

# Indium-111-DTPA-D-Phe-1-Octreotide and Technetium-99m-(V)-Dimercaptosuccinic Acid Scanning in the Preoperative Staging of Medullary Thyroid Carcinoma

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The early detection of all tumor sites in patients with medullary thyroid carcinoma (MTC) before primary surgery is important, because MTC tends to metastasize to regional lymph nodes of the neck and mediastinum early during the course of the disease.

**Methods:** In an approach to localize the primary tumor sites and to detect additional tumor involvement, we have performed in 22 patients with MTC either  $^{99m}\text{Tc}$ (V)-dimercaptosuccinic acid (DMSA) and/or  $^{111}\text{In}$ -diethylenetriamine pentaacetic acid-D-Phe-1-octreotide scintigraphy. **Results:** Indium-111-octreotide (150–200 MBq) identified the primary tumor in 10 of 14 patients (71%), whereas the primary tumor was visualized by  $^{99m}\text{Tc}$ -DMSA (300–370 MBq) in 10 of 17 patients (58%). In 8 of 22 patients (36%), lymph node metastases were present at the time of diagnosis, as confirmed by histopathology and histochemistry after surgery (all <2 mm). Preoperatively, neither scan was able to detect lymph node involvement in these patients (0/8). **Conclusion:** Both  $^{99m}\text{Tc}$ -DMSA and  $^{111}\text{In}$ -octreotide studies have similar sensitivity to localize primary MTC; however, these scans are not able to detect small lymph node involvement (micrometastases) before initial surgery. Unfortunately, both scans have no clinical implication for preoperative staging in patients with MTC.

**Key Words:** medullary thyroid carcinoma; technetium-99m(V)-dimercaptosuccinic acid; indium-111-diethylenetriamine pentaacetic acid D-Phe-1-octreotide; lymph node metastases

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Medullary thyroid carcinoma (MTC) is a slow-growing, malignant neuroendocrine tumor that accounts for 4%–9% of all thyroid malignancies (1–4). MTC arises from the parafollicular C cells of the thyroid and occurs in a sporadic form and as a part of the multiple endocrine neoplasia syndrome (1,2). Calcitonin and carcinoembryonic antigen (CEA) are used as biochemical tumor markers in patients with MTC. Therefore, the persistent elevation of these markers after primary surgery is suggestive of residual disease or metastases (5–7). In contrast, an undetectable basal calcitonin level without pathological increase after provocative stimuli indicates the cure of the disease (8). The earliest and primary sites of metastases are local lymph nodes of the neck and mediastinum (1,4,8). Because surgery is the only therapeutic option for this tumor and because more than 50% of patients with MTC have metastases at the time of the diagnosis (1,9,10), the localization of all tumor sites is important. Surgical strategy is based on this fact and on the occurrence and distribution of lymph node

metastases (9). If cervical or mediastinal lymph node metastases are already present at the time of initial surgery, an extensive lymph node dissection should be performed, because lymph node metastases seem to be the major prognostic factor in patients with MTC (11–13).

Besides radiological techniques such as sonography, CT or MRI, several radionuclides, including  $^{201}\text{Tl}$ -chloride,  $^{131}\text{I}/^{123}\text{I}$ -metaiodobenzylguanidine,  $^{111}\text{In}/^{131}\text{I}$ -anti-CEA,  $^{99m}\text{Tc}$ -hexakis-2-methoxyisobutyl isonitrile and  $^{99m}\text{Tc}$ (V)-dimercaptosuccinic acid (DMSA), have been used with variable success. Because of the image quality and relatively low radiation burden,  $^{99m}\text{Tc}$ -DMSA has been advocated by many authors for the localization of MTC; however, its limitations are its sensitivity and specificity (14–26). Recent interest has been shown in receptor-based radiopharmaceuticals, which have been successfully used to localize neuroendocrine tumors (27,28). As a neuroendocrine tumor, MTC may also express high-affinity somatostatin (SST) receptors, suggesting the use of the SST receptor scintigraphy in patients with MTC (28–35). Although recent studies with  $^{111}\text{In}$ -diethylenetriamine pentaacetic acid-D-Phe-1-octreotide are encouraging in patients with MTC, their potential value in detecting micrometastases remains controversial. The reported sensitivity of SST receptor scanning in patients with MTC using  $^{111}\text{In}$ -octreotide ranges between 17% and 72% (4,36).

