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Radioiodinated MIBG in paraganglioma and pheochromocytoma: previous results and early experiences using no-carrier-added MIBG

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Abstract

The majority of pheochromocytomas and paragangliomas are benign, with malignancy occurring in approximately 10% of pheochromocytoma patients. The malignancy rate among paragangliomas is 15–35% or higher if associated with succinate dehydrogenase B gene mutations. The 5-year mortality rate in malignant pheochromocytoma and paraganglioma is nearly 50%. Malignancy of both pheochromocytoma and paraganglioma is determined by the existence of metastasis or local invasion and not by the cellular characteristics. There are no known clinical, biochemical or histopathological differences between pheochromocytoma and paraganglioma.

Metaiodobenzylguanidine (MIBG) radiolabeled with either ^{123}I or ^{131}I has been used to diagnose neuroendocrine tumors such as paraganglioma and pheochromocytoma, and ^{131}I-MIBG has been used to treat these tumors. The role of radioiodinated MIBG in treating neuroendocrine tumors is still being evaluated. More recently, no-carrier-added (nca) MIBG has become available, and the advantages of nca MIBG over ca MIBG are being demonstrated. This article reviews the biology of paragangliomas and pheochromocytomas, the role of MIBG imaging in the diagnosis of these tumors and the role of both ca and nca ^{131}I-MIBG in the treatment of these tumors. New data on nca ^{131}I-MIBG in the therapy of these tumors are included.
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Keywords: Paraganglioma; Pheochromocytoma; MIBG; No-carrier-added

1. Introduction

Metaiodobenzylguanidine (MIBG) radiolabeled with either ^{123}I or ^{131}I has been used to diagnose neuroendocrine tumors such as paraganglioma and pheochromocytoma, and ^{131}I-MIBG has been used to treat these tumors. The role of radioiodinated MIBG in diagnosing and treating neuroendocrine tumors is still being evaluated. More recently, no-carrier-added (nca) MIBG has become available, and the advantages of nca MIBG over ca MIBG are being demonstrated. This article reviews the biology of paragangliomas and pheochromocytomas, the role of MIBG imaging in the diagnosis of these tumors and the role of both ca and nca ^{131}I-MIBG in the treatment of these tumors. New data on nca ^{131}I-MIBG in the therapy of these tumors are included.

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2. Biological and epidemiological considerations

Pheochromocytoma is a tumor arising from the chromaffin cells originating from the adrenal medulla that produces and secretes catecholamines. Paraganglioma is a tumor arising from the extra-adrenal chromaffin cells that are found in the sympathetic nervous system and usually occur in the retroperitoneum. The paragangliomas arising in the parasympathetic nervous system originate primarily in the neck.

Cesar Roux in Switzerland and Charles H. Mayo in the United States were first to recognize and successfully remove clinically significant pheochromocytoma in 1926. At that time, no documentation of catecholamine hypersecretion was available [1]. Since then, significant improvements have occurred in biochemical and histological testing as well as in anatomical and functional imaging.

Despite some of the autopsy studies showing a fairly high prevalence rate of pheochromocytomas [2], the incidence among the general population is estimated to be 1 to 6 out of 1 million per year [3–5]. Pheochromocytomas are

uncommon in individuals less than 20 years of age (age before which mostly extra-adrenal tumors occur), with an incidence peak in the fourth decade [6]. Occurrence of extra-adrenal disease is higher in children with nearly 50% of cases occurring in that population in one review. Despite that, clinical presentation of the disease is not different in the pediatric and adult populations. Only a small number of patients who present with pheochromocytoma have apparent metastases at the time of the presentation.

The majority of pheochromocytomas and paragangliomas are benign, with malignancy occurring in approximately 10% of pheochromocytoma patients [7]. The malignancy rate among paragangliomas is 15–35% or higher if associated with succinate dehydrogenase B (SDHB) gene mutations [8–10]. In the report by Amar et al. [8], 15 out of 21 patients with SDHB-related pheochromocytoma were found to have malignant lesions. However, mutations in the gene subunit D were reported to be associated with a much lower malignancy rate [11–13].

One of the difficulties encountered by clinicians in the management of these patients is that pheochromocytoma with benign histopathological profile may develop metastatic disease [14]. Malignancy of both pheochromocytoma and paraganglioma is determined by the existence of metastasis or local invasion and not by the cellular characteristics. It is not unusual for a patient to have had surgery for either tumor, thought to be cured of the tumor and for it to recur later as a malignant tumor. There are no known clinical, biochemical or histopathological differences between pheochromocytoma and paraganglioma [14].

Paragangliomas are the most frequent extracranial tumors found in children, comprising 8% to 10% of all pediatric malignancies and are responsible for approximately 15% of all childhood cancer deaths. The incidence is 10 per million in White children and 8 per million in Black children in the United States. Neuroblastoma is the most common malignancy diagnosed during infancy, with 50% of them presenting before 2 years of age and more than 90% before 5 years of age (see article in this supplement by DuBois et al.).

Nearly all of the pheochromocytomas in the multiple endocrine neoplasia (MEN) type II, 90% in the Von Hippel–Lindau syndrome and 90% in neurofibromatosis appear to be benign. The presentation of pheochromocytoma is highly variable, because it depends on the catecholamine production by the tumor.

Pheochromocytomas and paragangliomas are known to synthesize, store and secrete catecholamines that make them functional tumors; some of them, especially paragangliomas, are nonfunctional, that is, do not secrete any hormones. Clinical, biochemical and histopathological studies cannot reliably distinguish between the malignant and benign tumors. Features such as cellular hyperchromatism, increased number of mitoses and vascular and capsular invasion cannot safely distinguish malignancy from a benign tumor. There have been several biochemical, molecular and morphological markers proposed to differentiate benign from malignant tumors, but none of them so far have proved to successfully differentiate them.

3. Diagnosis

Malignant and benign functional pheochromocytomas have the same clinical presentation that include paroxysms of hypertension, palpitations, sweating, flushing, headaches, nausea, weakness, dyspnea, visual disturbances, weight loss and mental disturbances. Symptoms may be absent in nonfunctioning tumors that manifest themselves as a result of metastatic growth [15]. The most common metastatic sites and frequency for chromaffin-cell tumors are local lymph nodes (50%), bone (50%), liver (50%) and lung (30%) [15,16]. Many patients have metastatic disease in more than one organ.

3.1. Biochemical tests

Patients suspected of having pheochromocytoma initially undergo biochemical testing [17]. Because of the low incidence of pheochromocytoma, routine testing for it is not recommended. Documentation of elevated levels of plasma and urine catecholamines, urinary metanephrines and urinary vanillylmandelic acid has been used to make the diagnosis of pheochromocytoma. Although the incidence of pheochromocytoma is low, it is the devastating consequences of the disease that dictate the necessity of a reliable test to diagnose or exclude pheochromocytoma. Yet, despite the improved techniques employed for making the diagnosis of pheochromocytoma, the lag time between the initial symptoms and the final diagnosis remains nearly 3 years [18].

The approach in diagnosing pheochromocytoma varies greatly depending on the institution. Mayo Clinic used 24-h urinary excretion of catecholamines and total metanephrines for more than two decades. If the baseline 24-h urinary studies were normal, the study was repeated when the patient was symptomatic (e.g., with a spike in blood pressure). They did not find histamine and glucagon stimulation testing helpful in a study of 542 patients with high suspicion of pheochromocytoma and normal 24-h urinary catecholamine or total metanephrine excretion; none of these patients had a positive stimulation test in this setting [1].

Lenders et al. [19] have shown that plasma-free metanephrines or urinary fractionated metanephrines (normetanephrine and metanephrine separately) are the most sensitive tests for diagnosis and very useful in ruling out pheochromocytoma. High diagnostic sensitivities of the plasma-free or urinary fractionated metanephrines allow exclusion of virtually all pheochromocytomas if the results are negative. On the other hand, drugs, diet and conditions associated with increased levels of catecholamines, such as hypertension, heart failure and stroke, as well as inaccuracies in sampling methods, can cause false-positive results.

A multicenter cohort study was conducted from four referral centers for pheochromocytoma between 1994 and 2001 in order to determine the best test or combination of tests to diagnose pheochromocytoma. The analysis included 214 patients with a confirmed diagnosis of pheochromocytoma and 644 patients in whom it was determined not to have the tumor. The results of the test (sensitivity and specificity, respectively) are as follows: plasma-free metanephrines — 99% and 89%, urinary fractionated metanephrines — 97% and 69%, plasma catecholamines — 84% and 81%, urinary catecholamines — 86% and 88%, urinary total metanephrines — 77% and 93%, and urinary vanillylmandelic acid — 64% and 95%. The sensitivity and specificity values were highest for plasma-free metanephrines. Diagnostic yield was not improved by combining different tests beyond that of a single test of plasma-free metanephrines [20].

A Mayo Clinic review of benign paragangliomas reported that only 20% of patients had documented catecholamine hypersecretion, and most of the patients presented with mass effect symptoms or an incidental imaging finding. In patients with catecholamine hypersecretion, most tumors were localized to the abdomen and pelvis. Only 3.6% of patients with head and neck paraganglioma were documented to have catecholamine hypersecretion.

Malignant pheochromocytoma and paraganglioma have a defective expression of the catecholamine-synthesizing enzymes and, therefore, have a dominating noradrenergic phenotype. Malignant tumors can have other defects in synthesis of catecholamine precursors that result in elevated levels of dihydroxyphenylalanine (DOPA)/dopamine in plasma and urine [21].

