

Clinical importance of technetium-99m-methoxyisobutylisonitrile (MIBI) scintigraphy in differentiated thyroid carcinoma patients with elevated thyroglobulin levels and negative I-131 scanning results

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Aims and Background: The aim of this study was to evaluate the potential contribution of Tc-99m-MIBI scintigraphy to the follow-up of patients with differentiated thyroid carcinoma, who had elevated Tg levels and negative I-131 whole-body scan results. **Materials and Methods:** In this retrospective study, we evaluated 28 patients with differentiated thyroid carcinoma, who had total or near total thyroidectomy followed by an ablative dose of I-131 at various time intervals (15 women, 13 men; mean age 43 ± 17 years). All patients were treated with T4 suppression. After a mean follow-up period of 6.1 years (range 3–15) all patients were determined to have a high serum Tg concentrations (>2 ng/ml) and previous negative I-131 WBS results. All patients were examined for metastatic sites using Tc-99m-MIBI scan. Scans were visually evaluated for detecting lymph node metastases and/or local recurrence, lung metastases and skeletal metastases. **Results:** Tc-99m-MIBI scan demonstrated lesions in 23 patients (83.3%). In five patients with negative Tc-99m-MIBI scan findings (FN results):

* Chest CT showed small-sized mediastinal LN metastases in 2 patients and lung metastases in another 2 patients (<1 cm).

* Neck CT showed small-sized cervical LN involvement in 1 patient.

The sensitivity of detection for neck was 94.4%, for lung 63.6%, and for bone lesions 100%. For all scan sites taken together, the sensitivity of disease detection was 83.3%, the specificity was 50%, positive predictive value (PPV) was 96.2%, and finally negative predictive value (NPV) was 16.7%. **Conclusion:** We concluded that Tc-99m-MIBI scan should be considered as a supplementary scintigraphic method for the follow-up of patients with high serum Tg levels and negative I-131 WBS results, and it can help clinicians in making the decision to treat these patients.

Key words: Tc-99m-MIBI, I-131 whole body scan, serum thyroglobulin, differentiated thyroid carcinoma

INTRODUCTION

DIFFERENTIATED THYROID CARCINOMA (DTC) is a slow-growing cancer characterized by a favorable outcome due to the availability of effective therapeutic approaches: surgery, radioactive iodine and thyroid hormone suppression therapy with levothyroxine.^{1–5}

In the follow up of DTC several scintigraphic methods are used in addition to serum thyroglobulin (Tg) and ultrasonography (USG) of the neck. Iodine-131 whole body scintigraphy (I-131 WBS), is able to detect iodine positive recurrence, lymph node metastases and distant metastases in a very specific way.^{6–9}

However, the problem with I-131 WBS is the fact that only 67% of metastases from DTC accumulate iodine.^{10,11} Therefore, technetium-99m methoxyisobutyl isonitrile (Tc-99m-MIBI) scintigraphy has recently been used clinically for detecting thyroid cancer metastases, its role being considered supplementary to serum Tg measurements and I-131 WBS.^{12–14}

This article evaluates the potential contribution of

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Table 1 Results of MIBI scanning in respect of local disease, pulmonary and bone metastases

Results	Neck	Lung	Bone
True-positive	17	7	1
True-negative	1	0	0
False-positive	1	0	0
False-negative	1	4	0

Table 2 Clinical significance of MIBI scintigraphy in thyroid cancer

	Neck	Lung	Bone	All lesions
Sensitivity	94.4%	63.6%	100%	83.3%
Specificity	50%	—	—	50%
PPV	94.4%	100%	100%	96.2%
NPV	50%	—	—	16.7%

PPV: Positive Predictive Value
NPV: Negative Predictive Value

Tc-99m-MIBI scintigraphy in the follow-up of patients with differentiated thyroid carcinoma, who had elevated Tg levels and negative I-131 WBS results.

