$^{123/131}$I-MIBG SPECT/CT for Tumour Imaging

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7.1 Introduction

Metaiodobenzylguanidine (mIBG) is an aralkylguanidine norepinephrine analogue, which was clinically introduced in 1981 and developed to visualize tumours of the adrenal medulla [1]. It enters the neuroendocrine cells of postganglionic sympathetic neurons by an active uptake mechanism via the epinephrine transporter and is stored in the neurosecretory granule without being metabolized. This leads to a difference in the concentration compared to cells of other tissues [2, 3], whereas the storage intensity of mIBG-avid tissue is dependent on tissue uptake, and the storage capacity is proportional to the quantity of catecholamine-containing vesicles in the tumour and tracer turnover [4–6].

7.2 Physical Properties of ^{123}I and ^{131}I

^{123}I is a pure gamma-emitting radionuclide used only for diagnostic imaging. The physical half-life of ^{123}I is 13.13 h, and its principal gamma photon is emitted at 159 keV (83% abundance). It also emits multiple low-abundance, high-energy photons. ^{131}I emits a principal gamma photon of 364 keV (81% abundance) with a physical half-life of 8.04 days and also beta particles with a maximum energy of 0.61 MeV (mean 0.192 MeV) [2, 5].

mIBG can be labelled with ^{131}I or ^{123}I and allows scintigraphic delineation of neuroectodermal tumours [2, 5]. Although ^{131}I-mIBG can be applied for diagnostics, it is mostly used for therapeutic purposes. Its utilization for diagnostics is possible whether ^{123}I-mIBG is commercially unavailable (as was the case in several countries such as the USA until 2008) or in the case of estimation of tumour uptake for mIBG therapy planning [7].

Nonetheless, for diagnostic issues, ^{123}I-mIBG has some advantages over ^{131}I-mIBG, namely, its better physical characteristics, which result in better image quality. Its gamma energy (159 keV) is more appropriate for imaging than the 360 keV gamma photons of ^{131}I. Its higher photon efficiency in combination with shorter half-life (13.13 h vs. 8.04 days) induces a more suitable radiation dosimetry and lower radiation burden and therefore allows injection of higher tracer activities, resulting in higher count rates. In addition, the duration between injection and imaging is shorter (4–24 h) than with ^{131}I-mIBG scintigraphy (48–72 h), because, with ^{131}I-mIBG, delayed images may be required for optimal

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target-to-background ratios [6, 8]. Finally, ^{123}I-mIBG is the radiopharmaceutical of choice concerning diagnostic imaging, even if its use may be limited due to higher costs and inferior availability [3, 5].

7.3 Indications for mIBG Scan

There are several non-oncological indications for ^{123}I-mIBG scintigraphy, such as disorders of the sympathetic innervation of the myocardium (cardiomyopathy), differentiation between idiopathic Parkinson's disease and multisystem atrophy or hyperplasia of the adrenal medulla, which are not addressed in this chapter [3]; however, there is a wide spectrum of different oncological indications, especially for imaging of neuroendocrine neoplasms (e.g. neuroendocrine tumours (NET)/neuroendocrine carcinomas (NEC), phaeochromocytomas/paragangliomas, neuroblastoma and medullary thyroid carcinoma) [2].

7.4 Patient Preparation

Pre-treatment with a saturated solution of sodium perchlorate is required to protect the thyroid from ablation and absorption of free iodine, especially as the infantile thyroid is very sensitive to radiation. Thyroid blockade (130 mg/day of potassium iodide; equivalent to 100 mg of iodine) should be started 1 day before tracer injection and continued for 1–2 days for ^{123}I-mIBG or 2–3 days for ^{131}I-mIBG. In the case of intolerance of sodium perchlorate, potassium perchlorate (SSKI) should be applied (administered 4 h before tracer injection and continued for 2 days; 400–600 mg/day) [3]. After appropriate thyroid blocking, a slow intravenous injection (over about 1 min) reduces side effects such as hypertensive crisis and tachycardia, which can occur as rare side effects rather concerning with catecholamine-producing tumours such as phaeochromocytomas. Adverse allergic reactions are not expected.

7.5 Interfering Drugs

There are some drugs known to interfere with mIBG uptake, such as tricyclic antidepressants (amitriptyline, imipramine), sympathomimetics (phenylephrine, phenylpropanolamine, ephedrine, xylometazoline and cocaine) and also antihypertensive medications such as labetalol, reserpine or calcium channel blockers. If possible, these medications should be discontinued for sufficient time prior to scintigraphy [5, 9–12].

The use of non-prescription drugs should also be considered, especially in children, and the use of the nasal drops or sprays containing xylometazoline or bronchodilators such as fenoterol, salbutamol, sultanol and terbutaline.

However, there are no precise data as to whether there is an influence of the above-mentioned drugs on mIBG uptake. Therefore, it is unknown how often false-negative mIBG scans occur because of these medications [3].

7.6 Contraindications

Pregnancy is with very few exceptions classified as absolute contraindication. After an mIBG scintigraphy with ^{123}I, breastfeeding should be discontinued for 48 h, and the milk should be pumped out and discarded. After investigation with ^{131}I, ablactation is recommended. There is not any known contraindication in children [3].

