

Exploring the role of technitium-99m dimercaptosuccinyl acid (V) scan in medullary carcinoma thyroid patients with postoperative persistent hypercalcitoninemia in the era of positron emission tomography-computerized tomography

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ABSTRACT

Background: Many radio-pharmaceuticals have been used over the years to localize the recurrences in patients with medullary carcinoma thyroid (MCT), including iodine-131-metaiodobenzylguanidine, thallium-201, technitium-99m dimercaptosuccinyl acid [Tc-99m DMSA (V)], Tc-99m methoxyisobutylisonitril, Tc-99m ethylenediamine diacetic acid/hydrazinonicotinyl-Tyr (3)-octreotide, and In-111 diethylenetriaminepenta-acetic acid-octreotide with varying sensitivities and specificities. **Aims:** The aim of this study is to explore the role of Tc-99m DMSA (V) scan in MCT patients with postoperative persistent hypercalcitoninemia in the positron emission tomography-computerized tomography (PET-CT) era. **Materials and Methods:** A retrospective review of 53 patients with proven sporadic MCT, who presented to our institution over a period 28 years from 1985 to 2012, was performed. Patients with persistently elevated levels of serum calcitonin (> 150 pg/ml) were initially evaluated by a DMSA scan if conventional imaging failed to localize any focus of disease. **Results and Conclusions:** Our study showed that the postoperative levels of serum calcitonin significantly correlated with the overall survival of our patients and can possibly serve as a good prognostic marker. Tc-99m DMSA (V) scans demonstrated a sensitivity of 75%, specificity of 56%, a positive predictive value of 50%, and a negative predictive value of 80% in detecting metastasis in postoperative persistent hypercalcitoninemia. Our study showed that Tc-99m DMSA (V) scanning is an affordable and a reasonably sensitive imaging agent for localization of recurrent/metastatic disease. PET-CT seems to be a useful complementary tool and needs to be kept in the armamentarium for diagnosis of recurrence especially in cases of discordance between Tc-99m DMSA (V) scan and the serum calcitonin levels.

Keywords: Medullary carcinoma thyroid, positron emission tomography-computerized tomography scan, serum calcitonin, technitium-99m dimercaptosuccinyl acid scan

INTRODUCTION

Medullary carcinoma thyroid (MCT) is a rare malignant neuroendocrine tumor developing from the para-follicular

calcitonin producing cells of the thyroid gland. Serum calcitonin has been established as the most sensitive and specific marker for the preliminary diagnosis and subsequent follow-up of patients with MCT.^[1] Conventional imaging modalities such as ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) have been initially used to localize recurrences following total thyroidectomy. However, recurrent/metastatic disease is believed to frequently escape detection by the above modalities, even in the presence of elevated levels of serum calcitonin. Many radio tracers have been used over the years to localize the recurrences in patients with MCT. We present our experience with the use of technitium-99m dimercaptosuccinyl

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acid [Tc-99m DMSA (V)] scan in the management of MCT patients with persistent postoperative hypercalcitoninemia.

MATERIALS AND METHODS

A retrospective review of 53 patients with proven sporadic MCT, who presented to our institution over a period 28 years from 1985 to 2012, was performed. All patients underwent a total/completion thyroidectomy and a central compartment neck dissection. A lateral neck dissection was performed in the event of a clinically/histologically positive lateral neck node. All patients postoperatively received oral levothyroxine to maintain the euthyroid state and were followed-up for a median duration of 90 months, 3 monthly for the first 2 years, 6 monthly for the next 3 years and then annually thereafter. Serum calcitonin levels were measured postoperatively at 3 months and then subsequently 6-12 monthly (6 monthly for the first 3 years and then annually). Additional imaging (ultrasound, CT or MRI) was performed in the event of clinical or biochemical disease recurrence. Patients with persistently elevated serum calcitonin (>150 pg/ml) were initially evaluated by a DMSA scan if conventional imaging failed to localize any focus of disease.

