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THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

MIBG (metaiodobenzylguanidine) theranostics in pediatric and adult malignancies

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ABSTRACT

Metaiodobenzylguanidine, a guanithidine analog, labeled with ^{123}I and ^{131}I, is used for imaging and therapy of neuroblastomas and various neural crest tumors like paragangliomas, pheochromocytomas, medullary cancer of thyroid and carcinoids since the past three to four decades. In this review article, we shall revisit metaiodobenzylguanidine as a radiopharmaceutical and its various applications in neural crest tumors.

INTRODUCTION

Metaiodobenzylguanidine (MIBG) was first developed in USA, in Michigan University Medical Centre, in early 1970, for imaging the adrenal medulla and its disease.[1] MIBG, a guanithidine analog, is taken up by an active mechanism into the neuroendocrine cells due to its similarities with nor-epinephrine. It came into clinical practice in 1981 for localization of pheochromocytoma (pheo).[2] In course of time, MIBG demonstrated its ability to concentrate in tumors of the neural crest origin such as neuroblastoma (NBL),[3] carcinoids and medullary carcinoma of the thyroid.[4,5] Due to good selective uptake and retention of MIBG by these tumors, its potential was explored for therapy of neuroendocrine tumors (NETs) as well. MIBG is labeled with 123-Iodine (^{123}I) which is exclusively used for imaging and also with 131-Iodine (^{131}I); which can be used both for imaging and therapy of NBL or other MIBG avid neural crest tumors.

SECTION I—METAIODOBENZYLGUANIDINE (MIBG) IN DIAGNOSIS AND THERAPY

Part 1—Metaiodobenzylguanidine (MIBG) in diagnosis

MIBG labeled with ^{123}I or ^{131}I is useful for localization, staging and in follow-up evaluation of NETs like pheo, NBL, ganglioneuroblastoma, paragangliomas (PGLs), medullary carcinoma of thyroid, carcinoid, Merkel cell tumors and MEN (multiple endocrine neoplasia) syndrome and as a prelude to ^{131}I MIBG therapy. This is a useful tool for confirmation of suspected neural crest tumor. Dosimetric studies and evaluation of treatment response are other indications of MIBG scintigraphy.[6]

Apart from these oncological indications, few non-oncological indications are functional studies for sympathetic innervation of the myocardium and adrenal medullary hyperplasia.[6]

Mechanism of uptake

The uptake of MIBG, an analog of nor-epinephrine, into the neuroendocrine cell is by two mechanisms—active and passive. The active transport or the uptake-1 system is the dominant method of transport of MIBG into the cell. This is an active, sodium and energy dependent amine uptake mechanism in the cell membrane of the sympathomedullary tissues. Within the cell, it is actively transported into the storage granules by an energy dependent transport mechanism via vesicular monoamine transporters 1 and 2. This accumulation of MIBG in these neurosecretory granules forms the basis for imaging and therapy with 123I/131I-labeled MIBG. Small amounts of MIBG is also present in the cytoplasm.[7] The other mechanism is passive diffusion of MIBG into the cells. The active uptake is more efficient and specific than the passive uptake. Within the body, MIBG is not metabolized and is mainly excreted unaltered by the kidneys by glomerular filtration. Within the first 24 h, about 50% of the injected activity is excreted in urine and about 90% in 4 days after injection, in patients with normal renal function. The highest uptake in tumors

is reached after 24–96 h.[7] A very minimal amount is excreted in feces, sweat and saliva.[8]

Preparation of the patient

Interfering drugs

Many drugs are known to interfere with MIBG uptake and storage, resulting in altered biodistribution, which may interfere with correct interpretation of the study. Common medications such as pseudoephedrine, labetalol, phenothiazines, central nervous system stimulants (cocaine, amphetamine) tricyclic antidepressants, calcium channel blockers, sympathomimetics, antihistaminics, opioid analgesics (Tramadol) and reserpine are known to interfere with MIBG and should be stopped prior to MIBG scan and/or therapy. These should be withheld for 24–72 h.[6,9] Few neuroleptics like Haloperidol, Flupentixol and Fluphenazine need a withdrawal period of 24 h to 1 month.[6] Food containing vanillin and catecholamine, chocolate and blue-veined cheese are also known to interfere with MIBG uptake and should be avoided prior to MIBG scan.

Thyroid blockade

Oral potassium iodide (KI) in dosage of 100mg per day in adults and 2 mg per kg body weight in children is used for blocking the thyroid. KI should be started 24 h prior to the injection and continued for 3–5 days for ^{131}I-MIBG and 2 days for ^{123}I-MIBG. This is to prevent irradiation of the thyroid due to the presence of 3–5% free radioiodine in the preparation.[9,10] Oral potassium perchlorate may be substituted in patients who are allergic to iodine at a dose of 8 mg kg^{-1} in children and 400 mg in adults.

Procedure

Dose—18.5–74 MBq (0.5–2 mCi) of ^{131}I -MIBG (specific activity >74 MBq mg^{-1}) or 185–370 MBq (5–10 mCi) of ^{123}I-MIBG (specific activity >300 MBq mg^{-1}) is administered intravenously over 1–5 min to avoid side-effects like hypertensive crisis or tachycardia. There is no distinction between children and adult dosage. The correct amount of tracer to be injected is not based on any scientific basis, but dosages have been suggested from the available literature and current experience.[11] The exact dosing for children is not available. However, the minimum activity that should be injected in children is 20 MBq for ^{123}I-MIBG and 35 MBq for ^{131}I -MIBG, the maximum dosage being 400 MBq for ^{123}I-MIBG and 80 MBq for ^{131}I-MIBG.[11,12]

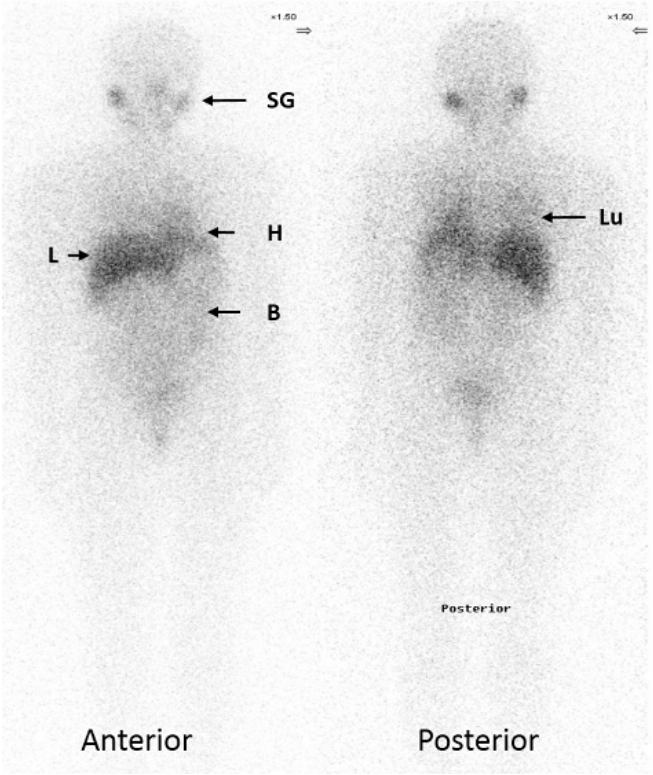
Image acquisition

The environment should be adapted for children with a friendly and caring attitude. The parents should be well-informed about the entire process and the technologists should be well-trained in pediatric procedures. All this will help in having a co-operative child for scanning and in building a good rapport with the patients. Sedation, if necessary may be given in small infants or in uncooperative children.[11]

Imaging with ^{123}I/^{131}I-MIBG

^{123}I is most suited for imaging due to its short half-life of 13h, γ emission of 159 keV γ photons, which is ideal for imaging with gamma camera and lack of β emission. The image quality of ^{123}I-MIBG is superior with lower radiation burden. However, due to lack of availability of ^{123}I-MIBG in few underdeveloped and developing countries, ^{131}I-MIBG is used for both imaging and therapy. ^{131}I has a half-life of 8.02days, γ emission of 364 keV and β of 606 keV.

