Evaluating Benign and Malignant Bone and Soft-Tissue Lesions with Technetium-99m-MIBI Scintigraphy

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This study compares the ability of 201TI and 99mTc-MIBI to detect and assess tumor response to chemotherapy in malignant and benign bone and soft-tissue lesions. Methods: Forty-two patients with various bone and soft-tissue pathologies (29 malignant and 13 benign lesions) were studied with 201TI and 99mTc-MIBI. Planar 201TI scintigraphy was performed 15 min after injection of 111 MBq of 201TI. Within 1 wk of the 201TI study, radionuclide angiography with 600–740 MBq of 99mTc-MIBI was performed and planar imaging was done 15 min later. Results: In visual analysis, 31 of 42 patients showed similar uptake of both tracers, 8 showed more intense uptake of 99mTc-MIBI than 201TI and 3 showed more intense uptake of 201TI than 99mTc-MIBI. In quantitative analysis, similar 201TI and 99mTc-MIBI uptake ratios were obtained (1.96 ± 1.25 versus 1.96 ± 1.02, respectively; p = ns). The perfusion index derived from 99mTc-MIBI radionuclide angiography was higher than 99mTc-MIBI uptake ratio (2.33 ± 1.23 versus 1.96 ± 1.02, respectively; p < 0.005), but correlated well with 99mTc-MIBI uptake ratio (r = 0.75). In 11 patients with malignant tumors, 201TI and 99mTc-MIBI scintigraphy was repeated after chemotherapy and the uptake of both tracers was significantly suppressed in patients with complete response confirmed by histological evaluation. In patients with complete response (n = 3), the uptake ratio of both tracers was reduced by more than 50%, whereas, less than 20% reduction of uptake ratio was observed in patients with nonresponse (n = 6). Conclusion: The ability of 99mTc-MIBI to detect malignant and benign bone and soft-tissue lesions and to assess tumor response to chemotherapy was comparable to that of 201TI. In addition, blood flow could be assessed by radionuclide angiography with 99mTc-MIBI. Technetium-99m-MIBI is a promising radiopharmaceutical for the evaluation of bone and soft-tissue lesions.

Key Words: technetium-99m-MIBI; thallium-201; bone tumor; soft-tissue tumor; chemotherapy

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Technetium-99m-hexakis-2-methoxyisobutylisonitrile (MIBI) was developed as a myocardial perfusion imaging agent. It has also been widely used as a tumor imaging agent in various benign and malignant lesions, including lung, breast, thyroid and brain tumors and lymphoma (1–6), because it accumulates in viable tumor cells through the potassium pathway with the ATPase-dependent Na+/K+ pump (7). Recently, 99mTc-MIBI has also been used in the detection of various benign and malignant tumors (8–15).

In bone and soft-tissue tumors, 201TI and 99mTc-MIBI scintigraphy was proven to be a valuable diagnostic method (16,17). However, no study has compared 201TI and 99mTc-MIBI in such tumors. Since 99mTc-MIBI is labeled with 99mTc, it is not only more appropriate for imaging than 201TI but also, since a higher dose can be used, tumor perfusion can be evaluated simultaneously by radionuclide angiography. Furthermore, 99mTc-MIBI is practical in routine practice because of its continuous availability as a kit-based agent. In this study, 201TI and 99mTc-MIBI accumulation and response to chemotherapy, in the same patients with bone and soft-tissue lesions, were evaluated and lesion perfusion by radionuclide angiography with 99mTc-MIBI was assessed.