DMSA (V) kit was procured from Baba Atomic Research Center, Mumbai and prepared as per instructions. About 25-30 mCi of Tc-99m pertechnetate was added to vial "A" (containing DMSA III) and then 0.5 ml of sodium bicarbonate from vial B was added to Vial "A", the resultant mixture was used after 15 min. Radio nucleotide imaging is performed in one of the two gamma cameras (Hitachi RC 1500 I). Low energy all-purpose collimators were used with peak energy at 140 keV. About 15-20 mCi of Tc-99m DMSA (V) was administered and the whole body planar scanning was performed after 2 and 4 h postinjection. Spot views of the neck and thorax were obtained, as well as additional views of any areas of interest. Whole body scans were acquired in 512×512 matrix continuous mode in anterior and posterior views.



Figure 1: Technetium-99m dimercaptosuccinyl acid (V) scan showing uptake in the anterior aspect of the left fourth rib in a follow-up patient of medullary carcinoma with persistently elevated serum calcitonin

Surgeries/systemic therapies for the extirpation of the metastatic foci were done whenever clinically indicated. Analysis of the outcome data was performed with the help of the statistical software package "SPSS 17".

RESULTS

Of the 53 patients, 45 patients underwent surgery, 8 patients were deemed inoperable (5 of whom were offered palliative radiotherapy and the remaining 3 declined any treatment) and were put on best supportive care.

Of the 45 patients who underwent surgery, only 34 patients had a baseline postoperative serum calcitonin 3 months postthyroidectomy done due to logistic issues. The reference value of ≤ 16 pg/ml was used to define normalcy. Nine patients had serum calcitonin level ≤ 16 pg/ml and 25 patients had serum calcitonin level >16 pg/ml (range: 4.8-21,254 pg/ml). The median overall survivals of the two subgroups were 72 months and 27 months, respectively, which was statistically significant ($P = 0.04$). The 10 years disease free survivals were also statistically significant thus suggesting that postoperative hypercalcitoninemia is a good predictor of long term outcome of patients.

On further follow-up, 19 patients had persistent postoperative hypercalcitoninemia (serum calcitonin >150 pg/ml with normal neck ultrasound/CT scan examination) and were considered for Tc-99m DMSA (V) scanning. Fourteen patients (73.68%) had an uptake in the scan, whereas five patients (26.31%) did not show any uptake. Seven patients had abnormal tracer uptake in the neck, followed by superior mediastinum in four patients, liver and bone in two patients, and bone only in one patient. [Figures 1-4]

Of the 14 patients who had uptake in Tc-99m DMSA (V) scan, six patients underwent surgery for removal of the metastatic nodal uptakes, two patients with liver metastasis underwent metaiodobenzylguanidine (MIBG) ablation therapy and the

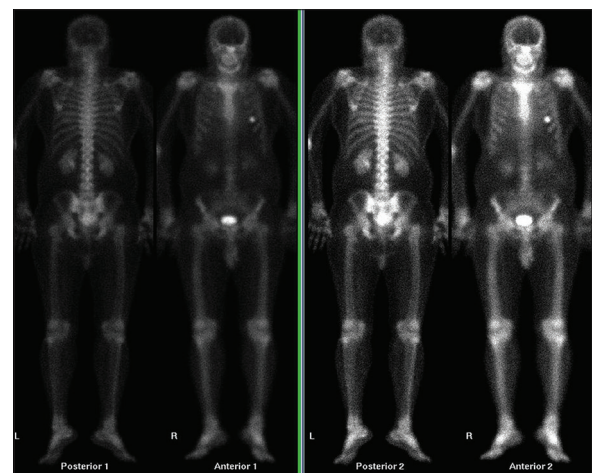


Figure 2: A technetium-99m bone scan corresponding to the uptake in uptake in the anterior aspect of the left fourth rib to that in Figure 1

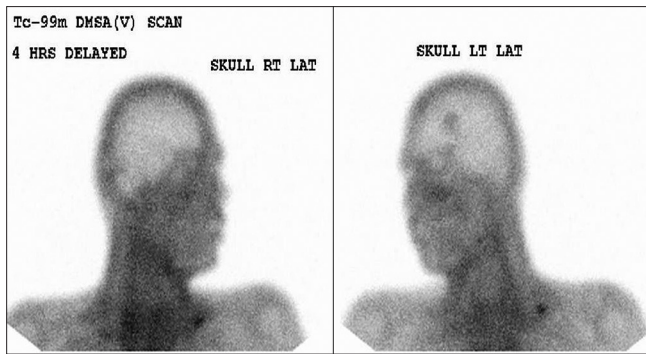


Figure 3: Technitium-99m dimercaptosuccinyl acid (V) scan showing uptake in the left parietal region of the skull bone

remaining six patients refused any form of intervention. Among the operated patients, 3 (50%) had confirmed metastasis on pathological examination and 3 (50%) demonstrated no cancerous tissue (two neck specimens showed lymph nodes with reactive changes and one specimen was reported as a benign cystic lesion). The postoperative levels of calcitonin did fall in 5 of the 6 patients who underwent surgery.