7.7 Dose Calculation

The recommended activities in adults are 200–400 MBq for ^{123}I-mIBG and 40–80 MBq for ^{131}I-mIBG. The activity administered to children should be calculated on the basis of a reference dose for an adult, scaled to body weight according to the schedule proposed by the EANM Paediatric Task Group [13].

7.8 Image Acquisition

The particular strength of mIBG scan lays in providing a whole-body evaluation with one single administration of the radiotracer. ^{123}I-mIBG scans are usually obtained 20–24 h after tracer injection. Selected delayed images (never later than day 2) may be useful in the case of equivocal findings on day 1. Early static images at 4–6 h after injection can be performed optionally to assess the dynamics of the tracer accumulation. Scanning with ^{131}I-mIBG is performed 1 and 2 days after injection and can be repeated at day 3 or later [3].

Planar and tomographic (SPECT/CT) images are performed with a multiple-head gamma camera with a large field of view. A high-energy parallel hole collimator is used for ^{131}I-mIBG and a low-energy high-resolution collimator (LEHR) for ^{123}I-mIBG. Whole-body imaging with additional spot images should be performed. With ^{123}I-mIBG, a total body scan with a speed of 5 cm/min or both anterior and posterior static spot views of the head and neck, chest, abdomen, pelvis and upper and lower extremities with about 500 k counts or 10–15 min acquisition per image using a 256 × 256 matrix or 128 × 128 matrix with zoom, and a 20% window centred at the 159 keV photo peak is usually performed. More useful information regarding acquisition, reconstruction parameters and camera settings for whole body and planar spot imaging have been described in detail elsewhere [2].

7.9 Acquisition of SPECT/CT

mIBG SPECT/CT should cover the region of interest (e.g. pelvis, abdomen or thorax), especially the anatomical regions showing pathological tracer uptake on planar images or reported suspected lesions by other modalities such as MRI.

Generally, SPECT images are obtained for a 360° orbit in 120 projections (128 × 128 matrix, 6° angle steps, 30–45 s per step or in 3° steps in continuous or step and shoot mode, 25–35 s per step). In the case of noncompliant patients or children, it is possible to reduce acquisition time (6° steps or a 64 × 64 matrix with shorter time per frame) [14, 15]. If only one mIBG SPECT/CT scan can be performed, acquisition at 24 h is preferred because of a higher target-to-background ratio.

SPECT/CT imaging is performed with co-registered CT images (100–130 keV, mAs modulation recommended) with high resolution in order to have a better characterization of the anatomical surroundings. This enables attenuation correction and facilitates precise localization of any focus of increased tracer uptake, which is particularly useful over the abdomen and head and neck region. Despite additional radiation burden of the (low-dose) CT, regardless, SPECT/CT should be performed in children in case of equivocal findings that, by SPECT alone, cannot be ascertained. Sedation of children is often necessary and is taken into account.

7.10 Reconstruction of SPECT/CT

Iterative reconstruction or other validated reconstruction protocols that allow accurate visualization of lesions and a CT-based attenuation correction should be performed. Scatter correction methods using spectral analysis can be used to improve the accuracy of quantification. Iterative reconstruction with a low-pass post-filter often provides better images than filtered back-projection. Any reporting should clearly state the methodology adopted for image processing and quantification [2].

7.11 Radiation Exposure

The radiation exposure depends on amount of the applied activity, which should be limited according to weight and age (for paediatric patients, see

guidelines for radioiodinated mIBG scintigraphy in children) [16].

The effective doses are 0.013 mSv/MBq for ^{123}I-mIBG and 0.14 mSv/MBq for ^{131}I-mIBG in adults and 0.037 mSv/MBq for ^{123}I-mIBG and 0.43 mSv/MBq for ^{131}I-mIBG in children (5 years old) [17, 18]; for example, a 5-year-old child's radiation exposure is about 5.6 mSv (18 kg for 124 MBq ^{123}I-mIBG) [3, 19]. Additional SPECT with low-dose CT implicates increased radiation dose (volume CT dose index: 3–5 mGy, depending on acquisition parameters).

7.12 Physiological mIBG Uptake and Distribution

mIBG is normally taken up mainly by the liver; lower levels of uptake have been described in the spleen, lungs, salivary glands, skeletal muscles and heart, based on the extensive sympathetic innervation of these tissues and/or catecholamine excretion [5].

One of the other variants in biodistribution of ^{123}I-mIBG is its accumulation in brown fat tissue in children which is more common in cold weather than in warm weather [20, 21]. This may be seen mainly in the neck and supraclavicular regions [21].

Therefore, evaluation and interpretation of mIBG scans should be considered thoroughly, especially if unknown suspicious findings are next to those regions or organs with physiological uptake, avoiding false-positive or false-negative results, e.g. in the liver with its diffuse, inhomogeneous tracer uptake, the discrimination between physiological enhancement and focal suspicious tracer accumulation is sometimes challenging, particularly in the case of small liver lesions.

Concerning the adrenal glands, symmetrical mIBG uptake less than or equivalent to liver uptake is described to be physiological. Normal, non-enlarged adrenal glands are sometimes difficult to localize on planar mIBG scans. The majority of mIBG is excreted unaltered by the kidneys (50% of the injected dose is recovered in the urine within 24 h), while faecal elimination is weak. In patients with phaeochromocytoma and paraganglioma, uptake in the heart and liver is significantly lowered by about 40% [22].