Figure 1. ^{131}I-MIBG scan showing physiological tracer uptake in SG, H, L, B and diffuse uptake in Lu. B, bowel; H, heart; L, liver; Lu, lungs; SG, salivary glands.



Whole body imaging is performed 24h after injection of ^{123}I-MIBG and 24–48 h after injection of ^{131}I-MIBG. Delayed imaging may be useful to resolve doubtful uptake in the bowel or kidneys. Additional spot views may be acquired for selected regions if needed. Single photon emission computed tomography (SPECT) or SPECT/CT may be performed with ^{123}I-MIBG for better delineation and cross-sectional imaging of the tumor and metastatic sites.

Normal biodistribution

Knowledge of normal physiological patterns of uptake avoids misinterpretation of images and false-positive results. Physiologic uptake of MIBG includes salivary glands, myocardium (due to sympathetic innervation), large intestine, urinary bladder (due to excretion of tracer through these routes) and liver. Other areas of physiological localization are nasal mucosa, gall bladder, colon, uterus. Occasionally, diffuse uptake may be noted in the lungs (Figure 1)[9,11,13] Usually the normal adrenals are not seen; but faint visualization may be seen 48–72 h after injection in 15% of patients with ^{131}I-MIBG.[6,11] The normal adrenals are commonly seen with ^{123}I-MIBG in upto 75% of patients.[6]

Normal variant

$^{123/131}$I-MIBG uptake may be seen in brown adipose tissue, usually in bilateral supraclavicular and axillary regions due to sympathetic innervation of brown adipose tissue[14,15]

Pitfalls

False-positive uptake of MIBG is rare, but few false-negatives have been reported in NBL.[16,17] Commonest cause for false-negative study is drug interference.[18] Other causes of error include small lesions which are below the resolution of the gamma camera, improper patient preparation (tiny lesions in the pelvis may be missed in a patient with a full bladder), lesions close to areas of high pathological or physiological uptake, lesions which are MIBG negative due to necrosis and changes in differentiation. Patient motion particularly in children, physiological uptakes in urinary tract and bowel; uptake in thyroid if not adequately blocked; urinary contamination, muscle uptake and supraclavicular brown fat uptake may also pose a problem in reporting.[6] PGL, in particular non-functioning tumors and tumors associated with SDH-B gene mutations may also be negative on MIBG study.[19]

Image interpretation

Intense tracer uptake is usually visualized in the diseased areas. Any tracer uptake beyond the normal physiological uptake should be taken into consideration and reported as abnormal. MIBG uptake in the skeletal system should be considered abnormal.

New MIBG tracer for imaging

^{124}I-MIBG is a relatively new positron emission tomography (PET) tracer for imaging NETs. As compared to other positron emitters, ^{124}I has a long half-life of 4.2days. It is produced in a cyclotron by using various reactions depending on the particles and energies available for irradiation. It is mainly produced by using enriched tellurium-124 as the target using ^{124}Te (d,2n) ^{124}I reaction or ^{124}Te (p,n) ^{124}I reaction. The later reaction is superior due to low levels of impurity.[20] ^{124}I-labeled MIBG provides high quality images and accurate tumor volume estimation and helps in better and appropriate dose planning with ^{131}I-MIBG therapy.[21] ^{124}I-MIBG is a better agent as compared to $^{123/131}$I-MIBG, due to its higher spatial resolution and provides additional information regarding the extent of the lesion and the overall disease extent. This information helps in appropriate management of the patient by triaging to surgical or medical management.[22] Its current use is limited by its non-availability at many centers.[21]

Part II—therapy with ^{131}I-MIBG

Being a γ and β emitter, ^{131}I-MIBG can be used for both imaging and therapy. The β rays emitted from ^{131}I have a cytocidal effect on the tumor cells. ^{131}I-MIBG was first used in treatment of patients of pheo.[23] Subsequently in 1986, NBL was treated with ^{131}I-MIBG.[24] Since then MIBG has been for treatment for NETs. Being a systemic agent coupled with the effective β emissions from ^{131}I; this agent achieves a higher therapeutic efficiency to multiple sites in one sitting, when compared to external beam radiation therapy.

Indications for ^{131}I- MIBG therapy

The pre-treatment MIBG scan should show avid concentration of the radiotracer in the primary and/or the metastatic sites to contemplate MIBG therapy. The indications are inoperable pheo, inoperable or Stage III/IV NBL, other inoperable neural crest tumors, and recurrent of metastatic medullary carcinoma thyroid (MTC).[25]

Prerequisites for ^{131}I- MIBG therapy

(1) Histopathologically proven NET with positive MIBG scintigraphy.
(2) Adequate thyroidal blockade as discussed in the previous (imaging) section.
(3) Drugs known to interfere with MIBG uptake should be withdrawn.

Contraindication for ^{131}I- MIBG therapy

The contraindications can be absolute and relative.

The absolute contraindications are:

(1) Pregnancy
(2) Breast feeding
(3) Renal insufficiency
(4) Life expectancy of<3 months.

The relative contraindications are:

(1) (i) Glomerular filtration rate of <30 ml min^{-1}. (ii) Myelosuppression (Total white cell count $<3\times10^{9}$ l^{-1}; platelets $<100\times10^{9}$ l^{-1}). (iii) Progressive renal or haematological toxicity. (iv) Unfit for isolation.
(2) In case of myelosuppression and renal impairment, the dose of the administered activity should be reduced.[25]

Patient instructions and preparation prior to MIBG therapy

(1) Patients should receive both written and verbal information regarding the entire therapy procedure. Informed consent form may be obtained if necessary.
(2) Prophylactic antiemetics should be started 72 h prior to therapy.
(3) Proper hygiene to avoid urinary contamination and soiling of clothes.
(4) The toilet should be flushed twice after use and hands should be washed thoroughly.
(5) Incontinent patients should be catheterized.

Planning and execution

A successful MIBG therapy program needs a multidisciplinary team effort. Pediatric oncologists, Nuclear Medicine Physicians, medical physicists, nuclear medicine technologists, radiopharmacists, Radiation Safety Officer and well-trained nursing staff are necessary for implementation and execution of MIBG therapy programme. Well-planned isolation therapy unit with an appropriate lead-lined isolation therapy room as well as hot lab with regulatory compliance is mandatory. The requirements of this facility depend on the individual national regulatory policy and should be abided. The facility should be well-equipped with adequate and appropriate personnel, radiation safety equipment, and proper procedures for waste management.[25] The isolation therapy room should be a private room with en-suite facilities and should not be shared by other patients or care-givers to minimize the radiation dose to others. Radiation safety precautions

that should be taken during the therapy and after discharge from the hospital should be well-informed to the care-givers, family members and also to the patient. The radiation exposure to the care-givers should be as low as reasonably achievable and should be within the established regulatory limits.[26]

Special care for needs to be taken while treating children with MIBG. To reduce the exposure time for the health personnel and parents'/care-givers, the time spend in patient room should be minimized. Ideally, the parent/care-giver should stay in a room adjacent the therapy room with a lead lined glass window so as to observe the child through the window and also to comfort the child. In case this is not available, a video-monitoring system should be in place.[26] Age-appropriate play materials can be given to the child to decrease the apprehension associated with admission into an isolation unit. Care should be taken to avoid contamination of these objects. To reduce the radiation exposure to the care-givers, it is best if two parents /care-givers are involved in the child's care and take turns to take care of the child. They should be monitored with personal dosimeters and should receive extensive basic training regarding the use of protective clothing, handling and disposal of body fluids; prior to MIBG treatment.[26] This training can be done by the use of proper written material with the use of cartoons on these topics, use of power point presentations and proper explanation by healthcare personnel and nursing staff.[26]

24–48 h prior to the therapy, thyroid protectors like KI or potassium perchlorate are started and continued for 3weeks after treatment.