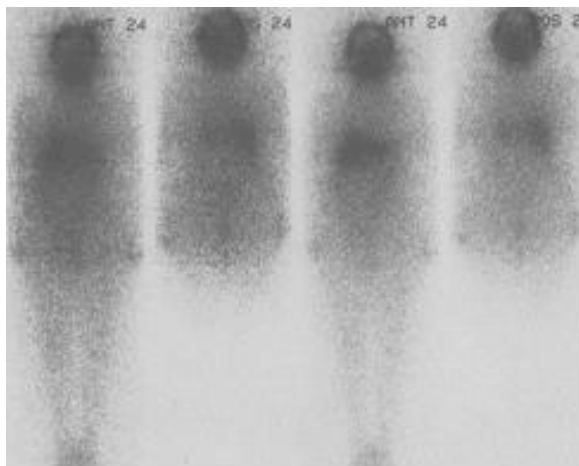
MATERIALS AND METHODS

Patients

In this retrospective study, we evaluated 28 patients with differentiated thyroid carcinoma, who had total or near total thyroidectomy followed by an ablative dose of I-131 at various time intervals (15 women, 13 men; mean age 43 ± 17 years). After thyroidectomy and radioiodine administration, all patients were on suppression therapy.

According to the histopathologic findings, 20 patients (71.4%) were diagnosed as having Papillary, 7 patients (25%) Follicular, and finally 1 patient (3.6%) Mixed Thyroid Carcinoma.

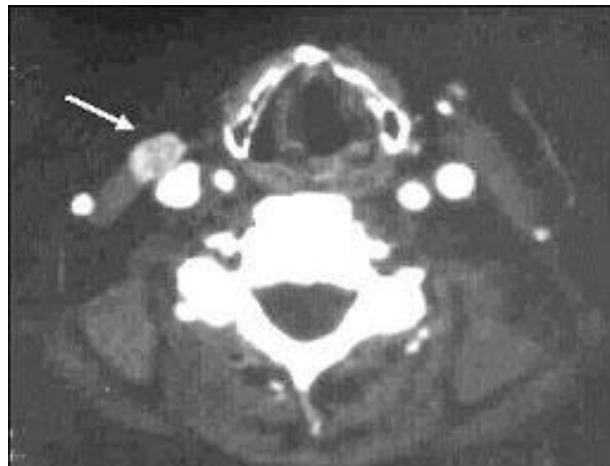
The follow-up schedule routinely used in our department in DTC patients consists of periodical clinical examination, laboratory tests (serum Tg and anti-Tg autoantibody measurement on and off HST), I-131 WBS and



A



B



C

Fig. 1 A 63-year-old female with history of Mixed Papillary and Follicular carcinoma of the thyroid gland, who had total thyroidectomy 20 years ago and also received high dose of radioiodine (total 22.2 GBq; 600 mCi) at different time intervals. In control thyroid function tests TSH was equal to 0.061 mIU/l, thyroglobulin was more than 3000 ng/ml, and finally anti-thyroglobulin-antibody was negative. In follow-up I-131 WBS of the patient—there was no detectable lesion in the neck (A). Tc-99m-MIBI scan was performed due to elevated serum thyroglobulin levels, and an increased uptake in the neck—right jugular region was observed. There was no palpable nodule on physical examination (B). Neck CT scan showed regional lymph node enlargements of which the highest size was below 1 cm. Neck dissection was performed and LN metastasis was proved histopathologically (C).

radiological imaging survey, as previously reported.⁵ After a mean follow-up period of 6.1 years (range 3–15) all patients were determined to have high serum Tg concentrations (>2 ng/ml) and previous negative I-131 WBS results.

Laboratory tests

Serum Tg concentrations were determined by immunoradiometric assay using a commercially available kit (IMMULITE 2000 TG kit/L2KTY2; normal range between 1.6–59.9 ng/ml). Anti-Tg antibodies that would affect Tg measurements were not detected in any of our patients (IMMULITE 2000 Anti-TG Ab kit/L2KTG; normal range between 0–40 IU/ml).

Scintigraphic techniques

For the scintigraphic examination Siemens E.CAM gamma camera was used (low-energy, high resolution, parallel-hole collimator). All patients undergoing thyroid hormonal treatment, were examined for metastatic sites using Tc-99m-MIBI scan, which was performed 20–30 min after iv injection of 555 MBq (15 mCi) Tc-99m-Sestamibi (anterior/posterior and static 10 min images were acquired). Scans were visually evaluated for detecting lymph node metastases and/or local recurrence (written as ‘neck’), lung metastases and/or mediastinal lymph node metastases (written as ‘lung’), and skeletal metastases (written as ‘bone’).

Radiological imaging

The final evaluation was made with other diagnostic methods including bone scans, chest x-rays, computed tomography (CT), ultrasonography, histopathology, and evolution of disease during follow-up.