This study evaluated the clinical value of  $^{111}\text{In}$ -octreotide and/or  $^{99m}\text{Tc}$ -DMSA scans in detecting lymph node micrometastases before initial surgery.

## MATERIALS AND METHODS

### Patients

Patient data are summarized in Table 1. Twenty-two patients (17 women, 5 men; age range 30–79; mean age 61 yr) with histologically confirmed sporadic MTC were studied. Germ-line mutations of the ret protooncogene (3) were excluded in all patients by analyzing exons 10, 11, 13, 14 and 16 of this gene on chromosome 10. MTC was suspected biochemically on the basis of elevated basal and pentagastrin-stimulated calcitonin levels. Indium-111-octreotide scintigraphy was performed in 14 patients, and  $^{99m}\text{Tc}$ -DMSA scintigraphy was performed in 17 patients (Table 1). Nineteen of 22 patients (86%) had a solitary, and 3 of 22 patients (14%) had bilateral tumor sites that were identified during surgery. In 8 of 22 patients (36%), lymph node metastases were present, either grossly involved ( $n = 1$ ) or as micro (<2 mm) metastases ( $n = 7$ ).

### Surgery

In all patients, a time-consuming, meticulous surgical technique was used in which, prophylactically, the fatty tissue with lymph node metastases was removed en bloc along both recurrent nerves

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**Table 1**  
Patient Data, Results of In Vivo Scintigraphy and Tumor Characteristics

Patient no.	Age	Sex	Primary tumor site(s) (mm)	Tumor Stage		Positive lesions		Postoperative elevated calcitonin
				pT	pN	DMSA	octreotide	
1	30	F	RTL (35), LTL (10)	2b	1b	RTL	np	No
2	68	F	LTL (35)	2a	1a	LTL	LTL	Yes
3	76	F	LTL (35)	2a	1a	LTL	LTL	Yes
4	73	F	RTL (20), LTL (3)	2b	0	na	np	No
5	35	F	LTL (7)	1a	0	LTL	nc	No
6	49	M	RTL (4)	1a	0	np	RTL	No
7	54	M	RTL (3), LTL (6)	1b	1b	na	np	No
8	51	M	RTL (60)	4a	1b	RTL	np	Yes
9	54	F	RTL (32)	2a	1b	np	RTL	Yes
10	73	F	LTL (37)	2a	0	na	np	No
11	71	F	RTL (12)	2a	0	RTL	RTL	No
12	49	F	RTL (24)	2a	0	RTL	RTL	No
13	47	F	RTL (14)	2a	0	np	RTL	No
14	69	F	RTL (7)	1a	0	np	LTL	No
15	61	F	LRL (50)	4a	1a	na	np	No
16	77	F	RTL (5)	1a	0	RTL	RTL	No
17	60	F	RTL (4)	1a	0	np	RTL	No
18	65	F	LTL (7)	1a	1a	na	na	Yes
19	58	M	LTL (3)	1a	0	na	np	No
20	79	F	LTL (13)	2a	0	LTL	np	Yes
21	73	F	LTL (7)	1a	0	nc	LTL	No
22	71	M	LTL (5)	1a	0	LTL	nc	No

pT = pathological tumor classification; pN = pathological lymph node classification; RTL = right thyroid lobe; LTL = left thyroid lobe; np = not performed; nc = not conclusive; na = no accumulation; DMSA = dimer-captosuccinic acid; OCT = octreotide.

(central compartment) and along the internal jugular veins of both sides (lateral compartment). All removed lymph node metastases were examined histopathologically and histochemically.

