Comparison of metabolic and receptor imaging in recurrent medullary thyroid carcinoma with histopathological findings

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Abstract. Early diagnosis of metastases of medullary thyroid carcinoma (MTC) provides the optimal condition for curative outcome. The aim of this study was to appraise the detection of metastases in patients with recurrent MTC using [^{111}In-DTPA-D-Phe^{1}]-pentetreotide and pentavalent technetium-99m dimercaptosuccinic acid [^{99m}Tc(V)-DMSA] in comparison with histopathological findings. Eighteen MTC patients with persistently elevated tumour marker (calcitonin, carcinoembryonic antigen) levels underwent somatostatin receptor scintigraphy using [^{111}In-DTPA-D-Phe^{1}]-pentetreotide (222 MBq) with early (4 h after injection) and delayed (24 h) whole-body scans and single-photon emission tomography (SPET) imaging. Metabolic whole-body and SPET imaging using 500 MBq ^{99m}Tc(V)-DMSA was performed 4 h after injection. Metabolic and receptor imaging revealed 51 sites of focal accumulation in the 18 patients investigated. Comparison with histological findings revealed that metabolic and receptor imaging had a sensitivity of 84% for the diagnosis of MTC. Using [^{111}In-DTPA-D-Phe^{1}]-pentetreotide, SPET discovered four lymph node metastases in two patients in whom planar views had previously identified only one lymph node metastasis, and provided no new information in the other 16 patients. In comparison, SPET studies [using ^{99m}Tc(V)-DMSA] additionally localized eight lymph node metastases in four patients and confirmed the diagnosis of hepatic metastases (n=5) in another patient in whom conventional imaging modalities and planar views had previously detected only three liver metastases. Overall, lesion detection sensitivities for ^{99m}Tc(V)-DMSA and [^{111}In-DTPA-D-Phe^{1}]-pentetreotide were 69% and 29%, respectively. Five surgically removed foci were adjudged false-positive with respect to MTC metastases. False-positve results were caused by lymphadenitis, an enchondroma and a pheochromocytoma (histologically proven). The smallest lesion identified by metabolic imaging was a 6 mm in diameter lymph node metastasis located in the upper mediastinum. Somatostatin receptor scintigraphy only demonstrated tumour sizes more than 1 cm in diameter. These preliminary results suggest that the combination of metabolic [^{99m}Tc(V)-DMSA] and receptor ([^{111}In-DTPA-D-Phe^{1}]-pentetreotide) imaging is more sensitive for tumour localization in patients with recurrent MTC than the use of only one radiopharmaceutical. However, neither ^{99m}Tc(V)-DMSA nor [^{111}In-DTPA-D-Phe^{1}]-pentetreotide is specific for MTC and false-positive scintigraphic findings have to be considered. Furthermore, somatostatin receptor scintigraphy cannot visualize small tumour sites (<1 cm). Further studies are needed to evaluate the role of combined metabolic and receptor imaging in the management of patients with recurrent MTC.

Key words: Medullary thyroid carcinoma – Neuroendocrine tumours – Metabolic and receptor imaging – [^{111}In-DTPA-D-Phe^{1}]-pentetreotide – ^{99m}Tc(V)-DMSA

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Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumour which tends to grow slowly and occurs in a sporadic and a familial form which is associated with other endocrine manifestations [1, 2]. The prognosis of MTC depends on tumour size, invasion of vessels by the tumour, grade of differentiation, tumour stage and the modality used to treat recurrence or metastases [3]. Woolner et al. demonstrated that the 10-year survival rate of patients without lymph node involvement reached 85%, but in patients with lymph node metastases it was significantly reduced to 42% [4]. In MTC surgical removal of the tumour is the first and most efficient treatment of the disease. Persistent or increasing serum calcitonin and carcinoembryonic antigen (CEA) levels imply tumour recurrence after thyroid ablation [5, 6]. There-

