2,39].

The response of tumor to treatment protocols (chemotherapy, radiotherapy and combined modality) is defined by the degree of tumor necrosis. This information can be obtained by detailed histological examination after resection, which is a lengthy procedure [3,5,9,16,33].

Diagnostic radiological procedures are helpful in outlining size of the tumor, its margin, integrity of adjacent bones, however it remains unsatisfactory in differentiating necrosis or fibrosis from viable tumor tissue following treatment [4,6,7,8].

Recently the use of radionuclide imaging techniques plays an important role in assessment of tumor response to treatment. They differentiate post-therapeutic necrosis or fibrotic changes from residual viable tumor tissue or local recurrence [37].

Tc99m MDP bone scan is widely used in

early detection of bony tumors, as it is very sensitive in detecting bone lesions, however, it is of less value in monitoring the response to treatment due to its low specificity. The mechanism of MDP uptake depends more on healing process and osteoblastic reaction rather than tumor viability.

Tc-99m SestaMIBI is used in myocardial perfusion imaging and has tumor imaging capability. It has the ability to differentiate post-therapeutic necrosis from residual viable tumor tissue or local recurrence. This is achieved by both qualitative and quantitative analysis of data obtained from its uptake and retention mechanism, which is dependent on mitochondrial metabolism and negative membrane potential [10,11,12,14,15,31,36].

Objectives:

Our objective is to study the reliability of Tc-99m sestamibi in assessment of treatment response of bone tumors to chemotherapy.

PATIENTS AND METHODS

Twenty-eight patients with bone sarcomas (18 patients with osteosarcoma and 10 patients with Ewing's sarcoma). Their age ranged from 8-19 years (mean age of 12 ± 2), 24 males and 4 females. Pre-chemotherapy assessment was done using 20 mCi of Tc-99m MDP WBS and local spot view on site of the primary lesion for a total of 500 Kc at 5 min and 3 hours. Bone scan was done to assess the primary lesion and exclude metastatic spread within one-week max. Tc-99m MIBI WBS was done following IV injection of 20 mCi with early images at 20 min and late images at 2 hours, both before treatment and 2 weeks after 3-4 courses of chemotherapy, applying the same technique and parameters. Tc-99m MIBI WBS was done with additional local spot view over site of the primary lesion for 5 min. Imaging was done on dual head gamma camera using low energy, parallel hole collimator with scan speed of 12 cm/min. Region of interest was drawn inside borders of the primary tumor uptake and contra-lateral normal site for calculation of lesion to normal (L/N) ratio both in early and late images. Image interpretation was evaluated both qualitatively and quantitatively. Qualitatively by classifying tumor uptake as high (+++) or low-grade uptake (+) and the degree of change in uptake from pre-to post chemotherapy scan was done.

Quantitative assessment: Was done by tumor uptake (L/N) ratio. L/N ratio > 1.5 is considered positive for viable tumor tissue while ratio ≤ 1.5 is considered negative for a definite viable tumor tissue.

Correlation of Tc-MIBI scan with percentage of tumor necrosis histo-pathologically was possible in 19 patients following surgery. The remaining 9 patients were assessed clinically and radiologically versus Tc-99m MIBI scan. Patients were divided into 3 groups according to degree of response.

Good responders: If there is change of their tumor uptake from high to low grade or even no abnormal uptake from Pre-to Post therapy scans with decrease of L/N ratio to ≤ 1.5 .

Partial responders: If there is decrease of L/N ratio from pre to post therapy scan but still L/N ratio > 1.5 with slight decrease in tumor tracer uptake in qualitative interpretation.

Non-responders: If they had no appreciable change in the qualitative images and L/N ratio remained the same or even increased from pre-to post therapy scan.

