

# Technetium-99m-Sestamibi Scanning in Recurrent Medullary Thyroid Carcinoma

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The presence of recurrent medullary thyroid carcinoma (MTC) can be detected early by measurement of serum calcitonin levels, but the localization of recurrent tumors is often difficult. **Methods:** We compared  $^{99m}\text{Tc}$ -sestamibi scans with computed tomographic (CT) scans in 10 patients with recurrent MTC, who had basal serum calcitonin values ranging from 220–61800 ng/liter. Two patients additionally had bone scans performed because of the clinical suspicion of bone metastases. **Results:** Seven of the 10 patients had at least one site of abnormal  $^{99m}\text{Tc}$ -sestamibi uptake, and all of these patients had basal serum calcitonin values  $>6000$  ng/liter. Only five of the 10 patients had abnormal CT scans. Technetium-99m-sestamibi scans detected 22 abnormal sites in the soft tissues of the neck and chest, while CT scans detected only 11 lesions in the neck and chest. Five of these sestamibi positive sites (in the neck and mediastinum of one patient) were confirmed histologically to represent MTC. When imaging the liver, CT scans detected 47 lesions in three patients while  $^{99m}\text{Tc}$ -sestamibi scans detected none. One of these liver lesions was confirmed as MTC histologically. When imaging bone in two of the patients, the bone scans detected 17 abnormal sites, while  $^{99m}\text{Tc}$ -sestamibi scans detected six abnormal sites. **Conclusion:** Technetium-99m-sestamibi scans complement CT and bone scans in the localization of recurrent MTC in patients with extremely high calcitonin levels. Technetium-99m-sestamibi scans are more sensitive than CT scans in the assessment of the soft tissues of the neck and chest, but CT is more appropriate for imaging hepatic lesions and bone scans are better for imaging bone lesions. Technetium-99m-sestamibi scans are unlikely to be abnormal in patients with only mild elevation of calcitonin.

**Key Words:** technetium-99m-sestamibi; computed tomography; bone scan; medullary thyroid carcinoma

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Medullary thyroid carcinoma (MTC) accounts for 5%–10% of all differentiated thyroid cancers (1). MTC may be sporadic in 75% of cases or occur as part of the inherited cancer syndromes multiple endocrine neoplasia type 2 and familial MTC in 25% of cases (1).

Approximately 35% of MTCs will have local lymph node spread at the time of diagnosis, and 50% will develop recurrent disease (2). The optimal mode of treatment for both the primary tumor and recurrence is surgery (3). While elevation of serum calcitonin and carcinoembryonic antigen (CEA) levels are used to demonstrate the presence of recurrent or residual disease, the preoperative localization of tumor tissue is problematic (4).

Imaging methods used to localize MTC include: ultrasound, CT, selective venous catheterization (SVC), MRI and radionuclide scanning, each of which has its limitations (5–9). Several radionuclide tracers have been used, but studies report small numbers and have shown poor sensitivity and/or specificity (6). These agents include  $^{201}\text{Tl}$ -chloride,  $^{131}\text{I}$ -MIBG,  $^{99m}\text{Tc}$  pen-

tavalent DMSA, labeled monoclonal antibodies, labeled somatostatin receptors and  $^{99m}\text{Tc}$ -sestamibi (6–9).

Technetium-99m-sestamibi is a radiopharmaceutical which has been used widely in the imaging of cardiac muscle (10) and parathyroid adenomas (11,12), but there are few reports of its use in MTC (9,13).

We report an evaluation of  $^{99m}\text{Tc}$ -sestamibi scanning in comparison to CT in 10 patients with recurrent MTC. We define a threshold of serum calcitonin above which the  $^{99m}\text{Tc}$ -sestamibi scan is likely to be positive and also define the sites of MTC recurrence where  $^{99m}\text{Tc}$ -sestamibi scanning is more sensitive than CT.

## MATERIALS AND METHODS

Ten patients (6 women, 4 men; age 21–76 yr; mean age 51 yr) with either sporadic or inherited MTC were studied. All patients underwent total thyroidectomy 1–20 yr previously with or without a local lymph node clearance. All patients had suspected MTC recurrence on the basis of elevated basal calcitonin values. The clinical residual disease varied from undetectable to extensive. Clinical data are summarized in Table 1.

CT scans of the neck and chest were performed in all patients. Seven patients also had views of the upper abdomen performed. The scans included 5 mm contiguous contrast scans through the neck and upper mediastinum. All CT scans were reviewed by the same radiologist and by at least one other independent radiologist.