7.13 The Importance of mIBG SPECT and SPECT/CT

Many studies indicate a high sensitivity and specificity of mIBG scintigraphy detecting tumours of the sympathetic nerve system. For neuroblastoma, sensitivity is about 80% for determining neuroblastoma lesions, while specificity is nearly 100% in the guidelines [3].

These data are mostly based on performing planar and whole-body images in many previous studies, as modern hybrid systems such as SPECT or SPECT/CT were not yet available [23, 24].

Based on these data, it could be concluded that whole-body imaging and planar imaging are sufficient enough, and additional diagnostic tools such as SPECT or SPECT/CT are not required to achieve good diagnostic results with respect to mIBG scintigraphy.

However, the use and benefit of SPECT for achieving better diagnostic accuracy has already been described in several studies and highlighted in the guidelines when it comes to smaller tumour lesions or suspicious findings next to organs, which physiologically accumulate mIBG, such as the urinary bladder or liver.

But despite this diagnostic benefit, SPECT is not sufficient in all cases and cannot achieve adequate diagnostic accuracy since differentiation between physiological structures and the findings is not always possible because of absent anatomical correlations.

Such difficulties occur regularly and require the best care and attention by the nuclear medicine physicians, as the interpretation of the findings in the mIBG scan often has far-reaching consequences and the results of an mIBG scan might influence the running therapy.

One way to overcome these limitations is the additional advantage of SPECT with potential of fusion with other radiological imaging methods (MRI/CT scan) [3, 14, 15, 25]. However,

this option may suffer from the problem that SPECT and MRI/CT images sometimes cannot be fused exactly, as the slices do not match to each other.

A way out of this dilemma is newly available hybrid SPECT/CT cameras, which enable direct correlation of anatomic and functional information [26–30]. Physiological activities can be delineated properly, which otherwise would have required additional imaging. With the help of low-dose CT of SPECT/CT, more accurate spatial resolution than using SPECT alone can be achieved. This results in a better localization and clearer delineation of small tumour lesions [31].

Besides detailed anatomic evaluation of suspicious findings such as mIBG avide or non-avide lesions, there is the above-mentioned possibility of fusion or co-registration SPECT/low-dose CT with diagnostic CT or MRI, whereas low-dose CT serves as a bridging tool for anatomical orientation. As a consequence, SPECT/CT findings may guide the diagnostic CT or MRI concerning equivocal findings. To summarize, SPECT/CT bridges the gap between mIBG scintigraphy and diagnostic CT or MRI scans, with guidance of diagnostic CT/MRI and characterization of its findings [30].

7.14 MIBG SPECT/CT in Neuroblastoma

Neuroblastoma is the third most common malignant solid tumour in childhood and the most common extra cranial malignant tumour (8–10%). This tumour entity arises in the adrenal gland (65%) or the sympathetic nervous system, as its cells are derived from the embryonic neural crest and remain as autonomous nervous tissue-neuroblasts in an immature state [32–34].

About 40% of children are diagnosed in the first year; the incidence decreases with age. Ninety percent of patients are younger than 6 years. The median age at diagnosis is 2 years. In a many of cases, there are already metastases of neuroblastoma at the time of diagnosis. It metastasizes to the liver, adrenal glands, lymph nodes, bone marrow and bone, whereas the primary can be localized at the cervical, thoracic and abdominal trunk, as well as the paraganglia [34, 35].

Approximately 40% of patients are at stage 4 (INSS classification) at the time of diagnosis with detection of distant metastases. Since the spread of the disease correlates with the prognosis and thus affects the extent of therapy, an accurate detection of all tumour foci is essential to determine the spread of the disease [3, 33, 34, 36].

In addition to the conventional radiological diagnostic modalities, such as ultrasound and CT, MRI plays an important role and may provide important information regarding to the basic staging, the tumour locations and choosing appropriate site for bioptic assurance.

Staging is completed with performing a ^{123}I-mIBG scan, which has the advantage of whole-body evaluation with one single administration of the radiotracer. This can provide important information about tumour localization and thus has an influence on the treatment planning with regard to chemotherapy strategy or possible operation plans [5]. The specificity of mIBG for detecting tumours of the sympathetic nervous system is nearly 100%. The sensitivity for the detection of an individual neuroblastoma lesion is stated to be 80% [3, 32, 37–44]. By using SPECT/CT, the sensitivity can be increased to 98% [45]. A recent published study reported that by using SPECT/CT in the follow-up of patients with high-risk neuroblastoma, the interpretation of planar imaging can be improved significantly and in 39% of cases SPECT/CT provided additional information [46].

7.14.1 Interpretation of the Findings: What Is Physiological?

To distinguish true-positive from false-positive findings, the knowledge of physiological distribution of mIBG in different organs or localizations is of importance (see above). Approximately 10% of patients show (usually symmetric) mIBG uptake in brown adipose tis-

sue of the neck and shoulder area [3]. Tracer uptake in the myocardium can be relatively high, especially in children under 1 year. At other ages, comparable mIBG-storage can also be found in the liver, which may complicate the detection and distinction of suspicious liver lesions, especially if whole-body imaging and planar imaging are performed without any additional SPECT/CT.