RESULTS

The first group (good responders) included 12/28 (43%) (6 with osteosarcoma, 6 with Ewing's sarcoma) showed good response to pre-operative chemotherapy. Six out of twelve patients showed initial high-grade uptake in early pre-chemotherapy scan and changed to low grade uptake in post therapy scan indicating good response to chemotherapy (Fig. 1). The remaining 6 patients had low-grade uptake from the start in pre-chemotherapy scan with almost no abnormal tracer uptake in post chemotherapy scan (Table 1).

Concerning the pattern of uptake, all the 12 patients showed homogenous pattern of uptake in the initial pre-therapy scan with low grade, homogenous uptake (6 patients) and absence of abnormal uptake (6 patients) in post-therapy scan (Table 2). Quantitatively, the mean early initial MIBI uptake before chemotherapy was 2.57 with marked improvement and decrease to 0.95 following chemotherapy. The difference between both ratios was statistically significant (p value < 0.01). Similarly, the mean late MIBI uptake ratio before and after chemotherapy

were 2.07 and decreased to 0.89. The difference was statistically significant (p value < 0.01) (Table 3). The percentage of tumor necrosis in this group (only performed in 6 patients) was $> 90\%$.

The second group (partial responders) included 6 (21.5%) patients (4 with osteosarcoma and 2 with E.S.). Two patients out of 6 had initial high-grade uptake in the pre-chemotherapy scan and change to low grade uptake in the post chemotherapy scan. The other four patients had high-grade uptake in pre-chemotherapy scan and showed mild degree of decreased uptake in post-therapy scan (partial response to chemotherapy) (Fig. 2). Concerning the pattern of uptake, two patients showed doughnut pattern of uptake in initial pre-chemotherapy scan with no change in the pattern in post chemotherapy scan. The other four patients had homogenous and heterogeneous uptake pattern, with no appreciable change in pattern in post therapy scan.

Quantitatively there is a decrease in the mean early Tc-99m MIBI uptake ratio, however it is still higher than 1.5 value. The initial mean early uptake before chemotherapy was 2.98 and decreased partially after chemo. to 2.17. The difference was statistically significant (p value < 0.05). Same results were found in the late images with mean uptake ratio of 3.02 pre-chemotherapy and decreased to 2.43 post chemotherapy. Percentage of tumor necrosis in 4 patients in this group was from 50-90%.

The third group (non-responders) showed no response to chemotherapy. They included 10 (35.5%) patients (8 osteosarcoma, 2 E.S.). All 10 patients showed high-grade uptake in early and late pre- & post chemotherapy scans (Fig. 3). Concerning pattern of uptake 7 patients had doughnut appearance and 3 patients had intense homogenous uptake in early and late pre- and post chemotherapy scans. Quantitatively the mean Tc-99m MIBI uptake in early and late pre-chemotherapy scans was 2.93 and 2.69 respectively with increase of tumor uptake mean ratio following chemotherapy with mean early and late Tc-99m MIBI uptake of 3.8 and 2.8 respectively. The difference was statistically non-significant (p value > 0.05). The percentage of tumor necrosis was $< 50\%$ (performed in 9 patients in this group).

Table (1): Qualitative assessment of response to chemotherapy using Tc-99m MIBI scan.

	High grade uptake		Low grade uptake	
	No.	%	No.	%
<i>Pre-therapy Tc-MIBI:</i>				
Good responders	6	21.5	6	21.5
Partial responders	6	21.5	-	-
Non-responders	10	35.5	-	-
<i>Post-therapy Tc-MIBI:</i>				
Good responders	-	-	6	21.5
partial responder	4	14	2	7
Non-responders	10	35.5	-	-

Table (2): Pattern of uptake in good, partial and non-responders.

	Pattern of uptake		
	Homogenous	Doughnut	Heterogeneous
<i>Pre-therapy Tc-MIBI:</i>			
Good responders	12	-	-
Partial responders	2	2	2
Non-responders	3	7	-
<i>Post-therapy Tc-MIBI:</i>			
Good responders	-	-	-
Partial responders	2 moderate	2	2 moderate
Non-responders	3	7	-

Table (3): Pre-and post chemotherapy mean Tc-99m uptake ratio in good, partial and non-responders.