### Somatostatin Receptor Imaging

SST receptor scintigraphy was performed using <sup>111</sup>In-octreotide (OctreoScan-111, Mallinckrodt, Inc., Petten, Holland). After labeling according to the manufacturer's instructions, planar images of the thyroid, thorax and abdomen were obtained using a medium-energy, parallel-hole collimator 6, 24 and, in some cases, 48 hr after administration of 150–200 MBq <sup>111</sup>In-octreotide. In all patients, SPECT studies of the neck and mediastinum were performed. Acquisition parameters for planar images were 300–500 kct for the images of head and neck and 500 kct for the remainder of the body, with a 256 × 256 pixel matrix. SPECT studies of the neck and mediastinum were performed with a 64 × 64 pixel matrix and 40–60 sec for each projection over 360°.

### Technetium-99m-DMSA Scintigraphy

Twenty minutes after injection of 300–370 MBq <sup>99m</sup>Tc-DMSA, whole-body (10 cm/min) scans were obtained with a low-energy, ultrahigh resolution collimation (double-head gamma camera, Toshiba, Japan). Thereafter, spot views of the neck were obtained (500–800 kct). In all patients, SPECT studies were performed with a 64 × 64 pixel matrix at 60 sec for each projection over 360° after planar scans.

### Preparation of Technetium-99m-DMSA

Labeling and analysis of the tracer was performed as follows: 2.7 μmol DMSA (FLUKA Chemie AG, Buchs, Switzerland) dissolved

in normal saline was buffered to pH 8 with 1 M NaHCO<sub>3</sub>. About 10 mCi <sup>99m</sup>Tc-O<sub>4</sub> were added and reduced by electrolytic Sn(II)-generation. The <sup>99m</sup>Tc-DMSA complex thus formed was stabilized by ascorbic acid and finally filtered through a sterile 0.2 μm membrane. Radiochemical purity was analyzed by thin-layer chromatography (silica-gel; n-butanol:HOAc:H<sub>2</sub>O 3:2:3) and paper chromatography developed in acetone and was better than 98%.

## RESULTS

### Indium-111-octreotide Scintigraphy

In 10 of 14 patients, a unilateral MTC lesion was correctly localized, resulting in a sensitivity of 71% for primary tumors. Two scintiscans in these 14 patients (14%) were considered to be nondiagnostic, because a diffuse accumulation and no well-delineated focal lesion was visualized. In the remaining two patients (14%), no accumulation was seen in the thyroid gland. None of the patients with bilateral MTC lesions underwent <sup>111</sup>In-octreotide scintigraphy.

Four of 14 patients (29%) who underwent <sup>111</sup>In-octreotide scintigraphy had lymph node metastases at the time of surgery that could be documented histopathologically; however, in none of these patients were lymph node metastases detectable scintigraphically.

### Technetium-99m-DMSA Scintigraphy

In 9 of 14 patients with unilateral primary MTC, <sup>99m</sup>Tc-DMSA scintigraphy correctly localized the tumor site with a sensitivity of 64%. In four patients with unilateral primary MTC, no accumulation was observed. In the remaining patient, diffuse accumulation of the tracer was seen, but it was considered to be nondiagnostic. Three patients had bilateral tumor sites (n = 6). Only one of these tumor sites was visualized correctly. The overall sensitivity for primary tumor was 58%.

Seven of 17 patients (41%) who underwent <sup>99m</sup>Tc-DMSA scintigraphy had lymph node involvement at the time of surgery that was documented histopathologically and histochemically. None of these lymph node metastases could be visualized by <sup>99m</sup>Tc-DMSA scintigraphy.