Some authors have suggested that high circulating levels of dopamine and the catecholamine precursor DOPA are more often associated with malignant rather than benign pheochromocytomas. Lenders et al. [19] retrospectively analyzed 120 consecutive patients (mean age=41±12 years) with histopathologically confirmed pheochromocytomas. They found that dopamine urinary excretion was increased in all patients with malignant pheochromocytoma, but abnormal levels were also observed in some patients with a benign tumor. Urinary excretion of DOPA was in the normal range in all subjects with malignant pheochromocytoma. The authors concluded that in some pheochromocytoma patients, excessive dopamine excretion may be indicative of malignant tumor, but it is not a discriminating marker for malignancy. However, these biochemical markers do indicate dedifferentiation. Purely dopamine-secreting tumors are very rare, and patients can be normotensive and asymptomatic [14].

The granular storage protein chromogranin A (CgA) is co-released together with amines/peptides from neuroendocrine tumor cells and is therefore a general tumor marker in plasma. It correlates with both secretory activity and tumor volume [22]. Rao et al. [23] have shown that patients with malignant tumors had higher CgA levels than those with benign tumors, which, in turn, were different from controls. During chemotherapy, CgA levels followed catecholamine markers and reflected the therapeutic response. Plouin and Gimenez-Roqueplo [24] recently showed that urinary metanephrines corresponded very well with the growth of malignant tumors and their response to treatment.

3.2. Molecular studies

Numerous studies have been done in areas of angiogenesis, DNA ploidy, adhesion molecules, gene expression abnormalities and new molecular markers in order to find new associations with malignant pheochromocytoma and paraganglioma [14]. Potential markers of malignancy are microvessel density and differential expression of vascular endothelial growth factor (VEGF) and VEGFR-2 [25–27], p53 and bcl2 [28], N-cadherin expression [29], tenascin C and cyclooxygenase-2 [30,31]. However, it was found that while a new marker for neuroendocrine tumor survivin (the apoptosis inhibitor) may represent a novel diagnostic agent, it did not appear to reliably distinguish benign from malignant pheochromocytomas or paragangliomas. It was found in the cytoplasm of both malignant and benign tumors and did not identify patients at risk for disease [32]. Immunohistological testing for connexin or cytoplasmic staining for galectin expression was not able to produce differentiation of benign from malignant pheochromocytomas [33,34]. The beta subunits of inhibin and activin were not found to be helpful in discriminating between the malignant and benign behavior of pheochromocytomas [35].

3.3. Anatomic imaging

Traditional imaging modalities such as MRI, CT and ultrasound are employed for anatomical location and tissue characterization. The functional modalities determine the activity of the tumor and receptor expression. CT can reliably identify primary tumors and metastases larger than 1 cm in diameter with a sensitivity of 77–98% and a specificity of 29–92% [36]. A CT density of the adrenal lesion of 40–50 Hounsfield units is suggestive of a tumor in the relevant clinical setting and appropriate biochemical profile [37]. MRI provides a higher sensitivity of 90–100% and specificity of 50–100% compared to CT, and it is superior in detecting extra-adrenal disease [36]. Increased signal on T_2-weighted images in the chromaffin-cell tumors is known to be characteristic yet not diagnostic of pheochromocytoma and paraganglioma. In some instances, large tumors may have hemorrhage and necrosis with a resulting low signal intensity on T_2-weighted images [36]. Ultrasound has limited diagnostic yield and is usually reserved for specific patients, for example, pregnant women and children. Some studies, however, have validated this modality for evaluation of neck paragangliomas [36,38].

3.4. Functional imaging

Because of the limitations of anatomic imaging in detecting pheochromocytomas and paragangliomas, functional modalities that image tumor-specific properties are used to detect these tumors. The accumulation of the catecholamine analogue MIBG, also known as iobenguane, labeled with either ^{131}I or ^{123}I, has been demonstrated in pheochromocytomas and paragangliomas. Iobenguane is a guanethidine analogue that structurally resembles norepinephrine. Various organs with rich adrenergic innervation and catecholamine secretion accumulate iobenguane, and it localizes in neuroectodermally derived tumors, such as pheochromocytoma, paraganglioma, carcinoid, Merkel's cell tumor, medullary thyroid cancer and neuroblastoma. The high sensitivity and specificity of this agent for the imaging purposes lead to a development of the treatment application of MIBG for neuroectodermally derived tumors. MIBG uptake by the chromaffin cells is similar to that of norepinephrine uptake and storage. MIBG is taken by the sympathetic nervous system cells by the active transporting mechanism involving a norepinephrine transporting molecule working at the cell membrane and concentrated into secretory granules via vesicular monoamine transporters (VMAT 1 and 2). This agent, however, has no affinity for the adrenergic receptors.

MIBG imaging has been shown to be able to detect pheochromocytoma/paraganglioma lesions that are not detected by CT or MRI [39]. The use of ^{123}I-labeled MIBG has advantages over ^{131}I-MIBG for imaging these tumors because of the superior imaging quality that results from its physical properties, which also produce less radiation dose to the patient. MIBG labeled with ^{123}I has a higher sensitivity (83–100% vs. 77–90%) than ^{131}I-labeled MIBG in detecting disease. Furthermore, with ^{123}I-MIBG, in addition to the whole-body planar body imaging, single photon emission computed tomography (SPECT) can be obtained [36,40]. Some preliminary data using the combined SPECT/CT devices suggest that the results from the hybrid imaging are better than those from SPECT alone or CT alone. Only ^{131}I-MIBG (iobenguane) is approved by the FDA for imaging these tumors at this time. Thus, if ^{123}I-MIBG is used, it is done under the practice of medicine/pharmacy exclusion to the FDA regulations. Several local radiopharmacies are making this radiopharmaceutical available on a routine basis.

Guller et al. [41] evaluated the role of ^{131}I-MIBG in the diagnosis of pheochromocytoma. They prospectively collected the data on 152 patients with pheochromocytoma. All urinary, plasma and platelet analyses were highly standardized and supervised by one investigator. ^{131}I-MIBG scans were independently reviewed by two nuclear medicine physicians; 55.3% of the patients were female, and patients were predominantly White (73.7%). Spells (defined as profuse sweating, tachycardia and headache) and hypertension at diagnosis were present in 51.4% and 66.6%, respectively. Bilateral disease was found in 12.5%, malignant pheochromocytoma in 29.6% and hereditary forms in 23.0%. The most sensitive tests were total urinary normetanephrine (96.9%), platelet norepinephrine (93.8%) and ^{131}I-MIBG scintigraphy (83.7%). In combination with ^{131}I-MIBG scintigraphy, platelet norepinephrine, plasma norepinephrine/MIBG, total urine normetanephrine/MIBG and urine norepinephrine/MIBG had a sensitivity of 100%, 97.1%, 96.6% and 95.3%, respectively. The investigators concluded that tests of choice to establish the diagnosis of pheochromocytoma are urinary normetanephrine and platelet norepinephrine. A combination of ^{131}I-MIBG scintigraphy and diagnostic tests in urine, blood or platelets does further improve the sensitivity. They advocated performing an MIBG scan if the diagnosis of pheochromocytoma is clinically suspected and catecholamine measurements are within the normal range [41].

Indium-111 pentetreotide (OctreoScan) is an eight-amino-acid analogue of octreotide that binds to somatostatin receptors (SSTRs) and has been shown to accurately detect many tumors that express SSTR. Although there are not many studies on SSTR expression using polymerase chain reaction, immunochemistry or autoradiography [14], some studies report expression of all five types of SSTR, whereas others describe a high prevalence of SSTR2, which has a high affinity for the somatostatin analogues octreotide and octreotate [42–45]. ^{123}I-MIBG imaging has been shown to have a higher detection rate of pheochromocytoma and paraganglioma in comparison to ^{111}In pentetreotide scintigraphy (100% vs. 75%) [46].

However, ^{111}In pentetreotide can serve as a complementary study to evaluate MIBG-negative lesions, selecting the appropriate approach for resection. Follow-up of pheochromocytomas is highly dependent upon reliable localization and exclusion of multifocal, bilateral or metastatic disease. MIBG scintigraphy was developed for functional localization of catecholamine-secreting tissues. SSTR imaging (SRI) has a high sensitivity for localizing head and neck paragangliomas, but studies of intra-abdominal pheochromocytomas are rare. A review on the results of ^{123}I-MIBG and SRI studies that were performed in the workup of primary and recurrent pheochromocytomas since 1983 and 1989, respectively, was reported [47]. Scintigraphic results were correlated with catecholamine secretion, tumor size and site, presence of malignancy, associated tumor syndromes and morphological features. ^{123}I-MIBG scans were performed in a total of 75 patients: before resection of primary pheochromocytoma in 70 cases and because of recurrent disease in 5 cases. Pheochromocytoma detection rate was 83.3% for all tumors and 89.8% if the tumor is larger than 1.0 cm. Multifocal disease was detected in four patients. MIBG uptake correlated with larger size of pheochromocytoma (r=.33; P=.008) and higher levels of plasma epinephrine (r=.32; P=.006). MIBG-negative pheochromocytomas (n=14) were (P=.01) smaller than MIBG-positive tumors. MIBG uptake was

significantly higher in unilateral (P=.02), benign (P=.02), sporadic (P=.02), intra-adrenal (P=.02) and capsular invasive (P=.03) pheochromocytoma than in bilateral, malignant, MEN2A/2B-related, extra-adrenal and noninvasive pheochromocytomas. SRI detected 25% (8 of 32) of primary benign pheochromocytomas. MIBG detected metastases in 8 of 14 cases. SRI detected metastases in seven of eight cases, including three MIBG-negative cases. MIBG uptake correlated with the size, epinephrine production and site of pheochromocytoma. Its role in detecting bilateral and MEN2A/2B-related pheochromocytomas seems limited [47].

