29 Radioiodine-Labeled Meta-Iodobenzylguanidine for Imaging and Treatment of Pheochromocytoma/Paraganglioma and Neuroblastoma

Manfred Fischer and Matthias Schmidt

29.1 Introduction

The main topic of the International Symposium – Theranostics/Precision Oncology at Bad Berka/Germany, 12–14th December 2019 was "Looking Back and Moving Forward" (Fig. 29.1).

Colleagues, already being specialists in radiology, starting specialization in nuclear medicine, were asked in 1973 (M.F.):"Why are you doing that, nuclear medicine is a dying specialty because of the development of computed tomography and high-sophisticated ultrasound?"Following the statement of the British physiologist Ernest Starling (1866-1927), "The physiology of today is the medicine of tomorrow," I was convinced that nuclear medicine would have a future as long as we would perform functional diagnostic and targeted therapeutic procedures. Manfred Fischer (MF) met Richard P. Baum in two special moments of his career. The very first time, when Richard Baum had to pass an exam to become specialist in nuclear medicine, I was one of the two examiners. After he answered (nearly) all our questions correctly, we decided after a brief confidential discussion that he was ready to become a specialist in nuclear medicine. Some years later, he asked me if I could perform a treatment of a peritoneal carcinomatosis of an ovarian cancer in my department in Kassel/Germany, because he did not have isolation beds for radionuclide therapy in his university hospital in Frankfurt at that time. This

Fig 29.1 Manfred Fischer (left) and Matthias Schmidt (right) at the International Symposium on the Occasion of the 20th Anniversary of Molecular Radiotherapy at Zentralklinik Bad Berka and Inauguration of the ICPO Foundation, December 12-14, 2019 | Zentralklinik Bad Berka

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was the first treatment with the radiolabeled monoclonal antibody in ovarian cancer in Germany.

In June 2010, Matthias Schmidt (MS) had the opportunity to spend a week with Prof. Baum in Bad Berka to learn about peptide receptor radionuclide therapy which had not yet been introduced at the department of nuclear medicine, University Hospital of Cologne. It is almost impossible to describe how inspiring it was to be with Prof. Richard Baum in his department. MS had known him from excellent talks before, but how Prof. Baum talks to patients was an outstanding experience. It is a very special combination of outstanding patient care, extraordinary enthusiasm for nuclear medicine, precision oncology and deep knowledge that makes him a very special colleague. He openly allowed to spread his knowledge. In 2011, MS attended the "1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (PRRNT) THERANOSTICS – On the Way to Personalized Medicine" with Prof. Baum being the congress president. It was most impressive how many colleagues from continents even as far away as Australia came to the rather remote location of Bad Berka, being in close proximity to Weimar – a location that stands for outstanding cultural and intellectual achievements. This event as well as the present congress in 2019 were highly enjoyable days combining outstanding presentations with an social evening event allowing to meet very interesting people from all over the world in person (Fig. 29.2).

Another regular opportunity to meet Prof. Baum are the "Hamburger Nuclear Medicine Days," a 3-day educational program once a year with MS being the scientific coordinator since 2013. Prof. Baum holds his very special Friday morning lecture about positron emission tomography and radionuclide therapies. Every year, Prof. Richard Baum presents vividly the most up-to-date information making his lectures an outstanding experience for about 30 doctors most of them being in their advanced years of specialization. For me, these times are a pleasure to experience his energy, his profound knowledge and his visionary ideas.

Fig 29.2 Michael Kreissl (left), Richard Baum with his wife (middle), and Matthias Schmidt (left) at the International Symposium on the Occasion of the 20th Anniversary of Molecular Radiotherapy at Zentralklinik Bad Berka and Inauguration of the ICPO Foundation, December 12-14, 2019 | Zentralklinik Bad Berka

"Molecular imaging: probes used to visualize, characterize, and measure biological processes in living systems. Both endogenous molecules and exogenous probes can be molecular agents" (SNM molecular center 2007). These probes may also be used for therapeutic procedures.

The World Health Organization (WHO) published in 2017 a new classification of tumors of endocrine organs [1]. In chap. 5, a new definition and description of tumors of the adrenal medulla and extra-adrenal paraganglia is given, including pheochromocytoma, extra-adrenal paraganglioma, neuroblastic tumors of the adrenal gland (neuroblastoma), composite pheochromocytoma, and composite paraganglioma. One characteristic clinical feature of all of them is an excessive synthesis of catecholamines.

In 1967, first time adrenal medullary hormone epinephrine and its precursors were radiolabeled with ^{14}C [2]. In the following decade, several groups studied mainly radiolabeled dopamine and its analogues. The first radioiodinated compound developed by the same group, was the bretylium analogue p-RIBA (III), showing a high affinity to the adrenal medulla [3]. Within 2 years, Donald M Wieland and coworkers developed by changing the chemical structure ^{131}ortho-iodobenzyldimethyl-2-hydroxyethyl ammonium. In tissue distribution studies with dogs, high tracer

uptake was observed in the adrenal medulla [4]. Labeling meta- (or para-) iodobenzylguanidine with ^{125}I, these tracers showed a significantly higher concentration in adrenomedullary tissue with a long retention in the chromaffin storage granules. Meta-iodobenzylguanidine as a derivative of guanethidine acts as an analogue of noradrenalin and can be used for anatomico-functional imaging and treatment. It enters the sympathetic cells via the norepinephrine transporters and is stored in the intracellular secretory granules and/or cytoplasm. The authors recommended to use these tracers for scintigraphic imaging of the adrenal medulla, pheochromocytomas, and neuroblastomas [5] (Fig. 29.3) (Chem structures).

29.1.1 Pheochromocytoma/ Paraganglioma

29.1.1.1 Manfred Fischer

WH Beierwaltes published an article [6] and mentioned the evaluation of the use of ^{131}I-mIBG for treating medullary hyperplasia. From diagnostic scans, his group suggested that similar to radioiodine therapy of thyroid cancer, a radiation dose to pheochromocytoma metastases of about 5000 rad/100 mCi of ^{131}I-mIBG may be reached. Using this approach, we started to treat three female patients (two of them 16 years., one of 73 years. of age) suffering from metastatic pheochromocytoma between July 1982 and May 1983, administering single dose of 2.4 upto 5 GBq (cummulative activities between 5 and 9.2 GBq) [7].