MATERIALS AND METHODS

Patients

The study comprised 42 patients with various bone and soft-tissue disorders proven pathologically in specimens obtained by biopsy and/or surgery. There were 21 men and 21 women (age range 8–87 yr; average age 47 ± 21 yr). Twenty-nine had malignant tumors (3 osteosarcomas, 1 parosteal osteosarcoma, 4 chondrosarcomas, 6 malignant fibrous histiocytomas, 1 epitheloid sarcoma, 1 synovial cell sarcoma, 3 malignant schwannomas, 1 myxoid liposarcoma, 1 multiple myeloma, 1 non-Hodgkin's lymphoma, 7 bone metastatic adenocarcinoma) and 13 had benign lesions (1 giant-cell tumor, 2 neurinomas, 2 neurilemmomas, 2 bone cysts (1 with traumatic fracture), 1 enchondroma, 2 abscesses, 1 osteomyelitis, 1 nonspecific lymph node swelling, 1 postchemotherapeutic nonspecific fibrous tissue).

Thallium-201 and Technetium-99m-MIBI Imaging

Planar 3-min 201TI imaging was performed 15 min after intravenous injection of 111 MBq of the radiopharmaceutical with a gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator. Within 1 wk of the 201TI study, radionuclide angiography was performed after injection of 600–740 MBq 99mTc-MIBI with a gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator. Data were acquired every 2 sec for 2 min. Then, planar 3-min 99mTc-MIBI images were obtained 15 min after radionuclide administration.

Image Analysis

Both 201TI and 99mTc-MIBI images were evaluated visually and quantitatively. For visual analysis, two blinded observers evaluated the degree of radionuclide uptake using a five-grade scoring system, with 0 = background activity, 1+ = slight increase in uptake, 2+ = moderate uptake, 3+ = strong uptake but less than heart, 4+ = strong uptake equal to or greater than heart. Radionuclide angiography with 99mTc-MIBI was also evaluated by two blinded observers and the degree of perfusion increase was classified into four grades, with 0 = no increase, 1+ = mild increase, 2+ = moderate increase, 3+ = marked increase in arterial phase.
For quantitative analysis, a manual ROI was set on the lesion and a symmetrical ROI was set on the contralateral normal area. Then, the uptake ratio was calculated by dividing the count density of the lesion by that of the contralateral normal area. In one patient with malignant fibrous histiocytoma adjacent to the spinal process and in a patient with vertebral metastasis, the reference ROI was set on the caudal side of the lesion.

The perfusion index was obtained by radionuclide angiography. Using the same ROI set to calculate the uptake ratio, the time-activity curve of each ROI was generated and the perfusion index was determined by dividing the peak count of the arterial phase of the lesion by that of the contralateral normal side. When a peak count was not obtained, the time-activity curve always showed a shoulder point, which was the ejection point between the rapid count increase due to arterial phase and steady state or gradual count increase due to 99mTc-MIBI accumulation to the lesion and normal tissue. Therefore, the count of the flexion point of the time-activity curve was used to calculate the perfusion index.

### Evaluation of Chemotherapy

Eleven patients with malignant tumors (3 osteosarcomas, 4 malignant fibrous histiocytomas, 1 malignant schwannoma, 2 bone metastasis (adenocarcinoma), 1 synovial cell sarcoma) underwent both pre- and postchemotherapy evaluation on both 99mTc-MIBI and 201Tl imaging. Postoperative histological assessment was performed on these 11 patients to evaluate tumor response to chemotherapy. Histologic grading of the effect of chemotherapy was based on the degree of cellularity and necrosis in the largest slice of the resected tumor. Grade IV (100% necrosis) was considered a complete response and Grade III (>90% to <100% necrosis) was considered a partial response. Grade II and I
responses (≤90% ~ >50% and 90%, respectively) were considered nonresponses.

To evaluate the effect of chemotherapy, percent changes in the perfusion index and uptake ratio (Δ%) were calculated by the following formula:

\[ Δ% = 100 \times \frac{\text{post-pre}}{\text{pre}} \]

where post = postchemotherapy value of perfusion index or uptake ratio and pre = prechemotherapy value of the perfusion index or uptake ratio.

**Statistical Analysis**

Values were presented as mean ± s.d. Statistical comparisons were done using a two-tailed paired Student’s t-test to compare the 201Tl and 99mTc-MIBI uptake ratios and the 99mTc-MIBI perfusion index. For comparisons of the perfusion index and uptake ratios between malignant and benign lesions and between low-grade and high-grade malignant lesions, a two-tailed unpaired Student’s t-test was used. Comparison of proportion was performed with chi-square analysis. A p value of < 0.05 was considered significant.