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fore, the precise localization of metastases is of utmost importance. A complete work-up with conventional imaging modalities (e.g. computerized tomography, ultrasonography) is used for preoperative localization of MTC metastases, but the sensitivity is low [7]. Various tumour-avid radiopharmaceuticals, such as thallium-201 chloride, iodine-131 or iodine-123 labelled metaiodobenzylguanidine (MIBG) and radiolabelled anti-CEA antibodies have been used for tumour imaging [8, 9]. Furthermore pentavalent technetium-99m dimercaptosuccinic acid [^{99m}Tc(V)-DMSA] imaging has been used for the diagnosis and follow-up of MTC [10]. [^{111}In-DTPA-D-Phe^{1}]-pentetreotide scintigraphy has been shown to localize gastroenteropancreatic tumours not detected by conventional imaging modalities [11]. In the case of MTC, high-affinity somatostatin receptors have been identified autoradiographically by Reubi et al. [12]. Using in vivo scintigraphy with the indium-111 labelled somatostatin analogue pentetreotide, tumour localizations were demonstrated in up to 65% of patients with persistent MTC [13, 14].

The aim of this study was to appraise the detection of metastases in patients with recurrent MTCs using [^{111}In-DTPA-D-Phe^{1}]-pentetreotide and ^{99m}Tc(V)-DMSA in comparison with histopathological findings.

Materials and methods

Patients

The study group consisted of 18 patients with relapsing MTCs (7 female and 11 male patients; mean age 56.5 years, range 21–78 years), all scheduled for surgery. All patients had undergone total thyroidectomy more than 3 years previously and 13 of the 18 patients had had repeated cervical lymph node dissection. A 67-year-old female patient with multiple endocrine neoplasia (MEN II) additionally demonstrated a follicular thyroid carcinoma and a pheochromocytoma. Two patients had undergone radiotherapy of the head and neck region 3 years before. Serum levels of calcitonin (mean: 5618 ng/ml; range: 550–19 500 ng/ml) and CEA (mean: 69.2 ng/ml; range: 15–256 ng/ml) were increased in all patients. Scintigraphic imaging, chest radiography, ultrasonography of the cervical region and abdomen, and thoracic computerized tomography (CT) had been performed within 2 weeks preceding surgery. Informed consent was obtained from all patients prior to the studies.

Radiopharmaceuticals

[^{111}In-DTPA-D-Phe^{1}]-pentetreotide. The somatostatin analogue pentetreotide (Octreoscan) was obtained from Mallinckrodt (Petten, The Netherlands) in lyophilized form (20 μg) as a single vial kit. Direct labelling was performed by adding 222 MBq ^{111}In chloride according to the manufacturer's instructions. The label-

