Sixth Conference on Radioimmunodetection and Radioimmunotherapy of Cancer

Supplement to ***Cancer***

Comparison of Technetium-99m Sestamibi and Indium-111 Octreotide Imaging in a Patient with Ewing's Sarcoma before and after Stem Cell Transplantation

Francis J. Giles, M.D.[1]
Alan D. Waxman, M.D.[2]
Kim N. Nguyen, M.D.[2]
Marie P. Fuerst, R.N.[1]
Donato A. Kusuanco[1]
Mercedes M. Franco, M.D.[1]
Howard Bierman, M.D.[1]
Stephen W. Lim, M.D.[1]

[1] Stem Cell/Bone Marrow Transplantation Program, Division of Hematology/Oncology, Department of Medicine, Cedars-Sinai Medical Center, University of California Los Angeles School of Medicine, Los Angeles, California.

[2] Department of Imaging Services, Cedars-Sinai Medical Center, Los Angeles, California.

Presented at the Sixth Conference on Radioimmunodetection and Radioimmunotherapy of Cancer, Princeton, New Jersey, October 10–12, 1996.

Address for reprints: Stephen W. Lim, M.D., University of California/Irvine Cancer Center, 101 City Drive South, Route 81, Building 23, Room 244, Orange, CA 92868.

Received August 12, 1997; accepted September 5, 1997.

BACKGROUND. We report the use of two novel nuclide agents, Technetium-99m (^{99}Tc)sestamibi (MIBI) and indium-111 (In-111) octreotide, in comparison with conventional computed tomography (CT) imaging in a patient with metastatic Ewing's sarcoma (ES) before and after high dose chemotherapy with autologous peripheral stem cell transplantation (PSCT). MIBI is taken up actively by metabolically active tumor cells. Octreotide, a somatostatin analog, binds specifically to somatostatin receptors.

METHODS. The patient was a 20-year-old male with recurrent metastatic ES to the lung. Before and sequentially after high dose chemotherapy and PSCT, the patient was imaged with MIBI. Whole body planar and single photon emission computed tomography (SPECT) images were obtained after the injection of 30 mCi of ^{99}Tc MIBI. Prior to PSCT the patient was imaged with 6 mCi In-111 pentreotide.

RESULTS. Conventional CT scans also were performed. Initial CT revealed pulmonary metastasis in the right lower lobe along with multiple left pleural-based lesions. These lesions were visualized clearly with MIBI. Octreotide detected only the left lung involvement. Sequential MIBI scans after PSCT correlated with tumor reduction in the right lung field and tumor progression in the left lung as well as the development of new pulmonary metastasis. These findings were confirmed on CT.

CONCLUSIONS. MIBI imaging was highly concordant with CT scanning in the detection of metastatic ES. MIBI scanning holds promise for the direct detection of a variety of human malignancies, and may prove useful as a rapid whole body imaging modality.
Cancer **1997;80:2478–83.**

KEYWORDS: Ewing's sarcoma, MIBI, octreotide, stem cell transplantation.

Ewing's sarcoma (ES) is the second most common bone tumor of the young, with 90% of cases occurring before age 30 years.[1] Patients present with disease primarily in the axial skeleton, but it may involve any bone. Current management is comprised of a combination of chemotherapy, surgery, and radiation therapy. Survival has improved with significant disease free survival of 55% at 69 months.[2] Metastasis is primarily hematogenous, most commonly to lung and bone. As therapy evolves, more accurate assessment techniques are needed for baseline staging, to determine response to preoperative chemotherapy, and to monitor for early recurrence.

Imaging of ES traditionally is comprised of plain radiographs, computed tomography (CT), radionuclide studies,[1] and more re-

