Imaging in Medullary Thyroid Cancer 18

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18.1 Introduction

Medullary thyroid cancer (MTC) results from malignant de-differentiation of the parafollicular cells ("C cells") in the thyroid [2]. It was recognized in 1959 by Hazard as a clinicopathological entity that is different from other forms of differentiated thyroid cancer [17], originating from the iodine-processing thyrocytes. Over the subsequent decade, investigators identified and described the parafollicular C cell, which produces calcitonin, which is involved in the regulation of calcium homeostasis and bone metabolism [13]. In 1966 and 1967, Williams suggested that MTC arises from this C cell population [38]. This hypothesis could be confirmed by several subsequent investigators who documented elevated serum calcitonin levels in MTC patients. In the 1970s, Wells and co-workers established a provocative test, the pentagastrin stimulation test, which rendered calcitonin one of the most sensitive and specific tumor markers in oncology [37].

MTC accounts for between 3% and 12% of all thyroid cancers [2]. Genetic studies in the 1980s and 1990s demonstrated that it does occur in distinct familial syndromes. Whereas 60%–80% of all MTC cases are sporadic, 20%–40% were demonstrated to be associated with mutations in the *RET* proto-oncogene (either as isolated MTC or in the context of a hereditary multiple endocrine neoplasia [MEN] syndrome) [1, 2, 27].

Embryologically, the parafollicular C cells arise from the neural crest and, thus, are identified as APUD cells with a high content of chromogranin and neuron-specific enolase. C cells secrete a variety of proteins and peptides, including the characteristic calcitonin, but also ACTH, serotonin, prostaglandins, vasoactive intestinal peptide (VIP), somatostatin, and a variety of other endocrine substances [2, 38]. Malignant C cells additionally secrete procalcitonin, which precipitates as stromal amyloid around the tumor cells. An extraordinarily high percentage of MTCs express and secrete high amounts of carcinoembryonic antigen, and occasionally also CA 19-9 [2, 28, 36].

Since the C cells are located primarily in the upper and middle thirds of the thyroid gland, with a particular concentration laterally and posteriorly, MTC primary tumors are usually found in this location (cf. Fig. 18.1). This has also important implications for the lymphatic drainage and for the location of lymph node metastases (see below; cf. Fig. 18.7c).

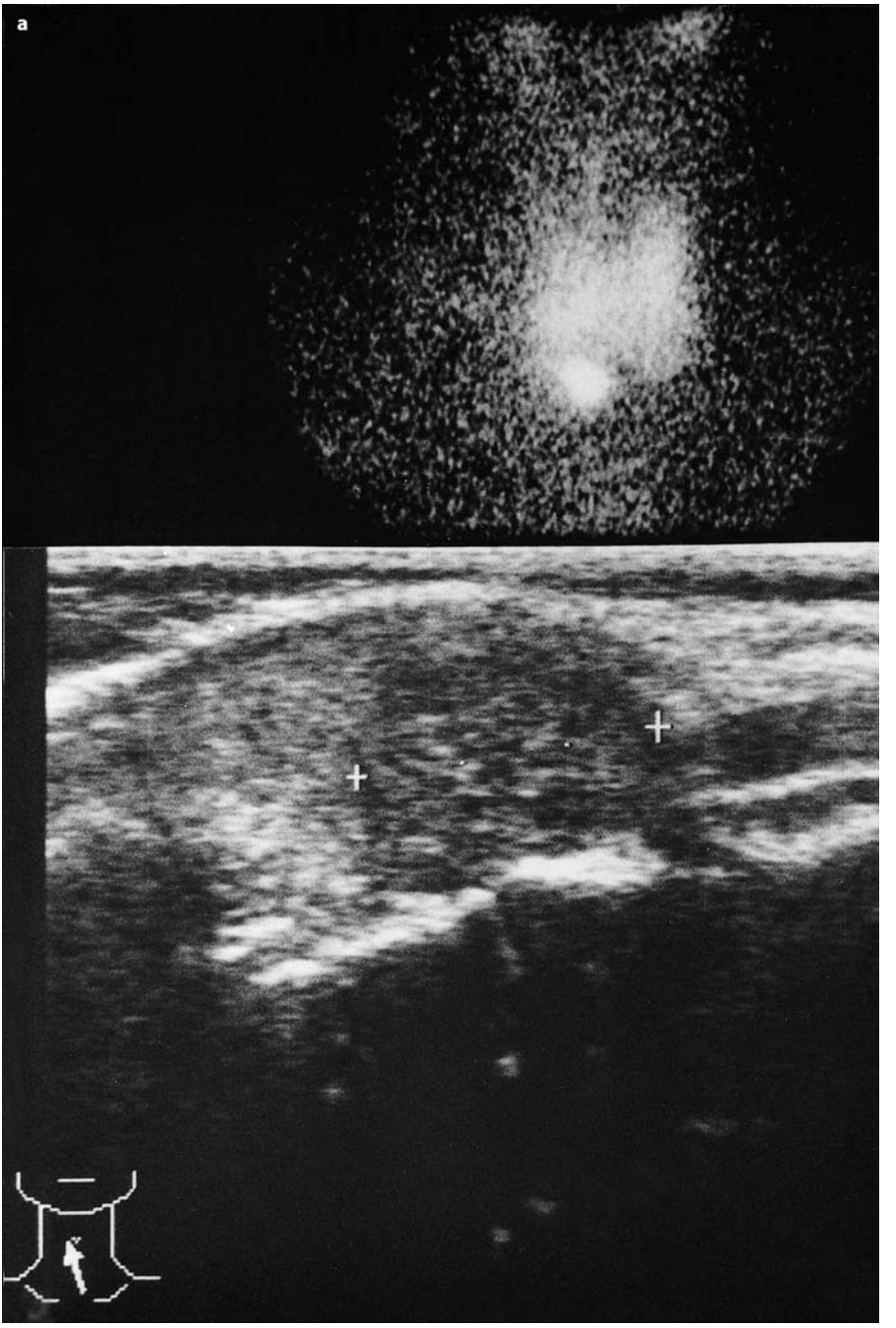
The 5-year survival of MTC patients is, at approximately 70% (10-year survival rates are approximately 30%), clearly worse than the survival rates of patients with other forms of differentiated thyroid tumors [2, 12, 34]. One of the major reasons is probably the fact that, with the exception of anecdotically reported mixed medullary/follicular thyroid cancers [23, 26], MTCs do not take up and do not concentrate radioiodine. This is the reason why, in contrast to the outstanding role of radioiodine in the staging, follow-up, and therapy of other forms of differentiated thyroid cancer, it is more or less useless in MTC patients [2].

Frequently, MTC remains occult or only slowly progressive for many years. It is diagnosed incidentally in a multinodular goiter or, occasionally, after a long diagnostic odyssey in patients with persistent and therapy-refractory diarrhea [19]. Frequently, postsurgically persisting tumor marker levels indicate the presence of metastatic disease, although imaging is unable to identify the responsible lesions ("occult disease"). Usually, even metastatic MTC remains clinically inapparent for many years, before eventually changing into an accelerated, more rapidly metastasizing form with endocrine symptomatology which may be hard to influence therapeutically. Therefore, the management of patients with MTC encounters three distinct clinical scenarios: (a) diagnosing and identifying the primary tumor, (b) identifying responsible lesions in patients with persistently elevated tumor marker levels following surgery (occult disease), and (c) staging of the manifest metastatic situation. This chapter intends to critically review the currently available radiological imaging modalities which can be used for primary staging or restaging of MTC patients in these different clinical settings.

18.2 Diagnosis and Localization of the Medullary Thyroid Primary Tumor; Presurgical Staging

Since MTCs cause symptoms only in very advanced tumor stages, most of them are diagnosed incidentally. Usually, MTC primaries appear as scintigraphically cold, sonographically hypodense nodules (Fig. 18.1). With respect to these sonographic and scintigraphic features, there is no difference between medullary and other forms of thyroid malignancies. For differentiation, fine-needle aspiration cytology may help to establish the diagnosis preoperatively (Fig. 18.1c, d). Also serum calcitonin determination may be helpful in differential diagnosis.