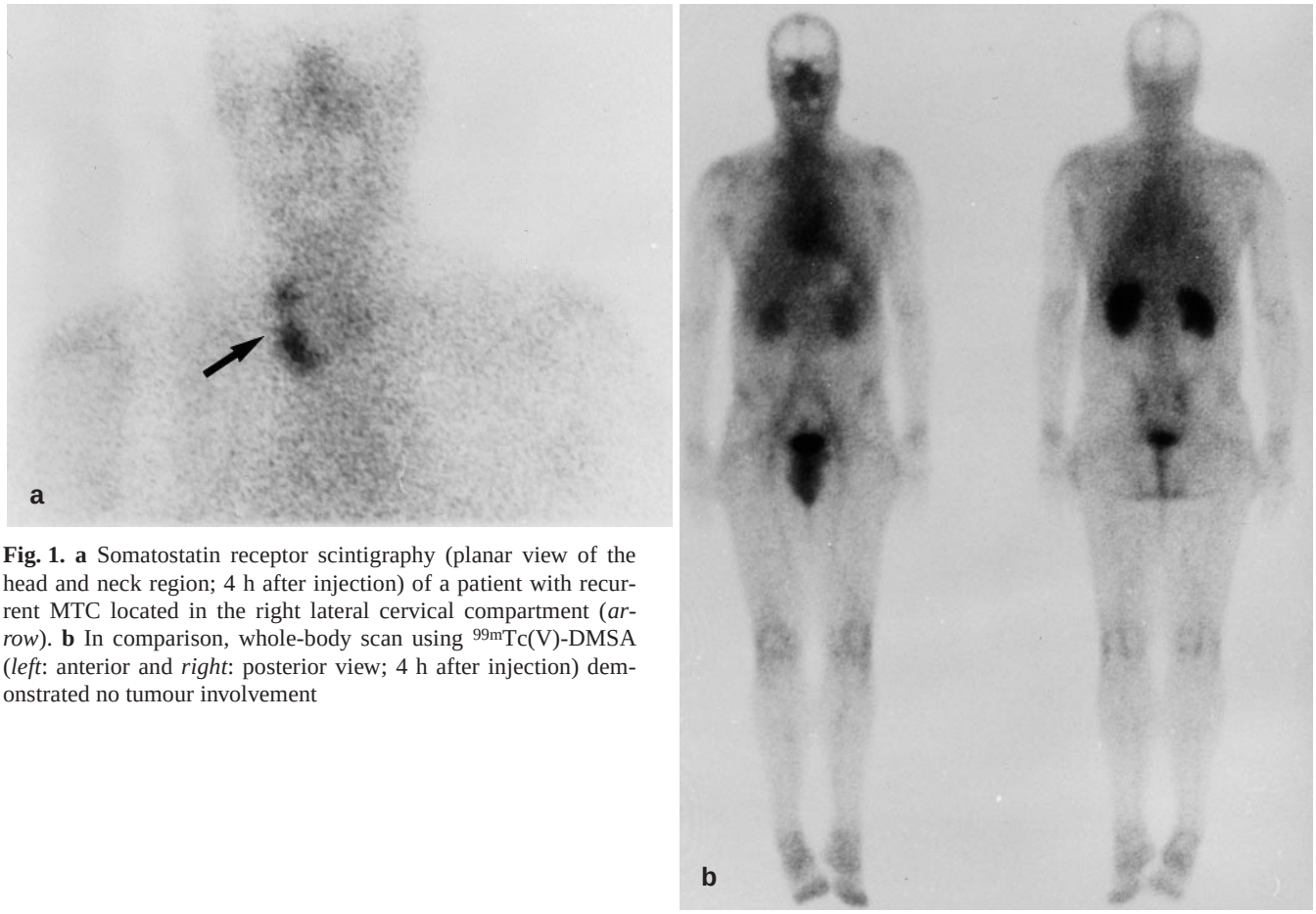


Fig. 1. a Somatostatin receptor scintigraphy (planar view of the head and neck region; 4 h after injection) of a patient with recurrent MTC located in the right lateral cervical compartment (*arrow*). **b** In comparison, whole-body scan using ^{99m}Tc(V)-DMSA (*left*: anterior and *right*: posterior view; 4 h after injection) demonstrated no tumour involvement

ling procedure was completed within 30 min with a labelling yield of more than 95% as measured by thin-layer chromatography using sodium acetate (0.1 mol) as running medium.

^{99m}Tc(V)-DMSA. All patients with relapsing MTC were examined using an original DMSA kit (vial 1) from CIS Diagnostica (Dreieich, Germany) to which solutions of $NaHCO_3$ (vial 2) and penta-DMSA (vial 3), obtained from our pharmacy, were added. The preparation was performed according to a modified protocol with regard to the manufacturer's instructions as follows: For the preparation of a bicarbonate solution (vial 2): 1.4% $NaHCO_3$ was dissolved in 10 ml of distilled water for injection and this aliquot was dispensed aseptically. For vial 3: DMSA (2.5 mg) and $NaHCO_3$ (4 mg) were dissolved in 1 ml distilled water and also dispensed aseptically for injection. One ml of vial 3 was added to the freeze-dried DMSA kit (vial 1) and then 1.3 ml of vial 2 and 2 ml ^{99m}Tc-pertechnetate (1 GBq/2 ml) were added simultaneously to the DMSA solution and shaken sufficiently. The labelling procedure was completed within 10 min with a labelling yield of more than 98% as measured by thin-layer chromatography.