All patients underwent scintigraphic studies using  $^{99m}\text{Tc}$ -sestamibi. An anterior view of the chest (300 sec) followed by anterior and posterior whole-body sweeps (12 min/meter) was performed in each patient, beginning 15 min after 800 MBq  $^{99m}\text{Tc}$ -sestamibi injection. A SPECT scan of the chest and neck was then performed (360°, 64 steps, 25 sec each, elliptical orbit). If an abnormality was identified on planar views in a region other than the neck and chest, a SPECT study of that region was considered. All images were acquired on a single-head gamma camera equipped with a high-resolution, parallel-hole collimator and interfaced to a nuclear medicine computer. All images were interpreted qualitatively by two experienced nuclear medicine physicians blinded to the clinical history and the results of other investigations. A consensus approach was used in the event of equivocal studies. Technetium-99m-sestamibi and CT studies were then reviewed together, and a comparison was made of the sites of abnormality. Two patients in the series underwent bone scanning. Whole-body planar images were obtained on the same camera and performed 3–4 hr after 800 MBq  $^{99m}\text{Tc}$ -methylene diphosphonate (MDP) injection.

Basal calcitonin values were measured by a commercially available enzyme-linked immunoassay. The normal range in this assay is  $<20$  ng/liter.

The chi-square statistic was used to compare  $^{99m}\text{Tc}$ -sestamibi scanning with CT for the number of lesions detected in the soft tissues of the neck and chest. The difference was considered significant for  $p < 0.05$ .

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**TABLE 1**  
Clinical Data

Patient no.	Basal calcitonin (ng/liter)	Extent of surgery and/or radiotherapy*	Clinical features	CT scan results (Lesions)	<sup>99m</sup> Tc-sestamibi results (Sites)
1	220	Reoperation to neck and mediastinum	N	N	N
2	308		N	N	N
3	5340	Two neck dissections	N	N	N
4	6240	Reoperation to neck and mediastinum† (9 × 2-cm mass of 12 MTC-containing nodes removed from mediastinum)	1-cm R neck node	R neck-1 cm normal mediastinum	Two in neck Three in mediastinum
5	7500		N	N	One in central neck
6	10000	L hepatic resection† (4 cm MTC lesion)	R and L axillary nodes	Liver, 2 cm	One in R axilla, 1 in L axilla
7	16000	Mediastinum opened at initial surgery	Known multiple metastases	L neck-1.5 cm, R lung—2 cm; or 30 lesions in liver (1 to 2 cm)	One in L neck, 1 in R lung, 1 in L lung, 3 in mediastinum
8	25400	Radiotherapy to neck and mediastinum	Known multiple metastases	R paratracheal lesion into R superior mediastinum—4 cm	One in R paratracheal region into R superior mediastinum, 1 in L mediastinum, 1 in L hilum
9	31000	Two reoperations to neck radioactive iodine (originally diagnosed as papillary cancer)	N	N	One in L femur, asymmetric parotid uptake
10	61800	Radiotherapy to bony metastases in thoraco-lumbar spine	Known multiple metastases	L supraclavicular lesion-1 cm R and L hilar lesions (2.5 and 2 cm) L neck—1-cm paratracheal lesions (0.8 and 0.9 cm); 16 liver lesions (1-2 cm)	One L supraclavicular R and L hilar sites, one in L axilla, one R parietal site, one R scapular site, one in R shoulder, one in L second rib, one in L1

\*Surgery subsequent to the initial thyroidectomy ± neck dissection in all patients.

†Surgery subsequent to the sestamibi study.

N = no abnormalities detected; R = right; L = left.