In addition, free iodine causes thyroid uptake and storage in the gastrointestinal tract. The bony skeleton has no mIBG storage. In the extremities, only slight activity is found in the muscles and the bones, whereas the knees and joints can be seen as cold areas [3, 20, 21].

7.14.2 Image Interpretation

7.14.2.1 False-Negative Findings

Lesions may be overlooked due to anatomical or physiological reasons: small lesions that are close to the primary tumour, next to large metastases or in regions with high physiological uptake (myocardium, thyroid, salivary glands, liver, kidney, bladder and colon) maybe overlooked [3, 43, 47]. These limitations can be solved by using SPECT/CT (Figs. 7.1 and 7.2).

7.14.2.2 False-Positive Findings

There are different benign accumulations which could cause false-positive results including accumulation in the lung correlating with pneumonia or because of atelectasis, mIBG uptake in the focal nodular hyperplasia, intense uptake in the liver because of prior radiation, because of accessory spleen [48] and also because of contamination, most often urine contamination or any other contamination (salivary secretion). Using SPECT/CT can avoid misinterpretation of these findings.

7.14.3 SPECT/CT: Reducing False-Negative and -Positive Results

As mentioned, SPECT/CT allows better anatomical localization of mIBG-avide findings, which is essential in most cases. In particular, fusion of SPECT with other imaging modalities (MRI/diagnostic CT) improves diagnostic accuracy, while low-dose CT of mIBG-SPECT/CT serves as anatomical orientation [30] (Fig. 7.3).

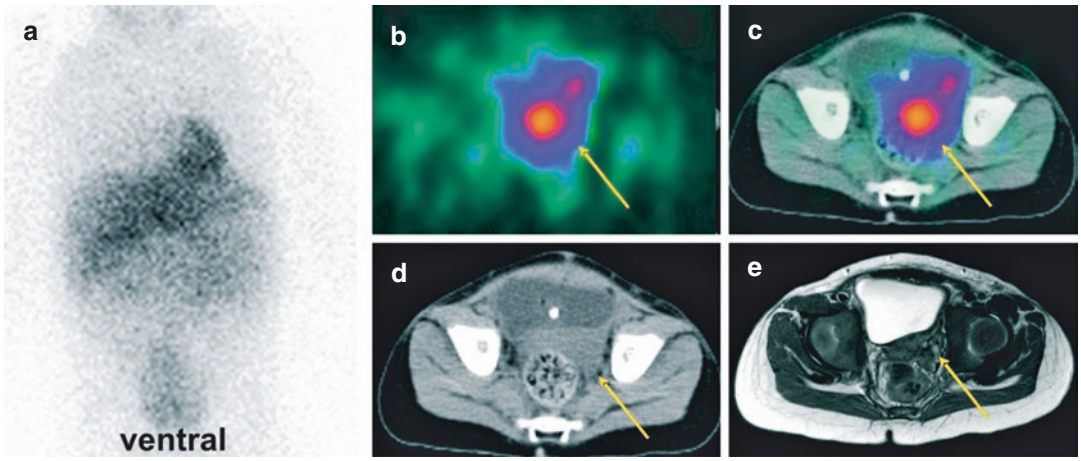

Fig. 7.1 A 2-year-old patient with retrovesical neuroblastoma (**e**: MRI, yellow arrow) underwent ^{123}I-mIBG scan, for evaluation of treatment possibility with ^{131}I-mIBG. (**a**) Planar scan was inconclusive because of bladder activity. (**b–d**) Exact localization, differentiation of the bladder and evaluation of mIBG uptake were made possible only by SPECT/CT (yellow arrows). A Foley catheter was used for emptying the bladder

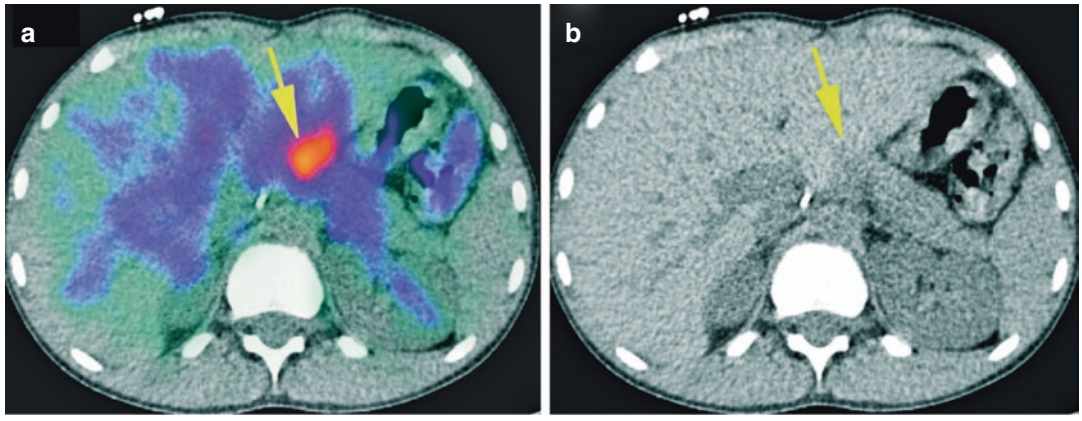

Fig. 7.2 A 9-year-old patient with stage IV neuroblastoma received ^{123}I-mIBG scan for restaging after chemotherapy. SPECT/CT revealed a suspected uptake beside the liver (yellow arrow), which had been overlooked by MRI. The patient underwent an operation. Histopathology showed a lymph node metastasis. (**a**) SPECT/CT transversal view, (**b**) CT transversal view