As in diagnostic scintigraphies, ^{131}I-mIBG uptake in pheochromocytomas may vary in a wide range from false negative to true positive. An overall sensitivity in diagnostic scans of 87.4% (range 78.4–94.3%) and specificity of 98.9–100% was observed in true positive pheochromocytomas [8]. This variability seems to be independent from the specific activity of the tracer. The same is evident, comparing tracer uptake versus plasma und intratumoral noradrenaline levels [9]. In a small group of other neuroendocrine tumors like medullary thyroid cancer, ganglioneuroma, neuroectodermal tumor, neurofibromatosis, oat cell carcinoma, and melanoma (n = 36) 25 were false negative in the ^{131}I-mIBG scintigraphy. In two patients with carcinoid and one with medullary thyroid cancer, following true positive diagnostic ^{131}I-mIBG scintigraphy, ^{131}I-mIBG therapy was performed with no change in disease in two patients and progressive disease in one patient. In 43 cases of pheochromocytoma or functional paraganglioma in children or adolescents (≤18 years) (24 m, 19 f) a positive

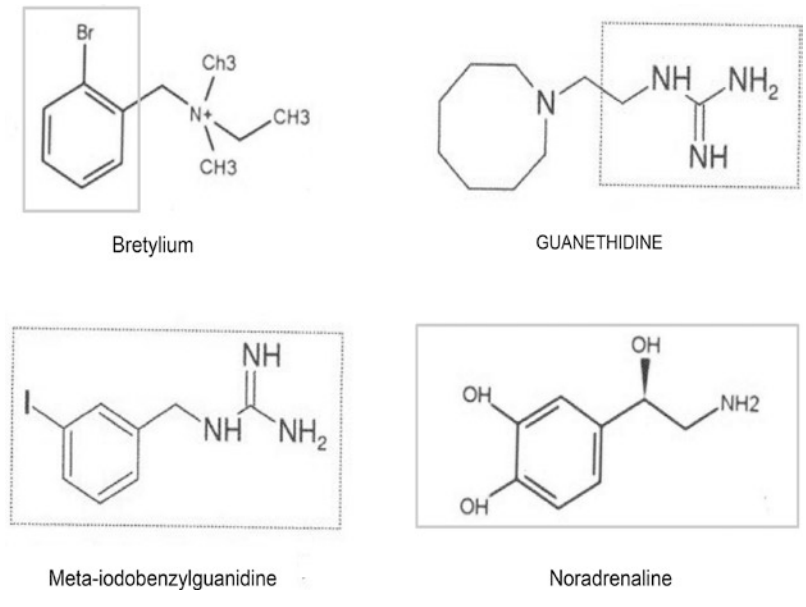

Fig. 29.3 Chemical structure of Bretylium, Guanethidine, meta-iodobenzylguanidine, and Noradrenaline

^{131}I-mIBG scintigraphy was observed in 36 patients (84%) whereas false negative results were observed in 12%. The false negative rate in computed tomography was higher (20%). Thirteen of 24 (54%) unifocal tumors, which were considered to be benign, proved to be multifocal and/or malignant. Only 15 tumors in this group were staged as malignant at the time of primary diagnosis. Ultimately 26 (60%) proved to have malignant tumors, confirmed by local recurrence or distant metastases upto 26 years after initial surgery. Therefore lifelong follow-up with effective diagnostic procedures like ^{123}I-MIBG seems to be mandatory [10].

In 1991, we summarized the results of 13 patients with malignant pheochromocytoma and one female patient with an intra-adrenal probably benign pheochromocytoma (Fig. 29.4). The first patient treated in our center got two times a sequential ^{131}I-mIBG therapy (cummulative

Fig. 29.4 ^{131}I-mIBG accumulation in an intra-adrenal pheochromocytoma

activity 50 GBq) with an ineffective chemotherapy in between. After a follow-up of about 10 years, she finally died from her progressive tumor. In a young boy (13 years at start of ^{131}I-mIBG therapy) with inoperable lymph node metastasis of a malignant pheochromocytoma, invading the liver, the tumor encapsulated totally after four courses of ^{131}I-mIBG treatment (cum. Activity 20.4 GBq) (Fig. 29.5). Surgical complete removal of the primary tumor and lymph node metastasis was possible. This patient now is father of a boy, who was diagnosed by MRI suffering from a bilateral adrenal tumor about 30 years later. Lab tests showed elevated catecholamines. By ^{123}I-MIBG whole body scan and PET/CT (Fig. 29.6) the bilateral neuroendocrine