## RESULTS

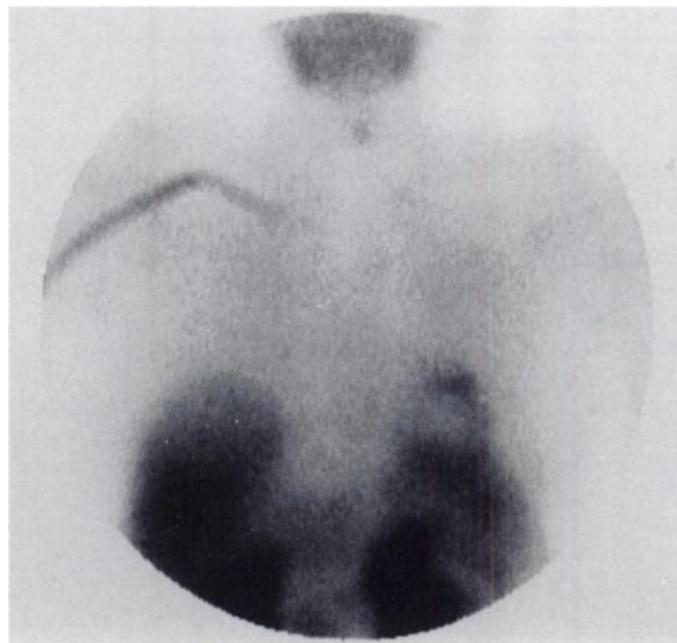
Of the 10 patients studied, seven patients (70%) showed at least one abnormal area on <sup>99m</sup>Tc-sestamibi scanning, compared with five patients (50%) on CT scanning. All of the seven patients with abnormal <sup>99m</sup>Tc-sestamibi scans had biochemical evidence of extensive disease with calcitonin values greater than 6000 ng/liter. Two of these patients had uptake in only one site, and the remaining five patients had uptake in multiple sites. Individual patient data are shown in Table 1. Results are divided according to the location of the abnormalities in either soft tissues, liver or bone.

### Soft Tissue

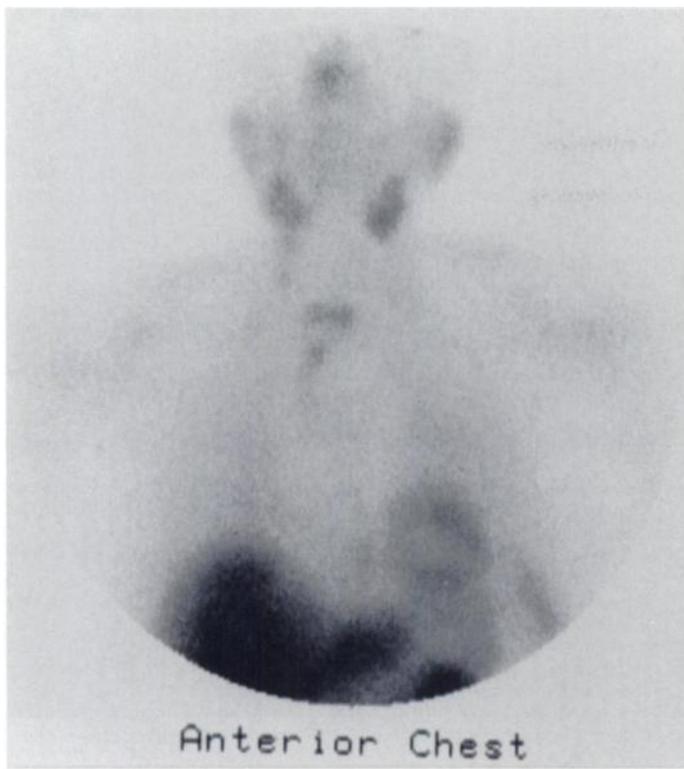
A total of 25 soft-tissue lesions in the neck and chest were detected in six patients on either <sup>99m</sup>Tc-sestamibi or CT scanning. Of these lesions, 14 (56%) were detected only on <sup>99m</sup>Tc-sestamibi imaging, 3 (12%) on CT scanning alone and 8 (32%) using both techniques. For example, <sup>99m</sup>Tc-sestamibi scans detected 22 of 25 soft-tissue sites, while CT scans detected 11 of 25 ( $p < 0.001$ ). Technetium-99m-sestamibi scans detected soft-tissue lesions in five patients in whom CT scans of the same site revealed no abnormality (Figs. 1 and 2). The benefit of <sup>99m</sup>Tc-sestamibi over CT scanning was particularly evident in the mediastinum. Three patients (Patients 4, 7 and 8) had mediastinal sites detected by <sup>99m</sup>Tc-sestamibi but not by CT. In Patient 4, the <sup>99m</sup>Tc-sestamibi scan showed two sites in the neck and three in the mediastinum (Fig. 2), while the CT scan showed only a 1-cm neck lesion. Histological confirmation was obtained when 16 and 12 MTC-containing lymph nodes were removed from the neck and the mediastinum, respectively. The mediastinal mass removed measured 9 cm × 2 cm and included 15 nodes (12 of which contained MTC). CT revealed soft-tissue abnormalities in only one patient (Patient 10) that

were not detected by <sup>99m</sup>Tc-sestamibi imaging, and two of these lesions were <1 cm in diameter.

While SPECT studies were more useful than planar images in defining the exact location of the lesions, no additional lesions were detected by SPECT in the neck and chest in any patient.