Paragangliomas of the head and neck arise from chemoreceptor tissue of the glomus bodies at the carotid bifurcation (carotid body paraganglioma), along the promontory of the middle ear (glomus tympanicum), at the jugular bulb (jugular paraganglioma) and along the vagus nerve high in the neck (vagal paraganglioma) [48]. Ninety-eight percent of patients with paraganglioma were determined to have SSR-2 and 2% were determined to have SSR-1, providing a high likelihood of ^{111}In pentetreotide binding in paraganglioma [49,50]. Therefore, several studies have shown better head and neck paraganglioma detection rate with pentetreotide scintigraphy, with a sensitivity of 97% and a specificity of 82% [48].

A prospective trial of ^{111}In pentetreotide, ^{123}I-MIBG scintigraphy and CT evaluated 12 patients with histologically proven malignant pheochromocytoma. At least one metastatic lesion was visualized by pentetreotide scintigraphy in eight patients, while the remaining four patients had negative findings. Of 54 known metastases, 43 (79.6%) were detected by MIBG, whereas 24 (44.4%) were detected by pentetreotide. Pentetreotide scintigraphy detected six metastases that were negative by MIBG. Thus, pentetreotide scintigraphy behaves, in part, complementary to MIBG and increases diagnostic sensitivity [51].

Kwekkeboom et al. [50] reported the results of ^{111}In octreotide scintigraphy in 34 patients referred because of known paragangliomas or in whom a paraganglioma was suspected and compared the results of octreotide scintigraphy with the outcomes of other imaging techniques used in the diagnosis or follow-up of these patients. Fifty of 53 (94%) known tumor sites in 25 patients with paragangliomas were detected. Additional sites of paraganglioma previously not detected were found in 9 of 25 patients (36%). In four of them, the tumor sites were subsequently demonstrated with other imaging modalities. In eight of nine patients who were referred because of symptoms consistent with paraganglioma or follow-up after surgical removal of a paraganglioma, neither routine imaging nor octreotide scintigraphy revealed any abnormalities indicative of paraganglioma. The investigators concluded that virtually all paragangliomas can be visualized using ^{111}In octreotide scintigraphy. Because conventional imaging is usually limited to the site where a paraganglioma is clinically suspected, octreotide scintigraphy, because of the information it provides on potential tumor sites in the whole body, may be useful in detecting multicentricity or metastases in patients with paraganglioma.

Approximately 10% of head and neck paragangliomas are reported to be familial. Myssiorek and Palestro [49] evaluated the utility of the Indium-111 pentetreotide for the screening purposes of the families with paraganglioma. Early diagnosis and treatment of familial paragangliomas (FPs) would decrease the morbidity of tumor excision. Patients from two kindred with FP were studied. Areas of increased uptake were further imaged with MRI. Altogether, five patients had positive ^{111}In pentetreotide scans. Two unsuspected glomus tympanicums and bilateral carotid body tumors were identified. Three people tested had no abnormal uptake. The authors conclude that ^{111}In pentetreotide scanning is a safe, noninvasive method for early diagnosis of FP and is useful in detecting multicentric lesions.

New data proposing somatostatin and DOPA analogues in PET/CT imaging are emerging. Hoegerle et al. [52] found 100% correlation between MRI and ^{18}F-DOPA PET results in 17 patients. They reported that ^{18}F-DOPA PET was better than MIBG imaging, which missed small tumors in 4 of 17 patients. The same investigators found good results for paragangliomas of the head and neck region, with MRI and PET correlation in 7 out of 10 patients; partial agreement was shown in 2 patients and disagreement in 1 patient, in whom a clearly defined lesion on PET was not confirmed by MRI. All tumors diagnosed by MRI were detected by PET; however, correlation of MRI and PET yielded an additional three lesions detected by PET alone [53].

^{18}F fluorodopamine is another promising PET radiotracer. Better sensitivity was found using ^{18}F fluorodopamine in comparison to MIBG in 16 patients with malignant pheochromocytoma. All patients had positive findings on PET, and 7 patients had negative ^{131}I-MIBG scans [54]. Pacak et al. [55] confirmed the high sensitivity of ^{18}F fluorodopamine in detecting malignant pheochromocytoma.

With high affinity of paragangliomas to SSTR type II, ^{68}Ga-based octreotide PET may be another promising tool in the imaging of these tumors [56]. Kayani et al. [57] studied 38 patients with primary or recurrent neuroendocrine tumors and found a sensitivity of 82% for ^{68}Ga-DOTATATE PET/CT and a sensitivity of 66% (25 of 38) for ^{18}F-FDG PET/CT. The sensitivity of combined ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT was 92%.

4. Therapy of pheochromocytoma/paraganglioma

The 5-year mortality rate in malignant pheochromocytoma and paraganglioma is nearly 50% [58]. The presence of chromaffin tissue, not connected with a primary tumor and where chromaffin tissue is not normally present, is a finding of distant metastasis and precludes surgical cure. Despite lack of outcome data, surgical debulking remains a mainstay of palliative therapy. Control of catecholamine excess

pharmacologically is necessary to control the symptoms in patients with metastases or incompletely resectable invasive pheochromocytoma. Other therapies, such as external irradiation, radiofrequency ablation, cryotherapy and arterial embolization, may be helpful for symptomatic relief [59].

4.1. Chemotherapy

One of the first treatments used for malignant chromaffin-cell tumors was cytotoxic chemotherapy. The use of streptozotocin alone, as well as in combined therapy with cyclophosphamide and 5-fluorouracil, did not offer significant improvement. In 1985, a combination of cyclophosphamide, vincristine, darcarbazine protocol was offered by Keiser et al. [60]. This scheme was shown to be effective at modest toxicity, yet with a short remission of time, which often was followed by therapeutic failure.

4.2. Previous experience with MIBG therapy

As noted previously in this article, iobenguane ^{131}I is a guanethidine analogue structurally resembling norepinephrine and localizes in neuroendocrine tumors such as pheochromocytoma and paraganglioma. Because ^{131}I undergoes beta decay and MIBG localizes in tissue and tumors with the noradrenaline transporter, a high radiation dose can be delivered to these tissues and tumors. The initial studies performed at the University of Michigan evaluated the distribution in animals [61]. They found that the adrenal medulla in dogs received the highest concentration. It is interesting to note that despite the very large radiation doses received by the adrenal glands, no evidence of adrenal dysfunction has been reported with the use of therapeutic doses of iobenguane ^{131}I. After the imaging studies demonstrated localization of the ^{131}I in tumors in patients, trials were performed, evaluating it as a therapeutic agent in tumors that accumulate the agent. There are several clinical trials that have evaluated ^{131}I-MIBG's effectiveness in treating pheochromocytoma and paraganglioma.

In 1982, Vetter et al. [62] described two patients with metastatic pheochromocytoma who received treatment with iobenguane ^{131}I. Metastases were reported to the skull, to the axial skeleton and to soft tissue in the abdomen; one patient also had metastases to the lung. CT was used to calculate the volume of metastatic disease. One patient received three doses over a 6-month period: 65 mCi (2.4 GBq), 80 mCi (2.9 GBq) and 103 mCi (4.0 GBq). Another patient was treated initially with 75 mCi (2.8 GBq), and after 3 months, an additional 110 mCi (4.1 GBq). The reduction in tumor size was reported to be 30% and 80% in the two patients. However, no alteration in biological catecholamine secretion was documented.

In 1984, Sisson et al. [63] treated five patients with malignant pheochromocytoma with ca iobenguane ^{131}I. The authors used two to four doses of the agent prepared with a specific activity of 8–11 Ci/mmol. Individual doses were given at 3- to 10-month intervals and in 97- to 197-mCi amounts (3.6–7.3 GBq). Total administered activity was 484 mCi (17.9 GBq) in four treatments over 15 months for the first patient, 373 mCi (13.8 GBq) in three treatments over 8 months for the second patient, 410 mCi (15.2 MBq) in three treatments over 17 months for the third patient, 270 mCi (9.9 GBq) in two treatments over 3 months for the fourth patient and 293 mCi (10.8 GBq) in two treatments over 3 months for the fifth patient. The first two patients had predominantly soft tissue metastases and demonstrated responses in terms of disappearance of symptoms and a reduction in tumor volume and hormone secretion to <50% of pretreatment values. The tumors of the patients who responded to ^{131}I-MIBG exhibited a more aggressive growth pattern before therapy, received a greater cumulative radiation dose and were more predominant in soft tissues than those in the patients who obtained little benefit. These partial remissions lasted over 1 year at the time of publication. Tumor-absorbed doses were stated to range between 13 and 120 Gy, but the dose estimation method was not described. No toxic effects were encountered during the treatments, and only minor and temporary untoward responses were seen.