Fig. 18.1 a–d MTC in a 59-year-old woman with a history of colorectal cancer and rising serum CEA levels (7.5 ng/ml at the time of presentation). **a** Ultrasonography of the neck shows a solid, hypoechoic nodule in the right lobe of the thyroid (*lower panel*), corresponding to a scintigraphically cold area in the pertechnetate scan (*upper panel*)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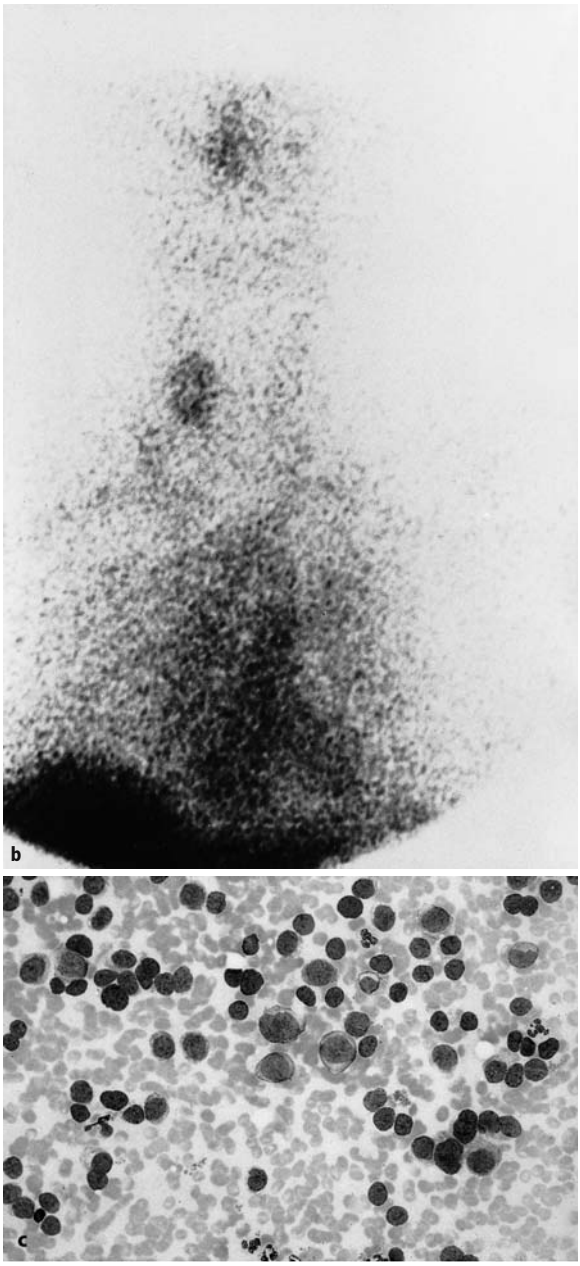

Fig. 18.1 b–c **b** Immunoscintigraphy with a ^{99m}Tc-labeled anti-CEA antibody, clone BW431/26, shows intense antibody accumulation in this nodule in the right lobe of the thyroid. **c** Fine-needle aspiration cytology

Interestingly, Pacini and co-workers published a study in 1994, investigating whether routine measurement of serum calcitonin could improve the preoperative diagnosis of sporadic MTC [29]. Almost 1,500 consecutive patients,

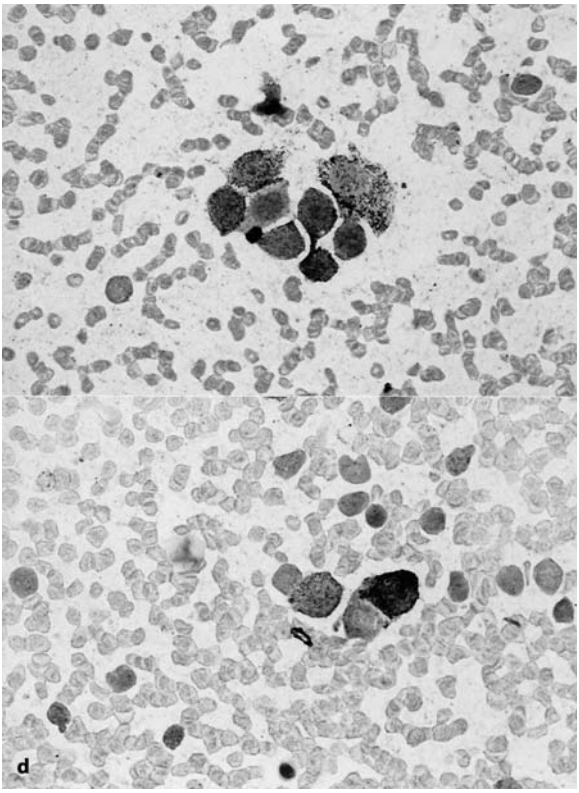

Fig. 18.1 d Immunohistochemical staining show calcitonin (*upper panel*) and chromo-granin-A (*lower panel*) expressing cells, proving their neuroendocrine origin, which is in accordance with a primary MTC

presenting for nodular thyroid disease during 1 year, were submitted to serum calcitonin determination and fine-needle aspiration cytology. The clinical diagnosis was nontoxic nodular goiter in 86% of these patients, toxic multinodular goiter in 5%, autonomously functioning thyroid nodule in another 5%, and autoimmune thyroid disease with nodules in the remaining 4%. As controls, almost 200 patients with nonnodular thyroid disease and more than 30 normal subjects were included. Patients with fine-needle biopsy suspicious of any kind of thyroid carcinoma and patients with elevated basal and pentagastrin-stimulated serum calcitonin, regardless of the results of biopsy, were submitted to surgery. Eight (0.6%) patients (seven with nontoxic nodular goiter and one with thyroid autonomy) had elevated basal serum calcitonin levels. The pentagastrin test was abnormal in all of them. Fine-needle biopsy was suggestive of MTC in two, thyroid carcinoma in one, and benign nodule in three, and was inadequate in two. By histology, immunohistochemistry, and Northern blot analysis of total tumor RNAs, MTC was confirmed in all patients, including the one with thyroid autonomy, who had the association of microfollicular adenoma and a small MTC in the same lobe. The authors concluded that these results indicate that serum calcitonin measurement is useful for the screening of sporadic MTC in patients with thyroid nodules. The prevalence of MTC, diagnosed by serum

calcitonin measurement, was surprisingly high: 0.6% of all thyroid nodules and 16% of all thyroid carcinomas [29].

Occasionally, pathologically elevated CEA serum levels can lead to the diagnosis of MTC as well. In no less than eight out of 235 (i.e., more than 3%) colorectal cancer patients who presented with an unexplained rise in serum CEA levels, we found an occult MTC primary as the reason for the tumor marker elevations (Fig. 18.1) [5].

Summarizing, presurgical staging of MTC includes, besides a thorough clinical examination, thyroid hormone, calcitonin, and CEA serum level determinations and ultrasonography of the neck, and optionally also chest radiography and computed tomography of the neck, chest, and abdomen.

18.3 Imaging and Disease Localization in the Follow-up of Patients with MTC

18.3.1 Conventional Radiological Techniques (Ultrasonography, X-ray, Computed Tomography, Magnetic Resonance Imaging, Bone Scanning)

Due to the extraordinarily high sensitivity and specificity of calcitonin, especially in the context of provocative tests, regular serum calcitonin determinations play a key role in the follow-up of MTC patients. Other peptides (e.g., somatostatin) and tumor markers, with the exception of CEA, have been shown to be much less sensitive, and thus do not play a relevant clinical role. Frequently, elevated calcitonin levels indicate the persistence or presence of malignant C cells even though all conventional imaging procedures [ultrasonography, X-ray, computed tomography (CT), magnetic resonance imaging (MRI)] fail to localize responsible lesions ("occult disease," cf. Fig. 18.2). This is mainly due to the fact that the total tumor mass is very small, with diffuse (micro-)metastatic spread to the lung, liver, or bone marrow, and with individual lesions being too small to be detectable by conventional radiological methods [2, 6].