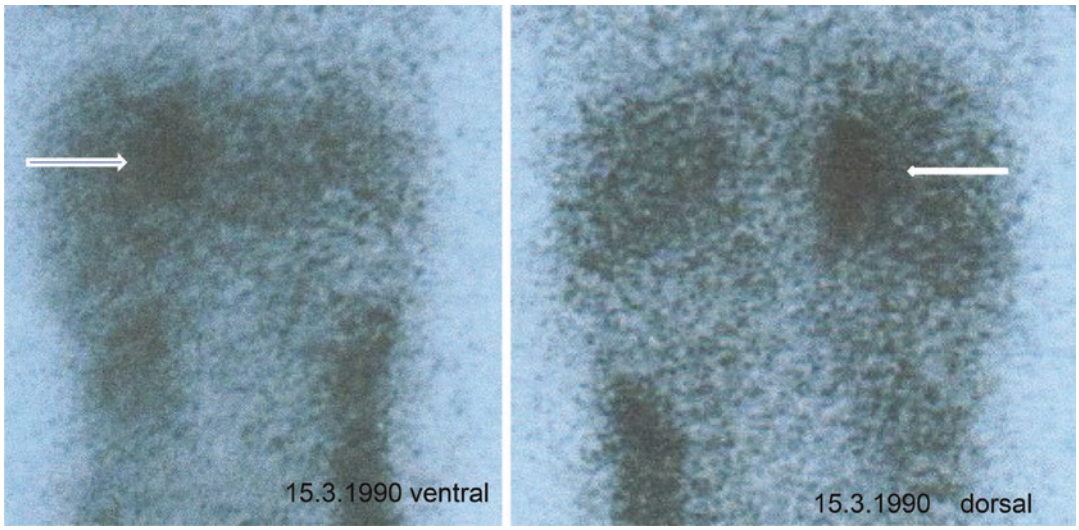

Fig. 29.5 N.D. (14yrs.), post-therpeutic scan: metastatic pheo.; lymph node metastasis infiltrating the liver. 3 cycles with a cum. activity of 18.5 GBq ^{131}I-mIBG

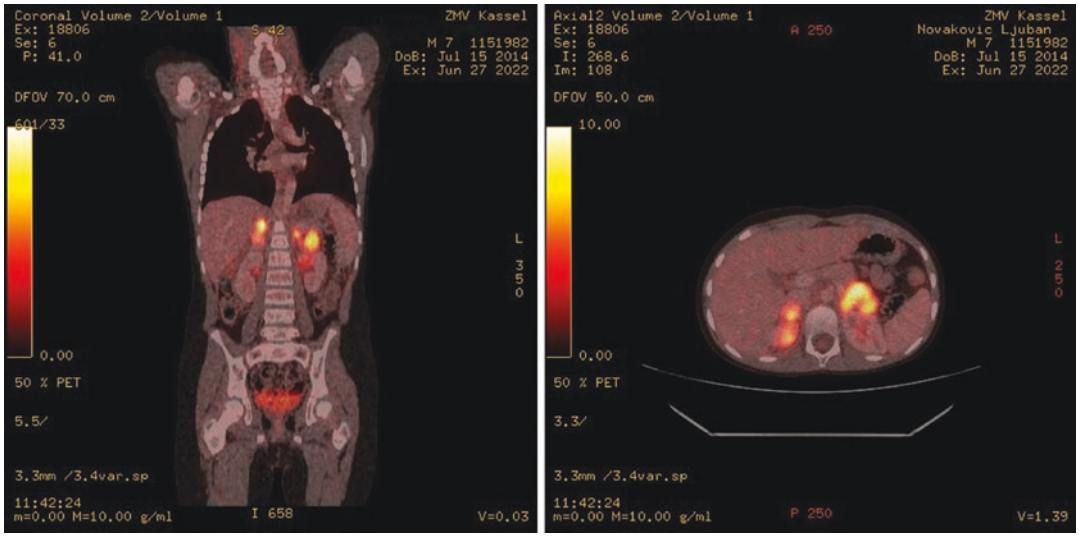

Fig. 29.6 ^{68}Ga-DOTATOC PET/CT of the 8 years old boy with a bilateral familial pheochromocytoma. The left tumor shows a lobulated structure with partly inhomogeneous intensive tracer uptake; the right gland shows an irregular structure with intensive tracer uptake. No extra-adrenal tracer uptake was shown in the pre-surgery whole-body scan (With courtesy of Dr. S. Ortega-Lawerenz)

tumor was confirmed without showing extra-adrenal tracer uptake, excluding metastatic disease. The son was transferred from Serbia to the same hospital, where we treated his father already. By surgery the tumor tissue was removed totally. During the follow-up period of nearly 2 year the patient is symptom-free. ^{131}I.MIBG therapy was not needed. One should keep in mind the "rule of 10" in this rare neuroendocrine disease with an incidence of 2–8 per million per year in the USA: in 1/10 patients the pheochromocytoma is bilateral, in 1/10 malignant, in 1/10 extra-adrenal and in 1/10 familial [11]. In this family, one can find three of them. The father suffered from a malignant, the son from a bilateral tumor and the disease is familial. The activity administered in patients we treated because of malignant disease ranged from 15 to 42.7 GBq. The mean follow-up time was 30.2 months (range 9–97 months). In one patient with malignant pheochromocytoma and a soft tissue metastasis in the mouth in one of five of the therapeutic courses the total activity was administered via an intra-arterial catheter into the arteria carotis externa. Tumor uptake and intratumoral residence time of the activity in this local metastasis was not significantly different from intravenous activity administration (Fig. 29.7). The clinical symptoms improved in all patients. Four of the patients died in the follow-up time [12].

Probably in all studies, mentioned above, low-specific-activity ^{131}I-mIBG (LSA-^{131}I-mIBG) was used for treatment of these patients. The disadvantage of this compound is a very high amount of unlabeled MIBG, competing for norepinephrine transporter binding sites and disrupting the norepinephrine-reuptake mechanism negatively. In an open, single-arm multicenter trial, 49 patients with pheochromocytoma and 19 patients with paraganglioma were treated with a very high-specific-activity ^{131}I-mIBG(HAS-^{131}I-mIBG) between 2009 and 2014. Thirty-three (49%) of all treated patients had a response regarding hypertension control with a reduction of at least 50% of hypertensive medication. Even 59 (92%) patients had an objective tumor response (partial response n = 15; stable disease n = 44). The median overall survival (OS) was 37 months (range 31–49 months) and 5-years OS 36%. These data suggest a broad tumor effect of HAS-^{131}I-mIBG. The number of severe adverse events in the long-term follow-up was comparable with those in earlier trials using LSA-^{131}I-mIBG two secondary malignancies (1 acute myeloid and 1 acute lymphocytic leukemia). Hematologic adverse events under HSA-^{131}I-mIBG therapy were higher than under LSA-^{131}I-mIBG [13].

In some of our patients, we observed decreasing tracer uptake following repeated ^{131}I-mIBG treatment courses (Fig. 29.8). Using ^{111}In-Octreotide scintigraphy in these patients, they might show positive tracer uptake. In those patients, we went on using unlabeled Somatostatin® for further treatment to improve or stabilize clinical symptoms.