Findings were classified as true-positive (TP) or false-positive (FP) when the positive Tc-99m-MIBI scan was confirmed or not confirmed by another diagnostic method (bone scans, chest X-rays, computerized tomography (CT), ultrasonography and histopathologic evaluation). True negative (TN) or false-negative (FN) scan was defined when the negative Tc-99m-MIBI scan was accompanied by absence or presence, respectively, of active thyroid cancer evaluated by other diagnostic modes.

Statistics

The following formulas were used: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); predictive value of positive test = TP/(TP + FP) and predictive value of negative test = TN/(TN + FN).

RESULTS

Results of MIBI scanning were evaluated for three disease categories: neck (local tumor and/or local lymph node metastases), chest (pulmonary metastases) and bone metastases.

The scintigraphic results for the 28 patients with confirmation of disease state by radiological imaging, biopsy or adequate follow-up are summarized in Table 1. Tc-99m-MIBI scan yielded 25 true-positive, 1 true negative, 1 false-positive and 5 false-negative results.

Tc-99m-MIBI scan demonstrated lesions in 23 patients (83.3%). In five patients with negative Tc-99m-MIBI scan findings (FN results):

- * Chest CT showed small-sized mediastinal LN metastases in 2 patients and lung metastases in another 2 patients (<1 cm).
- * Neck CT showed small-sized cervical LN involvement in 1 patient.

The sensitivity of detection for neck was 94.4%, for lung 63.6%, and for bone lesions 100%. For all scan sites taken together, the sensitivity of disease detection was 83.3%, the specificity was 50%, positive predictive value (PPV) was 96.2%, and finally negative predictive value (NPV) was 16.7% (Table 2).

In the present study, MIBI scan revealed the site of neoplastic foci in 83.3% of cases. Positive results have a very high predictive value, while the predictive value of negative results is lower.

DISCUSSION

MIBI is primarily used as a myocardial scanning agent, and also binds to the cytosol in the tumor cell.^{15,16}

The cationic charge and lipophilicity of Tc-99m-MIBI, the mitochondrial and plasma membrane potentials of tumor cells, and the cellular mitochondrial content are important in tumoral uptake of this agent.^{15,16}

In the detection of metastatic DTC, studies have found that Tc-99m-MIBI accumulated more often in lesions in which I-131 failed to accumulate.^{17,18,19} It was suggested that Tc-99m-MIBI uptake and concomitant loss of I-131 uptake is a sign of undifferentiation.^{17–19}

Patients with well-differentiated thyroid cancer are followed up after thyroidectomy by serum thyroglobulin (Tg) estimations and I-131 WBS.^{6–9}

Non-functioning metastases have been reported in 10–30% of patients with DTC.^{1,5,20,22} In these cases, the metastatic lesion loses the ability to uptake I-131 because of undifferentiation of the cancer cells. Obviously, in these cases I-131 cannot be used for diagnostic purposes. On the other hand, non-functioning metastases maintain an elevated metabolic cellular activity and, as a consequence, in the majority of cases preserve the ability to synthesize and secrete Tg.^{23,24} However, for those patients with elevated serum Tg levels but negative I-131 WBS, early determination if there are metastatic lesions is very important but difficult. Surgery, external radiotherapy or redifferentiation therapy can be performed if the lesions can be identified. There are some studies about the effectivity of MIBI scan in patients with DTC. Briele et al. reported that MIBI was helpful in patients with metastatic

and increased Tg level.²⁵ Yen et al. showed the MIBI could detect more lesions than I-131 and TI-201 scans.²⁶ Nemec et al. also investigated the value of MIBI in patients with distant metastatic lesions and concluded that MIBI scanning might play an important role in the follow-up of these patients. They reported the sensitivity of MIBI for bone metastasis was 100%, for pulmonary metastasis 94.7% and for tumor in the neck 80.9%. The specificity was 98.5%, 95.3%, 71.4% the PPV was 100%, 99.5% and 80.0% the NPV was 85%, 66.7%, 75.9%. Our results were similar to those of these studies except lung metastasis. We thought that we could not differentiate the mediastinal lymph node due to cardiac uptake and the small size of the lesions. In this retrospective analysis, we could not perform PET scan. We thought PET studies might increase the accuracy of the detection of these lesions. We are planning to perform PET soon.

CONCLUSION

We concluded that Tc-99m-MIBI scan should be considered a supplementary scintigraphic method for the follow-up of patients with high serum Tg levels and negative I-131 WBS results, and it can help clinicians in making the decision to treat these patients.

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