**FIGURE 1.** Technetium-99m-sestamibi scan in Patient 5 (a 51-yr-old woman, 13 yr post-thyroidectomy with a calcitonin of 7500 ng/liter) shows the abnormal site in the neck, midline. CT scan was normal.



**FIGURE 2.** Technetium-99m-sestamibi scan in Patient 4 (a 69-yr-old woman, 2-yr post-thyroidectomy with a calcitonin of 6240 ng/liter) shows three mediastinal and two neck sites. CT scan was abnormal only in the neck.

#### Liver

Forty-seven lesions up to 2 cm in diameter were detected by CT in three patients. None of these lesions were identified on  $^{99m}\text{Tc}$ -sestamibi imaging. MTC was confirmed histologically in the liver lesion of Patient 6 who underwent fine-needle aspiration biopsy and then surgical resection of this lesion (which measured 4 cm on removal).

#### Bone

Seventeen lesions were detected on  $^{99m}\text{Tc}$ -MDP bone scans in two patients who had clinically suspected bone metastases (Patients 9 and 10). Only six bone lesions (35%) were detected on  $^{99m}\text{Tc}$ -sestamibi scans in these patients. In each case, lesions were more clearly identified on bone scanning than on  $^{99m}\text{Tc}$ -sestamibi scanning due to a higher target-to-background ratio.

#### DISCUSSION

The mainstay of therapy for both primary and recurrent MTC is surgery (3), and thus accurate preoperative localization of tumor is required. Technetium-99m-sestamibi has been shown to be taken up by some malignancies including lung, nasopharyngeal carcinoma and lymphoma (14–16). The mechanism of tumor localization is thought to be uptake of the radiopharmaceutical by mitochondria (17). Technetium-99m-sestamibi is taken up by normal thyroid tissue and has been used to successfully image differentiated thyroid adenocarcinomas (18,19) and Hurthle cell tumors (20). However, published descriptions of  $^{99m}\text{Tc}$ -sestamibi uses in MTC are confined to case reports only (20). Lebouthillier et al. (9) describe two patients with metastatic MTC where  $^{99m}\text{Tc}$ -sestamibi scanning was performed along with  $^{201}\text{Tl}$ ,  $^{131}\text{I}$  MIBG and  $^{99m}\text{Tc}$  (V)DMSA scanning. A SPECT study with  $^{99m}\text{Tc}$ -sestamibi allowed the precise localization of a metastatic mediastinal lymph node in one case where the other studies were inconclusive. O'Driscoll et al. (13) describe one MTC patient where

$^{99m}\text{Tc}$ -sestamibi yielded higher target-to-background ratios than scanning with either  $^{201}\text{Tl}$  or  $^{111}\text{In}$  anti-CEA Ab fragments.

We compared  $^{99m}\text{Tc}$ -sestamibi scans with CT scans, which is the most frequently used imaging modality in patients with recurrent MTC in our institution. Our series of patients had basal calcitonin values from 220–61800 ng/liter, and 70% of these patients had an abnormal  $^{99m}\text{Tc}$ -sestamibi scan at one or more sites. Of the 25 soft-tissue sites detected by  $^{99m}\text{Tc}$ -sestamibi and/or CT scanning, significantly more (88%) were detected by  $^{99m}\text{Tc}$ -sestamibi than by CT (44%). Technetium-99m-sestamibi scanning was able to detect a greater number of abnormal soft-tissue sites than CT in all but one of the seven patients. The discrepancy between  $^{99m}\text{Tc}$ -sestamibi scanning and CT in individual patients may be due to differences in tumor biology. Technetium-99m-sestamibi is taken up by mitochondria, and uptake is clearly not related only to tumor size. Small lesions of 8 mm and 9 mm diameter in Patient 10 were detected by CT and not by  $^{99m}\text{Tc}$ -sestamibi scanning; however, a group of 12 tumor-containing lymph nodes in the mediastinum of Patient 4 was seen on the  $^{99m}\text{Tc}$ -sestamibi scan but not on the CT scan. It is possible that the discrepancy is due to modifications of anatomical planes, since Patient 8 had mediastinal radiotherapy and Patients 5, 7 and 10 underwent previous surgery in the region of the discrepancies. CT scans can be difficult to interpret when there has been previous surgery and normal tissue planes are lost (21).