^{131}I-MIBG is transported and stored in frozen form and should be thawed prior to administration. All quality control tests should be done prior to injection to ensure that the amount of free iodide in the radiopharmaceutical preparation is <10%. Carrier- free ^{131}I with high specific activity (upto 1.48 GBq mg^{-1}) labeled with MIBG is preferred. The prescribed dose [typically in the range of 3.7–11.2 GBq (100–300 mCi)] ^{131}I-MIBG is administered as an infusion after securing a patent intravenous line, by the nuclear medicine personnel. The infusion continues for 90–120 min. Blood pressure and heart rate should be monitored. ^{131}I-MIBG therapy may have cardiovascular effects due to changes in sympathetic activity; this makes cardiac and blood pressure monitoring mandatory. α or β blockers should always be available for any emergency/inadvertent situation. The patient is hospitalized for 3–5 days after ^{131}I-MIBG therapy and discharged after radiation levels are well-within the discharge limits. Prior to discharge, a post-therapy whole-body scan is done to assess the areas of ^{131}I-MIBG uptake.

Side-effects

There are no major toxicities and the therapy is well tolerated.

Early side effects

<10% of patients experience hypertension and tachycardia within few hours after the treatment, even after slow intravenous administration of ^{131}I-MIBG over 1–3h. Nausea and vomiting may occur due to acute radiation gastritis in 10–25% of patients in first few hours or 1–2 days after the treatment. This can be reduced by the use of antiemetics given 24 h prior to treatment and continued for 2 days. Hematopoietic toxicity can also occur with ^{131}I-MIBG therapy. Myelosuppression is seen 2–4 weeks after the therapy. Thrombocytopenia is common in patients of NBL receiving >15 mCi kg^{-1}. This requires treatment with stem cell rescue.[26–28]

Late side-effects

There is a possibility of few late side-effects due to ^{131}I therapy in general. Hypothyroidism may occur secondary to inadequate blockade of thyroid during ^{131}I-MIBG therapy. Rarely myelosuppression may occur. Rare possibility of developing second primary like leukemia of solid tumors due to use of radionuclide therapy in conjunction with chemotherapy.[25,29]

New MIBG tracer for therapy

New tracer for therapy of neural crest tumors is ^{211}At meta-astatobenzylguanidine (MABG), which is an α emitter. α-particle is a method of targeted radionuclide therapy that destroys cells by simple cytotoxic mechanism by DNA damage. Due to its high linear energy transfer and limited range in the tissue (<100 micron m), this form of therapy has strong therapeutic effects with minimal side-effects. In a recent study, Ohshima et al have shown strong tumor volume-reducing effect with this agent in mouse-pheo model. Moreover, there no severe adverse effects like weight reduction and reduction in number of myeloid cells in the bone marrow.[30] In the future, ^{211}At-MABG might prove to be an effective treatment option for neural crest tumors.

SECTION II

Specific role of iodine-labeled MIBG in various tumors

Role of MIBG in neural crest tumors

Neuroblastoma

NBL is a common childhood malignancy and the most common extracranial tumor seen in infancy and young children. It arises from primitive neural crest cells of the sympathetic nervous system. This tumor expresses nor-adrenaline transporter molecule and therefore,>90% of cases demonstrate uptake of MIBG.[31]

NBL can be found anywhere from the neck to the pelvis along the sympathetic chain, but the commonest location is in the abdomen (65–70%), with adrenal gland being the commonest organ of involvement.[32,33] The patient might be asymptomatic or may present with distention of the abdomen, abdominal pain, constipation and sometimes hypertension. NBL is seen in the thorax in 20% of patients.[32] These manifest with respiratory symptoms and features of Horner's syndrome, *i.e.* ptosis, myosis and anhydrosis.

Distant metastases are very common in NBL. About 50% of patients present with distant metastases at initial presentation. The commonest sites of metastases are bone, lymph nodes and liver.[34] 5–15% of patients present with intraspinal extension of tumor, which may result in compression of the spinal cord, resulting in paraplegia.[33,35] 2–3% of children present with opsoclonus myoclonus ataxia syndrome, which is associated with random eye movements and myoclonic jerks with associated ataxia in few. These children usually have a favorable outcome.[36]

Table 1. INSS (Source – Monclairet al. 2008)

Tumor stage	Description
1	• Localized tumor with complete gross excision, with or without microscopic residual disease. • Ipsilateral regional nodes are negative for tumor microscopically. Nodes attached to the primary tumor and removed with the primary may be positive.
2A	• Localized tumor with incomplete gross excision. • Ipsilateral regional nodes are negative for tumor microscopically.
2B	• Localized tumor with complete or incomplete resection • Ipsilateral (non-adherent) nodes positive for tumor • Enlarged contralateral nodes negative for tumor microscopically
3	• Unresectable tumor crossing the midline or • Localized tumor with contralateral nodal involvement • Midline tumor with bilateral extension via infiltration or by nodal involvement.
4S (Special)	• In <1 year of age, localized primary tumor (Stage 1, 2A or 2B) with distant metastases confined to skin, liver and/or bone marrow.
4	• Any tumor with dissemination to distant nodes, skin, liver , bones or any other organs; except those defined in Stage 4S.