Local recurrences and cervical lymph node metastases are usually detectable by ultrasonography, whereas in many cases, mediastinal and hilar lymph node metastases correspond to normally sized lymph nodes, escaping radiological diagnosis (the sometimes encountered calcifications are ambiguous, allowing for several differential diagnoses) (Fig. 18.2). Pulmonary lymphangiosis frequently escapes radiological diagnosis, as is the case in other forms of differentiated thyroid cancer, so that only biopsy is able to clearly prove its presence. In bone scanning, due to their low metabolic activity, bone metastases are difficult to distinguish from other, nonneoplastic processes, such as degenerative changes [2, 6]. Often, liver metastases are hypervascular so that they are solely visualized by CT without intravenous contrast agent, becoming isointense to the normal liver parenchyma after i.v. injection of contrast dye (Fig. 18.3a) [20].

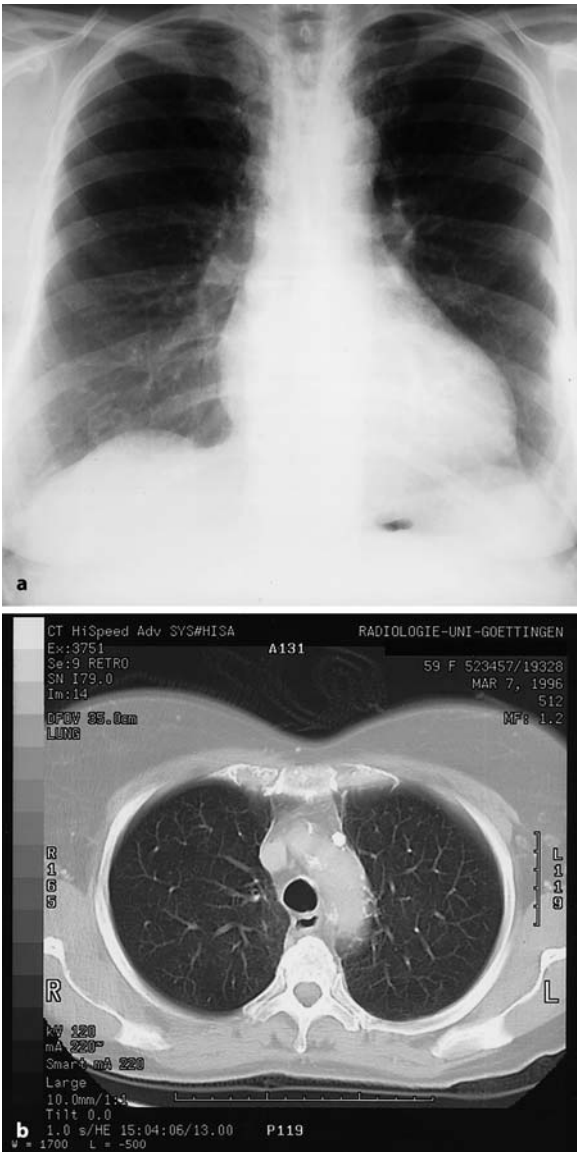

Fig. 18.2 a–d Metastatic involvement of mediastinal lymph nodes in a woman with occult metastatic MTC. Whereas the chest radiograph (**a**) is without pathological findings and a CT scan of the chest (**b**) merely shows some nonspecific calcified lymph nodes, somatostatin receptor scintigraphy (**c**) shows typical bilateral lymph node involvement ("chimney sign"). By contrast, FDG-PET (**d**) is false-negative

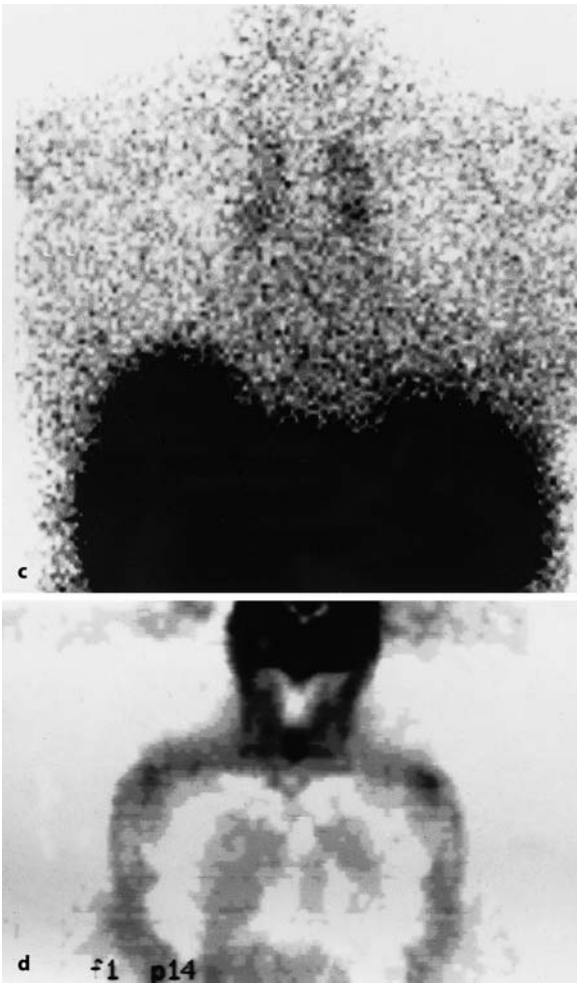

Fig. 18.2 c–d.

18.3.2 Traditional Scintigraphic Techniques [^{201}Tl Chloride, ^{99m}Tc-(V)-DMSA, $^{123/131}$I-MIBG, etc.]

In contrast to other forms of differentiated thyroid cancer, MTC usually does not concentrate radioiodine, with the very rare exception of mixed medullary follicular carcinomas [23, 26]. There is a multitude of studies on the diagnostic sensitivities and accuracies of a range of more or less non-MTC-specific tumor-seeking radiopharmaceuticals, such as ^{201}Tl chloride (uptake as K^+ analog via Na^+/K^+-ATPase) [2], ^{99m}Tc-labeled phosphonates (specific uptake in osteoblastic bone lesions or in calcifications of soft tissue metastases) [2], ^{67}Ga citrate [transchelation of gallium as iron analog into transferrin, uptake via CD71 (transferrin receptors)] or

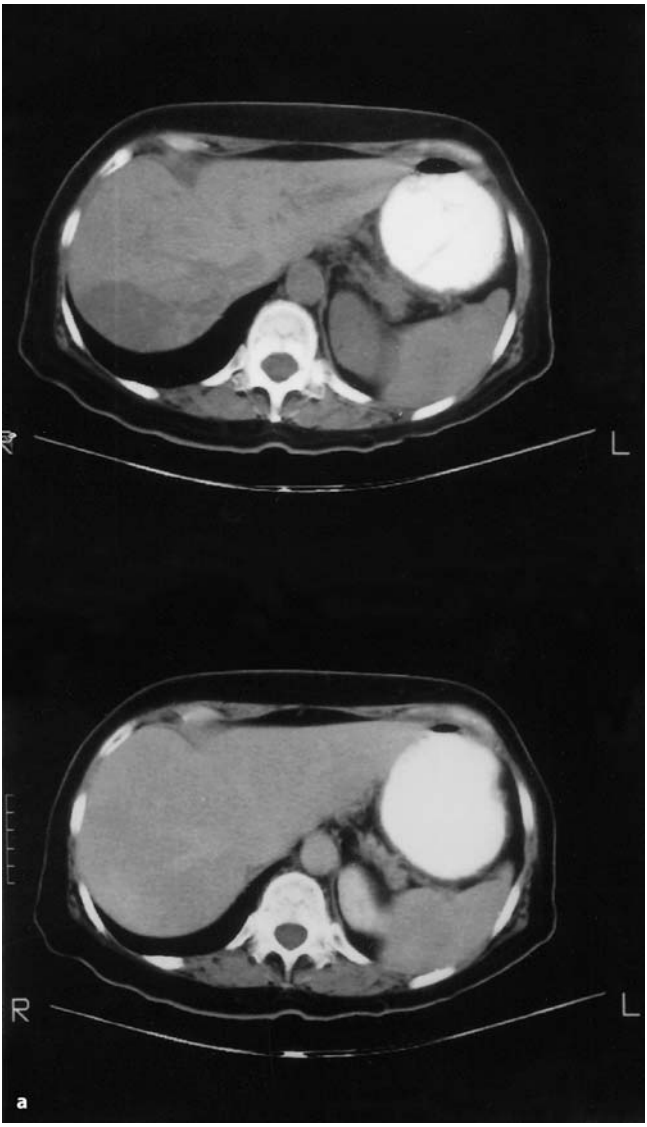

Fig. 18.3 a–c Imaging and therapeutic response with ^{131}I-labeled anti-CEA antibodies in a 72-year-old woman with advanced metastatic MTC (local recurrence and lung, pleural, and liver metastases). **a** Hypervascular liver metastasis is visible as hypodense lesions in the plain CT scan (*upper panel*) but becomes isointense to the normal liver parenchyma, and thus invisible, in the contrast-enhanced CT scan (*lower panel*)