## DISCUSSION

MTC metastasizes early to regional lymph nodes of the neck and mediastinum. In more than 50% of patients, lymph node metastases are present at the time of the presentation of the disease (1,10). The presence of lymph node metastases has been proven to be the main prognostic factor in MTC (12) and seems to increase the risk of cause-specific mortality (11). Therefore, the detection of lymph node involvement in MTC is important. After exclusion of possible distant metastases, all calcitonin-producing tissue (primary tumor tissue and lymph node metastases) has to be resected surgically to avoid persisting disease, which generally leads to a time-consuming, laborious reoperation. The surgical strategy should be based on this fact and on the occurrence and distribution of lymph node metastases (9). Recent reports have emphasized the value of a meticulous, microsurgical compartment-oriented dissection (37,38), because total thyroidectomy in combination with prophylactic central, lateral neck and mediastinal dissection seems to be the only curative therapeutic option in patients with MTC (9,11,37–41,42).

Noninvasive radiological methods to detect lymph node involvement of MTC include sonography, CT and MRI generally fail to localize micrometastases in a high proportion of patients, because these imaging techniques generally rely on the criteria of lymph node enlargement. When tumor deposits within a node are microscopic, detection of the tumor by CT

and MRI is impossible (43). Several nuclear medicine methods have been used to overcome this problem. Likewise, the detection of small lesions is limited (4,14–26). The most reliable localization technique seems to be selective venous catheterization, but this technique is invasive and also yields inconclusive results in a considerable proportion of patients (23–33).

Precise preoperative localization of tumor sites in patients with MTC is advocated by some authors to minimize potential surgical complications (22), as well as to avoid reoperations. In our study, because of unsuccessful preoperative localization, none of the patients benefited from scintigraphy, and extensive surgery had to be performed.

Sixteen of 22 patients (73%) had postoperatively undetectable basal and pentagastrin-stimulated calcitonin levels, indicating a curative surgical strategy (8). It can be concluded that these patients had no distant metastases at the time of surgery and were biochemically cured after initial surgery. However, despite meticulous initial surgery and extended surgical management, 6 of the 22 patients (27%) (Patients 2, 3, 8, 9, 18 and 20, Table 1) still had elevated basal or pentagastrin-stimulated calcitonin levels, indicating the presence of lymph node or other distant metastases (41). However, in no patient, could additional tumor sites be documented scintigraphically before initial surgery using either of these scans. The lack of sensitivity of <sup>111</sup>In-octreotide and <sup>99m</sup>Tc-DMSA scanning to detect lymph node metastases can be explained by the small size of the lesions, because all lesions were <2 mm.

In about one-third of the patients, despite extended surgical management and dissecting lymph node metastases in the central and lateral compartments, the metastatic lesions may still be undetected. The results of this study suggest that (a) the sensitivity of <sup>111</sup>In-octreotide and <sup>99m</sup>Tc-DMSA scans in the localization of primary MTC is similar and (b) neither scan is able to detect micrometastatic lymph node involvement in the neck and mediastinum before initial surgery. New imaging techniques are, therefore, needed to improve the clinical management of patients with MTC.

## CONCLUSION

The results of our study suggest that <sup>111</sup>In-octreotide and <sup>99m</sup>Tc-DMSA scans have similar sensitivity to localize primary MTC tumor sites; however, neither scan is able to detect early lymph node micrometastases. Therefore, a precise preoperative staging with <sup>111</sup>In-octreotide or <sup>99m</sup>Tc-DMSA scans in patients with MTC is not possible.