	Pre-chemotherapy uptake ratio	Post-chemotherapy uptake ratio	p -value
<i>Good responders:</i>			
Early	2.57	0.95	< 0.01
Late	2.07	0.89	
<i>Partial responders:</i>			
Early	2.98	2.17	< 0.05
Late	3.02	2.43	
<i>Non-responders:</i>			
Early	2.93	3.8	> 0.05
Late	2.69	2.8	

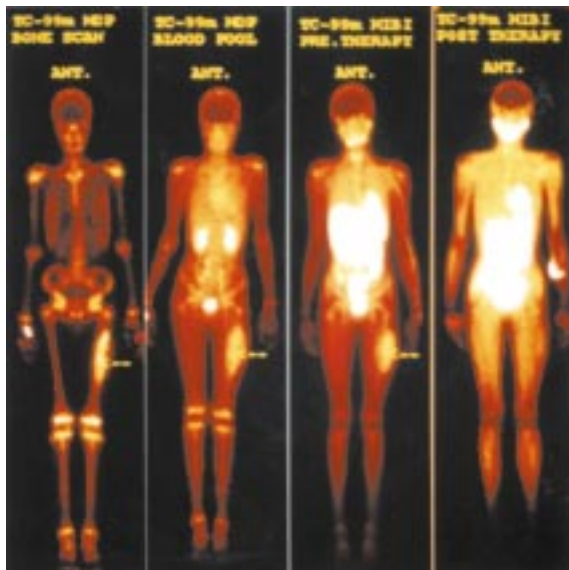


Fig. (1): *Good responders:*

A- Blood pool image showing hyper-perfusion of the tumor in Lt. mid thigh. B- Delayed whole body scan (WBS). C- Tc-99m MIBI WBS before chemotherapy. D- Tc-99m MIBI WBS after chemotherapy with disappearance of tumor uptake.

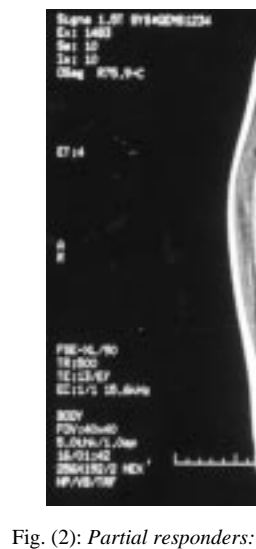
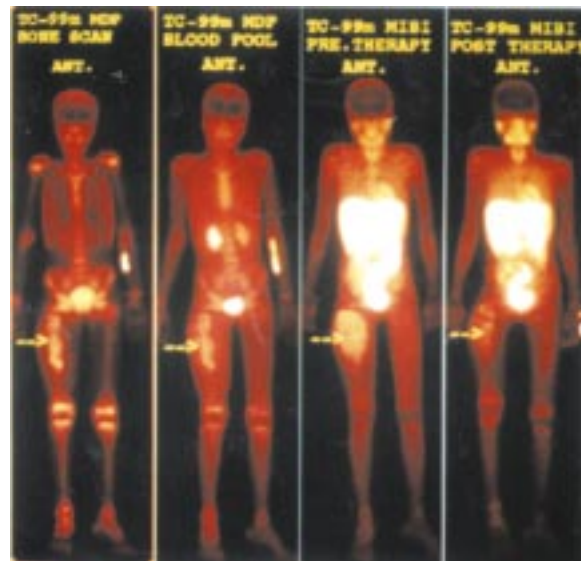


Fig. (2): *Partial responders:*

A- Blood pool image showing hyper-perfusion of the tumor in Rt. upper thigh. B- Delayed whole body scan (WBS). C- Tc-99m MIBI WBS before chemotherapy. D- Tc-99m MIBI WBS after chemotherapy with decrease of tumor uptake. E- MRI showing partial response.