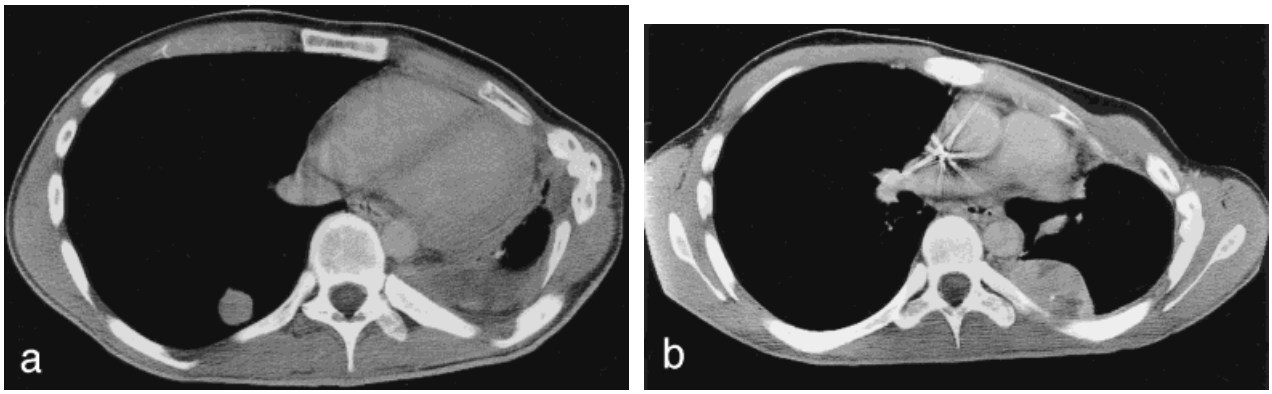

FIGURE 1. Computed tomography scans of the chest revealed a 2.5-cm right lower lobe mass with multiple pleural-based nodules along the posterior and left lateral pleural surfaces consistent with metastatic disease.

cently, magnetic resonance imaging (MRI).[3–5] Newer nuclide modalities for imaging in oncology include indium-111 (In-111) octreotide[6] and Technetium-99m (^{99}Tc) sestamibi (MIBI).[7] Octreotide, a somatostatin analog, has been found to image various APUD-derived tumors along with breast carcinoma and lymphomas.[8] MIBI, initially used in myocardial perfusion studies, also has been found to image human malignancies.[7] We report the use of octreotide and MIBI imaging compared with traditional CT scanning in a patient with metastatic ES performed before and after high dose chemotherapy followed by autologous peripheral stem cell transplantation (PSCT).

Case History

The patient was a 20-year-old male who was diagnosed with ES involving his right femur in June of 1988. He underwent therapy with cyclophosphamide, vincristine, methotrexate, and doxorubicin, followed by radiation therapy and surgical resection with placement of a titanium prosthesis. He then received adjuvant cyclophosphamide for four cycles. He did well, but the disease recurred in June of 1992 with pulmonary metastasis. This was treated with six cycles of etoposide, high dose ifosfamide, and radiation therapy, followed by surgical resection of the residual pulmonary lesions. The patient had a second recurrence with a malignant pleural effusion. He received carboplatin from June 1993 to November 1993 and radiation therapy from January 1994 to March 1994.

CT scans of the chest in August 1994 revealed a 2.5-cm right lower lobe mass as well as multiple pleural-based nodules along the posterior and left lateral pleural surfaces consistent with metastatic disease (Fig. 1). Whole body planar images using a dual detector Anger camera in anterior and posterior views along with triple-detector single photon emission computed tomography (SPECT) images were obtained after the injection of 30 mCi of ^{99}Tc MIBI. MIBI demonstrated multiple focal areas of increased uptake, with one focal area in the right lower chest and three foci in the left lung (Fig. 2), which corresponded to the findings on CT. Whole body planar images were obtained in the anterior and posterior views at 24 and 48 hours after injection of 6 mCi In-111 pentreotide. SPECT images of the chest also were obtained. This study demonstrated two areas of faintly increased uptake in the left lung (Fig. 3) and a focal area of increased uptake in the right upper thigh (not shown). Both octreotide and MIBI correlated with the CT findings, but SPECT MIBI was more strongly concordant.

The patient received high dose etoposide priming chemotherapy in August 1994 with subsequent peripheral stem cell collection. He then underwent myeloablative conditioning therapy with doxorubicin, ifosfamide, mesna, and carboplatin followed by stem cell reinfusion. He recovered his peripheral cell count without event.

A repeat MIBI scan performed in December 1994, 4 months after transplantation, showed decreased uptake in the left chest (Fig. 4). Repeat MIBI scanning February 1995 revealed increased intensity of the previously reported uptake in the left lung as well as new focal sites of uptake (Fig. 6). This correlated with a chest CT that showed no significant change in the right lower lung zone nodule but an increase in the left lung mass and new metastatic left lung lesions (Fig. 5).