Imaging procedures

Somatostatin receptor scintigraphy. [^{111}In-DTPA-D-Phe^1]-pentetreotide (222 MBq) was injected intravenously. No adverse reaction was noted. Multiple planar overlapping anterior and posterior images of the whole body were obtained 4 and 24 h after injection [The static images were acquired in a 256×256 matrix for 10 min, or until 1000 kcounts had been collected (Sopha Medical Gamma Camera D 7.0)]. Single-photon emission tomography (SPET) of the thorax and abdomen was performed 5 h after injection using a medium-energy parallel-hole collimator (360° rotation in 64 steps with 30 s per step, approximately 2 million total counts, frame reconstruction utilizing the Wiener filter, slice thickness 6 mm). Previous experience in the detection of gastroenteropancreatic tumours and MTC recurrences revealed no significant difference in the localization of lesions when SPET performed after 4 h was compared with SPET performed 24 h after injection [15, 16]. The analyser was set at both ^{111}In peaks (173 keV and 247 keV; window 20%).

Metabolic imaging using ^{99m}Tc(V)-DMSA. ^{99m}Tc(V)-DMSA (500 MBq) was injected intravenously. No adverse reaction was noted. Multiple planar overlapping anterior and posterior images of the whole body were obtained 4–5 h after injection. (1000 kcounts per view, 256×256 matrix, Sopha Medical Gamma Camera D 7.0). SPET of the head and thorax or the abdomen was performed 6 h after injection using a high-resolution collimator (360° rotation, 26 min rotation time; frame reconstruction was done using a modified Shepp-Logan filter). The analyser was set at the ^{99m}Tc peak (140 keV; window 20%).

All radiological and scintigraphic studies were interpreted by two experienced nuclear physicians and radiologists without any knowledge of the background of the patients. The sensitivity (true-positive ratio) of metabolic and receptor imaging was calculated for each scintigraphic technique using the formula: true-positive findings/(true-positive findings + true-negative findings).

Table 1. Histologically proven lesions detected by conventional imaging modalities

Patient	Calcitonin (ng/ml)	CEA (ng/ml)	CT	Site	Ultra-sono-graphy	Site
1	5600	25	1 (TP)	um	Negative	–
2	850	15	Negative	–	Negative	–
3	5500	35	Negative	–	Negative	–
4	6200	48	Negative	–	Negative	–
5	7500	67	3 (TP)	um	Negative	–
6	16600	210	2 (FP)	mm, rh	Negative	–
7	850	74	Negative	–	1 (FP)	rc
8	980	90	1 (TP)	um	1 (TP)	um
9	550	20	2 (TP)	rc	2 (TP)	rc
10	1250	23	Negative	–	Negative	–
11	3600	100	2 (TP)	lc	1 (TP)	lc
12	4500	86	Negative	–	Negative	–
13	7800	65	3 (TP)	liver	1 (TP)	liver
14	4300	52	Negative	–	Negative	–
15	950	15	2 (TP)	um	Negative	–
16	19500	256	1 (TP)	mm	Negative	–
17	5600	21	1 (TP)	rc	1 (TP)	rc
18	9000	45	Negative	–	Negative	–
Σ=18	Mean=5618	Mean= 69.2	16 (TP) 2 (FP)		6 (TP) 1 (FP)	
			Σ=18 lesions		Σ=7 lesions	

um, Upper mediastinum; mm, middle mediastinum; rh, right humerus; rc, right cervical compartment; lc, left cervical compartment; TP, true-positive, FP, false-positive