Fig. (3): *Non-responders:*

A- Delayed whole body scan. B- Tc-99m MIBI WBS before chemotherapy. C- Tc-99m MIBI WBS after chemotherapy with increase of tumor uptake.

DISCUSSION

Bony sarcomas are aggressive tumors treated by multimodality approaches. Assessment of response to chemotherapy as well as early detection of residual or recurrent tumor tissue after treatment is very important in further management of these patients [21,26-30].

Tc-99m MIBI uptake reflects functional imaging, compared to morphologic findings in CT and MRI, it serves as an indicator of tumor response. However, variation in tumor size, attenuation and photons scattering contribute to its uncertainty. By including only tumors of the extremities, it was possible to define a corresponding background reference and avoid disturbing activity coming from the visceral structures [4,13,17,23].

In our study 28 patients with malignant bone tumors of the extremities were included to assess the response of chemotherapy using Tc-

99m MIBI scan. Twenty two (78.5%) of these patients showed high-grade uptake in the pre-therapy scan with mean uptake of 2.91 ± 1.1 . All these 28 patients were re-evaluated after chemotherapy and classified according to the degree of change of their MIBI uptake into 3 groups, good, partial and non-responders.

Good responders: 12 (43%) patients showed marked decrease in post chemotherapy MIBI uptake with L/N ratio < 1.5 . *Partial responders:* 6 (21.5%) patients showed mild decrease in MIBI uptake, but still L/N ratio > 1.5 . *Non-responders:* 10 (35.5%) patients showed no decrease in uptake but even showed increased uptake ratios.

Pattern of radiotracer uptake in 28 patients of bone sarcomas was homogenous in 17 patients, 14/17 (82%) had response to chemotherapy (12 good, 2 partial), whereas no response to chemotherapy was seen in the other 3 patients. On the other hand, 9 patients who had doughnut pattern 7/9 (78%) of them showed no response to chemotherapy and 2/9 (22%) patients had partial response. This finding (doughnut pattern) with high percentage of non-responders may be related to associated tumor necrosis with diminished blood flow and/or presence of resistant more aggressive clones of tumor cells. Similar finding was reported by other investigators in 11 patients with malignant bone tumors treated by chemotherapy were assessed by histopathology examination and Tc-MIBI scan. Another study was done in twelve patients with osteosarcoma evaluated by Tc-MIBI before and after chemotherapy. They had clinical response with change of tracer uptake in 11 patients, while progressive clinical disease with no change in uptake is seen in only one patient. In all 11 patients histological examination showed cellular necrosis between 50% and 100% and reduced tumor uptake ratio of Tc-MIBI. While the single progressive tumor showed increased tumor uptake ratio [18,19,21,22,32,34,35,40].

It is widely accepted that post therapeutic tumor necrosis $< 90\%$ denotes a poor response to chemotherapy. A lower percentage of tumor necrosis following preoperative chemotherapy indicates the presence of hundreds of thousands of viable resistant tumor cells and correlates with a greater potential of distant metastases and local recurrence. Whereas, tumor necrosis $\geq 90\%$ indicates good response to preoperative

chemotherapy. This is important information not only for prognosis but also for selection of alternative chemo-therapeutic regimens in patients who failed to demonstrate good response to preoperative chemotherapy and in operative planning as well [20,24,25,38].

In the present study, response to chemotherapy with ^{99m}Tc -MIBI was correlated with percentage of necrosis in 19 patients, 6 patients had good response with mean MIBI uptake ratio < 1.5 and had percentage necrosis of 90%, 4 patients had partial response with percentage necrosis ranging from 50-90% and the other 9 patients had no response with mean MIBI > 1.5 and had percentage necrosis $< 50\%$.

Conclusion:

Tc-99m MIBI plays an important role in assessment of response to chemotherapy of bone sarcomas. The criteria of response in both qualitative and quantitative scan results are comparable to histopathological data. It is recommended to perform Tc-99m MIBI scan in patients with bone sarcoma before and during therapy to assess treatment success and guide any further change in treatment strategy for each individual patient.

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