The specificity of the two techniques could not be confirmed histologically in every patient, but in Patient 4, mediastinal abnormalities on  $^{99m}\text{Tc}$ -sestamibi scan, and in Patient 6, a liver lesion identified on the CT scan, were each confirmed histologically. All patients had extremely high calcitonin levels and clearly had metastatic MTC. Furthermore, the absence of abnormal  $^{99m}\text{Tc}$ -sestamibi uptake in any of the patients with calcitonin values less than 6000 ng/liter suggests that sites of false-positivity are uncommon.

The hepatic excretion of  $^{99m}\text{Tc}$ -sestamibi complicates its ability to identify hepatic metastases. In our study, lesions detected by CT could not be detected by  $^{99m}\text{Tc}$ -sestamibi planar imaging. While SPECT may have been more sensitive in the identification of hepatic metastases, it was not routinely performed because of the significant increase in the imaging time required, combined with the fact that physiological liver and bowel uptake could complicate image interpretation. SPECT was useful in precisely localizing lesions in the neck and chest but did not detect additional lesions to the planar images.

Conventional bone scanning with  $^{99m}\text{Tc}$ -MDP would still appear to be the preferred imaging modality for bone metastases, as 11 lesions seen on bone scanning were not visualized on  $^{99m}\text{Tc}$ -sestamibi scanning, and the avidity of  $^{99m}\text{Tc}$ -MDP for bone lesions was greater than that of  $^{99m}\text{Tc}$ -sestamibi.

The utility of  $^{99m}\text{Tc}$ -sestamibi scanning is greatest in patients with calcitonin values in excess of 6000 ng/liter. No patient with a value less than this showed any abnormality on either  $^{99m}\text{Tc}$ -sestamibi or CT scans. Technetium-99m-sestamibi scanning alone is thus not a suitable method for localizing disease not clinically apparent, although clearly it has value when combined with CT and bone scanning in the evaluation of patients who may potentially benefit from further surgery.

#### CONCLUSION

Technetium-99m-sestamibi scanning is a sensitive technique for detecting recurrent MTC in patients with calcitonin values in excess of 6000 ng/liter. Technetium-99m-sestamibi scanning should be considered complementary to CT and bone scanning in the overall assessment of patients with very high calcitonin

values. Technetium-99m-sestamibi scanning is more sensitive than CT for localizing soft-tissue disease, especially in the mediastinum, although liver metastases should be assessed on CT scans. Bone metastases from MTC are best assessed on bone scans.

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# Tin-117m(4+)DTPA: Pharmacokinetics and Imaging Characteristics in Patients with Metastatic Bone Pain

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Biokinetics and imaging characteristics of <sup>117m</sup>Sn(4+)DTPA have been studied in patients with metastatic bone pain. **Methods:** Seventeen patients with bone pain due to metastasis were given three dose levels: 180  $\mu$ Ci/kg (6.66 MBq/kg), 229  $\mu$ Ci/kg (8.47 MBq/kg) and 285  $\mu$ Ci/kg (10.55 MBq/kg) body weight. Periodic blood and daily urine samples were collected for 14 days to measure percent injected activity retained in blood and that excreted in urine. Simultaneous anterior and posterior view whole-body images were obtained under identical scan settings at 1, 3.5 and 24 hr and on Days 3 and 7 and between 4-6 and 8-10 wk postinjection. The total body retention was calculated using the geometric mean counts. **Results:** After intravenous injection, the total body clearance of <sup>117m</sup>Sn(4+)DTPA shows two components: a soft-tissue component and a bone component. The soft-tissue component accounts for 22.4% of the dose and consists of four subcomponents with an average biologic clearance half-time of 1.45 days (range 0.1-3.2

days). The bone component accounting for the remaining 77.6% of the dose shows no biologic clearance. A mean 22.4% of the dose is excreted in urine in 14 days; 11.4% within 24 hr. The uptake pattern appears similar to that of <sup>99m</sup>Tc-MDP. Peak uptake is observed in normal bone by 24 hr and metastatic lesions by 3-7 days. Pain palliation was observed with all three doses levels. **Conclusion:** Among the four potential bone pain palliation radionuclides, <sup>117m</sup>Sn(4+)DTPA demonstrates the highest bone uptake and retention. Some biokinetic and radionuclidic features of <sup>117m</sup>Sn(4+)DTPA are similar to other agents, but many features are different and unique and may make it an ideal bone pain palliation agent. Double-blind comparative studies are needed to determine its exact role in bone pain palliation.

**Key Words:** bone pain palliation; pharmacokinetics; tin-117m(4+)DTPA

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Of the estimated 1.35 million people in the U.S. who would be diagnosed of some form of cancer in 1996, slightly more than half will develop metastasis (1). In patients whose primary

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