^{99m}Tc-(V)-dimercaptosuccinic acid (DMSA) [18]. ^{123}I- or ^{131}I-metaiodobenzylguanidine ($^{123/131}$I-MIBG) is chemically related to the anti-sympathomimetic drug guanethidine, which is taken up by neuroendocrine cells via the norepinephrine

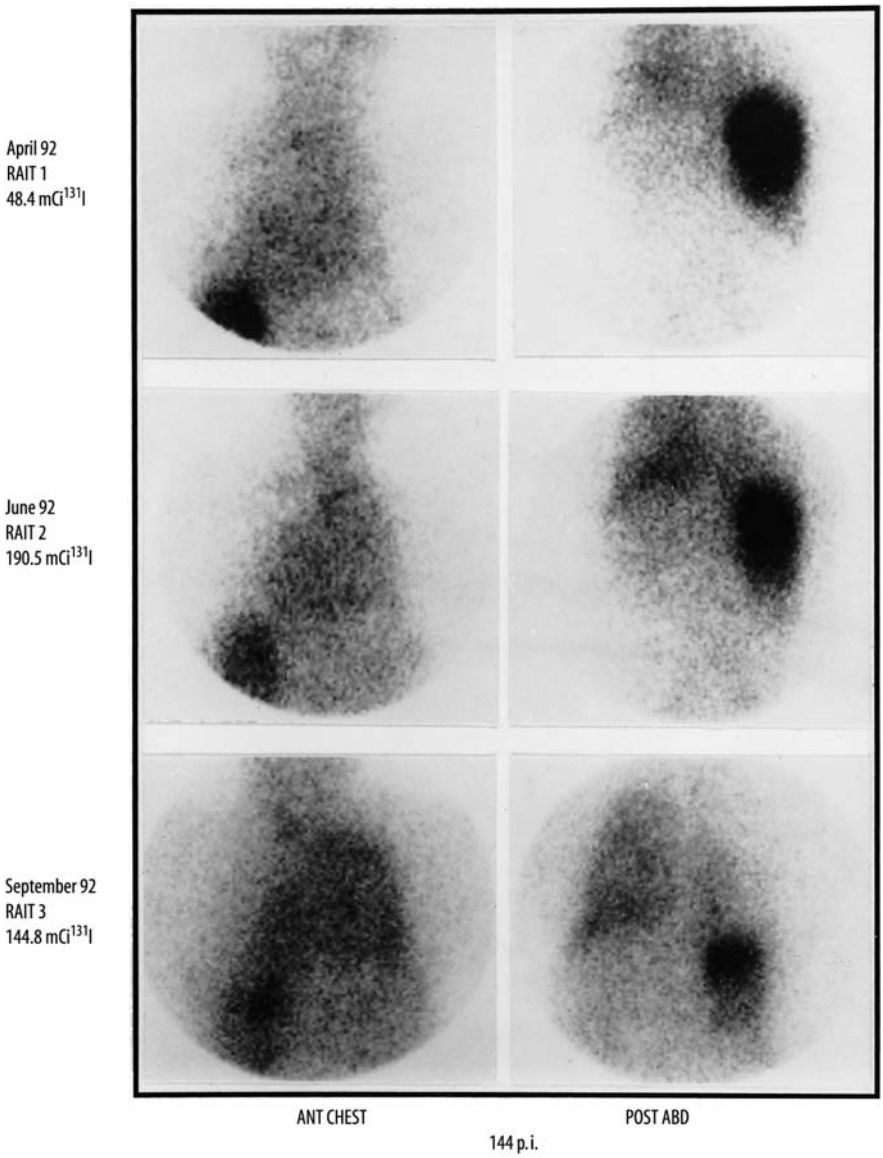

Fig. 18.3 b Tumor targeting in the same patient on the occasion of three therapy injections (144 h p.i. each)

reuptake mechanism. MIBG is stored intracellularly in chromaffin granules [3]. However, in contrast to pheochromocytoma and neuroblastoma, its uptake is rather low in MTC. Summarizing, all these scintigraphic techniques are more or less nonspecific and have yielded variable results clinically.

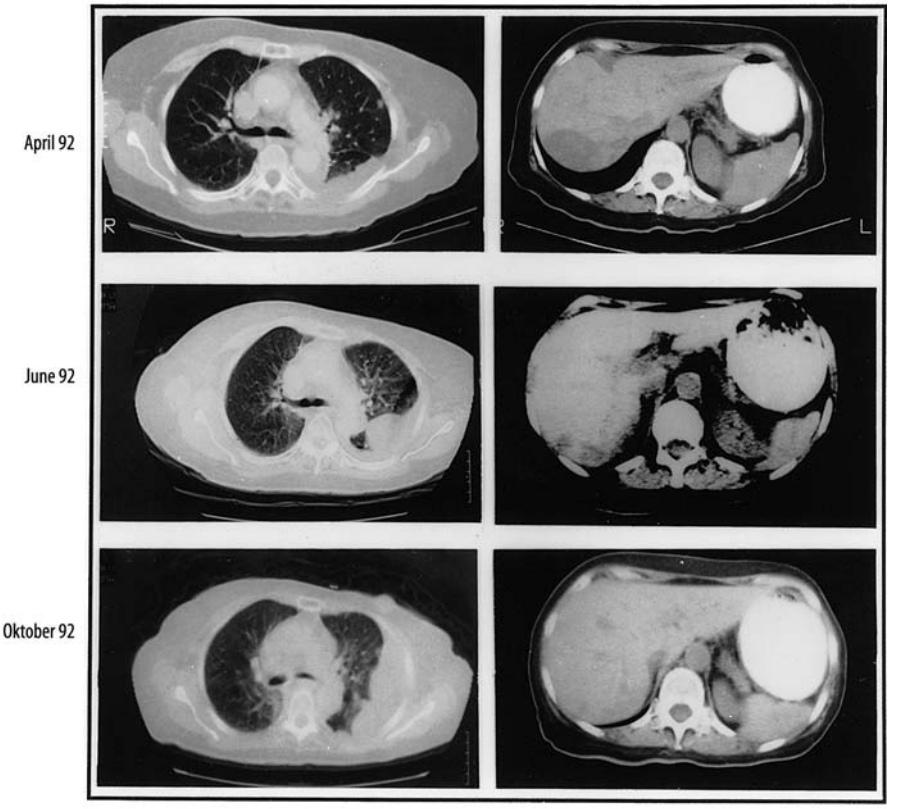

Fig. 18.3 c The large hyperperfused liver metastasis disappeared completely 1 month after the third therapy injection, having received a total dose of approximately 65 Gy, whereas the pleural effusion is progressing (thus representing a mixed response)

18.3.3 Modern Nuclear Medical Techniques (Anti-CEA Immunoscintigraphy, Somatostatin Receptor Scintigraphy, Positron Emission Tomography)

