

Role of Tc-99m DMSA (V) scanning and serum calcitonin monitoring in the management of medullary thyroid carcinoma

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ABSTRACT

Introduction: Medullary thyroid carcinoma (MTC) is a rare disease. Serum calcitonin levels and Tc-99m DMSA(V) scans are used in the follow-up of these patients after surgical resection. We present our experience in the follow-up of these patients at a tertiary institution.

Methods: A retrospective review of the medical records was performed. Patients with histologically -proven MTC, and who had serum calcitonin assays and DMSA (V) scans in their postoperative follow-up, were included.

Results: There were 17 patients with 56 DMSA (V) scans. Four out of seven patients with elevated preoperative calcitonin measurements had calcitonin normalisation within six months of surgery, and have remained disease-free. Two patients had persistently elevated calcitonin levels after six months, which predated positive DMSA (V) scans. Results of DMSA (V) scans and serum calcitonin levels were concordant in 38 of 48 instances (79.2 percent) and discordant in 10 of 48 instances (20.8 percent). Sensitivity of DMSA (V) scans for detecting recurrence was 71.4 percent. There were no false-positive scans.

Conclusion: Serum calcitonin level is a sensitive and specific indicator of disease recurrence in postoperative follow-up of patients with MTC. Early (within six months) normalisation of calcitonin levels postsurgery may predict subsequent disease-free status. Discordant results between serum calcitonin levels and DMSA (V) scans may be due to undetectable lesions and follow-up scans or alternative radionuclide imaging may be required.

Keywords: medullary thyroid carcinoma, serum calcitonin, Tc-99m DMSA (V) radionuclide scans, thyroid carcinoma

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INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare disease, accounting for 3%–10% of thyroid cancers. These cancers arise from the parafollicular calcitonin-secreting cells of the thyroid and are slow-growing. The inherited forms account for 25%, while the remainder (75%) are sporadic. The inherited form includes three well-defined syndromes, namely: familial MTC and multiple endocrine neoplasia (MEN) types 2A and 2B. In MEN type 2A, they are associated with pheochromocytoma and hyperparathyroidism. In MEN type 2B, they are associated with ganglioneuromatosis and a marfanoid habitus. Specific mutations in the rearranged during transfection (RET) proto-oncogene have been found in the familial form.⁽¹⁾ The average age of onset in the sporadic form is 60 years, while they tend to occur in adolescence in the familial form.

The survival rate of MTC is 40%–50% at ten years, and is significantly better when limited to the thyroid.⁽²⁾ Hence, early total thyroidectomy with dissection of nodes in the central and lateral neck compartments is the definitive treatment for all patients with MTC. Other sites of metastases include the lung, liver and bone. Monitoring of residual or recurrent disease following surgery is usually performed with serial serum calcitonin assays and pentavalent Technetium-99m (Tc-99m) dimercaptosuccinic acid [DMSA(V)] radionuclide scans. The production of calcitonin by proliferating parafollicular C cells form the basis for biochemical monitoring of disease activity using assays. Radionuclide imaging is used in the follow-up of patients to demonstrate metastatic sites and aid surgical planning. Various tumour-seeking imaging agents have been used. These include radiolabelled somatostatin receptor analogues, 201-Thallium, Tc-99m sestamibi, Tc-99m tetrofosmin and Tc-99m DMSA (V). We present our experience in the

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follow-up of these patients with serum calcitonin assays and Tc-99m DMSA (V) scans.

METHODS

Retrospective review of the records at the Department of Nuclear Medicine, Singapore General Hospital, was performed. Patients with histologically-proven MTC, who had serum calcitonin assays and DMSA (V) scans as part of their postoperative follow-up assessment, were included in the study. There were 17 patients in the study (12 men, 5 women; age range 32–71 years, median age 50 years). 56 DMSA (V) scans were performed for these 17 patients between 1993 and June 2006, and were analysed. All patients had prior total thyroidectomy and were referred to our department for imaging assessment. Two patients had synchronous papillary carcinoma of the contralateral thyroid lobe and one patient had MEN type 2A syndrome.

The reference level for basal serum calcitonin level was 26 pg/ml. Pentagastrin stimulation was not performed. Radionuclide imaging was performed on one of four gamma cameras (Argus, Genesys, Vertex Plus and Forte of Philips Medical Systems/ADAC Laboratories, Milpitas, California, USA). Low energy all purpose (LEAP) collimators were used with peak energy at 140 keV. 5–10 mCi (185–370 MBq) of Tc-99m DMSA (V) was administered and whole body planar scanning performed at one hour and four hours post-injection. Spot views of the neck and thorax were also obtained, as well as additional views of any areas of interest. All scans were interpreted by experienced nuclear medicine consultant physicians.