**RESULTS**

Patient data are summarized in Table 1 for malignant and benign lesions, respectively. Visual analysis of 31 of 42 patients showed similar uptake for both tracers, 8 (6 malignant and 2 benign lesions) showed more intense uptake of 99mTc-MIBI than 201Tl and 3 (all malignant lesions) showed more intense uptake of 201Tl than 99mTc-MIBI. In a patient with osteosarcoma (Patient 2), bone marrow extension was detected only with 99mTc-MIBI. A malignant fibrous histiocytoma in Patient 10 was detected by 99mTc-MIBI only, while a malignant schwannoma in Patient 18 was detected by 201Tl only. In 29 malignant lesions, 6 lesions (2 chondrosarcoma, 1 malignant fibrous histiocytoma, 1 myxoid liposarcoma, 1 malignant schwannoma, 1 vertebral bone metastatic adenocarcinoma) were not visualized on either 99mTc-MIBI or 201Tl images. In benign lesions, all inflammatory lesions (2 abscesses, 1 osteomyelitis) and a giant-cell tumor showed intense uptake on both 99mTc-MIBI and 201Tl images. A chondrosarcoma and a neurinoma in one patient each were detected only with radionuclide angiography.

Technetium-99m-MIBI background activity around the lesion was visually higher than 201Tl in 17 patients, equal to 201Tl in 19 patients and lower than 201Tl in 6 patients. In lung uptake of both tracers, each pattern was observed in 22, 17 and 3 patients, respectively.

In all patients, uptake ratios of 99mTc-MIBI and 201Tl were similar (1.96 ± 1.02 versus 1.96 ± 1.25; p = ns). Uptake ratios of 99mTc-MIBI in malignant and benign lesions were 2.01 ± 0.99 and 1.82 ± 1.11, respectively, and were similar to those of 201Tl (2.09 ± 1.34 and 1.65 ± 1.02, respectively; p = ns). In all patients, the perfusion index derived from dynamic 99mTc-MIBI study was 2.33 ± 1.23 and was significantly higher than that of the 99mTc-MIBI uptake ratio (1.96 ± 1.02; p < 0.005) and 201Tl uptake ratio (1.96 ± 1.25; p < 0.05). In malignant lesions, the 99mTc-MIBI perfusion index (2.36 ± 1.13) was higher than the 99mTc-MIBI uptake ratio (2.01 ± 0.99; p < 0.05) and 201Tl uptake ratio (2.09 ± 1.34; p = 0.19) but the difference was not significant between 99mTc-MIBI perfusion index and 201Tl. In benign lesions, the 99mTc-MIBI perfusion index (2.28 ± 1.48) was significantly higher than the 99mTc-MIBI uptake ratio (1.82 ± 1.11; p < 0.05) and 201Tl uptake ratio (1.65 ± 1.02; p < 0.01). Good correlation was obtained between the 201Tl and 99mTc-MIBI uptake ratios (r = 0.89), and fair ones were obtained between 201Tl uptake ratio and 99mTc-MIBI perfusion index (r = 0.70) and between the 99mTc-MIBI uptake ratio and perfusion index (r = 0.75) (Fig. 1).

Malignant lesions were not differentiated from benign lesion in both tracers (in malignant and benign lesions, respectively: perfusion index: 2.36 ± 1.13 versus 2.28 ± 1.48; 99mTc-MIBI uptake ratio: 2.01 ± 0.99 versus 1.82 ± 1.11; 201Tl uptake ratio: 2.09 ± 1.34 versus 1.65 ± 1.02). In 20 primary malignant lesions, both tracers did not accumulate in three of five low-grade tumors but did not accumulate in only three of 15 high-grade tumors, however, this was not significant (p = 0.01). There were no significant differences between low-grade and high-grade tumors in the perfusion index (1.61 ± 0.59 versus 2.35 ± 1.08), the 99mTc-MIBI uptake ratio (1.66 ± 1.23 versus 1.87 ± 0.78) and the 201Tl uptake ratio (1.60 ± 0.90 versus 1.86 ± 1.01).