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## REFERENCES

- Saad MF, Ordonez NG, Rashid RK, et al. Medullary carcinoma of the thyroid. *Medicine* 1984;63:319–342.
- Jensen MH, Davis RK, Derrick L. Thyroid cancer: a computer-assisted review of 5287 cases. *Otolaryngol Head Neck Surg* 1990;102:51–53.
- Vierhapper H, Raber W, Bieglmayer, et al. Routine measurement of plasma calcitonin in nodular thyroid diseases. *J Clin Endocrinol Metab* 1997;82:1589–1593.
- Kurtaran A, Leimer M, Kaserer K, et al. Combined use of <sup>111</sup>In-DTPA-Phe-1-octreotide and <sup>123</sup>I-vasoactive intestinal peptide in the localization diagnosis of medullary thyroid carcinoma. *Nucl Med Biol* 1996;23:503–507.
- Wells SA, Dilley WG, Farndon JA, et al. Early diagnosis and treatment of medullary carcinoma. *Arch Intern Med* 1985;145:1248–1252.
- van Heerden JA, Grand CS, Gharib H, et al. Long-term course of patients with persistent hypercalcitoninemia after apparent curative primary surgery for medullary thyroid carcinoma. *Ann Surg* 1990;212:395–401.
- Moley JF, Wells SA, Dilley WG, et al. Reoperation for recurrent or persistent medullary thyroid cancer. *Surgery* 1993;114:1090–1096.
- Raue F, Winter J, Frank-Raue K, et al. Diagnostic procedure before reoperation in patients with medullary thyroid carcinoma. *Horm Metab Res* 1989;21(suppl):31–34.
- Tisell LE, Hansson G, Jansson S. Surgical treatment of medullary carcinoma of the thyroid. *Horm Metab Res* 1989;21(suppl):29–31.
- Chong GC, Behrs OH, Sizemore GW, et al. Medullary thyroid carcinoma of the thyroid gland. *Cancer* 1975;35:695–704.
- Grebe SK, Hay ID. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. *Surg Oncol Clin N Am* 1996;5:43–63.
- Dralle H, Damm I, Scheumann GF, et al. Compartment-oriented microdissection of regional lymph nodes in medullary thyroid carcinoma. *Surg Today* 1994;24:112–121.
- Schröder S, Dralle H. Prognostic factors in medullary thyroid carcinomas. *Horm Metab Res* 1989;21(suppl):26–28.
- Hoefnagel CA, Delprat CC, Zanin, et al. New radionuclide tracers for the diagnosis and therapy of medullary thyroid carcinoma. *Clin Nucl Med* 1988;13:159–165.
- Clarke SEM, Lazarus CR, Wraight P, et al. Pentavalent <sup>99m</sup>Tc-DMSA, <sup>131</sup>I-MIBG, and <sup>99m</sup>Tc-MDP: an evaluation of three imaging techniques in patients with medullary carcinoma of the thyroid. *J Nucl Med* 1988;29:33–38.
- Lebouthiller G, Morais J, Picard M, et al. Tc-99m-sestamibi and other agents in the detection of metastatic medullary carcinoma of the thyroid. *Clin Nucl Med* 1993;18:657–661.
- O'Byrne KJ, Hamilton D, Robinson I, et al. Imaging of medullary carcinoma of the thyroid using <sup>111</sup>In-labeled anti-CEA monoclonal antibody fragments. *Nucl Med Commun* 1992;13:142–148.
- Berna L, Cabezas R, Mora J, et al. <sup>111</sup>In-octreotide and <sup>99m</sup>Tc(V)-dimercapto-succinic acid studies in the imaging of recurrent medullary thyroid carcinoma. *J Endocrinol* 1995;144:339–345.
- Ohta H, Yamamoto K, Endo K, et al. A new imaging agent for medullary carcinoma of the thyroid. *J Nucl Med* 1984;25:323–325.
- Parthasarathy KL, Shirmaoka K, Bakshi SP, et al. Radiotracer uptake in medullary carcinoma of the thyroid. *Clin Nucl Med* 1980;5:45–48.
- Senga O, Miyakawa M, Shirota H, et al. Comparison of Tl-201-chloride and Ga-67-citrate scintigraphy in the diagnosis of thyroid tumor: concise communication. *J Nucl Med* 1982;23:225–228.
- Udelsman R, Ball D, Baylin SB, et al. Preoperative localization of occult medullary carcinoma of the thyroid gland with single photon emission tomography dimercapto-succinic acid. *Surgery* 1993;114:1083–1089.