Of the five patients without uptake in Tc-99m DMSA(V) scan, two patients had evidence of cervical nodal uptake on fluorodeoxyglucose-positron emission tomography-computerized tomography (FDG-PET-CT) and underwent surgical removal of the same. One patient had evidence of cervical nodal metastasis and the other patient showed no tumor on final histopathology.

Tc-99m DMSA(V) scans thus demonstrated a sensitivity of 75%, specificity of 56%, a positive predictive value of 50%, and a negative predictive value of 80% in detecting metastasis in postoperative persistent hypercalcitoninemia.

DISCUSSION

MCTs accounts for about 3-4% of all thyroid carcinomas and originates from the para-follicular calcitonin producing cells of the thyroid gland. Most of MCTs are sporadic (80%), the rest represents a hereditary form, which includes three well-defined syndromes, namely: familial MCT and multiple endocrine neoplasia types 2A and 2B.^[1]

The most sensitive and specific marker for the preliminary diagnosis and subsequent follow-up of patients with MCT is serum calcitonin.^[2-4] Normalization of elevated preoperative levels of serum calcitonin has been deemed as biochemical cure following complete tumor extirpation.

The early detection of all metastatic foci is of prime importance and serum calcitonin has been established as the gold standard in the management of recurrent MCT. Postoperative persistent hypercalcitoninemia has been associated with significantly worse survivals in many studies^[5] including our study. In a structured meta-analysis of 10 studies with data on the postoperative kinetics of tumor markers, the doubling times of both serum



Figure 4: Technitium-99m dimercaptosuccinyl acid (V) scan showing uptake in a lymph node on the left of the superior mediastinum

calcitonin and carcinoembryonic antigen were independent prognostic factors for recurrences and deaths in MCT patients.^[5]

Numerous radio-pharmaceuticals have been evaluated in the detection of local and distant metastases of MCT namely iodine-131 MIBG, thallium-201 (Tl-201), Tc-99m DMSA(V), Tc-99m methoxyisobutylisonitril (MIBI), Tc-99 ethylenediaminediacetic acid (EDDA)/hydrazinonicotinyl-Tyr (3)-octreotide (HYNIC-TOC) and In-111 diethylenetriaminepenta-acetic acid-octreotide with varying sensitivities and specificities [Table 1]. Tc-99m DMSA(V) is taken up by the primary as well as recurrent tumor, along with its metastasis, with sensitivity ranging from 19% to 88%.^[3-11]

Verga *et al.* compared the diagnostic sensitivities of DMSA and MIBG among 12 patients with MCT and reported a sensitivity rate of 50% and 25%, respectively.^[4] Ugur *et al.* undertook a study in 14 MCT patients with postoperative hypercalcitoninemia to determine the sensitivities of Tl-201, Tc-99m MIBI, and Tc-99m DMSA (V) in the detection of recurrent or metastatic MCT. The overall lesion detection sensitivities for Tc-99m DMSA (V) scan, MIBI and Tl-201 were 95%, 47%, and 19%, respectively.^[6] In the study of Adams *et al.*, lesion detection sensitivities in patients with MCT for computed tomography, ¹¹¹In-pentetreotide, and Tc-99m DMSA(V) were 32%, 34%, and 65%, respectively.^[7]

In a study of 17 patients, DMSA scans and serum calcitonin levels were concordant in 79.2% of the scans and discordant in 20.8%. The sensitivity of Tc-99m DMSA (V) scans for detecting recurrence was reported at 71.4%.^[8]

In our study, Tc-99m DMSA (V) scan demonstrated a sensitivity of 75%, specificity of 56%, a positive predictive value of 50%, and negative predictive value of 80% in detecting metastasis in patients with persistent postoperative hypercalcitoninemia, which correlates with most of the above quoted trials.