RESULTS

Preoperative serum calcitonin levels (or performed within two weeks of surgery) were available in seven patients. All seven patients had elevated calcitonin levels greater than 100 pg/ml, with the lowest level of 272 pg/ml. Four of the seven patients showed normalisation of serum calcitonin within six months of surgery. They remained disease-free with follow-up periods ranging from 24 to 26 months. Two patients showed an initial decline in serum calcitonin at 12 months postsurgery up to 50 pg/ml, and subsequent increase. Both patients were found to have recurrent disease foci on subsequent DMSA (V) scans. The third patient with elevated postoperative calcitonin level was lost to follow-up (Fig. 1).

DMSA (V) scans and serum calcitonin levels performed within a month apart and were analysed. Findings were concordant if the serum calcitonin was elevated and the DMSA (V) scan showed a focus of abnormal uptake (Fig. 2), or both the serum calcitonin assay and DMSA (V)

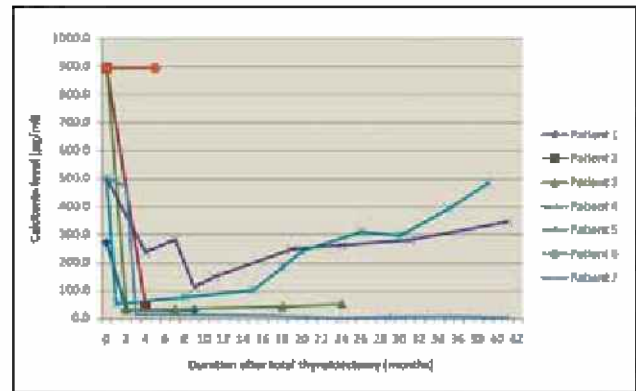


Fig. 1 Graph shows the pre- and postoperative calcitonin levels in seven patients.

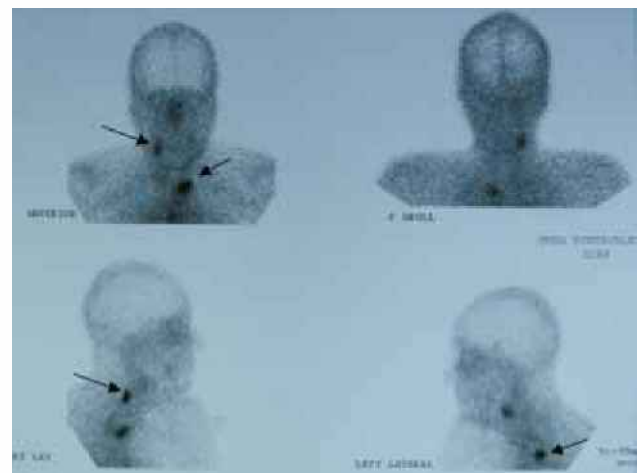


Fig. 2 Tc-99m DMSA (V) scan shows neck and superior mediastinal metastases in a patient with elevated postoperative serum calcitonin.

Table I. Results of Tc-99m DMSA (V) scans and serum calcitonin levels performed within a month apart.

	DMSA (V) positive	DMSA (V) negative
Elevated serum calcitonin	25	10
Normal serum calcitonin	0	13

scan were normal. Findings were discordant if the serum calcitonin level was elevated but the DMSA (V) scan was negative. Findings were concordant in 38 of 48 instances (79.2%) and discordant in 10 of 48 instances (20.8%). Sensitivity of DMSA (V) scans for detecting recurrence was 71.4%, using calcitonin levels as the reference (Table I). There were no false positive scans.

There was good agreement between sestamibi and DMSA (V) scans. Six patients had both sestamibi and DMSA (V) scans in their follow-up assessment, and the findings from both imaging modalities were concordant in all six patients. Two patients had additional F-18

fluorodeoxyglucose (FDG) whole body position-emission tomography (PET) imaging. In the first patient, PET detected residual hypermetabolic focus in a right paratracheal node which was not detected on the DMSA (V) scan performed two months after. Both imaging modalities detected the tibial bone metastasis. In the second patient, DMSA (V) scan showed residual disease in the neck, which was not detected in the corresponding PET.

Clinical follow-up periods for all patients ranged from nine to 142 months. Two patients were lost to follow-up. At the end of their follow-up periods, six of 15 patients (40%) had normal serum calcitonin levels and negative DMSA (V) scans, and were considered disease-free. Three patients (20%) had elevated serum calcitonin levels and positive DMSA scans, and were considered to have residual or recurrent disease. The remaining six patients (40%) had elevated serum calcitonin levels but negative DMSA scans, and were indeterminate.