After some disappointing results of immunoscintigraphy [30], more modern approaches with high-affinity antibodies were able to show excellent results in manifest as well as occult metastatic disease. Juweid et al. reported on 26 patients with known or occult MTC who were studied with radiolabeled anti-CEA antibodies [20, 22]. The targeting results of ^{99m}Tc-, ^{123}I-, and ^{131}I-labeled anti-CEA antibodies indicated that all these reagents were capable of detecting established and occult MTC. The sensitivity for detection of known sites of disease ranged from 76% to 100% for the various anti-CEA antibodies used, when compared with CT, MRI, bone scan, or other imaging modalities [20–22]. More-

over, the antibody scan was positive in seven of nine patients with occult disease (patients with negative conventional imaging studies, but who had elevated calcitonin and/or CEA levels). Three of these seven patients underwent surgery and the disease was confirmed by histopathology in all three. The authors concluded that anti-CEA antibodies are excellent agents for imaging recurrent, residual, or metastatic MTC. The high lesion sensitivity in patients with known lesions, combined with the ability to detect disease, may make these agents ideal for staging patients, for monitoring disease pretherapy or posttherapy, and especially for evaluating patients with recurrent or persistent hypercalcitonemia or CEA elevations after primary surgery. The authors even postulated that radiolabeled anti-CEA antibodies may achieve a role in diagnosing and monitoring patients with MTC similar to that of radioiodine in the evaluation of patients with differentiated thyroid cancer. Initially promising results were also reported by the same authors with the therapeutic use of radiolabeled anti-CEA antibodies (Fig. 18.3) [21].

Enthusiastic hopes accompanied the introduction of somatostatin receptor scintigraphy [15, 16]. In vitro data had shown that MTCs not only produce somatostatin themselves, but also express corresponding receptors. After initially very optimistic reports indicating sensitivities of more than 90% in known as well as occult MTC, subsequent studies were unable to reproduce these apparently excellent results in larger series of patients.

We were able to show in a series of almost 30 patients that somatostatin receptor scintigraphy of occult MTC has a good sensitivity which is superior to that of conventional radiological methods in the neck and mediastinum (cf. Figs. 18.2 and 18.4). We found a typical metastatic pattern: in patients with persistently elevated calcitonin levels in the immediate postsurgical period, cervical or supraclavicular lymph node metastases were identified in most cases. In patients with postsurgically normalized, but slowly increasing calcitonin levels, bilateral "chimney-shaped" mediastinal lymph node involvement was found, for which we coined the term "chimney-sign" (Figs. 18.2, 18.5 and 18.6) [6, 7].

In this context, we recently compared the sensitivity and diagnostic accuracy of immunoscintigraphy with anti-CEA antibodies and somatostatin analogs for the detection of recurrent or metastatic MTC [4, 6]. Additionally, we tried to assess whether there may be correlations between the scintigraphic behavior in both imaging modalities and the prognosis [4, 6]. A total of 26 patients with MTC were examined. Ten suffered from known disease, 14 from occult metastatic MTC, and two patients were free of disease at the time of presentation (as indicated by normal serum calcitonin after pentagastrin stimulation). All patients underwent conventional radiological evaluation (ultrasonography, CT, MRI) and/or biopsy within 4 weeks. Additional imaging was performed with ^{99m}Tc-(V)-DMSA, ^{123}I-MIBG, ^{201}Tl chloride, ^{99m}Tc-methylene diphosphonate (MDP), and/or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). Clinical follow-up for up to 10 years was obtained in all cases.

All patients with established disease had elevated plasma CEA (range 6.8–345 ng/ml) and calcitonin levels (92–11,497 pg/ml), whereas in 9/14 occult cases, CEA levels were, at ≤5 ng/ml, normal (overall range in occult disease patients: CEA 0.6–829 ng/ml; calcitonin 72–2,920 pg/ml). In patients with known

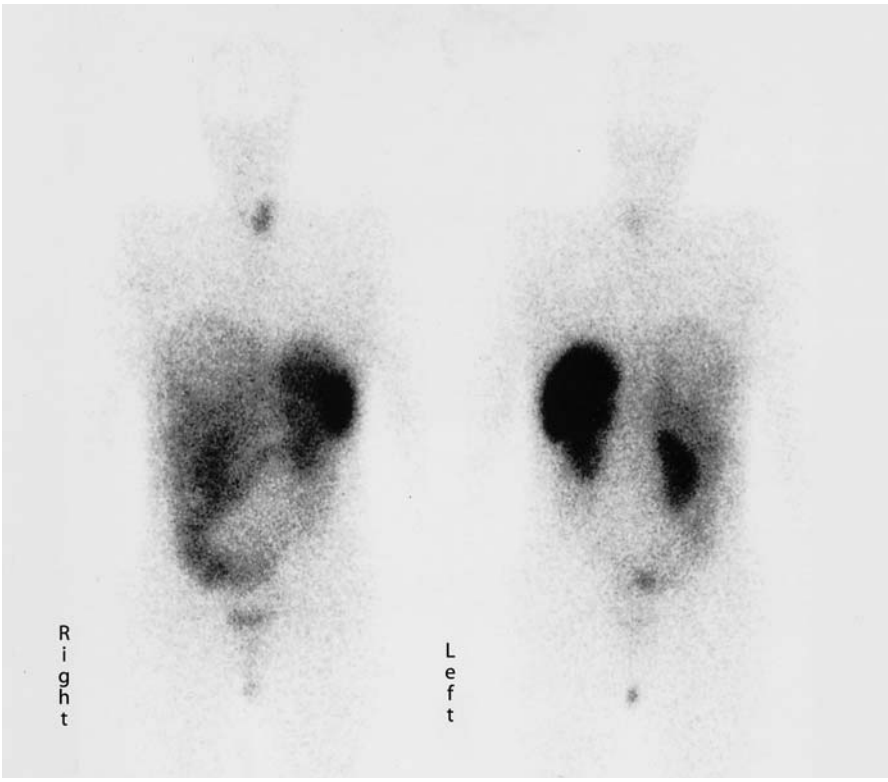

Fig. 18.4 Thirty-year-old woman with primary and metastatic MTC. Somatostatin receptor scintigraphy shows good ^{111}In-DTPA-octreotide uptake in the primary tumor in the left lobe of the thyroid, but no somatostatin receptor expression in a large liver metastasis (scan at 24 h p.i.). This is in accordance with the known loss of somatostatin receptor expression in dedifferentiating MTC

disease, the overall lesion-based sensitivity was 86% for anti-CEA immunoscintigraphy. In contrast, octreotide was unable to target any tumor in patients with rapidly progressing disease, or to detect distant metastases (resulting in an overall sensitivity of only 47%) (Figs. 18.4 and 18.6). However, in all patients with occult MTC, anti-CEA monoclonal antibodies as well as octreotide were able to localize at least one lesion (patient-based sensitivity virtually 100%). In patients with persistent hypercalcitoninemia following surgery, cervical lymph node metastases were identified as the most frequent site of disease, whereas in patients with occult and slowly progressing disease several years after primary surgery, immunoscintigraphy and octreotide showed bilateral involvement of mediastinal lymph nodes ("chimney sign") [7] (Figs. 18.2, 18.5 and 18.6); however, tumor/nontumor ratios were usually higher with octreotide in these cases. With anti-CEA antibodies, highest tumor/nontumor ratios were observed in clinically aggressive, rapidly progressing disease.