DISCUSSION

ES is a common malignant tumor of bone primarily affecting those age $<$ 30 years.[1] With the advent of

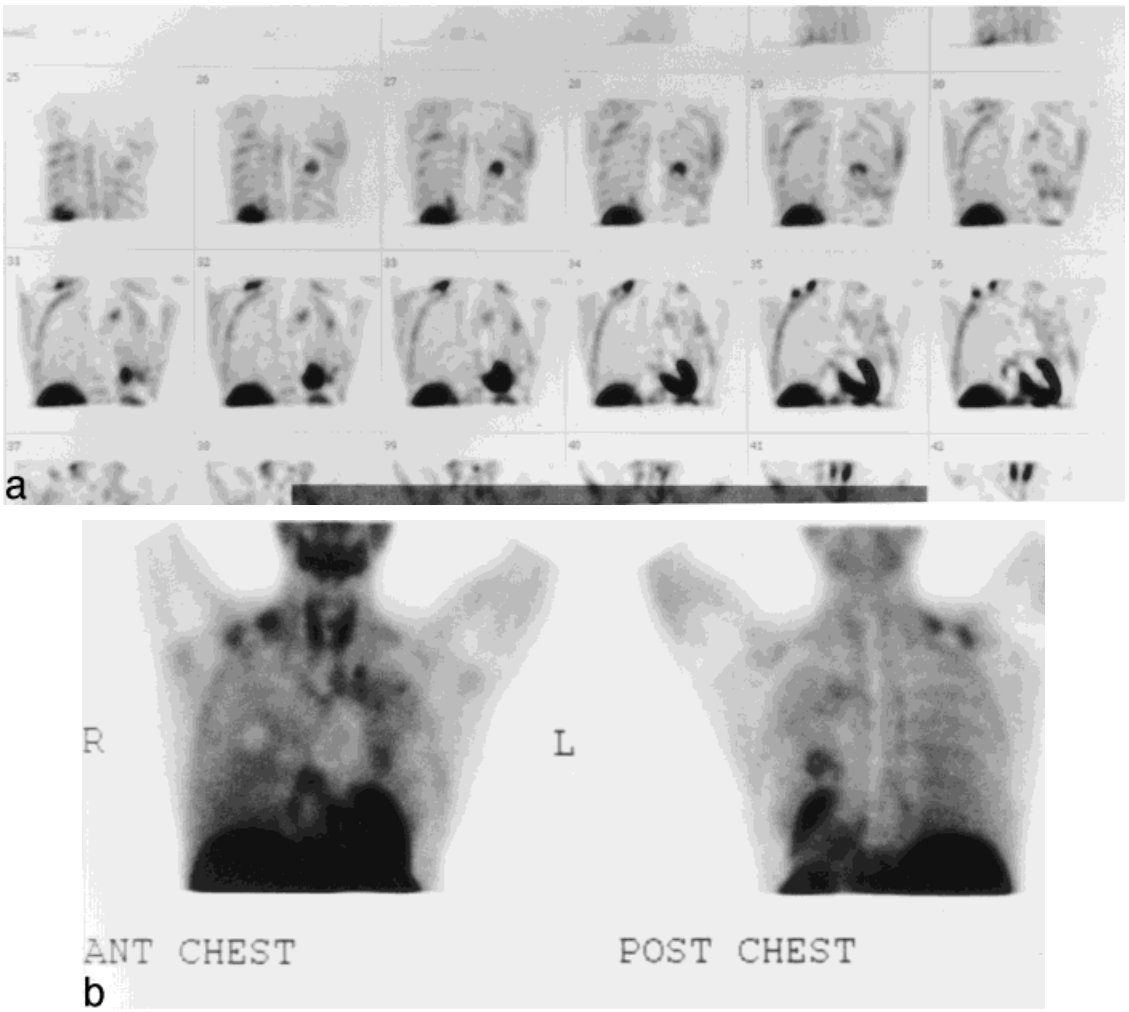

FIGURE 2. Technetium-99m sestamibi demonstrated multiple focal areas of increased uptake, with one focal area in the right lower chest and three foci in the left lung.

multimodality therapy, survival, even with metastatic disease, has improved.[2] Imaging of ES traditionally has utilized plain radiographs, CT scanning, and bone scan. MRI often is used to complement CT imaging.[5] In the initial diagnosis, plain radiographs often reveal the classic diaphyseal lytic tumor with lamellated or ''onion skin'' periosteal reaction.[9] CT then is used to define the tumor, both in size and anatomic location. ^{99}Tc phosphate bone scintigraphy also may demonstrate tumor involvement of bone.[1] Bone scans fail to give accurate information regarding initial therapeutic response because they remain abnormal throughout the osseous healing phase after treatment. Because the initial response to chemotherapy is a prognostic factor,[10] more sensitive imaging modalities are needed to assess the efficacy of the presurgical therapy. Sensitive as well as specific techniques also are needed in the surveillance of recurrent disease.