Changes in the perfusion index and uptake ratios of 99mTc-MIBI and 201Tl before and after chemotherapy are shown in Table 2. In all patients with a pathological complete response, the perfusion index and uptake ratio of both tracers decreased significantly to 1.2 or less after chemotherapy. On the other hand, in patients with pathological nonresponse, neither the perfusion index nor uptake ratio decreased to 1.2 or less. As shown in Figure 2, good correlation was observed between the percent change in 99mTc-MIBI and 201Tl uptake ratios as well as fair correlation between the percent change in the 99mTc-MIBI perfusion index in 201Tl uptake ratio (r = 0.83 and r = 0.69, respectively). The percent change in the 99mTc-MIBI uptake ratio and 99mTc-MIBI perfusion index also showed good correlation (r = 0.80). In all three patients with complete response, the percent change in 99mTc-MIBI and 201Tl uptake ratios was less than −50%. On the other hand, in all six patients with nonresponse, the percent change in both 99mTc-MIBI and 201Tl uptake ratios was more than −20%.

Representative patients are shown in Figures 3, 4 and 5. Figure 3 compares the 201Tl and 99mTc-MIBI images in a 67-yr-old woman with malignant fibrous histiocytoma of the...
right distal femur. Radionuclide angiography revealed a hyper-vascular lesion. Both $^{201}$TI and $^{99m}$Tc-MIBI demonstrated intense tracer uptake. The edge of the tumor was delineated slightly more sharply with $^{99m}$Tc-MIBI than with $^{201}$TI.

Figure 4 shows an 8-yr-old boy with osteosarcoma in the right proximal humerus (Patient 2). Markedly increased tumor perfusion was demonstrated by radionuclide angiography with $^{99m}$Tc-MIBI. Although both $^{99m}$Tc-MIBI and $^{201}$TI scintigraphy demonstrated increased uptake in the right proximal humerus, only $^{99m}$Tc-MIBI scintigraphy disclosed bone marrow extension to the humeral shaft. After chemotherapy, no significant increased tumor perfusion or $^{99m}$Tc-MIBI or $^{201}$TI accumulation was observed. The surgical specimen revealed complete tumor necrosis.

Figure 5 shows a 72-yr-old woman with non-Hodgkin’s lymphoma on the left buttock (Patient 29). Technetium-$^{99m}$MIBI showed stronger uptake than $^{201}$TI, but the $^{99m}$Tc-MIBI uptake ratio was lower than $^{201}$TI due to high background uptake.

**DISCUSSION**

Generally, bone, $^{67}$Ga and $^{201}$TI scintigraphy have been used to evaluate bone and soft-tissue lesions. Bone scintigraphy is quite sensitive for the detection of primary bone tumors as well as bone involvement by adjoining soft-tissue malignant tumors or metastasis. However, in defining the accurate extent of the tumor, $^{201}$TI scintigraphy is more helpful than bone scintigraphy, even in the case of primary bone tumors. In addition, $^{201}$TI scintigraphy is superior to bone scintigraphy and $^{67}$Ga imaging in predicting tumor response to chemotherapy (16,17).