MIBG sensitivity drops down in metastatic pheochromocytomas and paragangliomas to even <50% of paragangliomas with germline mutations with succinate dehydrogenase subunits. Most of these lesions strongly express somatostatin receptors [14]. Five somatostatin receptor subtypes are known. The overexpression of these subtypes may be different in benign or malignant pheochromocytomas. The majority (about 90%) of pheochromocytomas and paragangliomas overexpress somatostatin subtype 3 and/or 2A. Subtype 2A is overexpressed mainly in extra-adrenal pheochromocytomas [15]. Comparing the detection rate per lesion of pheochromocytoma and paraganglioma by different imaging procedures, PET studies using ^{68}Ga-DOTA-SST were significantly better than other PET-tracer studies and $^{123/131}$I-MIBG scintigraphy, especially in tumors overexpressing SSTR2, whereas ^{68}Ga-DOTATOC binds more to SSTR2 and SSRT5, ^{68}Ga-DOTANOC shows a high affinity to all SSTRs except SSTR1 [16].

Since several years, radiotagged somatostatin receptor agonists are developed for diagnostic and therapeutic procedures in patients suffering from such neuroendocrine tumors [17], which express somatostatin receptors. More recently for therapy β-emitters like ^{90}Y or ^{177}Lu are used for

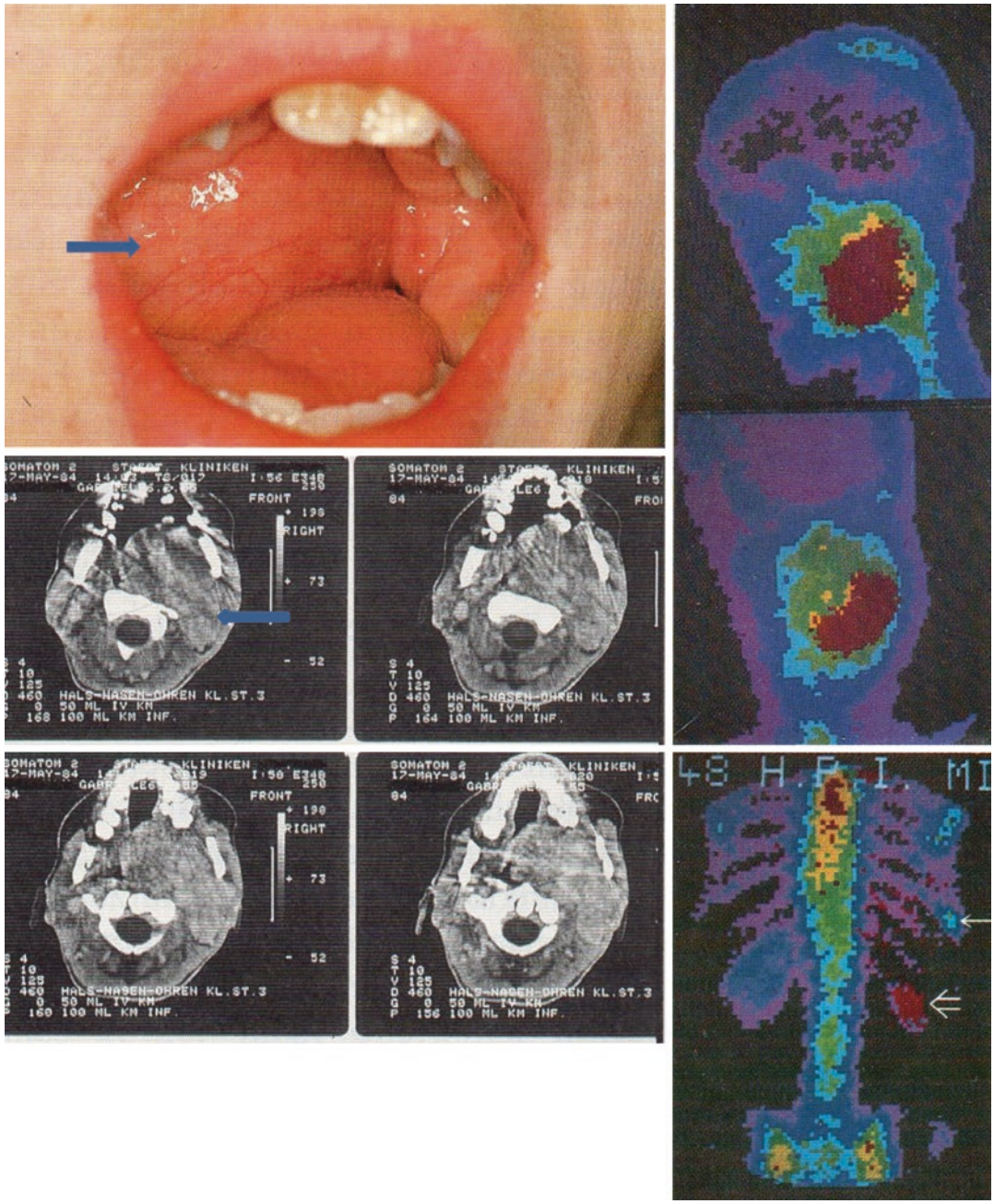

Fig. 29.7 Female pat. with malignant pheo: primary left adrenal gland, soft tissue metastasis right neck with compression in the mouth (blue arrow), bone mets

labeling either DOTATOC or DOTATATE. In a prospective observational trial in 200 patients with advanced neuroendocrine tumors, dosimetry of kidneys and bone marrow was performed to evaluate the impact on efficacy and outcome after treatment with ^{177}Lu-DOTA-octreotate. Most patients were suffering from advanced small intestine or pancreatic NET, only three from paraganglioma and one from a pheochromocytoma. Complete remission was reached in 1