Shapiro et al. [64] from the University of Michigan described the results of treating 28 patients with histologically proven metastatic pheochromocytoma or invasive, unresectable pheochromocytoma. All of the patients had tumors that accumulated tracer doses of ca iobenguane ^{131}I. Patients received between one and six doses of ca iobenguane ^{131}I, ranging from 97 to 301 mCi (3.6–11.1 GBq) for single administered doses and from 111 to 916 mCi (4.1–33.9 GBq) for cumulative doses. Minor degrees of leukopenia and thrombocytopenia were observed in 3/28 (10.7%) patients. There were three patients who developed hypothyroidism but no significant hepatic, renal, adrenocortical or autonomic nervous dysfunction. Mild radiation sickness (nausea, vomiting, anorexia) occurred in 21/28 (75.0%) patients. A partial response (PR) in tumor size was achieved in 8 of the 28 patients and a partial biochemical response in 12 of the 28 patients. No pharmacological toxicity was observed.

Lumbroso et al. [65] described the results of evaluating 20 patients with metastatic pheochromocytoma that included 16 men and 4 women (aged 11–76 years), in a single institution in France between 1985 and 1990. Metastases were reported in all patients: 11 patients had metastases at presentation, 7 patients had a 10- to 30-month delay in developing metastases and 2 patients developed metastases 9 and 28 years later. Hypersecretion of catecholamines was documented in all patients. On a diagnostic scan, MIBG uptake was found in 16 patients and only after a therapeutic dose in 1 patient. Surgery was performed on the primary tumor in 18 patients and on the distant metastases in 10 patients. ^{131}I-MIBG therapy was performed in 11 patients, 9 of whom were evaluable. The cumulative activity ranged from 3.7 to 26.3 GBq (100 to 711 mCi) in one to six courses. The authors reported symptomatic improvement in

five patients and partial tumor response, which lasted for 28 and 9 months, in 2 patients, terminating with a rapidly progressive disease (PD) involving the bone marrow. Stabilization was observed in three patients. Moderate myelosupression after therapy was observed in four patients. Fifteen patients died with a median survival of 16 months (range=3–60 months).

Krempf et al. [66,67] prospectively evaluated the results of iobenguane ^{131}I for treating 15 patients with malignant pheochromocytoma at six centers in France. Patients were 28 to 75 years of age and had tumor sites demonstrating good MIBG uptake. Four patients had only soft tissue metastases, four had only bone metastases and seven had both bone and soft tissue metastases. The patients received courses of administered doses that ranged from 78.4 to 250.0 mCi (2.9–9.2 GBq) of ca iobenguane ^{131}I every 3 months. The number of courses ranged from 2 to 11, and cumulative activity ranged from 300.0 to 2322 mCi (11.1–85.9 GBq). The cumulative absorbed dose in tumors ranged from 12 to 155 Gy. One patient with widespread bone metastases developed pancytopenia after three courses (348.6 mCi; 12.9 GBq); however, the pancytopenia resolved. The tumor response rate was 33.3% (5 of 15 evaluable patients); duration of tumor response ranged from 29 to 54 months. The biochemical response rate was 46.7% (7 of 15 evaluable patients), and the duration of biochemical response ranged from 5 to 48 months. All patients with a hormonal response had objective improvement in clinical status and blood pressure. Seven patients died during the 54-month follow-up period, four of whom never responded to treatment. The investigators reported finding no relationship between cumulative dose and response.

Bestagno et al. [68] evaluated six patients with metastatic pheochromocytoma, treated from a single institution in Italy with ^{131}I-MIBG. Single administered doses of 100–200 mCi (3.7–7.4 GBq) were given, in one to six courses, up to cumulative doses of 145–1021 mCi (5.4–37.8 GBq). Objective responses were observed in five patients (two tumor responses and five lowering of blood pressure), which were only temporary in three patients and stable in two. Complete disappearance of pain was obtained in two patients. No adverse side effects were observed.

Five patients including three men and two women, aged 26–43 years, with malignant pheochromocytoma treated using ^{131}I-MIBG were described by Troncone et al. [69]. One patient had a voluminous adrenal tumor and multiple distant metastases; two patients had a recurrent tumor; two others had postsurgical residual tumor. Patients were administered single doses (70–200 mCi; 2.6–7.4 GBq) of ^{131}I-MIBG by slow intravenous infusion, given in several therapeutic courses at 1- to 5-month intervals. The treatment resulted in a complete response in one patient with residual tumor and in a PR in the patient with disseminated disease. Two patients showed stabilization of the disease, whereas therapy was considered ineffective in the fifth case who did receive pain relief. The treatment had very little toxicity and was well tolerated by all patients.

Colombo et al. [70] reported four patients with malignant pheochromocytoma who were treated with ^{131}I-MIBG therapy between 1987 and 1991 in a single institution. They all were in an advanced stage of the disease and showed severe symptoms and poor response to traditional therapy. The cumulative activity given was 200–600 mCi (7.4–22.2 GBq). All patients demonstrated temporary subjective as well as biochemical and hemodynamic parameter improvement. Two patients showed a reduction in the size and number of metastases seen on scintigraphy. One patient died due to progression of the disease. Three patients were alive and in good condition at the time of report. No remarkable early or late side effects were reported. The authors concluded that ^{131}I-MIBG radiometabolic therapy in advanced-stage malignant pheochromocytoma could be useful in reducing symptoms. They proposed that further investigation might show whether a greater reduction in the size of the tumor could be achieved using different therapeutic schedules or by treating the disease in its earlier stages.

Arias Martinez et al. [71] presented one patient with a diagnosis of malignant pheochromocytoma with osseous metastasis. The patient was treated with ^{131}I-MIBG at a total dose of 1800 mCi (48.6 GBq), with an excellent tolerance and short adverse symptoms. There were a partial tumor response and a complete hormonal response, with a survival of 30 years after the diagnosis.

Fitzgerald et al. [72] treated 30 patients with malignant pheochromocytoma (n=11) or paraganglioma (n=19), with high-dose ^{131}I-MIBG. Patients were 11–62 years old (mean=39 years): 19 patients were male and 11 were female. Three patients with paraganglioma had multifocal tumor. Six paragangliomas were nonsecretory. All 30 patients had prior surgery. Fourteen patients were refractory to prior radiation therapy or chemotherapy before ^{131}I-MIBG therapy. Peripheral blood stem cells (PBSCs) were collected and cryopreserved. Doses ranged from 557 to 1185 mCi (15–32 GBq) and from 7.4 to 18.75 mCi/kg (0.25–0.5 GBq), with a median dose of 833 mCi (12.55 mCi/kg). Marrow effects began to occur 3 weeks after therapy. After the first ^{131}I-MIBG treatment, 19 patients required platelet transfusions; 19 received GCSF; 12 received epoetin or RBCs. Four patients received a PBSC infusion. High-dose ^{131}I-MIBG resulted in the following overall tumor responses in 30 patients: 4 sustained complete remissions, 15 sustained partial remissions, 1 sustained stable disease, 5 sustained PD and 5 initially responded but relapsed to PD. Of the 30 patients, 23 were alive at the time of the report; deaths were from PD (n=5), myelodysplasia (n=1) and unrelated cause (n=1). Overall predicted survival at 5 years is 75% (Kaplan Meier estimate). For patients who have good MIBG uptake on diagnostic scanning, high-dose ^{131}I-MIBG therapy was effective in producing a sustained response in 67% of patients, with tolerable toxicity.

Gedik et al. [73] retrospectively reviewed the charts of 19 patients with malignant pheochromocytoma (n=12) or paraganglioma (n=7), who were treated with ^{131}I-MIBG. Four patients (21%) received radiotherapy, three (16%) received chemotherapy and in one patient (5%), both chemotherapy and radiotherapy were given before ^{131}I-MIBG therapy. Of the 19 patients, 13 (68%) were men and 6 (32%) were women. Ages ranged from 22 to 68 years (median=47 years). The median initial dose was 7.4 GBq (200 mCi; range=6.7–25.9 GBq, 180–700 mCi); median cumulative dose was 22.2 GBq (600 mCi; range=6.8–81.4 GBq, 183–2200 mCi). Response to ^{131}I-MIBG treatment was evaluated by objective criteria as tumor response, biochemical response and subjective response. Objective tumor response was achieved in 47% of the patients. Biochemical response rate was 67%, and symptomatic response rate was 89%. Overall median follow-up was 29 months, with a range of 3–93 months. Hematologic complications were the most common side effects and were observed in 26% of the patients. The authors concluded that symptomatic and biochemical response can be reached with ^{131}I-MIBG therapy in patients with metastatic pheochromocytoma and paraganglioma. Although complete tumor response was not observed, the palliation and control of tumor by ^{131}I-MIBG therapy may be valuable for the patients.

Rose et al. [74] used higher levels of activity of ^{131}I-MIBG than previously reported for the treatment of malignant pheochromocytoma and paraganglioma. Following debulking surgery and stem cell harvest, 12 patients with malignant pheochromocytoma or paraganglioma were treated with ^{131}I-MIBG. Five had received previous external beam radiation and/or chemotherapy. The median single treatment dose was 800 mCi (37 GBq; range=386–866 mCi) or 11.5 mCi/kg (range=5.6–18.3 mCi/kg). The median cumulative dose was 1015 mCi (range=386–1690 mCi; 37.5 GBq; range=14.3–62.5 GBq). Three patients had a complete response, two of whom had soft tissue and skeletal metastases. Their median follow-up was 45 months (range=23–101 months). Seven patients had a PR, with a median follow-up of 43 months (range=6–47 months). Two patients without a response died with PD and two patients with an initial PR died of PD at 13 and 11 months, respectively. Grade 3 thrombocytopenia occurred after 79% (15 of 19) of treatments had been administered. Grade 3 and Grade 4 neutropenia followed 53% (10 of 19) and 19% (4 of 19) of treatments, respectively. One patient required stem cell infusion, and one developed primary ovarian failure. The single and cumulative doses of ^{131}I-MIBG were approximately 2–3.5 times higher than those used at other centers. Unlike previous reports, two patients with both skeletal and soft tissue metastases had a complete response. Hematologic toxicity was significant but tolerable. The investigators concluded that high-dose ^{131}I-MIBG may lead to long-term survival in patients with malignant pheochromocytoma [74].