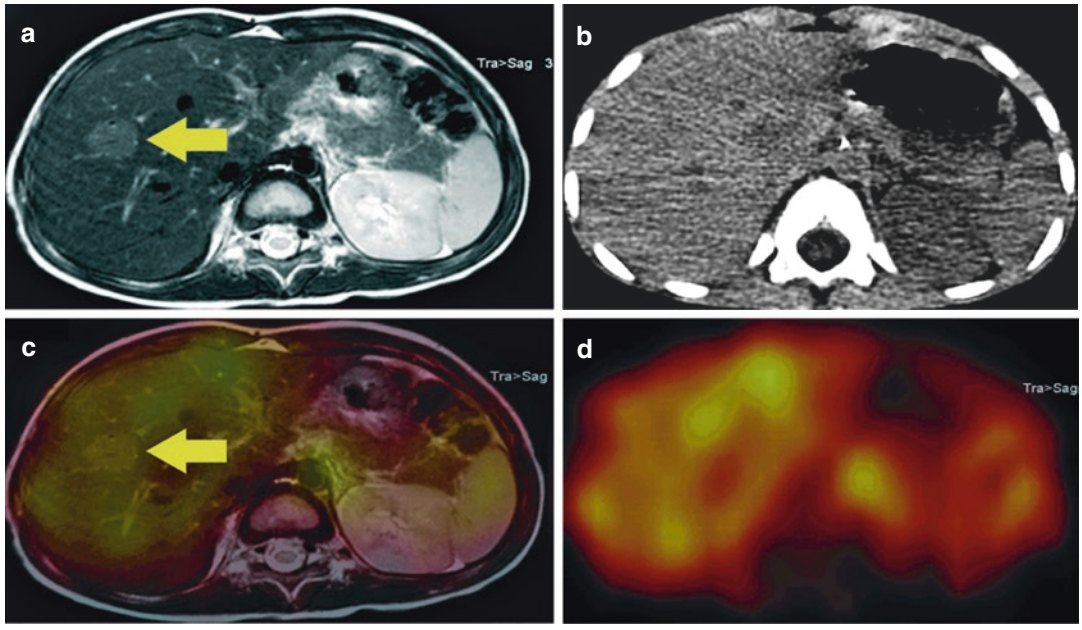

Fig. 7.3 A 3-year-old patient with suspected, new occurred liver lesion in MRI (**a**, yellow arrow), which was detected in his restaging examination after chemotherapy. The lesion showed no pathological ^{123}I-mIBG uptake (**c**, yellow arrow and **d**), reported as benign, which was confirmed by biopsy as FNH. A fusion with MRI (**c**) was possible with the help of the low-dose CT (**b**) of the SPECT/CT

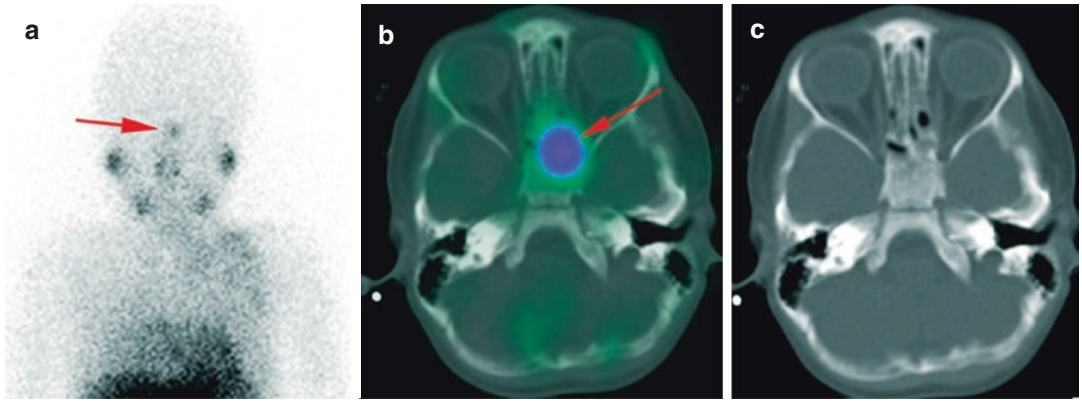

Fig. 7.4 A 4-year-old patient with tracer accumulation in the region of nasal mucosa (**a**, red arrow). SPECT/CT (**b**, **c**) revealed sphenoid bone involvement confirmed with MRI. This result resulted in further chemotherapy

Detection of small foci, which would have been mostly overlooked with planar imaging alone, is possible by using SPECT/CT (Fig. 7.4).

7.15 MIBG SPECT/CT in Pheochromocytoma and Paraganglioma

The pheochromocytoma is a catecholamine-secreting tumour of the chromaffin cells, and it is localized in the adrenal medulla to 85% and occurs with an incidence of 1/100,000 people p.a.