Staging and prognosis in NBL

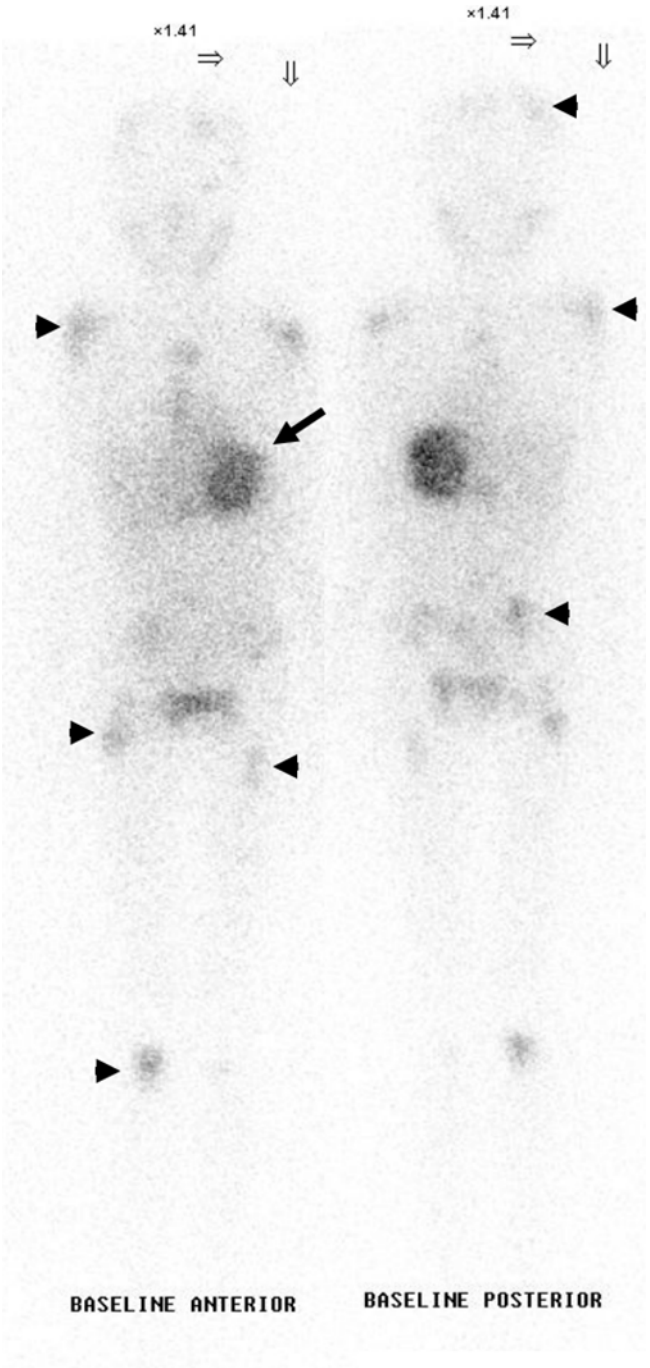
NBL is conventionally staged by the International Neuroblastoma Staging System (Table 1). This is based on resectability and histopathological assessment of the locoregional nodal involvement.[37] A more recent staging system is the International Neuroblastoma Risk Group Staging System; which is a pre-treatment staging system based on image defined risk factors.[38] This differentiates tumors that invade the adjacent organs, blood vessels and the nerves from those tumors that do not.

Age at diagnosis is an important prognostic factor in children with metastatic disease. Infants younger than 12 months of age have a favorable prognosis even with metastatic disease; as compared to children of more than 12 months of age.[39,40] Older children with metastatic disease are refractory to both chemotherapy and radiotherapy with overall survival of <40%.[41] The median age at diagnosis is 17 months[40] and it is rarely diagnosed beyond 10 years of age. Age >18 months, advanced disease stage, poorly or undifferentiated histology, diploid DNA and amplification of MYCN oncogene are poor prognostic factors. Patients are risk stratified into low, intermediate and high risk by the Children's Oncology Group based on these factors.

Role of MIBG imaging in NBL

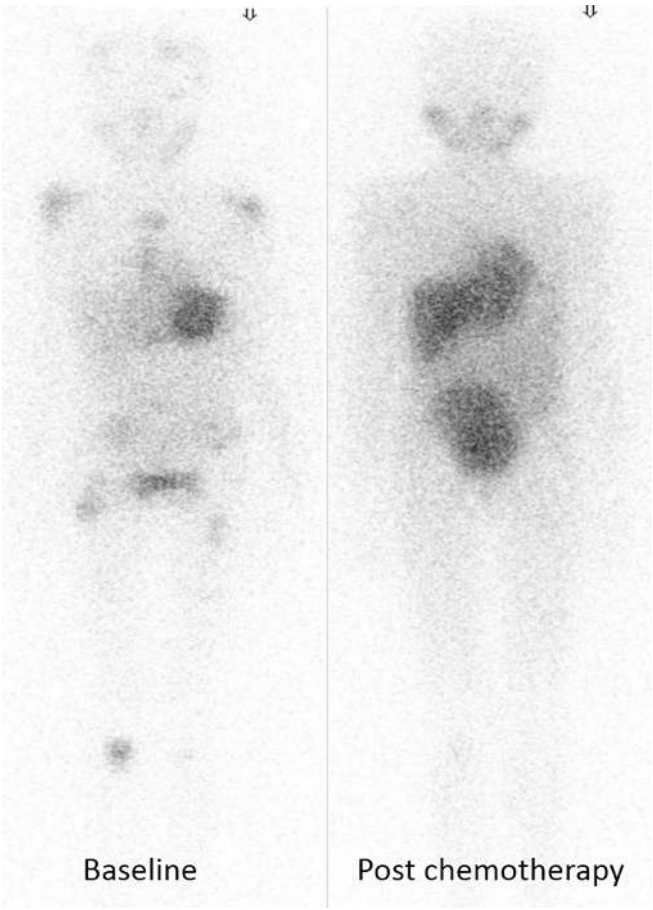
^{123}I/^{131}I-MIBG scintigraphy is a well-established imaging tool for diagnosis and staging of NBL (Figure 2). It is also used for restaging and detection of relapses.[37] More than 90% of NBLs are MIBG avid. The reported sensitivity of MIBG scintigraphy for NBL is 85–96% and the specificity is 95–99%.[42] MIBG scintigraphy documents MIBG avid disease and justifies the feasibility of MIBG therapy; because we treat what we see on the diagnostic

Figure 2. ^{131}I-MIBG scan of a 9-year-old female child showing MIBG avid large left suprarenal mass (arrow) with multiple sites of MIBG avid marrow lesions (arrow head). The scan was done for diagnosis and staging. Scan findings suggest left suprarenal Neuroblastoma with skeletal metastases. This was later confirmed by biopsy. MIBG, metaiodobenzylguanidine.



MIBG scan. For assessment of response of bone marrow disease MIBG (Figure 3) is superior to ^{18}F-fluorodeoxyglucose (FDG) PET/CT and MRI because it is not affected by post-treatment changes.[43] Due to hyperstimulation of marrow post-chemotherapy, FDG PET/CT shows diffuse FDG uptake in the marrow which may interfere which interpretation of the scan;

Figure 3. ^{131}I-MIBG scan of the same 9-year-old female child with left suprarenal neuroblastoma and skeletal metastases done for response assessment post COJEC chemotherapy. The image on the right shows significant reduction in the primary mass as well as the metastatic skeletal lesions. COJEC, Cisplatin (C), Vincristine (O), Carboplatin (J), Etoposide (E) and Cyclophosphamide (C); MIBG, metaiodobenzylguanidine.



but unlike FDG, MIBG scintigraphy is not affected by these post-treatment changes. MIBG has a sensitivity of 94% for detection of skeletal relapse, whereas FDG has a detection rate of only 43%.[44]

^{18}F-FDG PET/CT is complimentary to MIBG scintigraphy in MIBG-negative tumors. A study comparing ^{18}F-FDG and ^{123}I-MIBG showed that MIBG is superior to ^{18}F-FDG PET/CT in Stage IV NBL due to better delineation of skeletal disease and ^{18}F-FDG PET/CT was more superior in stages I and II.[45]

Scoring system in NBL

Semi-quantitative scoring methods have been proposed to assess the extent of metastatic involvement and also to assess the response to chemotherapy in NBL. Of all the scoring systems, the Curie score and the SIOPEN (International Society of Pediatric Oncology Europe Neuroblastoma) score are the most commonly used[46,47] (Table 2). Both the systems take into account the findings of planar MIBG imaging. Findings of SPECT or SPECT/CT are not considered.[41] These scoring systems are helpful in describing the extent of metastatic disease and bring about an objective dimension to reporting. The scoring systems are also excellent prognostic surrogates.[44] Both the Curie and the SIOPEN scoring systems are equally reliable and predictive with good inter observer reliability. A Curie score of <2 and a SIOPEN score <4 at initial staging have better event-free and overall survival.[48] MIBG scoring can also define patients with poor outcomes. Curie score >2 or SIOPEN score >3 at the end of induction chemotherapy have shown to have poorer outcomes.[49]