Loh et al. [15] have reviewed the literature on the use of ca iobenguane ^{131}I for treating malignant pheochromocytoma and paraganglioma. Data were analyzed from 1983 through 1996 from 24 centers in 10 countries. A total of 116 evaluable patients were included, with the majority of them selected for treatment based on MIBG imaging studies showing accumulation in the tumors. The cumulative administered activity of the iobenguane ^{131}I was between 96 and 2322 mCi (3.5–85.9 GBq), with a mean±S.D. of 490±350 mCi (18.1±12.9 GBq). The mean single therapy dose was 158 mCi (5.8 GBq), and the number of doses varied between 1 and 11 with a mean±S.D. of 3.3±2.2 doses. An initial symptomatic improvement was reported in 76% of patients, tumor response in 30% and hormonal response in 45%. Five patients had complete tumor and hormonal responses that varied from 16 to 58 months and were

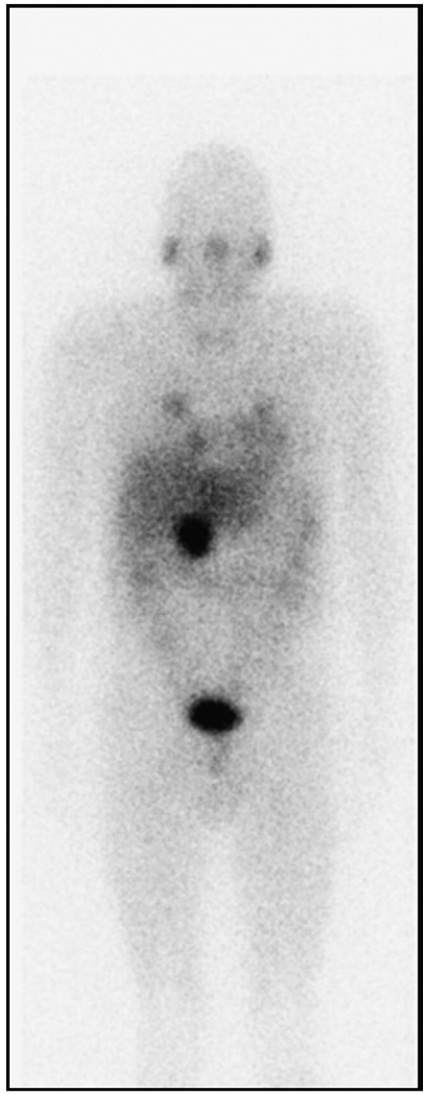

Fig. 1. Anterior image obtained 24 h after injection of 5 mCi of nca ^{131}I-MIBG in a patient with metastatic pheochromocytoma. Abnormal accumulation is noted in metastatic lesions in the upper abdomen and bilateral lungs.

sustained at the time of reporting. A more favorable response was noted in patients with metastasis to the soft tissue than in those with metastasis to the bone.

Safford et al. [75] reported the experience from Duke University Medical Center for the treatment of metastatic pheochromocytoma and paraganglioma. A retrospective review of 33 patients with metastatic pheochromocytoma (n=22) and paraganglioma (n=11) with ^{131}I-MIBG treatment over a 10-year period was performed. Patients received a mean dose of 388±131 mCi of ^{131}I-MIBG. Median survival after treatment was 4.7 years. Most patients experienced a symptomatic response leading to an improved survival (4.7 years vs. 1.8 years, P<.01). Patients with a measurable hormone response demonstrated an increased survival in comparison to those with no response (4.7 years vs. 2.6 years, P=.01). Patients who received a high dose (>500 mCi) as their initial therapy also had improved survival (3.8 years vs. 2.8 years, P=.02). Prolonged survival was best predicted by symptomatic and hormone response to ^{131}I-MIBG treatment. An initial dose of 500 mCi may be optimal. They also concluded that the benefit of ^{131}I-MIBG treatment for metastatic pheochromocytoma must also be weighed against its side effects.

4.3. nca MIBG

nca MIBG methodology was first introduced in 1993. The carrier molecule iobenguane is a biogenic amine, which may cause hypertension as well as nausea and vomiting when administered at high mass doses. High mass doses are currently the standard for therapeutic doses of ca iobenguane ^{131}I. Also, the selective active uptake by the norepinephrine transporter (NET) expressed on the neuroendocrine cell surfaces is a competitive process. Thus, the presence of cold "carrier" iobenguane molecules in the infusion solution can diminish the initial uptake in the target organs, such as neuroendocrine tumors (see article in the supplement by Mairs and Boyd). In vivo imaging and therapy studies in

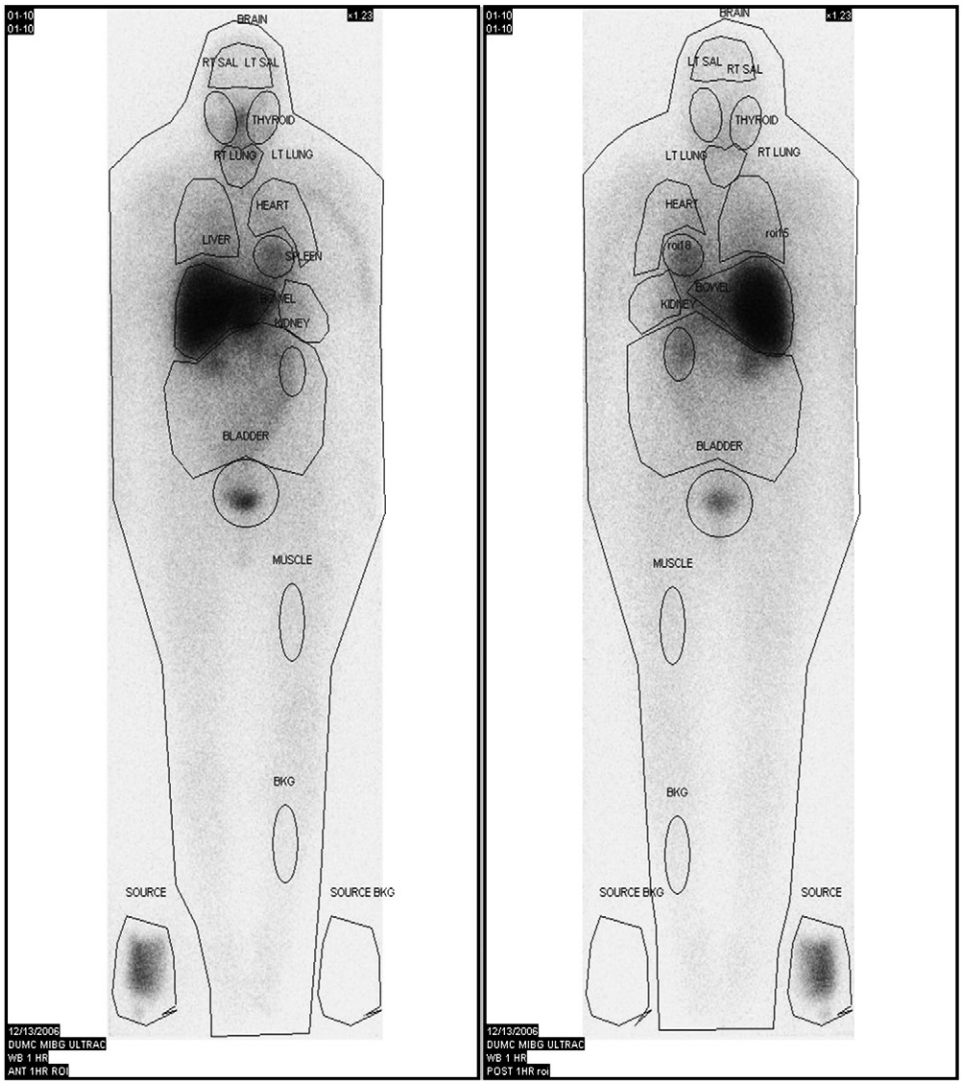

Fig. 2. Regions of interest on MIBG scan used for dosimetry calculations.

rodents confirm that target organ accumulation is at least twice as high for nca iobenguane as those obtained with ca preparations, and tumor kill is dramatically enhanced. In theory, the higher the specific activity of iobenguane ^{131}I, the greater the expected tumor uptake of radioactivity. In animal studies, the Ultratrace form of iobenguane ^{131}I has shown increased uptake by the normal tissues that express the NET such as the heart. In xenografts, the Ultratrace form demonstrated higher radiopharmaceutical concentration in PC-12 pheochromocytoma and in SK-N-BE (2c) neuroblastoma. An initial clinical study using iobenguane ^{123}I rather than iobenguane ^{131}I found enhanced tumor uptake of the Ultratrace form in a patient with malignant pheochromocytoma; however, no increased uptake was seen among four patients with benign pheochromocytoma. These findings suggest that, compared to ca iobenguane ^{131}I, the Ultratrace form may facilitate more radioiodinated iobenguane being taken up by malignant tumors.