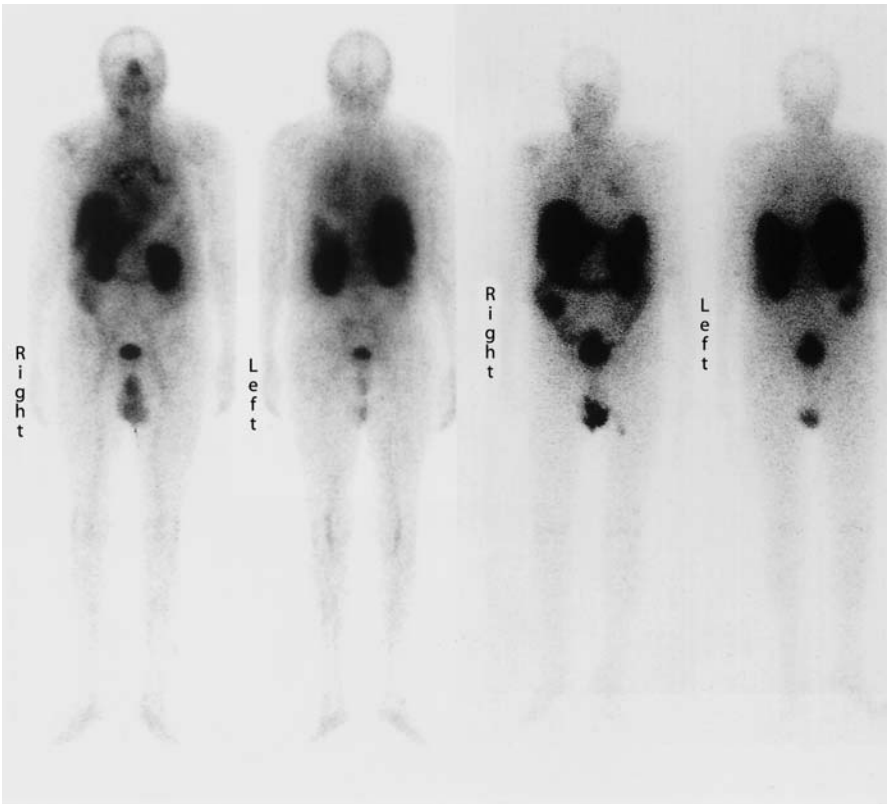

Fig. 18.5 Bilateral mediastinal lymph node involvement ("chimney sign") in a patient with the primary tumor in situ in the upper parts of the right lobe of the thyroid [*left panel*: anti-CEA immunoscintigraphy with ^{99m}Tc-labeled Fab' fragments, clone NP-4 (CEAScan); *right panel*: ^{111}In-DTPA-octreotide somatostatin receptor scintigraphy; both scans at 24 h p.i.]

We concluded from these data that for the detection of occult MTC, anti-CEA immunoscintigraphy and octreotide seem to have a sensitivity which is superior to conventional diagnostic modalities, especially when used in combination. However, better detectability with anti-CEA antibodies (probably corresponding to a higher tissue CEA expression) seems to be associated with more aggressive forms of MTC, whereas somatostatin receptor expression at normal plasma CEA levels and weaker antibody targeting is associated with a more benign clinical course [4, 6]. These data are in good accordance with the study of Busnardo et al. [14], who showed rising CEA and, at the same time, constant or decreasing serum calcitonin levels to be associated with a bad prognosis. These data also confirm the data of Mendelsohn et al. [25], who analyzed the relationship of tissue CEA and calcitonin expression to tumor virulence immunohistochemically; these authors found a clear increase in CEA and decrease in calcitonin expression with progressing dedifferentiation. Finally, our

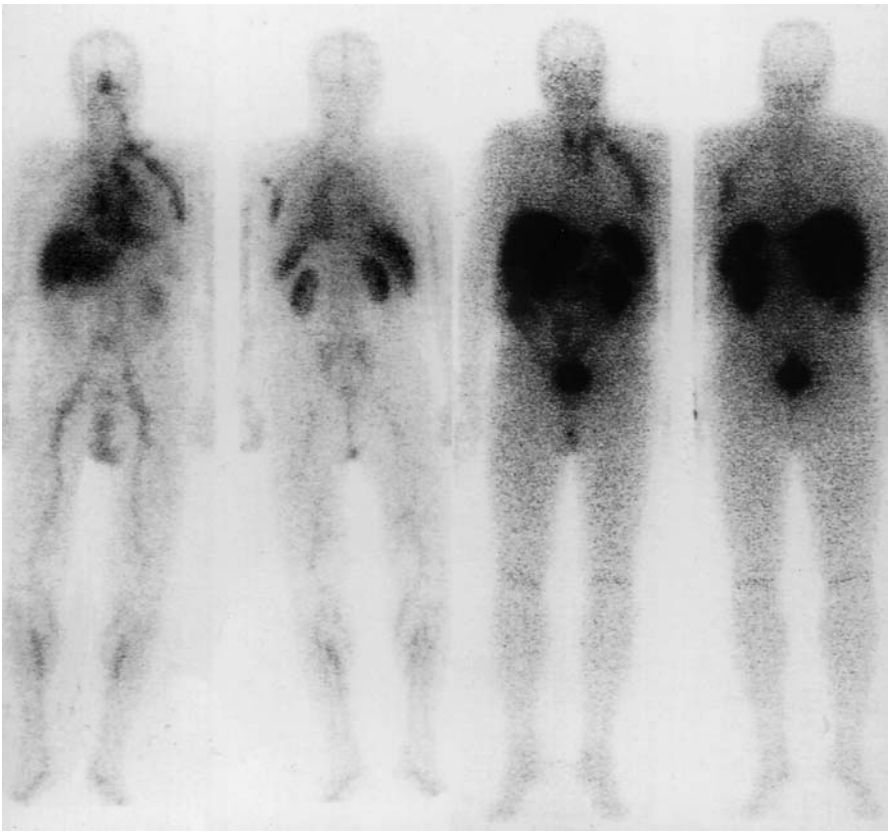

Fig. 18.6 Whole-body scans of a 67-year-old male with primary and metastatic MTC (*left panel*: ^{99m}Tc-anti-CEA IgG_1, clone BW431/26; *right panel*: ^{111}In-DTPA-octreotide; both scans at 24 h p.i.). Again, the primary tumor (in the cranial parts of the left lobe of the thyroid) seems to express both CEA and somatostatin receptors, as is the case for left supraclavicular and axillary lymph nodes, whereas more distant metastases (caudally located mediastinal lymph nodes, small liver metastases, and diffuse bone marrow involvement of the spine and sacrum) are merely positive with the CEA antibody, apparently lacking somatostatin receptors as a sign of their dedifferentiation

scintigraphic in vivo findings confirm in vivo the receptor autoradiographic in vitro data of Reubi et al. [32], who demonstrated the loss of somatostatin receptor expression in dedifferentiated MTC.

These scintigraphic findings even hold true within the same patient. As an illustration, Fig. 18.6 shows whole-body scans of a 67-year-old male with primary and metastatic MTC. The primary tumor (in the cranial parts of the left lobe of the thyroid) seems to express both CEA and somatostatin receptors, as is the case for left supraclavicular and axillary lymph nodes. In contrast, the chimney-shaped [7] cranial mediastinal lymph node involvement exhibits much stronger somatostatin receptor than CEA expression, whereas more distant metastases

(caudally located mediastinal lymph nodes, small liver metastases, and diffuse bone marrow involvement of the spine and sacrum) are only positive with the CEA antibody, apparently lacking somatostatin receptors. Thus: (a) the locoregional metastases (cervical and upper mediastinal lymph nodes), typically found in slowly progressing forms of MTC, preferentially express somatostatin receptors; (b) the more distant metastases (axillary and midmediastinal lymph nodes) express both CEA and somatostatin receptors; (c) lesions which originate from hematogenous spread and which are typical for aggressive metastatic MTC (liver and bone marrow) exclusively express CEA as a marker of their dedifferentiation [25]. Thus, scintigraphic visualization of MTC allows not only for lesion localization, but also for prediction of the patient's prognosis by means of tissue characterization in vivo [4].

Why, in contrast to other forms of differentiated thyroid cancer, MTC more frequently metastasizes in the more laterally located lymph node areas in the mediastinum, resulting in the typical chimney-shaped appearance in scintigraphic scans, is not completely clear at this point. It may be largely due to the fact that MTC primary tumors are usually located in the lateral parts of the thyroid (see above), which may have a different lymphatic drainage than the more medially located areas (Fig. 18.7).

In contrast to the outstanding diagnostic accuracy of FDG-PET in the staging of nonneuroendocrine tumors, FDG-PET has shown rather disappointing results in MTC (cf. Fig. 18.2). There is no larger study investigating the diagnostic accuracy of FDG-PET in a homogeneous MTC patient population, but the data available to date clearly demonstrate sensitivities and diagnostic accuracies of below 60% in MTC [24]. This is most likely due to the comparatively slow growth pattern as well as the comparatively good vascularization of MTC lesions, with a consequently low rate of anaerobic glycolysis and thus low glucose turnover.