- Abdelmoumene N, Schlumberger M, Gardet P, et al. Selective venous sampling catheterisation for localization of persisting medullary thyroid carcinoma. *Br J Cancer* 1994;69:1141–1144.
- Anderson RJ, Sizemore GW, Wahner HW, et al. Thyroid scintigraphy in familial medullary carcinoma of the thyroid gland. *Clin Nucl Med* 1978;3:147–151.
- Cannell JMC, Hilditch TG, Elliot A, et al. <sup>131</sup>I-MIBG and medullary carcinoma of the thyroid. *Lancet* 1984;2:273–274.
- Vuillez JP, Peltier P, Caravel JP, et al. Immunoscintigraphy using <sup>111</sup>In-labeled F(ab')<sub>2</sub> fragments of anticarcino-embryonic antigen monoclonal antibody for detecting recurrences of medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1992;74:157–163.
- Virgolini I, Raderer M, Kurtaran A, et al. Vasoactive intestinal peptide-receptor imaging for the localization of intestinal adenocarcinomas and endocrine tumors. *N Engl J Med* 1994;331:1116–1121.
- Krenning EP, Bakker WH, Breeman WA, et al. Localization of endocrine-related tumors with radioiodinated analogue of somatostatin. *Lancet* 1989;1:242–244.
- Dorr U, Frank-Raue K, Sautter-Bühl ML, Guzman G, Buhr HJ, Bühl H. The potential value of somatostatin receptor scintigraphy in medullary thyroid carcinoma. *Nucl Med Commun* 1993;14:439–445.
- Krenning EP, Kwekkeboom DJ, Reubi JC, et al. <sup>111</sup>In-octreotide scintigraphy in oncology. *Digestion* 1993;54:84–87.
- Kwekkeboom DJ, Reubi JC, Lamberts SWJ, et al. In vivo somatostatin receptor imaging in medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1993;76:1413–1417.
- Reubi JC, Chayvialle JA, Franc B, et al. Somatostatin receptors and somatostatin content in medullary thyroid carcinomas. *Lab Invest* 1991;64:567–573.
- Frank-Raue K, Raue F, Buhr HJ, et al. Localization of occult persisting medullary thyroid carcinoma before microsurgical reoperation: high sensitivity of selective venous catheterization. *Thyroid* 1992;2:113–117.
- Rohrer L, Raulf F, Bruns C, et al. Cloning and characterization of a fourth human somatostatin receptor. *Proc Natl Acad Sci USA* 1993;90:4196–4200.
- Bakker WH, Albert R, Bruns C, Breeman WA, et al. <sup>111</sup>In-DTPA-D-Phe-1-octreotide, a potential radiopharmaceutical for imaging of somatostatin receptor-positive tumors: synthesis, radiolabeling and in vitro validation. *Life Sci* 1991;49:1583–1591.
- Behr TM, Gratz S, Markus PM, et al. Enhanced bilateral somatostatin receptor expression in mediastinal lymph nodes (chimney sign) in occult metastatic medullary thyroid cancer: a typical site of tumor manifestation? *Eur J Nucl Med* 1997;24:184–191.
- Tisell L, Hansson G, Jansson S, et al. Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. *Surgery* 1986;99:60–66.
- Buhr HJ, Lehnert T, Raue F. New operative strategy in the treatment of metastasizing medullary carcinoma of the thyroid. *Eur J Surg Oncol* 1990;16:366–369.
- Jackson CE, Talpos GB, Kambouris JB, et al. The clinical course after definitive operation for medullary thyroid carcinoma. *Surgery* 1983;94:995–1001.
- Baylin SB, Wells SA. Management of hereditary medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1981;10:367–378.
- Ellenhorn JDI, Shah JP, Brennan MF. Impact of therapeutic regional lymph node dissection for medullary carcinoma of the thyroid gland. *Surgery* 1993;114:1078–1082.
- Gimm O, Dralle H. Medullary thyroid cancer: reoperation. *Acta Chir Austriaca* 1997;29:15–17.
- Som PM. Detection of metastasis in cervical lymph nodes: CT and MR criteria and differential diagnosis. *AJR* 1991;158:961–969.