Ultratrace iobenguane allows every molecule of MIBG to carry ^{131}I as compared with ca MIBG; only 1 in 2000 molecules of MIBG contains ^{131}I. By the benefit of high specific activity, the mass of the MIBG is much smaller with Ultratrace technology. The previously used methods for preparing the nca ^{131}I-MIBG resulted in the mass of MIBG for a 1-mCi diagnostic dose being approximately 0.3 mg and for a 350-mCi (12.95 GBq) therapeutic dose being 21 mg. For a 350-mCi dose of nca MIBG, the mass is 0.039 mg, that is, 1000th of the amount using Ultratrace technology.

A phase I study was performed in 11 patients to evaluate safety, distribution and radiation dosimetry of the Ultratrace iobenguane. The study included seven patients with carcinoid tumor and four patients with metastatic pheochromocytoma. All patients had documented ^{131}I-MIBG avid disease. The study was performed using 5 mCi (185 MBq) of Ultratrace iobenguane with a mass of cold MIBG that was equivalent to a 1-Ci dose of Ultratrace iobenguane. The patients had seven anterior and posterior whole-body images obtained over 5 days (Fig. 1). Computed tomography scans were obtained and used to determine tumor volumes in these patients. Regions of interest were drawn on the conjugate

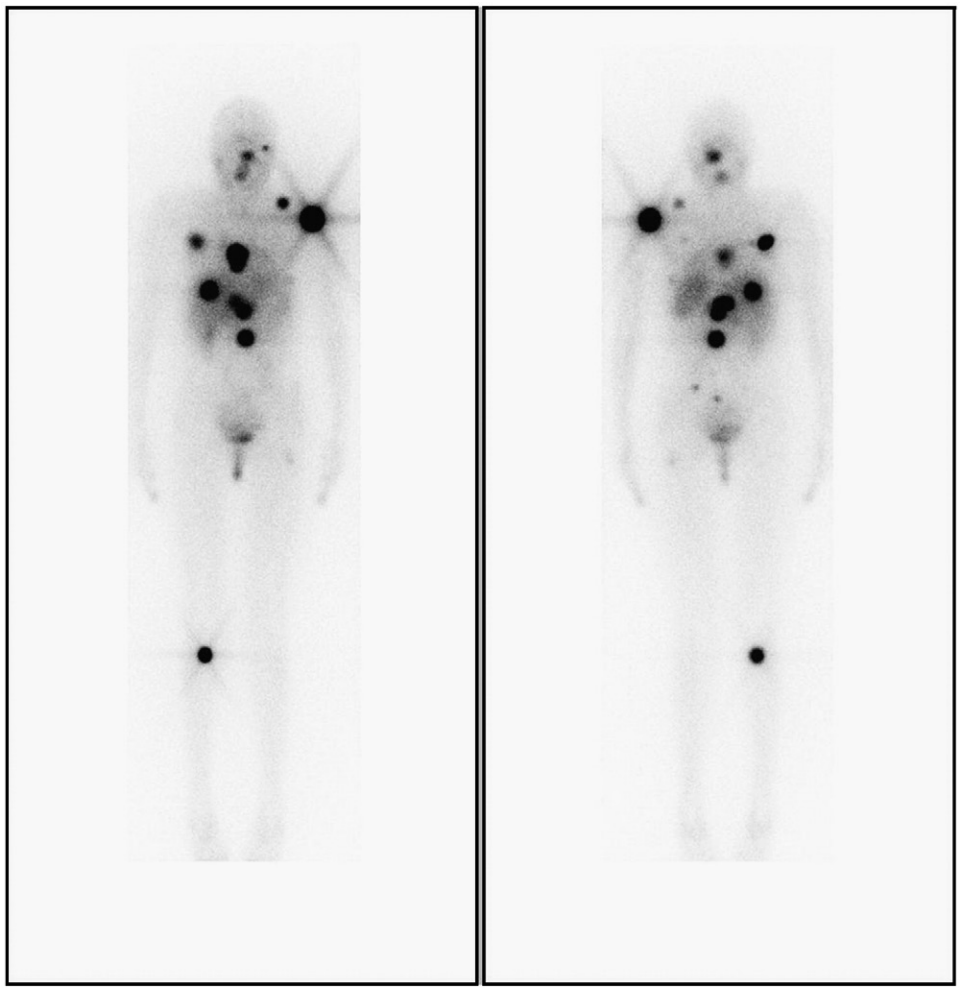

Fig. 3. A 36-year-old female with a history of carotid body paraganglioma in 1997 with metastases to the skull, sternum and abdomen in 2006. She underwent surgical removal of T12 vertebral lesions, base of skull metastases and abdominal metastases. The patient was diagnosed with sternal metastases in 2007. The patient was treated with 428 mCi of MIBG (11.6 GBq). Anterior and posterior images obtained 1 week after the therapy dose are shown.

views and geometric means computed for each source organ. A dosimetric analysis was performed by Radiation Dosimetry Systems, Inc. (Fig. 2).

No side effects were reported from the administration of radiopharmaceutical. The largest mean dose was in the thyroid (2.6±0.81 mGy/MBq). Mean calculated renal dose was 0.56±0.21 mGy/MBq. If 23 cGy is a limiting dose, maximum administered activity would be 1221 mCi (456 Bq). The only other organ with radiation dose exceeding 1.0 mGy/MBq was the salivary glands (1.8±0.56 mGy/MBq). Tumor doses ranged from 11 rad/mCi (3.0 mGy/MBq) to 46 rad/mCi (12 mGy/MBq).

A phase I evaluation of maximum tolerated dose, safety and efficacy of Ultratrace iobenguane in the treatment of malignant pheochromocytoma and paraganglioma is being performed.

The protocol was performed in cohorts of three patients starting at an administered dose of 6 mCi/kg (222 MBq) not to exceed 450 mCi (16.6 GBq) and increased to 7 mCi/kg (259 MBq) not to exceed 525 mCi (19.4 GBq) (Fig. 3), 8 mCi/kg (296 MBq) not to exceed 600 mCi (22.2 GBq) and 9 mCi/kg (333 MBq) not to exceed 675 mCi (24.9 GBq). If there was no dose-limiting toxicity (DLT) in the three patients, we progressed to the next level. If one patient developed DLT, three more patients were treated at that level. If none of those three developed DLT, we progressed to the next level. If two of the six patients had DLT, we went back to the previous level as the therapy dose for the phase II study. Three patients were treated at 6 mCi/kg, six patients treated at 7 mCi/kg (259 MBq) — one DLT, six patients treated at 8 mCi/kg — one DLT, six patients treated at 9 mCi/kg (333 MBq) — one DLT at this time.

For the therapy, the venous access was documented, and patients were premedicated with antiemetics. The MIBG was infused over 15–30 min with a flush of 10 min. Some patients experienced burning at the site of injection, but no other side effects were reported during procedure. Patients were advised to stay well hydrated. Patients may experience nausea starting 8–12 h after the therapy and may last for 4–5 days. Parotid gland tenderness may be noted at 12–24 h

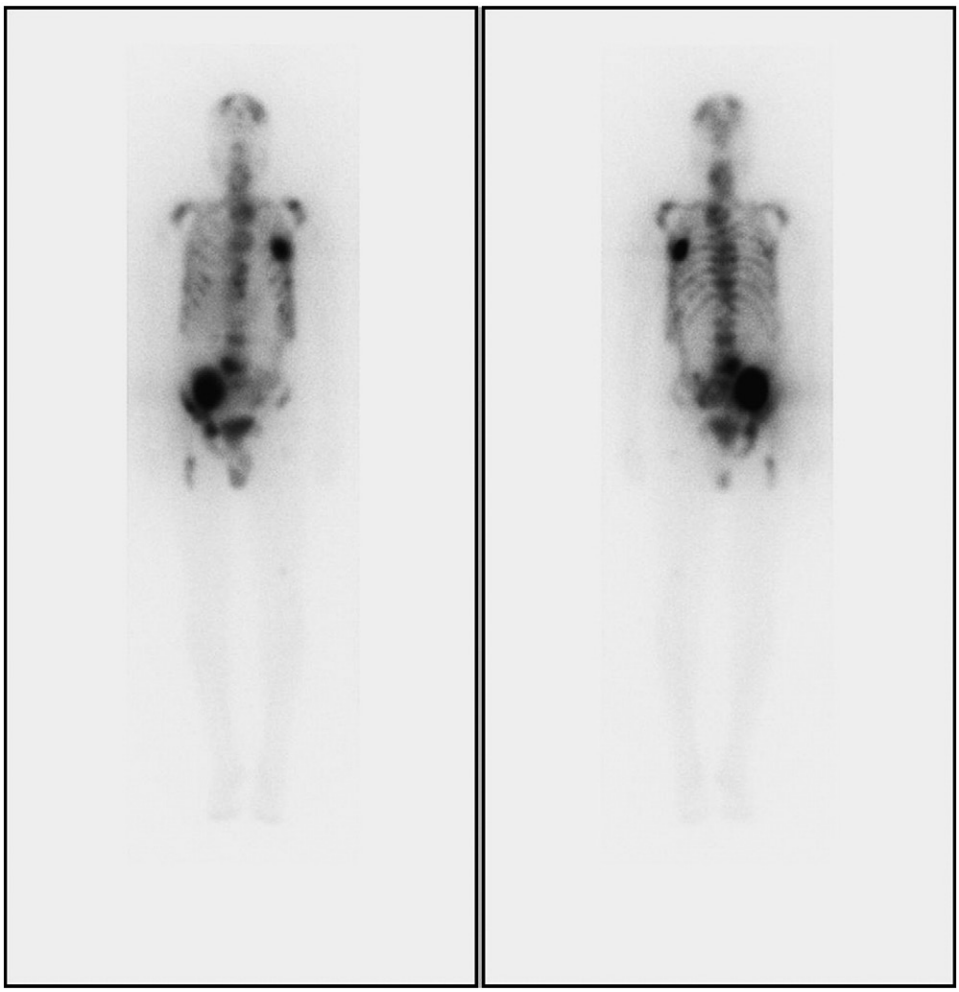

Fig. 4. A 35-year-old Asian male with paraganglioma first diagnosed in 1989 with bone metastases detected in 1990. The patient was treated with external beam therapy and MIBG in January 1999 (513 mCi; 13.8 GBq) and May 2005 (503 mCi; 13.5 GBq). The patient was treated with 405 mCi of nca MIBG (10.9 GBq) on July 2007. Anterior and posterior images obtained 1 week after the therapy dose are shown.