Its characteristic symptoms are episodic headaches, palpitations, diaphoresis and paroxysmal or sustained hypertension [7]. The pheochromocytoma occurs in isolation or as part of a syndrome, e.g. MEN 2 syndrome, von-Hippel-Lindau syndrome or neurofibromatosis type 1 (M. Recklinghausen). With widespread use of cross-sectional imaging, an increasing number of pheochromocytomas are diagnosed incidentally, without the presence of symptoms or complaints by the patient. Incidental tumours, as well as tumours detected while screening patients with hereditary syndromes, tend to be smaller than symptomatic ones.

The first diagnostic method is plasma or urine measurements of catecholamines and their metabolites [7, 49]. If there is positive biochemical testing, further imaging is required, such as ultrasound, CT of the abdomen or MRI.

mIBG scintigraphy for detecting pheochromocytomas or paragangliomas has been widely used for more than 25 years and have a reported high sensitivity and specificity of about 83–100% and 85–100%, respectively [50]. In the last 5 years, however, image quality and spatial resolution of other imaging methods, such as MRI with a high sensitivity for detection of tumours in the adrenal gland (which are usually hyper-intense on T2-weighted images and hypointense on T1-weighted images), increased significantly [7, 51]; in addition, other functional imaging modalities such as ^{18}F-DOPA PET/CT have been increasingly applied. Regarding this, some studies have been published compared sensitivity and specificity of those other imaging methods to mIBG SPECT. They all share a significantly lower sensitivity for mIBG scintigraphy, from which it might be concluded that the mIBG scan has lost its monopoly position as the gold standard functional imaging method for pheochromocytoma/paraganglioma. Critics find fault in its low-spatial resolution, the long examination time of 24 h, the necessity of thyroid blockade, the interference with several medications and the significant tracer-uptake in the normal adrenal medulla [52].

The disadvantage of the low spatial resolution may be largely compensated by the use of mIBG SPECT/CT; however, the other "disadvantages" remain. Additionally, limitations in

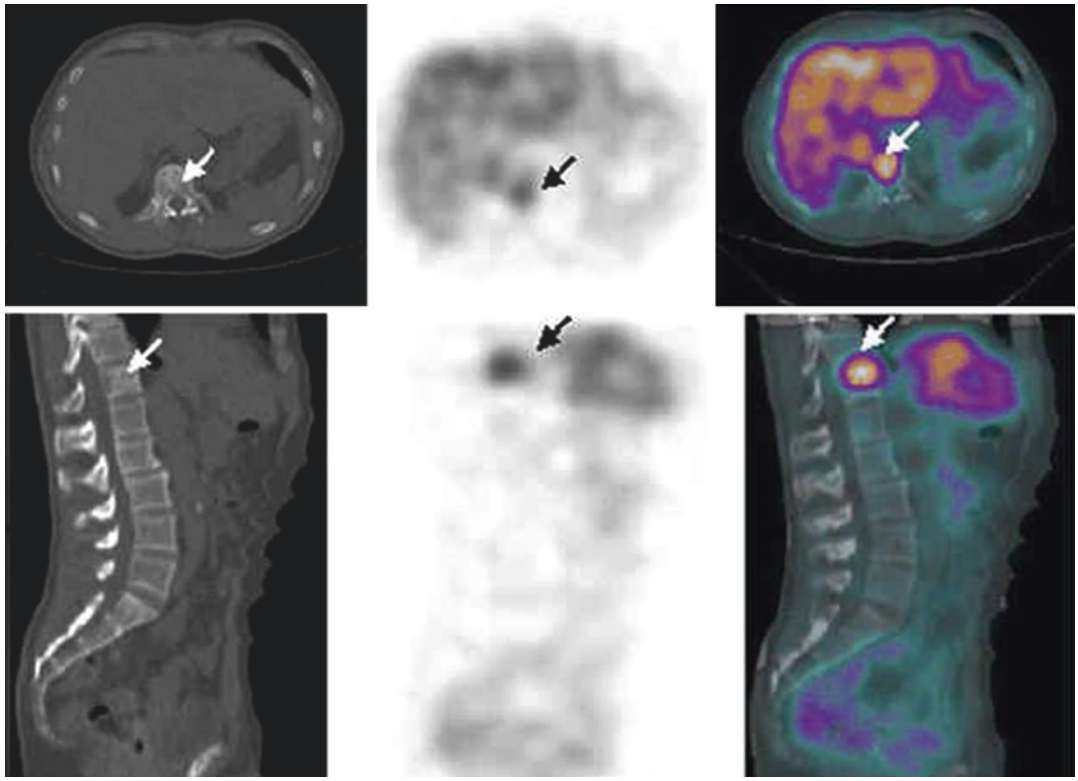

Fig. 7.5 CT, mIBG SPECT and fused mIBG SPECT/CT images of phaeochromocytoma metastasis to the body of T12 vertebra (white arrow). (With kind permission from Springer Science + Business Media: Meyer-Rochow et al. [29]. Fig. 1B)

terms of decreased sensitivity and specificity exist in several diseases, such as MEN2-related phaeochromocytoma, extra-adrenal, multiple or hereditary paragangliomas or metastatic disease, which may lead to a significant underestimation of the extent of disease in the mIBG-scan with potentially inappropriate management. The particular strengths of mIBG SPECT/CT are detection of local recurrence, small extra-adrenal pheochromocytomas, multifocal tumours or the presence of metastatic disease [29]. In patients with clinical or biochemical suspicion of pheochromocytoma, SPECT/CT, compared to SPECT and planar imaging, has a significantly higher accuracy (Fig. 7.5) [53]. ^{123}I-mIBG scintigraphy, precisely with assistance of SPECT/CT, can serve for evaluation and dose calculation for ^{131}I-mIBG therapy, from which patients may benefit [7, 54, 55].