Recently, $^{99m}$Tc-MIBI has been introduced as a myocardial perfusion imaging agent to replace $^{201}$TI. Technetium-$^{99m}$MIBI has lipophilic cationic properties, accumulating largely in mitochondria by its negative transmembrane potential. Moreover, its accumulation depends on cell viability and metabolic conditions (18–20). In human carcinoma cell lines, mitochondria and plasma membrane potentials may also contribute to $^{99m}$Tc-MIBI uptake, and carcinoma cells accumulate $^{99m}$Tc-MIBI like myocardial cells (21,22). In addition, high-level expression of p-glycoprotein that is encoded by multidrug-resistance gene restricts $^{99m}$Tc-MIBI uptake in animal and human cell lines (23–25). Thallium-201 accumulation in a tumor largely depends on the sodium-potassium pump activity and, to some extent, tumor blood flow (26,27). Despite these suggested differences in uptake mechanisms, accumulation of $^{201}$TI and $^{99m}$Tc-MIBI in various tumors was broadly similar to that reported in previous studies (8–10). Aktolun et al. (8) compared $^{99m}$Tc-MIBI and $^{201}$TI uptake in 17 patients with malignant tumors, mainly lung and breast cancer, and found that both tracers accumulated in tumors except for one patient with breast cancer, in whom tumors were detected only by $^{99m}$Tc-MIBI. In six patients with brain tumors, O’Tuama et al. (10) showed that both $^{99m}$Tc-MIBI and $^{201}$TI accumulated similarly, but the tumor-to-normal brain ratio was higher with $^{99m}$Tc-MIBI. In this study, 31 of 42 patients showed visually similar accumulation of both tracers, but eight showed greater $^{99m}$Tc-MIBI accumulation and three showed greater $^{201}$TI uptake. The lesion-to-contralateral normal side uptake ratio of all patients was similar for $^{99m}$Tc-MIBI (1.96 ± 1.02) and $^{201}$TI (1.96 ± 1.25), and for good correlation was observed between the uptake ratios of both tracers (r = 0.89), suggesting that similar factors were involved in the uptake of both tracers by lesions in spite of different cellular uptake mechanisms.

The uptake of both $^{99m}$Tc-MIBI and $^{201}$TI tended to be higher in malignant lesions but not significantly so. In our experience

**TABLE 2**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Diagnosis</th>
<th>$^{99m}$Tc-MIBI perfusion index</th>
<th>$^{99m}$Tc-MIBI uptake ratio</th>
<th>$^{201}$TI uptake ratio</th>
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<td></td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>% change</td>
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<tr>
<td>1</td>
<td>Osteosarcoma</td>
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<td>2.09</td>
<td>−15</td>
</tr>
<tr>
<td>2</td>
<td>Osteosarcoma</td>
<td>1.99</td>
<td>1.12</td>
<td>−44</td>
</tr>
<tr>
<td>3</td>
<td>Osteosarcoma</td>
<td>3.33</td>
<td>1.00</td>
<td>−70</td>
</tr>
<tr>
<td>9</td>
<td>Malignant fibrous histiocytoma</td>
<td>2.84</td>
<td>5.35</td>
<td>+88</td>
</tr>
<tr>
<td>10</td>
<td>Malignant fibrous histiocytoma</td>
<td>1.83</td>
<td>1.73</td>
<td>−5</td>
</tr>
<tr>
<td>12</td>
<td>Malignant fibrous histiocytoma</td>
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<td>1.93</td>
<td>−45</td>
</tr>
<tr>
<td>13</td>
<td>Malignant fibrous histiocytoma</td>
<td>3.58</td>
<td>1.82</td>
<td>−49</td>
</tr>
<tr>
<td>16</td>
<td>Synovial cell sarcoma</td>
<td>2.50</td>
<td>1.20</td>
<td>−52</td>
</tr>
<tr>
<td>19</td>
<td>Malignant schwannoma</td>
<td>1.18</td>
<td>1.26</td>
<td>+7</td>
</tr>
<tr>
<td>23</td>
<td>Metastatic adenocarcinoma</td>
<td>2.94</td>
<td>1.79</td>
<td>−39</td>
</tr>
<tr>
<td>25</td>
<td>Metastatic adenocarcinoma</td>
<td>4.06</td>
<td>4.65</td>
<td>+15</td>
</tr>
</tbody>
</table>