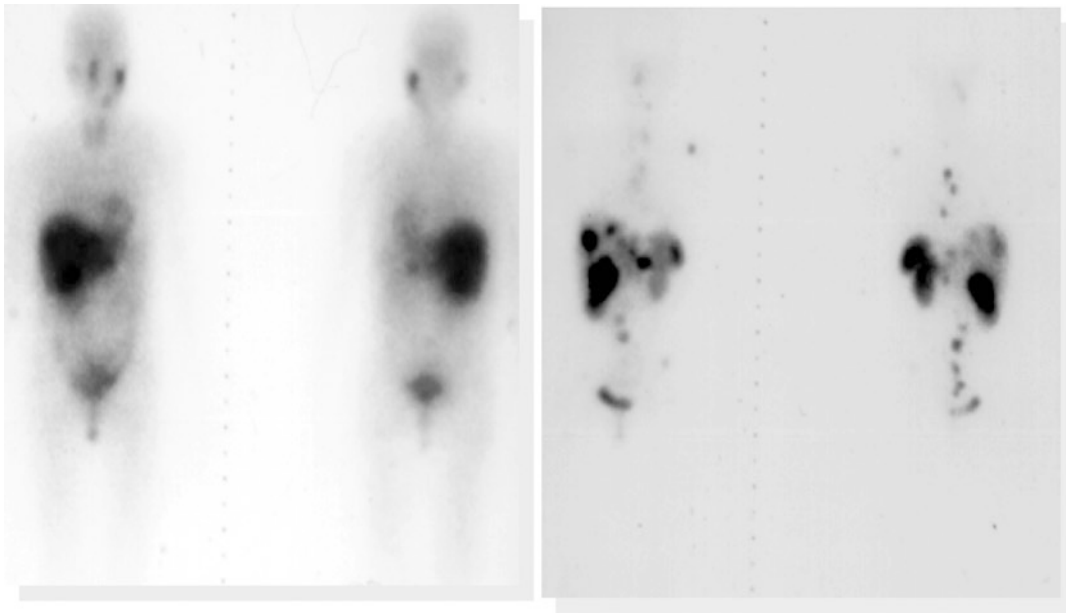

Fig 29.8 Malignant pheochromocytoma after 3 cycles with ^{131}I-mIBG with negative 123-I MIBG scintigraphy (left), but positive ^{111}In Octreotide scintigraphy. (right). Pat. was then treated with Sandostatin®

patient (0.5%), partial response in 47 (23.5%) and stable disease in 135 (67.5%) patients. The overall survival was 54 months in those who reached an absorbed dose in kidneys of 23 Gy in multiple treatment cycles, 25 months in those with lower absorbed doses. Toxicity was very similar to those observed in ^{131}I-mIBG therapy, resulting in acute leukemia (1.5%) and chronic leukemia (0.5%) of all patients in long-term observation [18]. Puranik and coworkers published results about more inoperable head and neck paragangliomas treated with ^{90}Y and or ^{177}Lu DOTATATE. Five patients were treated two times, one received three, and four others four courses. Mean follow-up time was 2.1 years (range 0.5–7 years). None of the patients developed new lesions, four of them showed partial response, five stable disease [19].

During the annual meeting of the European Association of Nuclear Medicine 2019 in Barcelona, the group of R.P. Baum presented a poster about a new somatostatin receptor antagonist for NET therapy [20]. For therapy, this NOGADA-LM3 was labeled with ^{177}Lu. In diagnostic scans with 68Ga NOGADA-LM3, high uptake in the tumors was observed, also fast whole-body clearance. In comparison with post-therapeutic scans with 68Ga DOTATATE, more metastases were observed because of a better tumor-to-background ratio (Fig. 29.9). Because of these promising aspects, further clinical studies are needed.

29.1.2 Neuroblastoma

29.1.2.1 Matthias Schmidt

Neuroblastoma is the most common extracranial pediatric solid tumor, first recognized in 1910 by Dr. James Homer Wright Homer Wright [21]. Neuroblastoma commonly presents in children younger than 2 years of age, with 90% being younger than 5 years of age. There is marked variability in clinical behavior ranging from spontaneous regression or differentiation into benign tumors to rapid and progressive disease with fatal outcome. One subgroup, high-risk neuroblastoma, is difficult to treat and requires multimodal therapy (Table 29.1).

Current treatment for high-risk neuroblastoma patients consists of induction chemotherapy followed by a consolidation therapy including