^{131}I-MIBG therapy in NBL

Surgery is the preferred treatment option for localized NBL with favorable tumor biology. In patients with locally advanced disease with favorable tumor biology, surgery with chemotherapy is preferred. Children with metastatic disease or with unfavorable tumor histology and/or biological features are at high-risk and need aggressive multimodality treatment with chemotherapy, surgery, radiotherapy, high-dose chemotherapy with autologous

Table 2. Curie and SIOPEN scoring systems [Source—Sucet al. (1996) and Decarolis et al. (2013) reference][47,48]

	Curie (COG) scoring	SIOPEN scoring
No of segments	10 (9 skeletal+1soft tissue)	12
Soft tissue accounted	Yes	no
Score in each segment	0–3	0–6
Maximum score (sum)	30	72
Skeletal score	1=one distinct lesion 2=two distinct lesions 3=>50% of segment	1=one distinct lesion 2=two distinct lesions 3=three distinct lesions 4=>3or<50% diffuse involvement 5=50–95%diffuse involvement 6=100% diffuse involvement.
Soft tissue score	1=1 MIBG avid soft tissue lesion 2=>1 MIBG avid soft tissue lesion 3=>50% of the region is involved (chest or abdomen/pelvis)	

COG, Children's Oncology Group; SIOPEN, International Society of Pediatric Oncology Europe Neuroblastoma;

bone marrow transplantation.[50,51] High-risk NBL patients initially respond to first-line treatment, but relapses are seen in 50–60%and the prognosis is often dismal. To our knowledge, there are no curative salvage treatments available, till date. It is in this scenario that ^{131}I-MIBG has been widely investigated as a potential therapeutic radiopharmaceutical.

^{131}I-MIBG therapy is reserved for relapsed or refractory NBLs, where there is disease progression after initial chemotherapy or in patients who fail to respond to induction chemotherapy.[52,53] >90% of NBL concentrate MIBG in primary tumors as well as metastases. This high avidity of MIBG for NBL makes it an ideal radiopharmaceutical for therapy as well as imaging.[54] Few studies have shown the use of MIBG as "induction therapy"—where MIBG has been used as first-line of treatment in newly diagnosed patients.[55] MIBG has also been given in conjunction with myeloablative chemotherapy after response with initial chemotherapy—in this setting, it is termed as "consolidation therapy".[56] Response rates of MIBG vary widely in different studies, a recent systematic review has quoted median response rates of 30% in relapsed and refractory NBL.[57] For refractory NBL, ^{131}I-MIBG has been used in escalating doses ranging from 111 to 666 MBq kg^{-1} (3–18 mCi kg^{-1}) in a Phase 1 study.[58] The adverse effects reported were mild nausea and vomiting seen within the first few days of the treatment. Significant hematologic toxicity in terms of thrombocytopenia can occur and is dose dependent. In this Phase 1 study, no patient who received 444 Mbq kg^{-1} (12 mCi kg^{-1}) or less of ^{131}I-MIBG needed an autologous stem cell rescue. The overall response rate was 37%.[58] In a Phase 2 study, comprising of 164 patients of relapsed or refractory NBL, the objective response rate was 37% for 147 patients who were treated with 666 MBq kg^{-1} (18 mCi kg^{-1}) ^{131}I-MIBG and 25% for 16 patients treated with 444 Mbq kg^{-1} (12 mCi kg^{-1}). Disease stabilization was seen in 39%.[59]

Higher dose intensification with cumulative dosing ranging from 814–1887 Mbq kg^{-1} (22–51 mCi kg^{-1}) followed by stem cell rescue was investigated in New approaches to Neuroblastoma therapy Phase I study.[60] ^{131}I-MIBG has also been used in combination with other agents such as cisplatin, irinotecan and topotecan. These are mainly feasibility studies with combination therapies and have been reported to be well-tolerated.[61–64]

Clinical data have also shown that pre-treatment with chemotherapeutic agents like cisplatin, doxorubicin and topotecan with ^{131}I-MIBG therapy, helps to significantly increase the MIBG uptake in tumor cells.[65–67] This is likely due to increase in nor-epinephrine transporter gene and thus, increase in norepinephrine receptor expression.[66]

Paraganglioma/Pheochromocytoma

PGLs arising from the chromaffin cells in adrenal medulla are called as pheo. Tumors arising from chromaffin cells located at extra-adrenal sites are referred to as PGL.[68] They are located in paravertebral and para-aortic areas in the abdomen. Rarely small PGLs may be found in the viscera like the urinary bladder and gall bladder. The clinical manifestations are mainly due to catecholamine hypersecretion and manifest as headache, palpitations and sweating. Hypertension though a common finding is often non-specific.[69] Prognosis of these masses depends on the malignant status. Currently, there are no validated histological criteria for determining malignancy. The diagnosis of malignant PGL is established only by the detection of metastasis. Metastases are typically seen in lymph nodes, lung, liver and bone.[70,71]

PGLs found in the head and neck and anterior mediastinum are related to the parasympathetic nervous system and are chromaffin negative tumors. In head and neck, the parasympathetic PGL usually occur in carotid body, jugular foramen and middle ear. In the anterior mediastinum, the location is in the aortopulmonary window. These tumors rarely produce significant amount of catecholamines and are non-functional. They usually present as painless masses. Only 1% of head and neck PGLs may be functional. Being non-functional, these are usually negative on MIBG. These masses are usually imaged by ^{18}F-FDG PET/CT or by somatostatin receptor (SSTR) tracer ^{68}Ga-DOTA PET/CT or octreotide based SPECT scintigraphy. Somatostatin receptor scintigraphy (SRS) has better sensitivity of 89–93% as compared to 42–44% of ^{123}I-MIBG.[72] PET tracers like ^{18}F-fluodihydroxyphenylalanine (DOPA) and ^{18}F-fluodopamine (FDA) have excellent sensitivity for detection of these tumors but are limited by their lack of availability.[73]

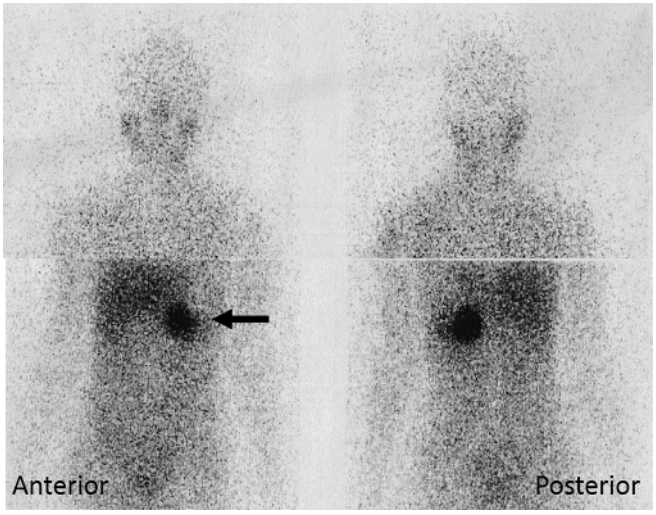
PGL can be sporadic or hereditary. Sporadic PGL presents in older age group in the fourth-fifth decade. Those with genetic predisposition present at a younger age group in the second or third decade and are often multiple and bilateral. These are often associated with hereditary syndromes like MEN 2 (MEN Type 2), neurofibromatosis Type 1, von Hippel-Lindau disease (VHL) and hereditary PGLs. These syndromes are caused by mutations in rearranged during transfection (RET), neurofibromatosis Type 1, VHL, succinate dehydrogenase (SDH)-B, C and D genes. SDH-related tumors are generally extra-adrenal. SDH-B gene mutation is the commonest, associated with aggressive tumors with high risk of malignancy and poor prognosis.[74]