FIGURE 2. Changes in uptake ratio and perfusion index after chemotherapy. There are good correlations between percent changes in $^{201}$TI and $^{99m}$Tc-MIBI uptake ratios and between $^{99m}$Tc-MIBI uptake ratio and perfusion index. There is fair correlation between percent changes in $^{201}$TI uptake ratio and of $^{99m}$Tc-MIBI perfusion index.
from this study and from our previous $^{201}$TI study, we feel that the differentiation of malignant from benign lesions should be carefully judged because tracer uptake depends on several factors, including blood flow, proportion of viable parenchymal tumor cell component to stromal tissue and presence of tumor necrosis. For example, giant-cell tumors ($n = 11$) always showed intense $^{201}$TI uptake (we have only one patient studied with $^{99m}$Tc-MIBI) and malignant schwannoma and chondrosarcoma usually showed poor or low $^{201}$TI and $^{99m}$Tc-MIBI uptake.

Since $^{99m}$Tc-MIBI is a technetium-labeled radiopharmaceutical, administration of a sufficient dose for radionuclide angiography is possible. Therefore, tumor blood flow can be assessed simultaneously as well as $^{99m}$Tc-MIBI tumor uptake. Additional information on blood flow may be useful in some patients. For example, in Patient 8 with chondrosarcoma, only radionuclide angiography detected the lesion, and in Patient 5 with chondrosarcoma, both tracers showed faint uptake. However, radionuclide angiography showed an obviously hypervascular lesion, suggesting a malignant tumor. As shown in Figure 1, a significant correlation was observed between perfusion index and $^{99m}$Tc-MIBI uptake ratio although it was not a rigid correlation, suggesting that perfusion was not the sole determinant of tracer uptake.

In the evaluation of tumor response to chemotherapy, several modalities are used, including CT, MRI, angiography and radionuclide imaging. Although tumor size can be evaluated well by CT and MRI, estimation of residual tumor cell viability is somewhat difficult. In radionuclide imaging, Ramanna et al. (16) reported that $^{201}$TI was superior to gallium and bone.
scintigraphy, and Caner et al. (17) showed that 99mTc-MIBI was superior to bone scintigraphy in the assessment of residual tumor viability. In this study, both 201Tl and 99mTc-MIBI uptake ratios could evaluate tumor response to chemotherapy precisely and equally. In addition, radionuclide angiography with 99mTc-MIBI might provide more objective information about tumor blood flow by quantification, whereas quantification of blood flow is difficult in conventional angiography with contrast media. In this study, the percent change in the perfusion index overestimated tumor response to chemotherapy in two patients with pathological nonresponse, although in both patients (Patients 12 and 23), postchemotherapeutic perfusion indices were still high (1.93 and 1.79), suggesting presence of hyperperfused residual tumor. Consequently, we believe that 99mTc-MIBI imaging deserves to be considered one of the best methods for evaluating tumor response to chemotherapy.

When the lesion is located in the pelvic or abdominal area, 99mTc-MIBI uptake might be significantly affected by bladder or gastrointestinal uptake. In these areas, 201Tl may be favorable because of the lower activity of the abdominal and pelvic organs. In case of disuse atrophy of the extremities due to pain or other factors, careful interpretation of uptake ratio and perfusion index are needed because muscle tracer uptake of both extremities may differ significantly and may affect these quantitative data. As shown in Figure 5, both original images and quantitative data should be always interpreted simultaneously because the uptake ratio affected significantly by the background activity in some patients.

CONCLUSION

This study revealed that 99mTc-MIBI has similar potential compared with 201Tl for detecting bone and soft-tissue lesions, but both tracers could not delineate benign from malignant lesions. Due to the high dose of 99mTc-MIBI administered, the degree of blood flow can be evaluated by radionuclide angiography, which is difficult in 201Tl scintigraphy. In addition, 99mTc-MIBI scintigraphy accurately assessed tumor response to chemotherapy as did 201Tl. Technetium-99m-MIBI scintigraphy is a promising method for evaluating bone and soft-tissue lesions, including detection and therapeutic response.

REFERENCES