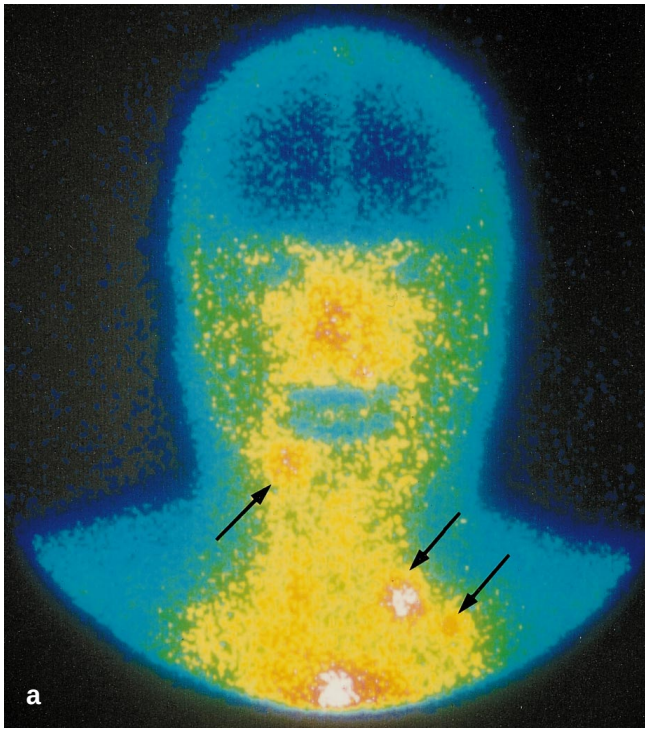
Results

Computerized tomography localized 16 lesions representing MTC recurrence in nine patients. Ultrasonography successfully detected only five tumour-involved lymph node metastases (in four patients) and one malignant liver lesion in another patient. Two reactively enlarged lymph nodes [one in the right cervical compartment (ultrasonography) and another one in the middle mediastinum (CT scan)] were caused by lymphadenitis. Furthermore an enchondroma was detected in the proximal metaphysis of the right humerus by CT (Table 1).

Metabolic and receptor imaging revealed 51 sites of focal accumulation in the 18 patients investigated. Using [^{111}In-DTPA-D-Phe^{1}]-pentetreotide, SPET discovered four lymph node metastases (size 1 cm in diameter) in two patients (nos. 2+12) in whom planar views had previously identified only one lymph node metastasis. SPET provided no new information in the other 16 patients. In comparison, SPET studies of the thorax using ^{99m}Tc(V)-DMSA additionally localized eight lymph node metastases in four patients. SPET confirmed the diagnosis of hepatic metastases (n=5) in another patient (no. 13) in whom conventional imaging modalities and planar views had previously detected only three liver metastases. The smallest lesion identified by scintigraphy was a 6 mm in diameter lymph node metastasis [^{99m}Tc(V)-DMSA positive] located in the upper mediastinum. Somatostatin receptor scintigraphy only demonstrated tumours more than 1 cm in diameter. Metastases localized by [^{111}In-DTPA-D-Phe^{1}]-pentetreotide in the mediastinum exceeded 2.5 cm in diameter. Eighteen sites of increased uptake could be shown by [^{111}In-DTPA-D-Phe^{1}]-pentetreotide and 41 lesions were detected by ^{99m}Tc(V)-DMSA (Figs. 1, 2). Details of tumours detected are given in Table 2.

Eight true-positive lesions could be visualized by both scintigraphic techniques. Eight lesions (true-positive) could be shown only with the ^{111}In-labelled somatostatin analogue, whereas 30 tumour-involved lesions demonstrated only ^{99m}Tc(V)-DMSA uptake. At surgery a total of 60 lesions (true-positive=55; false-positive=5) could be removed and nine metastases not previously detected by scintigraphy were found. Overall, lesion detection sensitivities for ^{99m}Tc(V)-DMSA and [^{111}In-DTPA-D-Phe^{1}]-pentetreotide were 69% and 29%, respectively. Comparison with histological findings revealed that metabolic and receptor imaging had a sensitivity of 84% (n=46/55) for the diagnosis of MTC.