In addition to traditional technetium bone scan agents and gallium, other radiopharmaceuticals are being investigated in the imaging of malignant disorders. Two of these new agents are MIBI and octreotide. MIBI is a radionuclide agent currently used primarily to assess myocardial perfusion. Noncardiac uses of MIBI are under increasing study. Recent reports have shown that MIBI is preferentially taken up in carcinoma cells lines versus normal cell lines and it has been shown to accumulate within the mitochondria and cytoplasm of cells.[11] Malignant tumors maintain higher (more negative) mitochondrial and cytoplasmic transmembrane potentials than normal cells and thus have increased metabolic demands. The increased

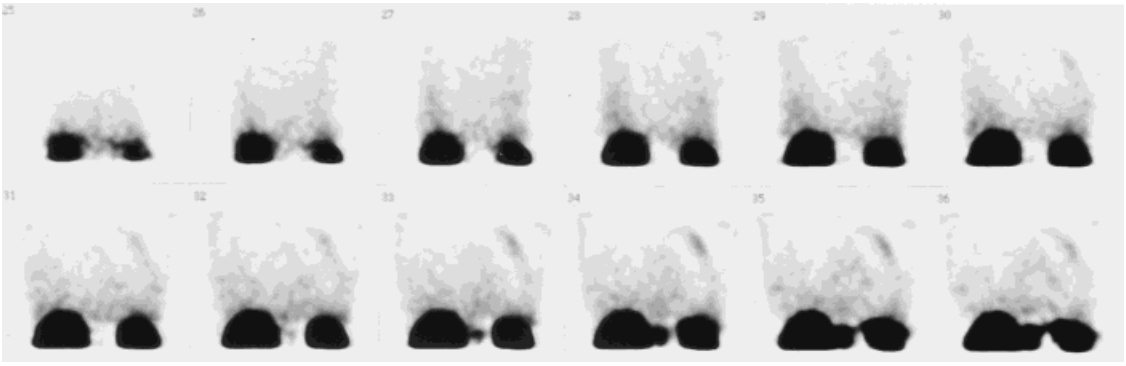

FIGURE 3. Single photon emission computed tomography demonstrated two areas of faintly increased uptake in the left lung.

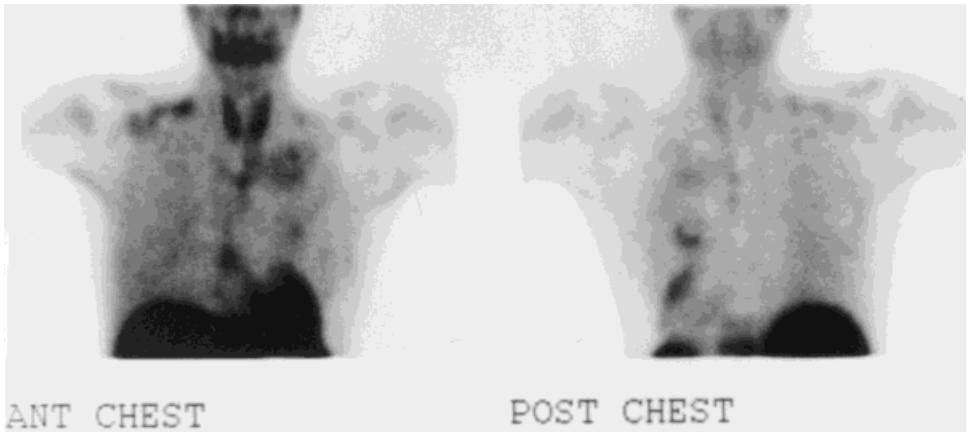

FIGURE 4. A repeat technetium-99m sestamibi scan performed 4 months after transplantation showed decreased uptake in the left chest.

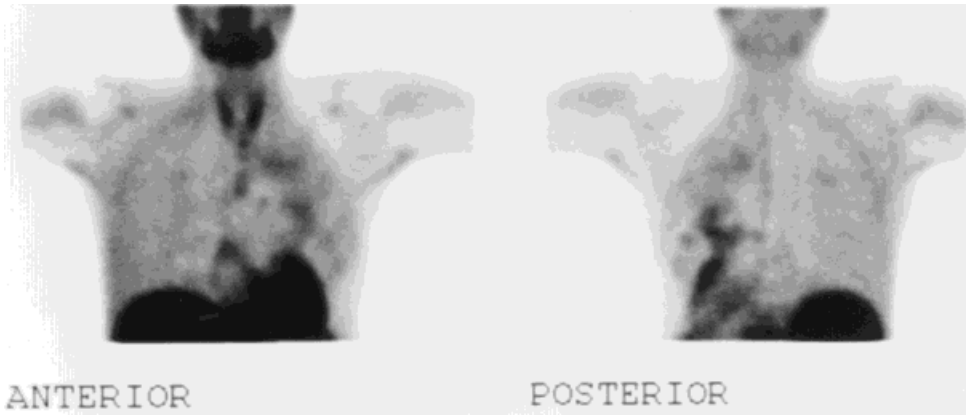

FIGURE 5. A chest computed tomography scan showed no significant change in the right lower lung zone nodule but an increase in the left lung mass and new metastatic left lung lesions.