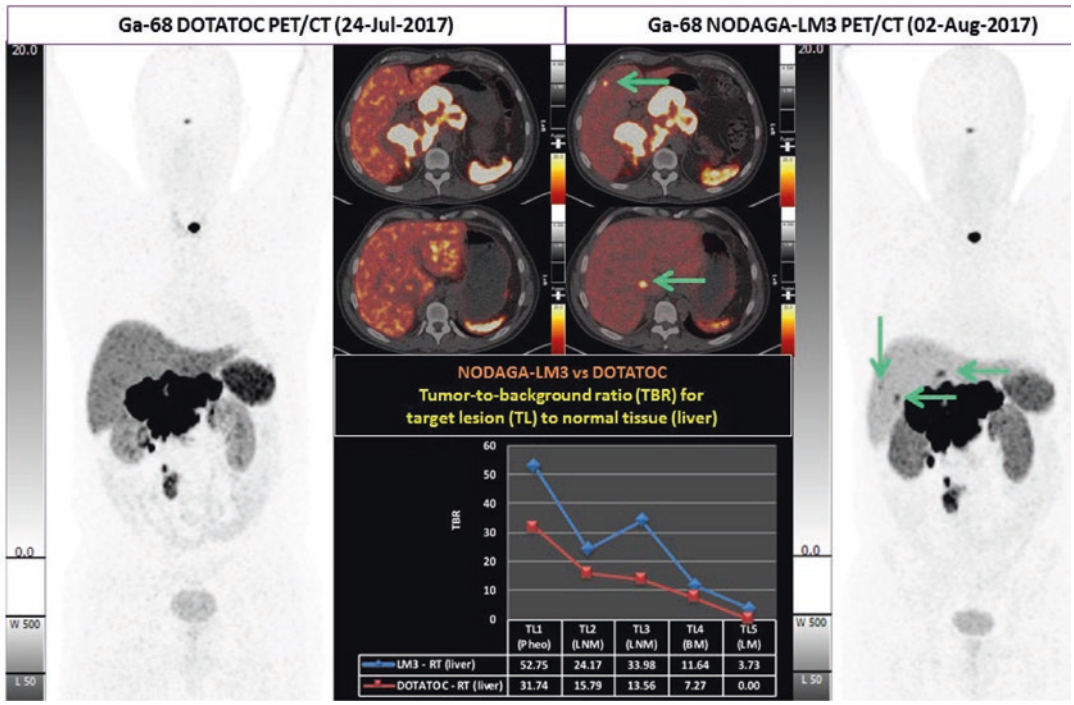

Fig. 29.9 Malignant pheochromocytoma: higher tumor-to-normal liver ratio on Ga-68 NOGADA-LM3 PCT/CT compared to Ga-68 DOTATOC PET/CT allows detection of 3 additional liver metastases (blue arrows). (Courtesy Prof. Dr. RP. Baum)

Table 29.1 Stage according to the International Neuroblastoma Risk Group (INRG) stages [22]

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of imaging-defined risk factors and confined to one body part
L2	Loco-regional tumor with presence of one more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

autologous stem cell transplantation. Surgery for the primary tumor and/or metastases and external radiation therapy are additional therapeutic modalities. Despite aggressive treatment regimens, high-risk neuroblastoma continues to have a devastating mortality rate of more than 40% and 5-year overall survival of patients with stage IV neuroblastoma only 30–50% [23]. ^{131}I-mIBG therapy is one treatment option [24–26]

29.2 ^{131}I-mIBG for Initial Therapy

First-line ^{131}I-mIBG therapy was developed in The Netherlands [27]. In 1991, Hoefnagel and coworkers recommended the use of ^{131}I-mIBG therapy in advanced neuroblastoma as a first-line treatment just after diagnosis. They stated that children's better general condition prior to following surgery and/or chemotherapy might be more unaffected, and shrinkage of the primary tumor would be advantageous for a surgical resection [28]. Kraal et al. analyzed response rates of ^{131}I-mIBG therapy in patients with newly diagnosed high-risk neuroblastoma. In one study, the objective response rate (ORR) was 73% after surgery; the median overall survival was 15 months (95% confidence interval (CI) 7 to 23); 5-year overall survival was 14.6%; median event-free survival was 10 months (95% CI 7 to 13); and 5-year event-free survival was 12.2%. In

the other study, the ORR was 56% after myeloablative therapy and autologous stem cell transplantation; 10-year overall survival was 6.25%; and event-free survival was not reported. With regard to short-term adverse effects, one study showed a prevalence of 2% (95% CI 0% to 13%; best-case scenario) for death due to myelosuppression. After the first cycle of ^{131}I-mIBG therapy in one study, platelet toxicity occurred in 38% (95% CI 18% to 61%), neutrophil toxicity in 50% (95% CI 28% to 72%), and hemoglobin toxicity in 69% (95% CI 44% to 86%); after the second cycle this was 60% (95% CI 36% to 80%) for platelets and neutrophils and 53% (95% CI 30% to 75%) for hemoglobin. In one study, the prevalence of hepatic toxicity during or within 4 weeks after last the ^{131}I-mIBG treatment was 0% (95% CI 0% to 9%; best-case scenario). Neither study reported cardiovascular toxicity and sialadenitis. There were no secondary malignancies observed (0%, 95% CI 0% to 9%), but only five children survived more than 4 years [29].

29.3 ^{131}I-mIBG in Stage III or IV Neuroblastoma

^{131}I-mIBG therapy in high-risk neuroblastoma patients started in 1984 [25], and these early studies focused on feasibility and toxicity. There is a lack of prospective randomized controlled trials about ^{131}I-mIBG therapy in neuroblastoma patients. Data are mostly taken from retrospective series. Seven studies with a total of 151 patients reported on highly variable ^{131}I-mIBG activities per treatment cycle 2.59–16.65 GBq (70–450 mCi) and on a response rate (complete or mostly partial response) of 17–66%. Phase I/II studies used ^{131}I-mIBG in progressive, refractory or relapsed high-risk neuroblastoma. In 1998, Matthay et al. reported on the treatment of 30 patients with escalating doses from 96.2–673.4 MBq/kg. None of the patients treated with 444 MBq/kg (12 mCi/kg) or less experienced prolonged neutropenia and therefore did not require autologous stem cell rescue. In contrast, two of five patients treated with 555 MBq/kg (15 mCi/kg) and four of nine patients treated with 666 MBq/kg (18 mCi/kg) required stem cell rescue. The maximum tolerated dose for patients without stem cell support was 444 MBq/kg (12 mCi/kg) being nowadays a usually used activity. The objective response rate was 37%, with most of the responses observed in patients receiving 444 MBq/kg (12 mCi/kg) or higher ^{131}I-mIBG. Median survival time following ^{131}I-mIBG therapy was 6 months [30]. Summarizing the results of 25 studies, Wilson et al. reported about an objective tumor response ranging from 0% to 75%, mean 32% [24, 26]. In Germany, ^{131}I-mIBG is given at the end of induction chemotherapy in case of persistent mIBG-avid disease before autologous stem cell transplantation [31].