Five surgically removed foci were adjudged false-positive with respect to MTC metastases. Histologically, three suspicious hot spots [^{99m}Tc(V)-DMSA positive n=2; [^{111}In-DTPA-D-Phe^{1}]-pentetreotide positive n=1] showed lymphadenitis. The other false-positive lesions, an enchondroma of the right humerus [^{99m}Tc(V)-DMSA positive] and a pheochromocytoma of the right adrenal



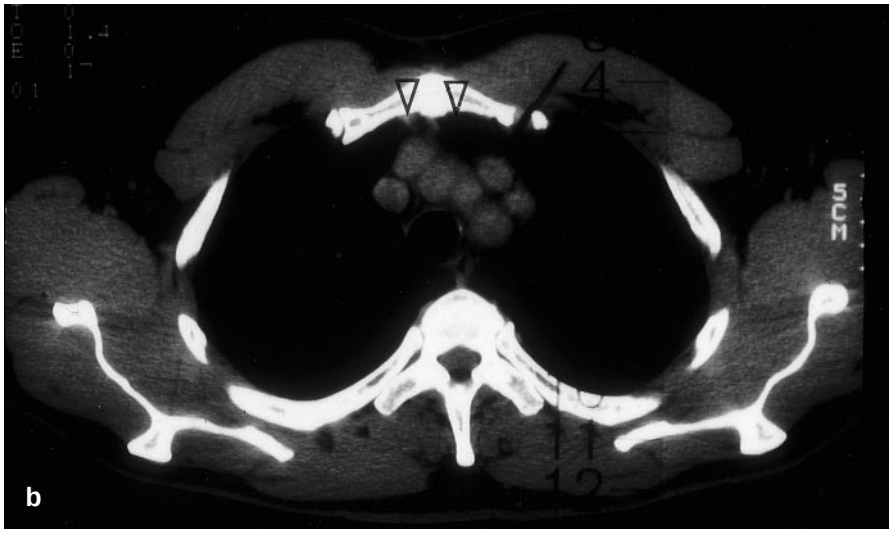


Fig. 2a, b. Multiple metastases of recurrent MTC. **a** ^{99m}Tc(V)-DMSA scan of the upper mediastinum and right cervical compartment; anterior planar view, 4 h after injection. **b** CT scan of the chest (transverse slice) showing the metastases. *Arrows*: site of tumour

Table 2. Comparison of histologically proven lesions detected by metabolic and receptor imaging in patients with recurrent MTC

Patient	SMS identical to DMSA	SMS additional to DMSA	Site	DMSA identical to SMS	DMSA additional to SMS	Site	Lesions detected by CT	Lesions identified by surgery
1	2 (TP)	–	um	2 (TP)	–	um	1 (TP)	2 (TP)
2	–	2 (TP)	rc	Negative	Negative	–	–	2 (TP)
3	Negative	Negative	–	–	7 (TP)	rc, lc	–	8 (TP)
4	Negative	Negative	–	–	3 (TP)	rc	–	3 (TP)
5	Negative	Negative	–	–	5 (TP)	um	3 (TP)	5 (TP)
6	–	1 (TP)	Sternum	–	1 (FP)	rh	2 (FP)	1 (TP) / 1 (FP)
7	2 (TP)	–	mm	2 (TP)	1 (TP)	mm	–	3 (TP)
8	Negative	Negative	–	–	3 (TP)	um	1 (TP)	3 (TP)
9	–	2 (TP)	rc	Negative	Negative	–	2 (TP)	2 (TP)
10	–	1 (FP)	lc	–	3 (TP)	um	–	3 (TP) / 1 (FP)
11	Negative	Negative	–	–	2 (FP)	rc	2 (TP)	2 (TP) / 2 (FP)
12	–	2 (TP) 1 (FP)	tb ag	Negative	Negative	–	–	2 (TP) / 1 (FP)
13	Negative	Negative	–	–	5 (TP)	liver	3 (TP)	7 (TP)
14	2 (TP)	–	lc	2 (TP)	–	lc	–	2 (TP)
15	2 (TP)	–	um	2 (TP)	–	um	2 (TP)	2 (TP)
16	Negative	Negative	–	–	2 (TP)	mm	1 (TP)	3 (TP)
17	Negative	Negative	–	–	1 (TP)	rc, lc	1 (TP)	3 (TP)
18	–	1 (TP)	rc	Negative	Negative	–	–	2 (TP)
Total	Σ=8 lesions	8 (TP) 2 (FP)		Σ=8 lesions	30 (TP) 3 (FP)		16 (TP) 2 (FP)	55 (TP) 5 (FP)
		Σ=10 lesions			Σ=33 lesions		Σ=18 lesions	Σ=60 lesions