Both CT and MRI have high sensitivity for detection of pheo and PGLs. CT has a sensitivity of 93–100% for detection of pheo and about 90% for detection of PGLs.[75] MRI has better sensitivity as compared to CT. The specificity of CT/MRI varies from 50 to 90% because of multiple false-negative studies.[76,77] Previous interventions like surgery may hamper the results of CT/MRI in the recurrent setting; when functional imaging becomes the most important imaging tool to detect recurrence and residual disease.[78]

MIBG imaging in PGL/pheo

The advantage of performing nuclear medicine imaging over anatomical imaging is better specificity and advantage of doing a whole-body imaging, which is helpful in detecting the presence of multiple tumors as well as metastases. ^{131}I-MIBG has a sensitivity of 77–90%and specificity of 95–100% in detection of abdominal PGL/pheo (Figure 4).[79] Reported sensitivity of ^{123}I-MIBG is slightly higher at 83–100%, the specificity being the same.[80] In a prospective study including 140 patients, the sensitivity and specificity of ^{123}I-MIBG for detection of pheo has been reported as 88and70%. The same study reported a sensitivity of 75% and specificity of 100% for detection of PGL and sensitivity for detection of metastatic disease was 83%.[81] Also, the role of

Figure 4. ^{131}I- MIBG scan in a 23-year-old male patient who presented with hypertension and palpitations. The clinical suspicion was of pheochromocytoma. The scan shows MIBG avid left suprarenal mass (arrow) suggestive of pheochromocytoma. The patient underwent surgery and diagnosis of pheo was confirmed. MIBG, metaiodobenzylguanidine.

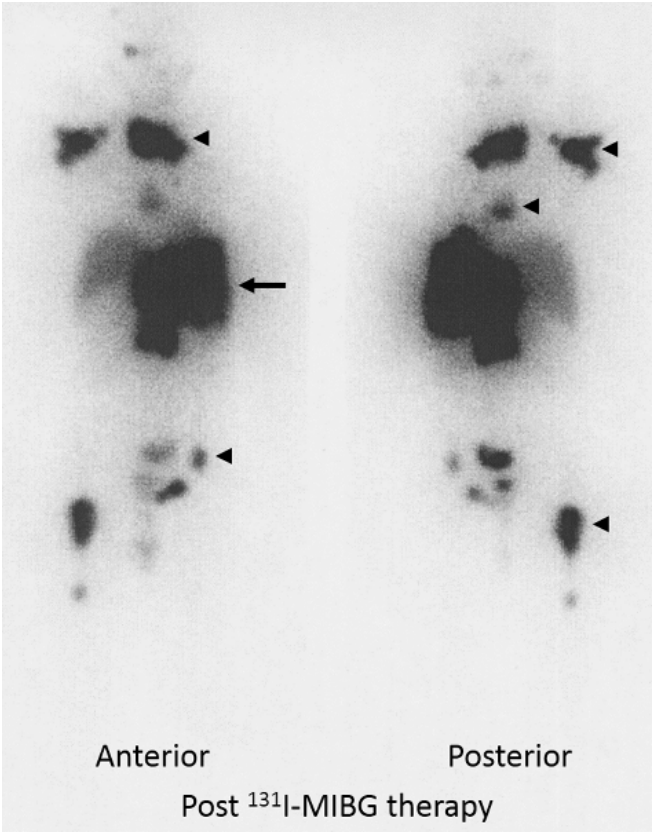


SPECT/CT in detection of PGL cannot be undermined. Addition of SPECT CT to planar imaging results in improved sensitivity due to precise localization of the lesion and better specificity due to better characterization of the lesions.[82] Timmers et al, in a prospective study have compared ^{18}F-fluoDOPA, ^{18}F-FDG and ^{18}F-FDA PET/CT and ^{123}I-MIBG for localization of pheo and PGL and have stated that ^{18}F-FDA PET/CT is the best modality for localizing primary PGL and for ruling out metastasis. Next best with similar sensitivities are ^{18}F-DOPA and ^{123}I-MIBG.[83] MIBG scintigraphy has low sensitivity in patients with malignant pheo/PGL, dedifferentiated tumor, mutation-associated (SDHB, VHL) pheo/PGL due to lower nor-adrenaline transporter expression.[84,85] In such cases alternate imaging modalities like ^{18}F-FDG and ^{68}Ga DOTATATE PET/CT are found to be useful. In patients with SDH-B-associated pheo/PGL ^{18}F-FDG PET is superior to $^{123/131}$I-MIBG, ^{111}In-pentreotide and 18F-FDA PET detection of metastatic lesions with sensitivity reaching upto 100%.[86] ^{68}Ga DOTA-peptide PET/CT imaging which targets SSTRs present on the cell membrane of these tumors has also shown promising results. ^{68}Ga DOTA-peptide PET/CT has high sensitivity for detection of pheo/PGL which are negative on MIBG scintigraphy and particularly in small head and neck PGLs which are non-functional and thus not visualized on MIBG scan.[87,88] In a study comparing SRS and MIBG scintigraphy in patients with SDH-X related syndromes; Michalowska et al have shown high sensitivity of 77 and 91.4% for SRS scintigraphy for benign and head and neck PGL respectively. The sensitivity of ^{123}I-MIBG in the same group was found to be very poor—22% for benign tumors and 3.7% for head and neck PGL.[89]

B^{131}I-MIBG therapy in pheo and PGL

Surgery is the only curative option for patients with pheo/PGL.[90] External beam radiotherapy has limited role in these tumors.[71] ^{131}I-MIBG is a good treatment option for pheo/PGL (Figure 5) in whom the diagnostic scan is positive done either with ^{123}I/^{131}I-MIBG.

Figure 5. 30-year-old male, a case of left para-aortic paraganglioma (arrow) with multiple metastases (arrow head). The patient was treated with 180 mCi of ^{131}I-MIBG. The post-therapy scan demonstrates the MIBG avid lesions. MIBG, metaiodobenzylguanidine.



^{131}I-MIBG therapy dose ranges from 3.7 to11.1 GBq (100–300 mCi) and can be repeated after 3 months.[91] A retrospective study with 116 patients documented tumor response in 30%, biochemical response in 45% and improvement of symptoms in 75% of patients with cumulative doses ranging from 3.55 to 85.91 GBq (96–2322 mCi).[92] The responses seen with MIBG therapy are mostly stabilization of the disease or partial response. Complete response is rare with MIBG treatment. In a systematic review with 243 patients, 52% showed stable disease, 27% showed partial response and only 3% showed complete response.[93] Reductions in symptoms is also noted after MIBG therapy.

The presence of SSTRs in pheo/PGL has facilitated the treatment of these tumors with Yttrium-90- DOTA-peptides (^{90}Y-DOTA) and Lutetium-177-DOTA peptides (^{177}Lu-DOTA), in patients who are negative on MIBG scintigraphy. The results with this therapy are encouraging in terms of tumor stabilization, regression and symptomatic relief.[94]

Medullary carcinoma thyroid

MTC is a NET arising from the parafollicular C cells of thyroid. It is a relatively rare tumor of thyroid comprising 5–10% of all thyroid cancers. It releases calcitonin and carcinoembryonic antigen primarily and also chromogranin, serotonin, somatostatin and gastrin releasing peptide. MTC exists in a more

common sporadic form (approx. 70–80%) and a less common inherited form (approx. 20–30%), as an autosomal dominant trait due to RET proto-oncogene mutation. The hereditary form can occur as a component of MEN 2 syndrome. MEN 2A is associated with pheo, hyperparathyroidism and MTC. MEN 2B with pheo, MTC, ganglioneuromatosis, and marfanoid habitus.[95] MTC with disease confined to the thyroid have better 10 year survival rate of 95% as compared to those with distant metastases where the 10year survival decreases to 40%.[96] MTC commonly metastasizes to cervical lymph nodes, mediastinum, lungs, liver and bone.