Table 1: Comparison of the sensitivities of the various radio-pharmaceuticals that have been evaluated in the detection of local and distant metastases of MCT

Study	Tc-99m DMSA (%)	In-111 (%)	CT scan (%)	Tc-99m MIBI (%)	Thallium-201 (%)	FDG-PET (%)	DOPA PET (%)	DOTA Ga-68 (%)
Verga <i>et al.</i> ^[4]	50	-	-	25	-	-	-	-
Ugur <i>et al.</i> ^[6]	95	-	-	44	19	-	-	-
Adam <i>et al.</i> ^[7]	65	34	32	-	-	-	-	-
Adalet <i>et al.</i> ^[9]	82	-	-	81	72	-	-	-
Koopmans <i>et al.</i> ^[10]	19	-	64	-	-	30	89	-
Arslan <i>et al.</i> ^[11]	57.1	78.5	-	-	-	-	-	-
Conry <i>et al.</i> ^[15]	-	-	-	-	-	77.8	-	72.2
Naswa <i>et al.</i> ^[16]	-	-	-	-	-	63.4	-	75.61
Ong <i>et al.</i> ^[21]	-	20	-	-	-	78	-	-
Beuthien-Baumann ^[22]	-	-	-	-	-	78	63	-
Hoegerle <i>et al.</i> ^[23]	-	-	81	-	-	44	63	-
Treglia <i>et al.</i> ^[25]	-	-	-	-	-	28	85	-

MCT: Medullary carcinoma thyroid, DMSA: Dimercaptosuccinyl acid, CT: Computed tomography, MIBI: Methoxyisobutylisonitril, FDG: Fluorodeoxyglucose, PET: Positron emission tomography, DOPA: Dihydroxyphenylalanine, DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid

The serum calcitonin levels and Tc-99m DMSA (V) scans were discordant in 26.31% our patients (DMSA uptake negative in patients with elevated serum calcitonin). The reason for this discordance may be due to the presence of dedifferentiated tumor or extra nodal microscopic metastasis.

MCTs in fact overexpress somatostatin receptors on their cell surface and this represents the rationale for using somatostatin analogs for diagnosis and therapy of these tumors. However, some authors report a heterogeneous distribution, thus making traditional somatostatin receptor scintigraphy of limited usefulness for detection of metastatic MCT. Tc-99 EDDA/HYNIC-TOC, a newer somatostatin analog has been reported to be clinically useful for scintigraphy in the preoperative evaluation and for localization of local recurrence or distant metastases.^[12] More recently, PET-CT using somatostatin analogs labeled with gallium-68 is being explored as a promising diagnostic tool for patients with recurrent/metastatic MCTs.^[13-17]

In addition, there is growing interest in the use of PET with different radiotracers,^[11,18-25] that is, 3,4-dihydroxy-6-F-18-fluoro-l-phenylalanin PET-CT (F-18 DOPA PET-CT) and F-18 FDG PET-CT. Although the literature focusing on the use of PET-CT in the detection of recurrent MCT is limited, the available studies have suggested a complementary role for PET-CT and have found it to be especially useful in cases of discordance between conventional radionucleotide imaging and the serum calcitonin levels. Many authors have suggested F-18 DOPA PET-CT to be the most useful PET radiopharmaceutical in detecting recurrent MCT based on rising levels of serum calcitonin.^[11,24,25]

CONCLUSION

Our study reiterates the importance of serum calcitonin as a sensitive and specific follow-up tumor marker in patients with MCT. Further, we found that the postoperative level of serum calcitonin significantly correlated with the overall survival of our patients and can possibly serve as a good prognostic marker.

In patients with persistent postoperative hypercalcitoninemia, Tc-99m DMSA (V) scanning is an affordable and a reasonably sensitive imaging for localization of recurrent/metastatic disease. PET-CT seems to be a useful tool and needs to be kept in the armamentarium for diagnosis of recurrence. The choice of investigations would further depend on the availability of the investigation, financial implications and ultimately the comfort of the treating clinician. Further, prospective studies comparing different radiopharmaceuticals in recurrent setting are needed for better understanding of this intriguing disease.

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