SMS, [^{111}In-DTPA-D-Phe^{1}]-pentetreotide; DMSA, ^{99m}Tc(V)-DMSA; um, upper mediastinum; mm, middle mediastinum; rc, right cervical compartment; lc, left cervical compartment; tb, thyroid bed; rh, right humerus; ag, adrenal gland; TP, true-positive, FP, false-positive

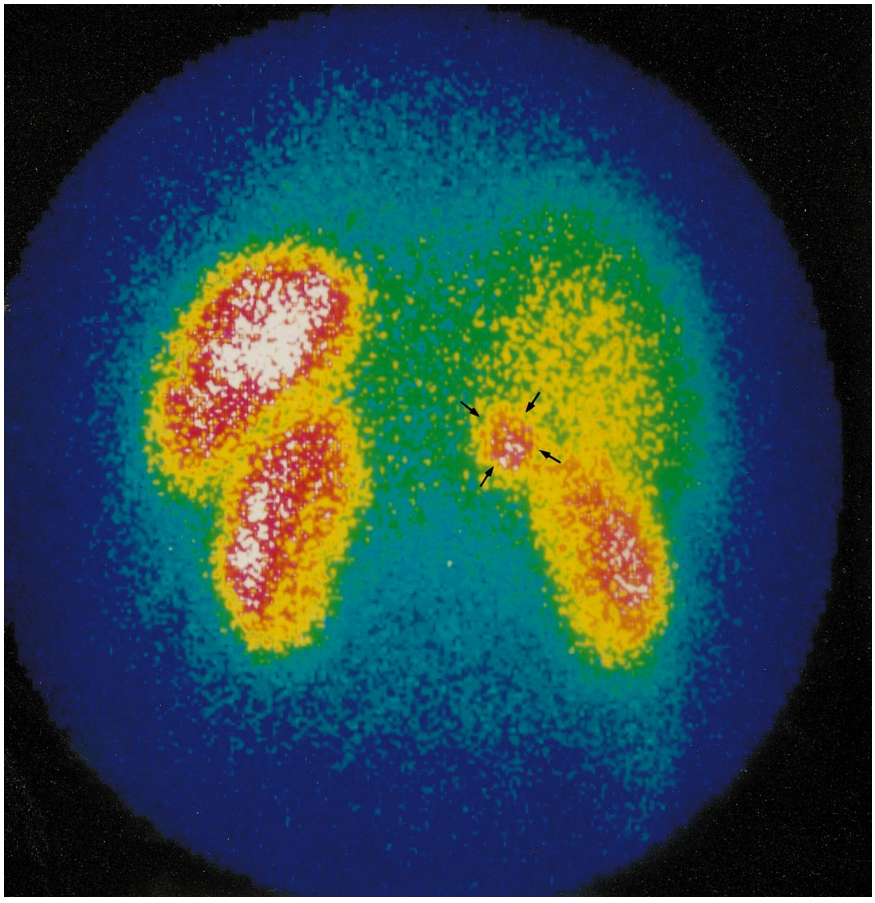


Fig. 3. Posterior planar [^{111}In-DTPA-D-Phe^{1}]-pentetreotide scintigram (posterior planar view; 24 h after injection). The localization of a histologically proven pheochromocytoma (right adrenal gland) in a patient with MEN II syndrome has to be adjudged as a false-positive scintigraphic finding only with respect to MTC. *Arrows*: site of tumour

gland ([^{111}In-DTPA-D-Phe^{1}]-pentetreotide positive; ^{123}I-metaiodobenzylguanidine [MIBG] scintigraphy negative) in the patient with MEN II syndrome were scintigraphically identified by planar imaging (Fig. 3).