and lasts for a few days. Dry mouth and decreased taste can start at 12–24 h and last 1–2 weeks. WBC and platelets start decreasing at 2 weeks, with a nadir at 6 weeks. Patients generally feel tired for 1 or 2 weeks. The DLT for patients treated to date include Grade 4 thrombocytopenia and leukopenia. All patients have recovered from the bone marrow toxicity.

Some preliminary observations have been made from the patients treated in the phase II study. Patients with bone pain (Fig. 4) and pain in the liver from metastatic disease report a decrease in the amount of pain or absence of pain a few weeks after therapy. Patients with hypertension note a decrease in the amount of drug therapy needed to control their abnormal blood pressure. Decreases in catecholamines and CgA levels have been documented.

5. Summary

Metastatic pheochromocytoma and paraganglioma may be insidious at the time of diagnosis. After diagnosis, the therapy options are limited if surgical removal is not possible. Chemotherapy has not been very successful in the management of these patients. ca ^{131}I-MIBG has been used successfully to treat patients with metastatic pheochromocytoma and paraganglioma, but the response has not been uniform. Although all the patients treated have evidence of MIBG accumulation by imaging, no factor that predicts response has been determined. More recently, nca ^{131}I-MIBG has been shown to have advantages over ca ^{131}I-MIBG. Recent phase I and phase II studies document that the nca ^{131}I-MIBG can be safely administered to patients, and doses of 9 mCi/kg (333 MBq) [maximum of 675 mCi (24.9 GBq)] have been administered in the phase II study. The efficacy of treatment is still being evaluated.

References

[1] Kudva YC, Sawka AM, Young Jr WF. Clinical review 164: the laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. J Clin Endocrinol Metab 2003;88:4533–9.

[2] McNeil AR, Blok BH, Koelmeyer TD, Burke MP, Hilton JM. Phaeochromocytomas discovered during coronial autopsies in Sydney, Melbourne and Auckland. Aust N Z J Med 2000;30:648–52.

[3] Andersen GS, Toftdahl DB, Lund JO, Strandgaard S, Nielsen PE. The incidence rate of phaeochromocytoma and Conn's syndrome in Denmark, 1977–1981. J Hum Hypertens 1988;2:187–9.

[4] Stenstrom G, Svardsudd K. Pheochromocytoma in Sweden 1958–1981. An analysis of the National Cancer Registry Data. Acta Med Scand 1986;220:225–32.

[5] Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1983;58:802–4.

[6] Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev 2003;24:539–53.

[7] Goldstein RE, O'Neill Jr JA, Holcomb III GW, Morgan III WM, Neblett III WW, Oates JA, et al. Clinical experience over 48 years with pheochromocytoma. Ann Surg 1999;229:755–64 [discussion 64-6].

[8] Amar L, Bertherat J, Baudin E, Ajzenberg C, Bressac-de Paillerets B, Chabre O, et al. Genetic testing in pheochromocytoma or functional paraganglioma. J Clin Oncol 2005;23:8812–8.

[9] Brouwers FM, Eisenhofer G, Tao JJ, Kant JA, Adams KT, Linehan WM, et al. High frequency of SDHB germline mutations in patients with malignant catecholamine-producing paragangliomas: implications for genetic testing. J Clin Endocrinol Metab 2006;91:4505–9.

[10] Brouwers FM, Elkahloun AG, Munson PJ, Eisenhofer G, Barb J, Linehan WM, et al. Gene expression profiling of benign and malignant pheochromocytoma. Ann N Y Acad Sci 2006;1073:541–56.

[11] Benn DE, Gimenez-Roqueplo AP, Reilly JR, Bertherat J, Burgess J, Byth K, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. J Clin Endocrinol Metab 2006;91:827–36.

[12] Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, Muresan M, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA 2004;292:943–51.

[13] Gimenez-Roqueplo AP, Favier J, Rustin P, Rieubland C, Crespin M, Nau V, et al. Mutations in the SDHB gene are associated with extra-adrenal and/or malignant phaeochromocytomas. Cancer Res 2003;63:5615–21.

[14] Ahlman H. Malignant pheochromocytoma: state of the field with future projections. Ann N Y Acad Sci 2006;1073:449–64.

[15] Loh KC, Fitzgerald PA, Matthay KK, Yeo PP, Price DC. The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine (^{131}I-MIBG): a comprehensive review of 116 reported patients. J Endocrinol Invest 1997;20:648–58.

[16] Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. Endocr Rev 1994;15:356–68.

[17] Ilias I, Pacak K. Diagnosis and management of tumors of the adrenal medulla. Horm Metab Res 2005;37:717–21.

[18] Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Plouin PF. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocrinol Metab 2005;90:2110–6.

[19] Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet 2005;366:665–75.

[20] Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287:1427–34.

[21] van der Harst E, de Herder WW, de Krijger RR, Bruining HA, Bonjer HJ, Lamberts SW, et al. The value of plasma markers for the clinical behaviour of phaeochromocytomas. Eur J Endocrinol 2002;147:85–94.

[22] Baudin E, Bidart JM, Bachelot A, Ducreux M, Elias D, Ruffie P, et al. Impact of chromogranin A measurement in the work-up of neuroendocrine tumors. Ann Oncol 2001;12(Suppl 2):S79–S82.

[23] Rao F, Keiser HR, O'Connor DT. Malignant pheochromocytoma. Chromaffin granule transmitters and response to treatment. Hypertension 2000;36:1045–52.

[24] Plouin PF, Gimenez-Roqueplo AP. Pheochromocytomas and secreting paragangliomas. Orphanet J Rare Dis 2006;1:49.

[25] Favier J, Plouin PF, Corvol P, Gasc JM. Angiogenesis and vascular architecture in pheochromocytomas: distinctive traits in malignant tumors. Am J Pathol 2002;161:1235–46.

[26] Middeke M, Hoffmann S, Hassan I, Wunderlich A, Hofbauer LC, Zielke A. In vitro and in vivo angiogenesis in PC12 pheochromocytoma cells is mediated by vascular endothelial growth factor. Exp Clin Endocrinol Diabetes 2002;110:386–92.

[27] Zielke A, Middeke M, Hoffmann S, Colombo-Benkmann M, Barth P, Hassan I, et al. VEGF-mediated angiogenesis of human pheochromocytomas is associated to malignancy and inhibited by anti-VEGF antibodies in experimental tumors. Surgery 2002;132:1056–63 [discussion 63].