7.15.1 Interpretation of the Findings

In some cases, there are quite unequivocal true-positive findings with a convincing focal mIBG-uptake, matched to an obvious size of adrenal masses in additional imaging such as CT. These unequivocal findings can even be detected only by using whole-body and planar imaging. In such cases, SPECT/CT may be useful to rule out any extra-adrenal manifestations; otherwise, does not have any additional benefit.

Concerning less conclusive accumulations or small masses in the adrenal, low-dose CT of SPECT/CT serves as an anatomical landmark. In SPECT/CT, the left adrenal is often detected much more easily than the right adrenal due to the anatomical location of the liver and large vessels, such as vena cava, with their physiological uptake. Especially for the detection of the right adrenal, the use of SPECT/CT is very valuable;

even when it only provides an inconspicuous finding, this can thus be diagnosed.

Additionally, there are several other difficulties and challenges besides localization, namely the distinction between a significantly increased uptake, therefore interpreted as pathological, and a mildly enhanced uptake, slightly above or similar to that of the liver. This is because there are no cut-off values from which an uptake can be considered significantly positive for a pathological finding. A dissociation of benign findings, such as adrenal adenoma with a moderate uptake, is not always easy.

The risk of misinterpreting any positive uptake as pathologic may lead to an increased rate of false-positive findings. On the other hand, smaller or extra-adrenal findings bear a great challenge, precisely because they can be easily overlooked, particularly if planar imaging is performed or if the findings are located next to physiological accumulations or organs.

It should be noted at least that larger adrenal masses, already considered to be suspicious in other imaging tools such as MRI because of their density, might show no or very low mIBG uptake. In such cases, an adrenal carcinoma cannot be ruled out. An operation with histological confirmation is so far the only opportunity to definitively assure diagnosis.

Some hints to reduce false-positive or -negative results:

- Correct patient selection criteria are required, which means positive biochemical testing and/or evaluation of suspicious masses of the adrenal in other imaging modalities.
- In utilization of SPECT/CT, the particular strengths of mIBG SPECT/CT are detection of local recurrence, small extra-adrenal pheochromocytomas and multifocal tumours (Fig. 7.6).

7.16 mIBG SPECT/CT in Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) is a quite rare thyroid tumour which occurs in 5–10% of all thyroid carcinomas and arises from thyroid parafollicular C cells, which are embedded in the thyroid, but do not belong to the thyrocytes. It releases calcitonin, CEA and several other substances, such as chromogranin, serotonin, somatostatin and gastrin-releasing peptide.

A sensitive and specific marker for the occurrence of MTC is calcitonin, which is produced by the C-cells. An elevated calcitonin level (hypercalcitoninaemia) reflects a disorder, a reactive stimulation of the C-cells or impaired/disturbed degradation for calcitonin. There is a wide range of differential diagnoses for increased calcitonin levels, such as alcohol consumption, intake of various drugs (calcium, proton pump inhibitor, medication with calcitonin), hypercalcaemia and andrenal insufficiency. Also, a severe bacterial infection, a serious illness or a para-neoplastic syndrome can also cause a hypercalcitoninaemia. If reasons such as these are excluded, only C-cell hyperplasia (CCH, C-cell hyperplasia) and MTC remain as the two most frequent diagnoses. It should be noted that C-cell hyperplasia is associated specifically with males, in combination with autoimmune thyroiditis, or hyperparathyroidism-associated hyper-gastrinaemia.

The reference values for basal calcitonin are higher in men than in women. Hypercalcitoninaemia should be confirmed in a second measurement. The interpretation of an elevated calcitonin level between 10 and 100 pg/ml is ambiguous; only a basal calcitonin level >100 pg/ml is almost always accompanies an MTC. If available, for further diagnosis, a pentagastrin test should be carried out. If pentagastrin stimulation is not available, stimulation can also be performed with calcium, noting that after calcium stimulation, false-positive findings appear to be more common in female patients and patients with thyroiditis and thyroid neoplasia, other than MTC [56]. $^{131/123}$I-mIBG uptake in MTC appears via the same molecular mechanisms, just as in other neuroendocrine tumours such as pheochromocytoma [7].