Discussion

Early diagnosis of small and occult metastases of MTC provides the optimal condition for curative outcome. The possibility of surgical removal depends on whether the malignant lesions are multifocally spread or localized. The tumour marker calcitonin is very sensitive in the follow-up of MTC and may be elevated long before any imaging technique can localize metastases or recurrences [7]. Tumour-avid radiopharmaceuticals such as ^{99m}Tc phosphates and ^{201}Tl chloride have been used with limited success to localize MTC. ^{131}I- or ^{123}I-MIBG, which has already been successfully applied as a scintigraphic agent for adrenergic tissue, has been suggested as a metabolic tracer for MTC [17]. The limited uptake of ^{131}I-MIBG by MTC (25%–30%) indicates that this radiopharmaceutical has questionable value in the detection of recurrence, but its potential role in therapy in patients with significant uptake warrants further investigation [17, 18].

The biological behaviour of MTC is generally regarded to be intermediate between anaplastic and differentiated thyroid carcinomas [19]. The tumour marker CEA has been suggested for evaluating the prognosis of patients with recurrent MTC [20]. Increasing CEA levels are frequently associated with increased mitotic activity and often lack somatostatin receptors, whereas somatostatin receptor expression is associated with differentiation and slow proliferation [13, 21]. In our study, using the somatostatin analogue [^{111}In-DTPA-D-Phe^{1}]-pentetreotide only 29% of all lesions were detected and verified as recurrent MTC. Other working groups have described positive scintigraphic results ranging from 37% up to 77% [13, 14, 22–24]. One explanation for these divergent results may be the fact that a minority of neuroendocrine tumours such as MTC and insulinomas express subtypes of somatostatin receptors, characterized by low affinity for [^{111}In-DTPA-D-Phe^{1}]-pentetreotide [12]. Furthermore, endogenous production of somatostatin by some human MTCs might hamper both, the in vitro and the in vivo detection of somatostatin receptors [13]. In agreement with the findings of Baudin et al. [24], in our study [^{111}In-DTPA-D-Phe^{1}]-pentetreotide was not able to localize small tumour sites (<1 cm), whereas ^{99m}Tc(V)-DMSA localized metastases which had a size of at least 6 mm in diameter.

Ohta et al. have postulated that because pentavalent DMSA resembles the phosphate ion, this is the mechanism by which ^{99m}Tc(V)-DMSA accumulates in tumours, particularly in MTC, in which calcification is a well-recognized phenomenon [25]. Radionuclide scanning with tumour-seeking agents such as ^{99m}Tc(V)-DMSA has previously been used for scintigraphic imaging of recurrent MTC with a sensitivity from 23% up to 95% [26, 27]. In our study ^{99m}Tc(V)-DMSA detected recurrent MTC with a sensitivity of 69%. In one patient an enchondroma of the right humerus was identified scintigraphically in accordance with the observation that ^{99m}Tc(V)-DMSA tumour uptake occurs in patients with soft tissue sarcoma, osteosarcoma, prostatic carcinoma and other benign and malignant head and neck tumours [28, 29].

We found that the combination of metabolic and receptor imaging had a sensitivity of 84% for the detection of MTC lesions, as assessed by histological findings; however false-positive ^{99m}Tc(V)-DMSA and [^{111}In-DTPA-D-Phe^{1}]-pentetreotide accumulation was caused by chronic inflammation. The localization of a histologically proven pheochromocytoma in the patient with MEN II syndrome has to be judged as a false-positive scintigraphic finding only with respect to MTC. However, pheochromocytoma is known to express somatostatin receptors and due to the co-occurrence of pheochromocytoma and MTC in MEN II syndrome, it is impossible to attribute metastatic lesions to one of these diseases based on scintigraphic results [30].

Conclusion

These preliminary results suggest that the combination of metabolic [^{99m}Tc(V)-DMSA] and receptor ([^{111}In-DTPA-D-Phe^{1}]-pentetreotide) imaging is more sensitive for tumour localization in patients with recurrent MTC than the use of only one radiopharmaceutical. However, neither ^{99m}Tc(V)-DMSA nor [^{111}In-DTPA-D-Phe^{1}]-pentetreotide is specific for MTC and false-positive scintigraphic findings have to be considered. Furthermore, somatostatin receptor scintigraphy cannot visualize small tumour sites (<1 cm). Further studies are needed to evaluate the definite role of combined metabolic and receptor imaging in the management of patients with recurrent MTC.

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