[28] de Krijger RR, van der Harst E, van der Ham F, Stijnen T, Dinjens WN, Koper JW, et al. Prognostic value of p53, bcl-2, and c-erbB-2 protein expression in phaeochromocytomas. J Pathol 1999;188:51–5.
[29] Khorram-Manesh A, Ahlman H, Jansson S, Nilsson O. N-cadherin expression in adrenal tumors: upregulation in malignant pheochromocytoma and downregulation in adrenocortical carcinoma. Endocr Pathol 2002;13:99–110.
[30] Salmenkivi K, Haglund C, Arola J, Heikkila P. Increased expression of tenascin in pheochromocytomas correlates with malignancy. Am J Surg Pathol 2001;25:1419–23.
[31] Salmenkivi K, Haglund C, Ristimaki A, Arola J, Heikkila P. Increased expression of cyclooxygenase-2 in malignant pheochromocytomas. J Clin Endocrinol Metab 2001;86:5615–9.
[32] Koch CA, Vortmeyer AO, Diallo R, Poremba C, Giordano TJ, Sanders D, et al. Survivin: a novel neuroendocrine marker for pheochromocytoma. Eur J Endocrinol 2002;146:381–8.
[33] Willenberg HS, Schott M, Saeger W, Tries A, Scherbaum WA, Bornstein SR. Expression of connexins in chromaffin cells of normal human adrenals and in benign and malignant pheochromocytomas. Ann N Y Acad Sci 2006;1073:578–83.
[34] Gimm O, Krause U, Brauckhoff M, Hoang-Vu C, Dralle H. Distinct expression of galectin-3 in pheochromocytomas. Ann N Y Acad Sci 2006;1073:571–7.
[35] Hofland J, van Nederveen FH, Timmerman MA, Korpershoek E, de Herder WW, Lenders JW, et al. Expression of activin and inhibin subunits, receptors and binding proteins in human pheochromocytomas: a study based on mRNA analysis and immunohistochemistry. Clin Endocrinol (Oxf) 2007;66:335–40.
[36] Ilias I, Pacak K. Anatomical and functional imaging of metastatic pheochromocytoma. Ann N Y Acad Sci 2004;1018:495–504.
[37] Sahdev A, Reznek RH. Imaging evaluation of the non-functioning indeterminate adrenal mass. Trends Endocrinol Metab 2004;15:271–6.
[38] Blake MA, Kalra MK, Maher MM, Sahani DV, Sweeney AT, Mueller PR, et al. Pheochromocytoma: an imaging chameleon. Radiographics 2004;24(Suppl 1):S87–99.
[39] Shulkin BL, Ilias I, Sisson JC, Pacak K. Current trends in functional imaging of pheochromocytomas and paragangliomas. Ann N Y Acad Sci 2006;1073:374–82.
[40] Shapiro B, Gross MD, Shulkin B. Radioisotope diagnosis and therapy of malignant pheochromocytoma. Trends Endocrinol Metab 2001;12: 469–75.
[41] Guller U, Turek J, Eubanks S, Delong ER, Oertli D, Feldman JM. Detecting pheochromocytoma: defining the most sensitive test. Ann Surg 2006;243:102–7.
[42] Reubi JC, Waser B, Khosla S, Kvols L, Goellner JR, Krenning E, et al. In vitro and in vivo detection of somatostatin receptors in pheochromocytomas and paragangliomas. J Clin Endocrinol Metab 1992;74:1082–9.
[43] Kubota A, Yamada Y, Kagimoto S, Shimatsu A, Imamura M, Tsuda K, et al. Identification of somatostatin receptor subtypes and an implication for the efficacy of somatostatin analogue SMS 201–995 in treatment of human endocrine tumors. J Clin Invest 1994;93: 1321–5.
[44] Kimura N, Pilichowska M, Date F, Kimura I, Schindler M. Immunohistochemical expression of somatostatin type 2A receptor in neuroendocrine tumors. Clin Cancer Res 1999;5:3483–7.
[45] Epelbaum J, Bertherat J, Prevost G, Kordon C, Meyerhof W, Wulfsen I, et al. Molecular and pharmacological characterization of somatostatin receptor subtypes in adrenal, extraadrenal, and malignant pheochromocytomas. J Clin Endocrinol Metab 1995;80: 1837–44.
[46] Kaltsas G, Korbonits M, Heintz E, Mukherjee JJ, Jenkins PJ, Chew SL, et al. Comparison of somatostatin analog and meta-iodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. J Clin Endocrinol Metab 2001;86:895–902.
[47] van der Harst E, de Herder WW, Bruining HA, Bonjer HJ, de Krijger RR, Lamberts SW, et al. [(123)I]Metaiodobenzylguanidine and [(111) In]octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metab 2001;86:685–93.
[48] Bustillo A, Telischi F, Weed D, Civantos F, Angeli S, Serafini A, et al. Octreotide scintigraphy in the head and neck. Laryngoscope 2004;114:434–40.
[49] Myssiorek D, Palestro CJ. ^{111}Indium pentetreotide scan detection of familial paragangliomas. Laryngoscope 1998;108:228–31.
[50] Kwekkeboom DJ, van Urk H, Pauw BK, Lamberts SW, Kooij PP, Hoogma RP, et al. Octreotide scintigraphy for the detection of paragangliomas. J Nucl Med 1993;34:873–8.
[51] Kopf D, Bockisch A, Steinert H, Hahn K, Beyer J, Neumann HP, et al. Octreotide scintigraphy and catecholamine response to an octreotide challenge in malignant phaeochromocytoma. Clin Endocrinol (Oxf) 1997;46:39–44.
[52] Hoegerle S, Nitzsche E, Altehoefer C, Ghanem N, Manz T, Brink I, et al. Pheochromocytomas: detection with ^{18}F DOPA whole body PET — initial results. Radiology 2002;222:507–12.
[53] Hoegerle S, Ghanem N, Altehoefer C, Schipper J, Brink I, Moser E, et al. ^{18}F-DOPA positron emission tomography for the detection of glomus tumours. Eur J Nucl Med Mol Imaging 2003;30:689–94.
[54] Ilias I, Yu J, Carrasquillo JA, Chen CC, Eisenhofer G, Whatley M, et al. Superiority of 6-[^{18}F]-fluorodopamine positron emission tomography versus [^{131}I]-metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. J Clin Endocrinol Metab 2003;88:4083–7.
[55] Pacak K, Eisenhofer G, Carrasquillo JA, Chen CC, Li ST, Goldstein DS. 6-[^{18}F]fluorodopamine positron emission tomographic (PET) scanning for diagnostic localization of pheochromocytoma. Hypertension 2001;38:6–8.
[56] Koukouraki S, Strauss LG, Georgoulias V, Eisenhut M, Haberkorn U, Dimitrakopoulou-Strauss A. Comparison of the pharmacokinetics of ^{68}Ga-DOTATOC and [^{18}F]FDG in patients with metastatic neuroendocrine tumours scheduled for 90Y-DOTATOC therapy. Eur J Nucl Med Mol Imaging 2006;33:1115–22.
[57] Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using (68)Ga-DOTATATE (DOTA-DPhe(1),Tyr(3)-octreotate) and (18)F-FDG. Cancer 2008.
[58] Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB. The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer 2007;14:569–85.
[59] Scholz T, Eisenhofer G, Pacak K, Dralle H, Lehnert H. Clinical review: current treatment of malignant pheochromocytoma. J Clin Endocrinol Metab 2007;92:1217–25.
[60] Keiser HR, Goldstein DS, Wade JL, Douglas FL, Averbuch SD. Treatment of malignant pheochromocytoma with combination chemotherapy. Hypertension 1985;7:I18–24.
[61] Wieland DM, Wu J, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with [^{131}I]iodobenzylguanidine. J Nucl Med 1980;21: 349–53.
[62] Vetter H, Fischer M, Muller-Rensing R, Vetter W, Winterberg B. 131-I-meta-iodobenzylguanidine in treatment of malignant phaeochromocytomas. Lancet 1983;2:107.
[63] Sisson JC, Shapiro B, Beierwaltes WH, Glowniak JV, Nakajo M, Mangner TJ, et al. Radiopharmaceutical treatment of malignant pheochromocytoma. J Nucl Med 1984;25:197–206.
[64] Shapiro B, Sisson JC, Wieland DM, Mangner TJ, Zempel SM, Mudgett E, et al. Radiopharmaceutical therapy of malignant pheochromocytoma with [^{131}I]metaiodobenzylguanidine: results from ten years of experience. J Nucl Biol Med 1991;35:269–76.
[65] Lumbroso J, Schlumberger M, Tenenbaum F, Aubert B, Travagli JP, Parmentier C. [^{131}I]metaiodobenzylguanidine therapy in 20 patients with malignant pheochromocytoma. J Nucl Biol Med 1991;35: 288–91.
[66] Krempf M, Lumbroso J, Mornex R, Brendel AJ, Wemeau JL, Delisle MJ, et al. Treatment of malignant pheochromocytoma with

[^{131}I]metaiodobenzylguanidine: a French multicenter study. J Nucl Biol Med 1991;35:284–7.

[67] Krempf M, Lumbroso J, Mornex R, Brendel AJ, Wemeau JL, Delisle MJ, et al. Use of *m*-[^{131}I]iodobenzylguanidine in the treatment of malignant pheochromocytoma. J Clin Endocrinol Metab 1991;72:455–61.

[68] Bestagno M, Pizzocaro C, Maira G, Terzi A, Panarotto MB, Guerra P. Results of [^{131}I]metaiodobenzylguanidine treatment in metastatic malignant phaeochromocytoma. J Nucl Biol Med 1991;35:277–9.

[69] Troncone L, Rufini V, Daidone MS, De Santis M, Luzi S. [^{131}I] metaiodobenzylguanidine treatment of malignant pheochromocytoma: experience of the Rome group. J Nucl Biol Med 1991;35:295–9.

[70] Colombo L, Lomuscio G, Vignati A, Dottorini ME. Preliminary results of [131]metaiodobenzylguanidine treatment in metastatic malignant pheochromocytoma. J Nucl Biol Med 1991;35:300–4.

[71] Arias Martinez N, Barbado Hernandez FJ, Couto Caro R, Gil Guerrero L, Coronado Poggio M, Navarro T, et al. Treatment of malignant pheochromocytoma with ^{131}I MIBG: a long survival. An Med Interna 2003;20:575–8.

[72] Fitzgerald PA, Goldsby RE, Huberty JP, Price DC, Hawkins RA, Veatch JJ, et al. Malignant pheochromocytomas and paragangliomas: a phase II study of therapy with high-dose ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG). Ann N Y Acad Sci 2006;1073:465–90.

[73] Gedik GK, Hoefnagel CA, Bais E, Valdes Olmos RA. (131)I-MIBG therapy in metastatic phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging 2007.

[74] Rose B, Matthay KK, Price D, Huberty J, Klencke B, Norton JA, et al. High-dose ^{131}I-metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. Cancer 2003;98:239–48.

[75] Safford SD, Coleman RE, Gockerman JP, Moore J, Feldman JM, Leight Jr GS, et al. Iodine-131 metaiodobenzylguanidine is an effective treatment for malignant pheochromocytoma and paraganglioma. Surgery 2003;134:956–62 [discussion 62-3].