Imaging modalities in MTC include CT/MRI, ultrasound and bone scan. Many nuclear medicine studies with different radiopharmaceuticals have been used for imaging and therapy of MTC. ^{99m}Tc(V) DMSA, ^{131}I MIBG, ^{18}F-FDG, ^{18}F-DOPA, and more recently, ^{68}Ga-DOTATOC have been used for imaging MTC. Therapy with ^{131}I-MIBG, ^{177}Lu- DOTATOC and ^{90}Y-DOTATOC have been attempted. MIBG has a poor diagnostic accuracy in MTC with very low sensitivity of 25–30%, but with high specificity of 95%.[97,98] In most cases of MTC, the uptake of MIBG is very low and good therapeutic benefit cannot be expected. The reported response rates with MIBG therapy are 30% partial response and 30% stable disease.[99] Symptom relief is reported in 60% of patients.[100] ^{177}Lu/90Y-DOTA offers good treatment opportunity in MTC. ^{131}I-MIBG therapy can be contemplated in cases which are not DOTA avid or do not respond to any other form of treatment.

Carcinoids

Carcinoids are tumors derived from the cells of neuroendocrine system, present in the bronchial epithelium, gastrointestinal tract and the urogenital system. Carcinoids can arise from lung, thymus, stomach and duodenum (foregut tumors), distal ileum and proximal colon (midgut), distal colon and rectum (hindgut) and also from endocrine pancreas which may be divided based on hormone secretion into insulinomas, gastrinomas, VIPomas, glucagonomas. About 15–30% of pancreatic NETs are non-functional. Radiolabeled MIBG has a limited role in evaluation of carcinoids. The detection rate of carcinoids with MIBG varies from 40 to 85% in various studies. Compared to MIBG, SSTR imaging has much better sensitivity of >80% in detection of primary as well as metastatic lesion.[101–105]

^{131}I MIBG therapy is for treatment of metastatic carcinoids offers good palliation of symptoms and effective disease stabilization. This can be used as an adjunct or alternative therapy regime in addition to the existing treatment modalities that are currently available.[106]

CONCLUSION

$^{123/131}$I-labelled MIBG imaging for neural crest tumors is unique because of its specific uptake mechanism due to its similarity with nor-epinephrine. This makes it an ideal imaging and a targeted therapeutic agent for imaging and treatment of these tumors. New agent ^{211}At-MABG, an α emitter has lesser bone marrow toxicity and strong therapeutic effect due to high linear energy transfer. It remains to be seen whether the use of ^{211}At-MABG in patients with neural crest tumors gives better therapeutic effect than ^{131}I-MIBG. At present, ^{131}I -MIBG remains the best targeted therapy option for these tumors.

REFERENCES

1. Wieland DM, JL W, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron blocking agents: adrenomedullary imaging with 131I-iodobenzylguanidine. *J Nucl Med* 1980; **21**: 349–53.
2. Sisson JC, Frager MS, Valk TW, Gross MD, Swanson DP, Wieland DM, et al. Scintigraphic localization of pheochromocytoma. *N Engl J Med Overseas Ed* 1981; **305**: 12–17. doi: https://doi.org/10.1056/NEJM198107023050103
3. Kimmig B, Brandeis WE, Eisenhut M, Bubeck B, Hermann HJ, zum Winkel K. Scintigraphy of a neuroblastoma with I-131 meta-iodobenzylguanidine. *J Nucl Med* 1984; **25**: 773–5.
4. Geatti O, Shapiro B, Sisson JC, Hutchinson RJ, Mallette S, Eyre P, et al. Iodine-131 metaiodobenzylguanidine scintigraphy for the location of neuroblastoma: preliminary experience in ten cases. *J Nucl Med* 1985; **26**: 736–42.
5. Von Moll L, McEwan AJ, Shapiro B, Sisson JC, Gross MD, Lloyd R, et al. Iodine-131 MIBG scintigraphy of neuroendocrine tumors other than pheochromocytoma and neuroblastoma. *J Nucl Med* 1987; **28**: 979–88.
6. Bombardieri E, Giammarile F, Aktolun C, Baum RP, Bischof Delaloye A, Maffioli L, et al. European association for nuclear medicine. 131I/123I-metaiodobenzylguanidine (mIBG) scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging* 2010; **37**: 2436–46.
7. Vallabhajosula S, Nikolopoulou A. Radioiodinated metaiodobenzylguanidine (MIBG): radiochemistry, biology, and pharmacology. *Semin Nucl Med* 2011; **41**: 324–33. doi: https://doi.org/10.1053/j.semnuclmed.2011.05.003
8. Wafelman AR, Hoefnagel CA, Maes RA, Beijnen JH. Radioiodinated metaiodobenzylguanidine: a review of its biodistribution and pharmacokinetics, drug interaction, cytotoxicity and dosimetry. *Eur J Nucl Med* 1994; **1994**: 545–59.
9. Bombardieri E, Giammarile F, Aktolun C, Baum RP, Bischof Delaloye A, Maffioli L, et al. 131I/123I-Metaiodobenzylguanidine (mIBG) scintigraphy: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging* 2010; **37**: 2436–46. doi: https://doi.org/10.1007/s00259-010-1545-7
10. Wood DE, Gilday DL, Kellan J. Stable iodine requirements for thyroid gland blockage of iodinated radiopharmaceuticals. *J Can Assoc Radiol* 1974; **25**: 295–6.
11. Giammarile F, Chiti A, Lassmann M, Brans B, Flux G. EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy. *Eur J Nucl Med Mol Imaging* 2008; **35**: 1039–47. doi: https://doi.org/10.1007/s00259-008-0715-3
12. Piepsz A, Hahn K, Roca I, Ciofetta G, Toth G, Gordon I, et al. A radiopharmaceuticals schedule for imaging in paediatrics.