metabolic demand of tumor cells may promote MIBI uptake. MIBI has been shown to be taken up by various malignant tumors, including breast carcinoma, malignant thymoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, thyroid papilloma, and lung carcinoma.[7] We recently demonstrated that MIBI uptake was concordant with disease activity before and after high dose chemotherapy and stem cell transplantation in a patient with multiple myeloma.[12] With respect to bone lesions, the uptake by malignant bone lesions is greater than that of benign bone lesions.[13] In a study by Aktolun et al., MIBI was believed to be more sensitive for the detection of viable tumor than thallium-201.[7]

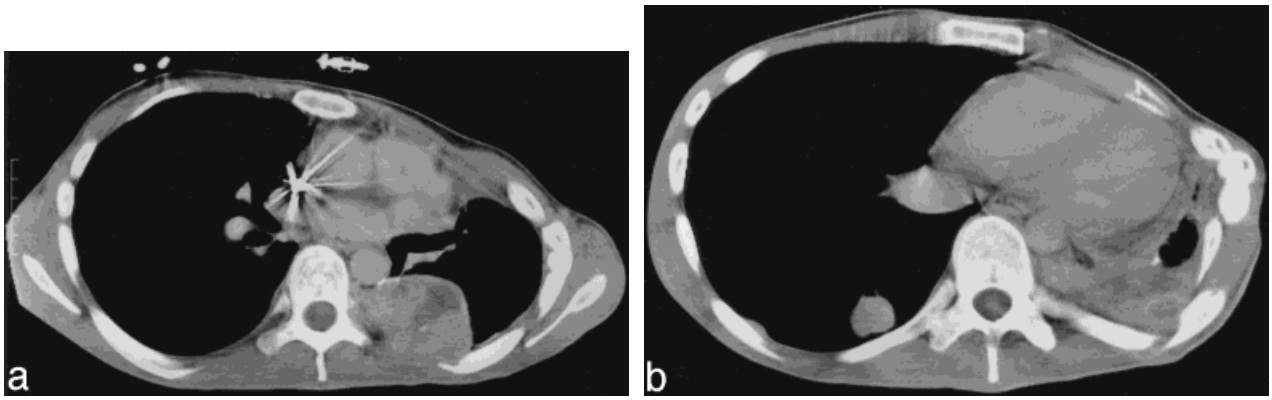

FIGURE 6. Repeat technetium-99m sestamibi scan revealed increased intensity of the previously reported uptake in the left lung as well as new focal sites of uptake.

Octreotide, an eight-peptide somatostatin analog, also has been shown to be able to image various human neoplasms, especially neuroendocrine tumors (i.e., growth hormone and thyrotropin-producing tumors) endocrine gastroenteropancreatic tumors, paragangliomas, pheochromocytomas, medullary thyroid carcinomas, and small cell lung carcinomas.[8] Other tumors that contain somatostatin receptors (SSR) include malignant lymphomas, several brain tumors, and breast carcinoma. The ability to detect these tumors radiographically correlates with the presence of SSR in vitro.

In the patient presented in the current study with known recurrent metastatic ES, staging chest radiograph and chest CT revealed metastatic pulmonary disease. MIBI planar and MIBI SPECT were concordant with CT, demonstrating metastatic lesions in the right and left lungs. After stem cell transplant, MIBI remained concordant, demonstrating tumor regression both immediately after high-dose therapy and then eventually with tumor progression. Despite ES being considered a neuroendocrine tumor, the octreotide scan was less concordant than MIBI scans. This may be due to either the lack of SSR on the relatively poorly differentiated tumor or if there are SSR, they may be of the lower affinity SSR-2 type.[14]

There has been significant progress in the management of ES, both with the use of multimodality therapy and more recently with high dose myeloablative chemotherapy followed by stem cell support.[15] Because of this, improved imaging techniques are needed to better determine the tumor burden at initial diagnosis, the response to preoperative chemotherapy, a prognostic factor,[10] and for the detection of early recurrence. In our patient, MIBI was most concordant with disease both before and after autologous PSCT. MIBI may prove useful in the development of a noninvasive imaging technique to determine tumor viability before and after therapy.

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