DISCUSSION

Serum calcitonin is the most sensitive and specific marker of MTC for primary diagnosis and follow-up.⁽²⁾ This has been corroborated by several studies, which report sensitivities of 98%–100% and specificities of 95%–100%.⁽²⁻⁴⁾ A preoperative serum calcitonin level has been found to be more sensitive than fine-needle aspiration cytology for the diagnosis of MTC, and has the added benefit of alerting the clinician to the need for total thyroidectomy and exploration of the neck nodes.⁽⁴⁾

Preoperative calcitonin levels have been shown to correlate with tumour size and prognostic significance. A calcitonin level of less than 100 pg/ml was associated with a median tumour size of 3 mm, compared to 20 mm for a calcitonin level above 100 pg/ml. A lesion less than 3 mm would only be detected using basal calcitonin measurements and histology, and this obviates the need for preoperative imaging with scintigraphy and ultrasonography. A threshold of 50 pg/ml was shown to be predictive of better outcomes and postoperative normalisation of the calcitonin level. This threshold has been suggested both to predict outcome and tumour size.⁽²⁾

We were unable to correlate the preoperative calcitonin levels with prognostic significance as all seven patients who had preoperative calcitonin levels, had initial values above the threshold of 50 pg/ml. All four patients who had calcitonin levels declining to below 50 pg/ml within six months of surgery remained disease-free at the end of their follow-up periods. The two patients, who had disease recurrence, had an initial decline in their serum calcitonin levels up to 50 pg/ml before a subsequent increase in

calcitonin levels. Both had extracapsular spread of disease at surgery. This suggests that the initial decline in serum calcitonin may be a predictor of subsequent disease status.

Pentagastrin (PG) stimulation is performed at some centres in order to exclude the possibility of calcitonin secretion related to pathological conditions other than MTC. A rise in calcitonin level following PG stimulation⁽²⁾ is diagnostic of MTC, whereas false positively elevated basal calcitonin levels will not show a rise following PG stimulation. It is not performed routinely in our centre. The imaging diagnosis and follow-up of patients with MTC has been less sensitive and specific. Various tumour-seeking agents such as Tl-201 and Tc99m-sestamibi (MIBI) have been utilised besides DMSA (V). Some studies have shown these agents to be complementary, having different sensitivities in different tissues.⁽³⁾ Other studies showed superiority of DMSA (V) over MIBI and Tl-201.⁽⁴⁾ In our study, DMSA (V) showed a sensitivity of 71.4% in detecting disease recurrence in comparison with serum calcitonin levels. This is comparable with reported sensitivities of 69% and 95%, respectively.⁽⁵⁾ There was also a good correlation between MIBI and DMSA (V) scans in our study.

The serum calcitonin levels and DMSA (V) scans were frequently discordant (20.8% in our study). This may be due to presence of microscopical metastases, extra-nodal metastases not detectable by DMSA (V) scan or dedifferentiated tumours. In a multicentre study, F-18 FDG PET showed the highest lesion detection probability compared with In-111 pentetretotide (somatostatin receptor imaging), DMSA(V), MIBI, computed tomography (CT) and magnetic resonance (MR) imaging.⁽⁶⁾ The high sensitivity was independent of the calcitonin level, whereas the other imaging techniques yielded poor results at lower calcitonin levels. Therefore, it has been suggested that FDG-PET is superior to the other imaging techniques, particularly in dedifferentiated tumours. Although FDG PET was superior over CT and MR imaging in localising lymph node involvement, small (< 1 cm) pulmonary metastases detected by CT were not visualised by PET.⁽⁷⁾ The use of other PET tracers has also been reported. In a small study of 11 patients with MTC examined using 18F-dihydroxyphenylalanine (DOPA) PET, F-18 FDG PET and somatostatin receptor scintigraphy, 18F-DOPA PET was reported to be more accurate in detecting local tumour recurrence and lymph node involvement than the latter two agents.⁽⁶⁾

In conclusion, calcitonin levels are a sensitive and specific indicator of disease recurrence in postoperative follow-up of patients with MTC. Calcitonin normalisation

within six months of curative surgery may be a predictor of disease-free status, whereas a less than complete normalisation of calcitonin may predict eventual disease recurrence. In cases of elevated calcitonin, DMSA (V) is an affordable, readily available and reasonably sensitive imaging agent for disease localisation. In cases of discordance between calcitonin and DMSA (V), evaluation with F-18 FDG PET may increase disease detection, particularly in tumours with mildly-elevated calcitonin.

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