7.16.1 Imaging Procedures

Cross-sectional imaging studies employing neck, chest and three-phase abdominal CT scans or

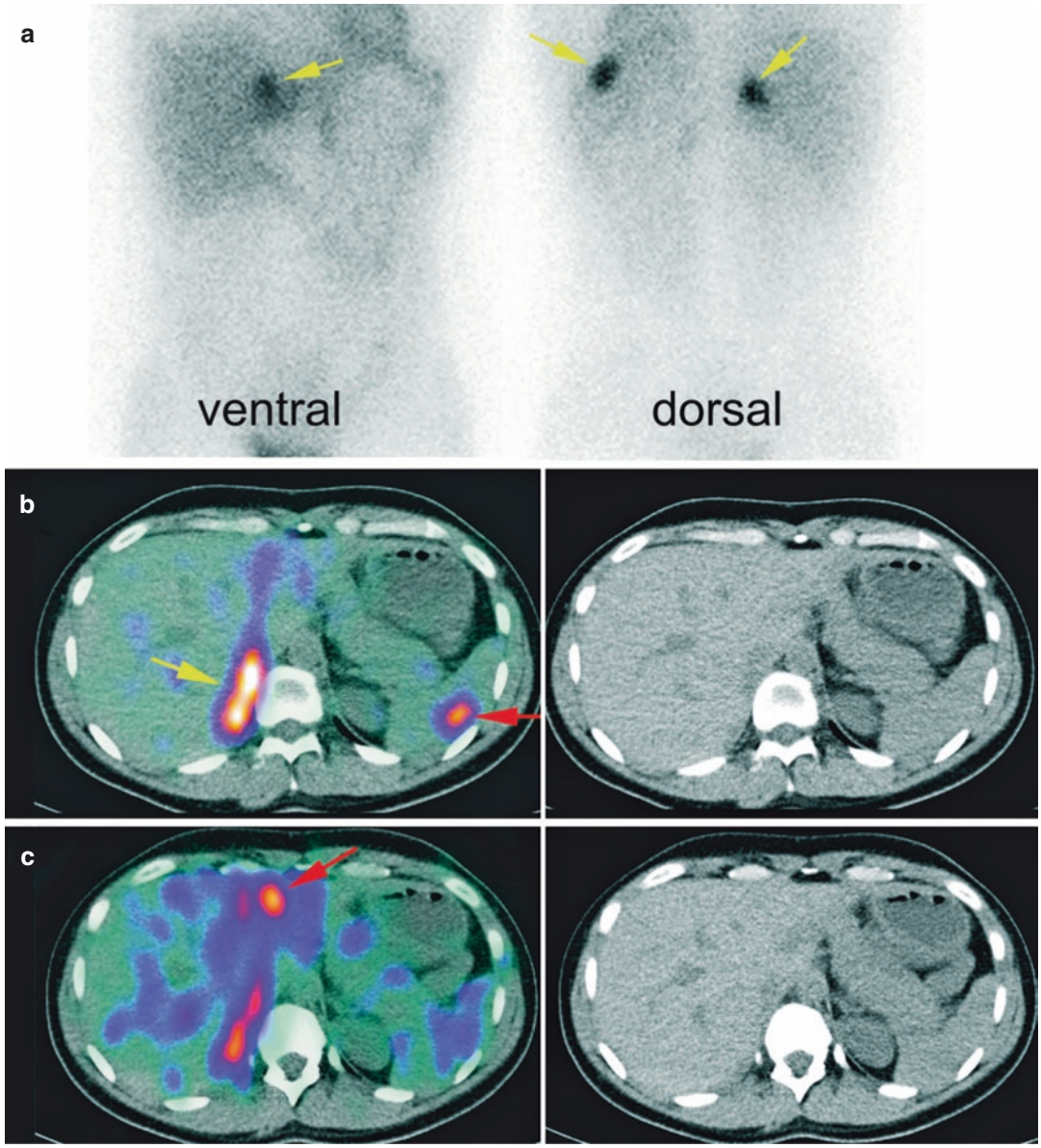

Fig. 7.6 Planar images of a patient with suspected recurrence of phaeochromocytoma showed three suspected abdominal uptake (**a**, yellow arrows). SPECT/CT revealed the exact anatomical localization of these uptakes (**b**, **c**) local recurrence (yellow arrow), a spleen metastasis and a liver metastasis (red arrows)

contrast-enhanced MRIs are recommended to rule-out distant metastases, especially when suspicious lymph nodes are identified or when calcitonin levels are >400 pg/ml [57, 58].

There are also several radiotracers to mention, such as ^{99}Tc-DMSA, ^{123}I-mIBG, ^{111}In-labelled somatostatin analogue and the PET pharmaceuticals ^{18}F-FDG, ^{68}Ga-DOTATOC and ^{18}F-DOPA [59].

The use of ^{123}I-mIBG in MTC is not the gold standard procedure because of its low sensitivity, which is said to be approximately 35% especially for familial/MEN-associated MTC. For sporadic MTC, data are superior. The specificity of mIBG is quite high and is approximately 95% [59–63].

In summary, the role of $^{131/123}$I-mIBG in the diagnostic evaluation of MTC is limited, but it

still serves as an evaluation method for tentative therapy with ^{131}I-mIBG [7].

Moreover, a combined diagnosis of $^{131/123}$I-mIBG scan and somatostatine receptor scintigraphy (SRS) increases the sensitivity up to 100% and seems to be the best practice to choose the most effective radiopharmaceutical with regard to therapy options [59].

The use of $^{131/123}$I-mIBG SPECT/CT can serve as a follow up to individual metastases and their responses to therapy, as SPECT/CT, more than planar imaging, simplifies localization and evaluation of the tumour burden.

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