18.4 Future Developments: Will Cholecystokinin-B/Gastrin Receptor Scintigraphy Allow for More Sensitive Staging of MTC?

The high sensitivity of pentagastrin stimulation in detecting primary or metastatic MTC suggests widespread expression of the corresponding receptor type on human MTC cells [8, 37]. Indeed, autoradiographic studies have demonstrated cholecystokinin (CCK)-B/gastrin receptors not only in over 90% of MTCs, but also in a high percentage of small cell lung cancers [31, 33] and potentially a variety of gastrointestinal adenocarcinomas [35]. In a pilot study, we demonstrated the feasibility of using radiolabeled gastrin-I to target CCK-B receptor expressing tissues in vivo in animals and patients [8]. The aim of our subsequent work was to systematically optimize, in a preclinical model, suitable radioligands for targeting CCK-B receptors in vivo. For this purpose, a variety of CCK/gastrin-related peptides, all having in common the C-terminal CCK-receptor binding tetrapeptide sequence Trp-Met-Asp-PheNH_2 or derivatives thereof, were studied

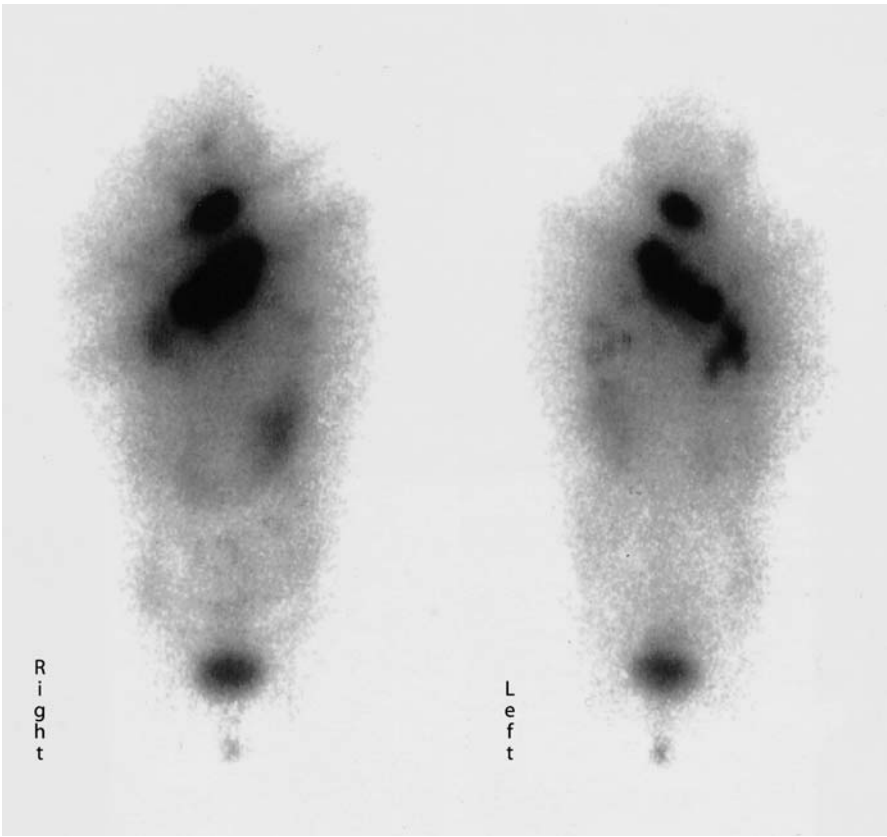

Fig. 18.7 a–c Differences in the lymphatic drainage between medullary and other forms of differentiated thyroid cancer. In papillary (a) as well as follicular (**b**) thyroid cancer (both $Na^{131}I$ posttherapy scans), mediastinal lymph node metastases are more randomly distributed, whereas in MTC (**c**), a typical bilateral lymph node involvement ("chimney sign") is commonly found (cf. Figs. 16.2, 16.5 and 16.6). This most likely reflects the different localization of the primary tumors (MTC is located more laterally than the other histological types; cf. the *hatched area*) and their respective draining lymph nodes, which, in the case of MTC, are localized more laterally in relation to the large vessels in the mediastinum

[9, 10]. They were radioiodinated by the Iodogen or Bolton-Hunter procedures. The peptides tested were members of the gastrin or CCK families, or possessed characteristics of both, which differ by the intramolecular position of a tyrosyl moiety (occurring in native or sulfated form). Their stability and affinity were studied in vitro and in vivo; their biodistribution and therapeutic efficacy were tested in nude mice bearing subcutaneous human MTC xenografts. DTPA derivatives of suitable peptides were synthesized and evaluated, labeled with ^{111}In.

All members of the CCK or gastrin family were stable in serum (with $t_{1/2}$'s of several hours at 37°C); nevertheless, the highest stability was found for those

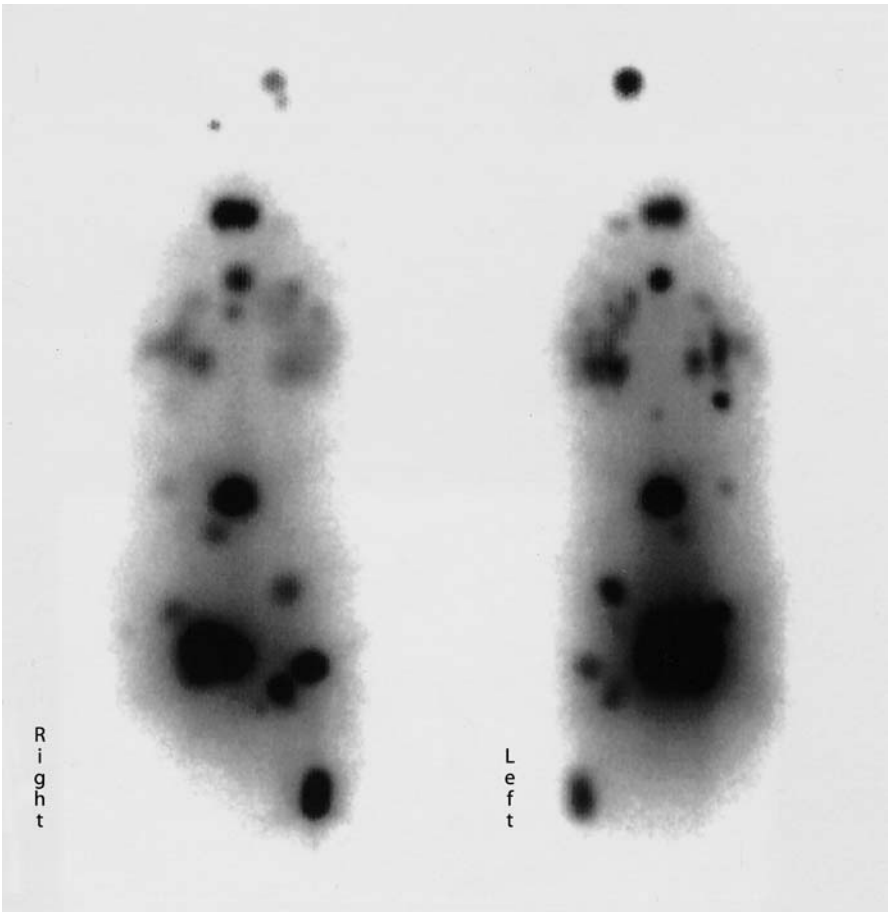

Fig. 18.7 b

peptides which bear N-terminal pGlu residues (e.g., big gastrin, gastrin-I, cerulein, etc.) or D-amino acids [9, 10]. In accordance with their comparatively low affinity, nonsulfated members of the CCK family showed fairly low uptake in the tumor and other CCK-B receptor-expressing tissues (e.g., the stomach). Sulfated CCK derivatives performed significantly better, but additionally displayed a high uptake in normal, CCK-A receptor-expressing tissues (such as the liver/gallbladder, pancreas, and bowel). Best tumor uptake and tumor-to-nontumor ratios were obtained with members of the gastrin family, probably due to their selectivity and affinity for the CCK-B receptor subtype. Pilot therapy experiments in MTC-bearing animals showed significant antitumor efficacy as compared to untreated controls. ^{111}In-labeled DTPA derivatives of minigastrin showed excellent targeting of CCK-B receptor-expressing tissues in animals and a normal human volunteer [9, 10].