29.4 ^{131}I-mIBG after Induction Chemotherapy

In the German NB85 trial, 47 high-risk neuroblastoma patients without complete response after induction chemotherapy were treated with a mean activity of 330 MBq (8.9 mCi) ^{131}I-mIBG/kg resulted in a response rate of 46.8%. In the German NB2004 study (End of study 31.12.2016), ^{131}I-mIBG therapy was scheduled in patients with non-progressing I-123-mIBG positive tumor tissue at the end of induction therapy. The effect of ^{131}I-mIBG therapy was analyzed retrospectively in 111 high-risk neuroblastoma patients: Forty patients received ^{131}I-mIBG therapy using a median activity of 444 MBq ()/kg body weight. By univariate analysis, patients who underwent ^{131}I-mIBG therapy had a better 3-year event-free survival (3-y-EFS 46 ± 8%) and 3-year overall survival (3-y-OS 58 ± 9%) than 71 patients without ^{131}I-mIBG therapy (3-y-EFS 19 ± 5%, $p = 0.003$; 3-y-OS 43 ± 6%, $p = 0.037$). However, subgroup analysis of 66 patients who underwent high-dose chemotherapy with autologous stem cell transplantation (ASCT) during treatment found a very similar outcome with ^{131}I-mIBG (3-y-EFS 49 ± 9%, 3-y-OS 59 ± 10%) and without ^{131}I-mIBG therapy (3-y-EFS 33 ± 9%, $p = 0.171$; 3-y-OS 59 ± 9%, $p = 0.285$) due to the dominating effect of ASCT. By multivariate anal-

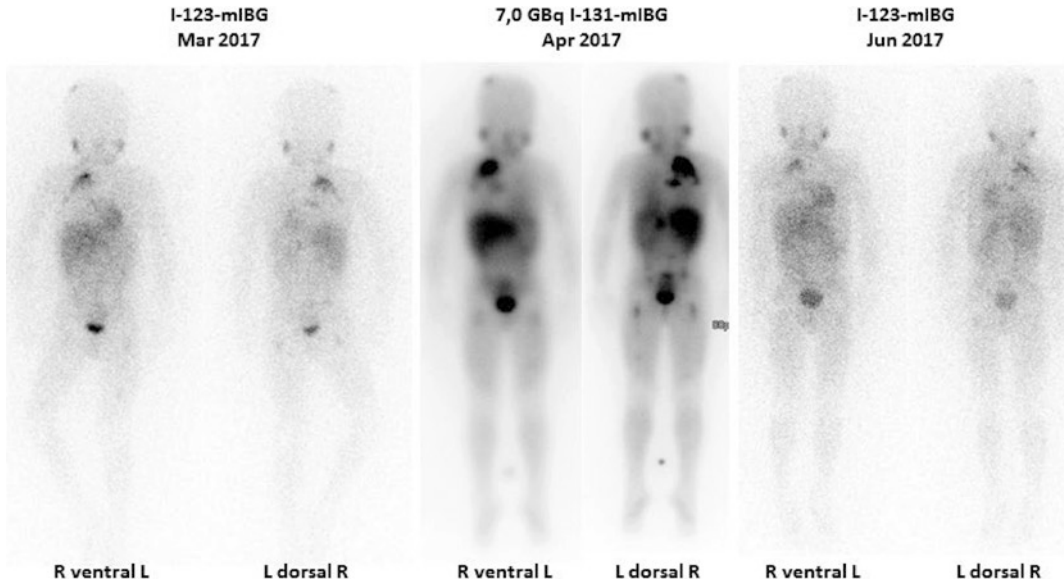

Fig. 29.10 Four year old male child with neuroblastoma IV with primary tumor in the right thoracic apex with infiltration of neuroforamina C7-Th4 and multiple skeletal lesions in the skull, ribs and vertebrae, pelvis and femora. Post-therapy ^{131}I-mIBG WBS shows more extensive skeletal disease. Subsequent ^{123}I-mIBG WBS demonstrates a decrease in number of lesions and intensity of uptake in the primary tumor and skeletal lesions

ysis, ^{131}I-mIBG therapy had no independent impact on EFS (p = 0.494) and OS (p = 0.891). Only ASCT, external beam radiation therapy and MYCN amplification were important for EFS and OS. Thus, an independent advantage of ^{131}I-mIBG therapy could not be proven in this retrospective analysis. Several problems have been addressed with this study: ^{131}I-mIBG therapy was delivered in multiple hospitals with highly variable activities of ^{131}I-mIBG (median activity 0.45 GBq (12 mCi), range: 0.14–1.46 GBq (3.8–39.5 mCi) / kg body weight). Results were influenced by local decisions as only 40 patients from 111 potentially eligible patients with ^{123}I-mIBG-positive residual disease at the end of induction chemotherapy actually received ^{131}I-mIBG therapy. As the patient numbers would allow detection of a difference between ^{131}I-mIBG therapy and no ^{131}I-mIBG therapy exceeding 20%, a smaller difference between these treatment options seemed likely from a clinical perspective, but was impossible to detect. As this study was based on the retrospective evaluation of the German NB97 trial, no dosimetric data were available. The pattern and intensity of ^{123}I-mIBG uptake were not analyzed with regard to treatment selection and outcome. In this group of heavily pretreated children, mIBG uptake was highly variable [31]. Fig. 29.10 is an example for treatment response after ^{131}I-mIBG therapy in a 4-year-old male child with neuroblastoma IV being initially treated with chemotherapy according to NB-2004 trial protocol HR including 7.0 GBq of ^{131}I-mIBG at the end of the induction chemotherapy before autologous stem cell transplantation.

29.5 Side Effects of ^{131}I-mIBG Therapy

The most important and usually intermediate complication of ^{131}I-mIBG therapy is related to hematotoxicity due to bone marrow irradiation. Neutropenia and thrombocytopenia are the most likely side effects and can be effectively overcome in combination with autologous stem cell transplantation. Matthay et al. demonstrated in a phase I trial that 30% of patients receiving ≥555 MBq (15 mCi)/kg of ^{131}I-mIBG had pro-

longed and significant myelosuppression which could be abrogated with infusion of autologous hematopoietic stem cells. Hematological toxicity is more noticeable in patients with bone marrow metastases and patients who received higher whole-body radiation doses. Hematopoietic cell transplantation was required in about one-third of patients treated with 666 MBq (18 mCi)/kg ^{131}I-mIBG. In contrast, all patients treated with less than 444 MBq (12 mCi)/kg of ^{131}I-mIBG did not need hematopoietic cell transplantation.