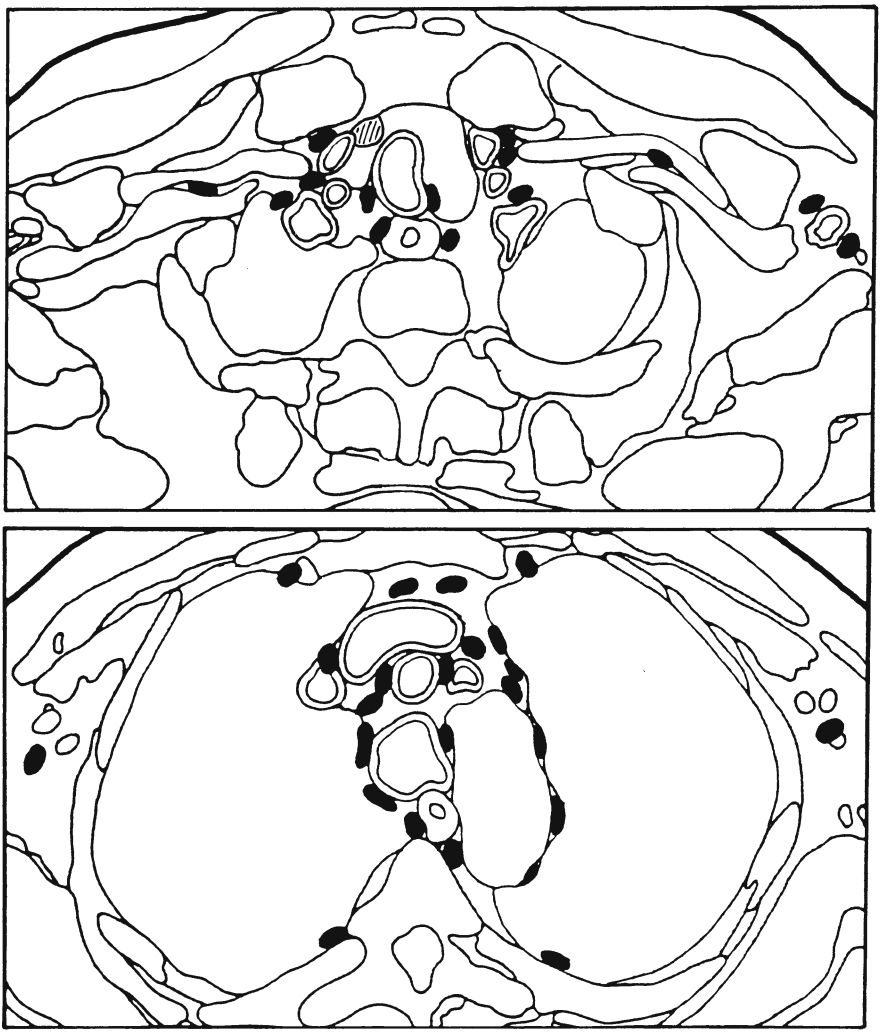

Fig. 18.7 c

These data suggested that CCK/gastrin analogs may be a useful new class of receptor binding peptides for the diagnosis and therapy of CCK-B receptor-expressing tumors, such as MTC or small cell lung cancer. Nonsulfated gastrin derivatives may be preferable due to their CCK-B receptor selectivity, and hence lower accumulation in normal CCK-A receptor-expressing organs.

Subsequently, 35 patients with metastatic MTC were studied [11]. All had undergone ultrasonography, whole-body CT, and MRI, as well as bone scanning and somatostatin receptor scintigraphy. As a result, 19 had known disease, and 16 occult disease. CCK-B receptor scintigraphy was performed with 3–5 mCi of

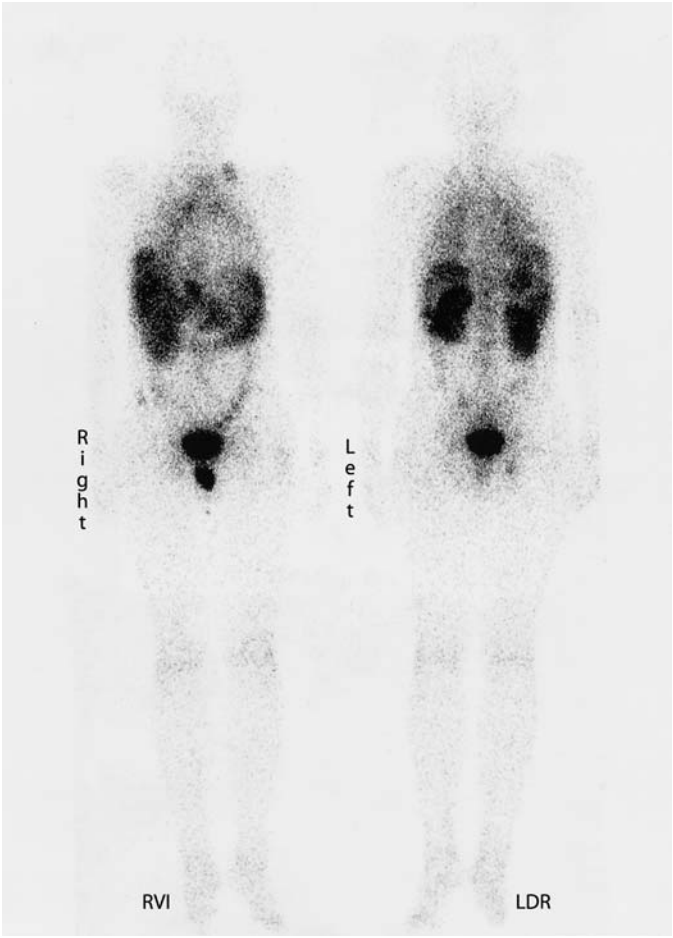

Fig. 18.8 Cholecystokinin-B/gastrin receptor scintigraphy with ^{111}In-labeled DTPA-D-Glu^{1}-minigastrin in a 34-year-old patient with advanced metastatic MTC, showing intense uptake in lymph node, diffuse lung, bone (marrow), and liver metastases. Physiological uptake is confined to the stomach, as the organ with the highest normal CCK-B receptor expression, and the kidneys, as excretory organs

a ^{111}In-labeled DTPA derivative of minigastrin (13 amino acids long; affinity in the n*M* range). Whole-body scans were performed at 10 min and 1, 4, and 24 h, and SPECT at 4 and 24 h p.i. The normal organ uptake of the radiopeptide was confined to the stomach (and to a much lesser extent, the gallbladder) as a result of CCK-B receptor-specific binding, and to the kidneys as excretory organs. No physiological uptake was observed in any other organ, such as the liver or spleen. All tumor manifestations known from conventional imaging were visualized as early as 1 h p.i., with increasing tumor-to-background ratios over time; at least one lesion was detected in 15/16 patients with occult disease (pa-

tient-based sensitivity 94%; eight cases surgically confirmed, seven remaining unconfirmed positive). Among them were local recurrences and lymph node, pulmonary, hepatic, splenic, and bone metastases (Fig. 18.8). We concluded that these data suggest that CCK-B receptor ligands are a promising new class of receptor binding peptides for the staging of MTC.

18.5 Conclusion

Imaging of MTC and especially of its (occult) metastatic forms remains a challenge which has not been satisfactorily solved. The new molecular targeting approaches, such as cholecystokinin-B/gastrin receptor binding peptides, offer a novel and promising tool. However, larger clinical studies are warranted before their potential future role can be appreciated more adequately. On the other hand, these molecular targeting approaches may also offer new therapeutic options in this otherwise therapy-resistant cancer type.

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