Early complications include nausea and vomiting in 10–20% of patients. Sialadenitis is seen with a relatively high frequency, while permanent xerostomia is rare. Modak et al. reported on transient sialadenitis in nine neuroblastoma patients who had received 444–666 MBq (12–18 mCi)/kg of ^{131}I-mIBG. Five patients had bilateral parotid swelling, two patients with associated buccal discomfort within 24 h of injection which subsided within 48 h. Grade 3 or 4 serum amylase elevation was documented in 8/8 patients tested [median 1336; range: 576–8830 U/L] which normalized [25–125 U/L] within 4–14 [median 5.5] days. Serum lipase remained normal. Patients did not develop subsequent dry mouth or dysphagia.

Blood pressure-related adverse advents are rare: antihypertensive drugs were required in 2.8% of 218 ^{131}I-mIBG administrations.

Veno-occlusive liver disease (VOLD) is an important early complication in patients who received ^{131}I-mIBG therapy followed by myeloablative chemotherapy and hematopoietic cell transplantation. The new approaches to neuroblastoma therapy (NANT) consortium reported that 6 of 22 patients had VOLDs after the therapies and an apparently high rate of VOLD was seen in the patients with a low glomerular filtration rate. In contrast, no VOLD was seen in patients receiving double infusions of high-dose ^{131}I-mIBG without chemotherapy. A decreased clearance of the chemotherapeutic agents was considered a major cause of VOLD.

Late complications include persistent hematotoxicity and thyroid dysfunction. Van Santen et al. reported about the development of a TSH ≥4.5 mU/L in 16 (64%) out of 25 neuroblastoma patients treated with ^{131}I-mIBG and concluded that occurrence of thyroid dysfunction after treatment with ^{131}I-mIBG for neuroblastoma is high, in spite of potassium iodide prophylaxis requiring close thyroid follow-up. In addition, they reported on an improved thyroid blockade with thyroxine, methimazole and potassium iodide with 19 / 23 patients (86%) of patients having a normal thyroid function after a mean follow-up of 19 months. Clement et al. reported on long-term efficacy of thyroid prophylaxis. Defining thyroid dysfunction as a plasma TSH > 5.0 mU/L or the use of levothyroxine thyroid disorders was seen in 12/24 patients available for long-term evaluation with a mean follow-up of 9.0 years after ^{131}I-mIBG treatment demonstrating the significant risk of thyroid damage. Thus, the incidence of thyroid disorders was high and increases with advancing time. No deleterious effects of ^{131}I-mIBG therapy on the parathyroid glands were found. As hypothyroidism can be easily treated, this side effect is usually not considered as serious.

Other less likely complications include fatigue secondary to anemia, sterility, and amenorrhea but these side effects are usually an effect of the combination with other therapies such as chemotherapy. Clement et al. published two patients with ovarian insufficiency after treatment with ^{131}I-mIBG therapy. Hepatic, adrenal, or cardiac dysfunction have rarely been reported.

Secondary malignancies have been reported with an incidence of less than 5%. In a report from Italy, two leukemia, one angiomatoid fibrous histiocytoma, one schwannoma, and one rhabdomyosarcoma occurred in 119 patients with neuroblastoma after ^{131}I-mIBG therapy. The University of California group from San Francisco described that leukemia was observed in 3 of 95 patients with refractory neuroblastoma at 7, 11, and 12 months after ^{131}I-mIBG therapy. It was difficult to clarify the main factors of the secondary malignancies, because all patients received several intensive therapies including chemotherapy and ^{131}I-mIBG therapy. Papillary thyroid carcinomas have been reported in two of nine patients with thyroid nodules [32].

29.6 Radiation Exposure/ Dosimetry

Heterogeneity in ^{131}I-mIBG uptake, tumor characteristics, and radiation resistance, as well as limitations of the current equipment and methods make correlation of dosimetry with response a continuing challenge [33]. Tumor dosimetry is an extensive topic on which progress has been achieved [34–37]. The main problem is that acquisition of serial whole body imaging in children is usually not possible. Usually, empirical treatment activities are usually chosen, and posttherapeutic whole-body and SPECT examinations are performed. Without stem cell support, the maximum allowable bone marrow absorbed dose consists of 2 Gy for adults and 2.5 Gy for children. If stem cell rescue is available, higher bone marrow doses are possible. In a series of 16 neuroblastoma patients in whom serial imaging after ^{131}I-mIBG was possible, typical whole-body absorbed doses were found in the region of 2 Gy (range: 1.0–2.9 Gy) whereas tumor absorbed doses in turn covered a span between 10 and 60 Gy using a therapeutic activity of 444 MBq/kg body weight [37].

In sum, ^{131}I-mIBG therapy is a long-standing established treatment modality. Upfront ^{131}I-mIBG therapy was mainly used in the Netherlands. ^{131}I-mIBG in case of residual mIBG-avid disease at the end of induction chemotherapy was included in the German protocol. ^{131}I-mIBG therapy was used in case of relapse in international studies. Due to the rarity of the disease, data are limited and there is only little innovation so far. The optimal timing of ^{131}I-MIBG therapy within the multidisciplinary therapy in not yet defined [38]. A new therapeutical aspect may be the use of ^{211}At metaastatobenzylguanidine, causing less hematotoxicity, shown in animal experiments [39].

With the recent establishment of new therapies, it may be possible to develop more effective therapeutic strategies in high-risk neuroblastoma patients. Few data are available on the effectiveness of PRRT [40]. A British trial was set up to evaluate how effective ^{177}Lu-DOTATATE is in children with high-risk relapsed or refractory neuroblastoma and determine the safety and adverse events of the treatment experienced by patients on the study (Eudra-CT-Nr. 2012-000510-10, https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-000510-10/results).

It may be concluded as stated by Kayano D and Kinuya S still in 2018 “MIBG therapy indicate their efficacy, especially in patients with advanced neuroblastoma and pheochromocytoma/paragangliomas [41].

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