Paediatric Task Group European Association Nuclear Medicine. *Eur J Nucl Med* 1990; **17**: 127–9.
13. Nakajo M, Shapiro B, Copp J, Kalff V, Gross MD, Sisson JC, et al. The normal and abnormal distribution of the adrenomedullary imaging agent m-[I-131] iodobenzylguanidine (I-131 MIBG) in man: evaluation by scintigraphy. *J Nucl Med* 1983; **24**: 672–82.
14. Okuyama C, Sakane N, Yoshida T, Shima K, Kurosawa H, Kumamoto K, et al. ^{123}I- or ^{125}I-metaiodobenzylguanidine visualization of brown adipose tissue. *J Nucl Med* 2002; **43**: 1234–40.
15. Gelfand M. 123I-MIBG uptake in the neck and shoulders of a neuroblastoma patient: damage to sympathetic innervation blocks uptake in brown adipose tissue. *Pediatr Radiol* 2004; **34**: 577–9. doi: https://doi.org/10.1007/s00247-003-1136-x
16. Hoefnagel CA, Voute PA, De Kraker J, Marcuse HR. Radionuclide diagnosis and therapy of neural crest tumors using iodine-131metaiodobenzylguanidine. *J Nucl Med* 1987; **28**: 308–14.
17. Gordon I, Peters AM, Gutman A, Morony S, Dicks-Mireaux C, Pritchard J. Skeletal assessment in neuroblastoma-the pitfalls of iodine-123-MIBG scans. *J Nucl Med* 1990; **31**: 129–34.
18. Boubaker A. Bischof Delaloye A: MIBG scintigraphy for the diagnosis and follow-up of children with neuroblastoma. *Q J Nucl Med Mol Imaging* 2008; **52**: 388–402.
19. Taïeb D, Timmers HJ, Hindié E, Guillet BA, Neumann HP, Walz MK, et al. EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging* 2012; **39**: 1977–95. doi: https://doi.org/10.1007/s00259-012-2215-8
20. Braghirolli AMS, Waissmann W, da Silva JB, dos Santos GR. Production of iodine-124 and its applications in nuclear medicine. *Appl Radiat Isot* 2014; **90**: 138–48. doi: https://doi.org/10.1016/j.apradiso.2014.03.026
21. Hartung-Knemeyer V, Rosenbaum-Krumme S, Buchbender C, Pöppel T, Brandau W, Jentzen W, et al. Malignant pheochromocytoma imaging with [124I I] mIBG PET/MR. *J Clin Endocrinol Metab* 2012; **97**: 3833–4. doi: https://doi.org/10.1210/jc.2012-1958
22. Cistaro A, Quartuccio N, Caobelli F, Piccardo A, Paratore R, Coppolino P, et al. 124I-MIBG: a new promising positron-emitting radiopharmaceutical for the evaluation of neuroblastoma. *Nucl Med Rev Cent East Eur* 2015; **18**: 102–6. doi: https://doi.org/10.5603/NMR.2015.0024
23. Sisson J, Shapiro B, Beierwaltes WH, Nakajo M, Glowniak J, Mangner T, et al. Treatment of malignant pheochromocytoma with a new radiopharmaceutical. *Trans Assoc Am Physicians* 1983; **96**: 209–17.
24. Treuner J, Klingebiel T, Feine U, Buck J, Bruchelt G, Dopfer R, et al. Clinical experiences in the treatment of neuroblastoma with ^{131}I-metaiodobenzylguanidine. *Pediatr Hematol Oncol* 1986; **3**: 205–16. doi: https://doi.org/10.3109/08880018609031220
25. Giammarile F, Chiti A, Lassmann M, Brans B, Flux G. EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy. *Eur J Nucl Med Mol Imaging* 2008; **35**: 1039–47. doi: https://doi.org/10.1007/s00259-008-0715-3
26. Shusterman S, Grant FD, Lorenzen W, Davis RT, Laffin S, Drubach LA, et al. Iodine-131–labeled Meta-iodobenzylguanidine therapy of children with neuroblastoma: program planning and initial experience. *Semin Nucl Med* 2011; **41**: 354–63. doi: https://doi.org/10.1053/j.semnuclmed.2011.06.001
27. Modak S, Pandit-Taskar N, Kushner BH, Kramer K, Smith-Jones P, Larson S, et al. Transient sialoadenitis: a complication of131I-metaiodobenzylguanidine therapy. *Pediatr Blood Cancer* 2008; **50**: 1271–3. doi: https://doi.org/10.1002/pbc.21391
28. Polishchuk AL, Dubois SG, Haas-Kogan D, Hawkins R, Matthay KK. Response, survival, and toxicity after iodine-131-metaiodobenzylguanidine therapy for neuroblastoma in preadolescents, adolescents, and adults. *Cancer* 2011; **117**: 4286–93. doi: https://doi.org/10.1002/cncr.25987
29. Weiss B, Vora A, Huberty J, Hawkins RA, Matthay KK. Secondary myelodysplastic syndrome and leukemia following 131I-MIBG therapy for relapsed neuroblastoma. *J Pediatr Hematol Oncol* 2003; **25**: 543–7Jul. doi: https://doi.org/10.1097/00043426-200307000-00009
30. Ohshima Y, Sudo H, Watanabe S, Nagatsu K, Tsuji AB, Sakashita T, et al. Antitumor effects of radionuclide treatment using α-emitting meta-^{211}At-astato-benzylguanidine in a PC12 pheochromocytoma model. *Eur J Nucl Med Mol Imaging* 2018; **45**: 999–. doi: https://doi.org/10.1007/s00259-017-3919-6
31. Leung A, Shapiro B, Hattner R, Kim E, de Kraker J, Ghazzar N, et al. Specificity of radioiodinated MIBG for neural crest tumors in childhood. *J Nucl Med* 1997; **38**: 1352–7.
32. Lonergan GJ, Schwab CM, Suarez ES, Carlson CL. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. *Radiographics* 2002; **22**: 911–34. doi: https://doi.org/10.1148/radiographics.22.4.g02jl15911
33. Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. *Hematol Oncol Clin North Am* 2010; **24**: 65–86. doi: https://doi.org/10.1016/j.hoc.2009.11.011
34. Matthay KK, Blaes F, Hero B, Plantaz D, De Alarcon P, Mitchell WG, et al. Opsoclonus myoclonus syndrome in neuroblastoma a report from a workshop on the dancing eyes syndrome at the advances in neuroblastoma meeting in Genoa, Italy, 2004. *Cancer Lett* 2005; **228**: 275–82. doi: https://doi.org/10.1016/j.canlet.2005.01.051
35. De Bernardi B, Pianca C, Pistamiglio P, Veneselli E, Viscardi E, Pession A, et al. Neuroblastoma with symptomatic spinal cord compression at diagnosis: treatment and results with 76 cases. *J Clin Oncol* 2001; **19**: 183–90. doi: https://doi.org/10.1200/JCO.2001.19.1.183
36. Gorman MP. Update on diagnosis, treatment, and prognosis in opsoclonus-myoclonus-ataxia syndrome. *Curr Opin Pediatr* 2010; **22**: 745–50. doi: https://doi.org/10.1097/MOP.0b013e32833fde3f
37. Brodeur GM, Pritchard J, Berthold F, Carlsen NL, Castel V, Castelberry RP, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 1993; **11**: 1466–77. doi: https://doi.org/10.1200/JCO.1993.11.8.1466
38. Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG task force report. *J Clin Oncol* 2009; **27**: 298–303. doi: https://doi.org/10.1200/JCO.2008.16.6876
39. Maris JM. Recent advances in neuroblastoma. *N Engl J Med Overseas Ed* 2010; **362**: 2202–11. doi: https://doi.org/10.1056/NEJMra0804577
40. Evans AE, D'Angio GJ. Age at diagnosis and prognosis in children with neuroblastoma. *J Clin Clinical Oncology* 2005; **23**: 6443–4. doi: https://doi.org/10.1200/JCO.2005.05.005
41. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13- *cis* -retinoic acid. Children's Cancer Group. *N Engl J Med Overseas Ed* 1999; **341**: 1165–73. doi: https://doi.org/10.1056/NEJM199910143411601

42. Shapiro B. Summary, conclusions, and future directions of [131I] metaiodobenzylguanidine therapy in the treatment of neural crest tumors. *J Nucl Biol Med* 1991; **35**: 357–63.
43. Lebtahi N, Gudinchet F, Nenadov-Beck M, Beck D, Bischof Delaloye A. Evaluating bone marrow metastasis of neuroblastoma with iodine-123-MIBG scintigraphy and MRI. *J Nucl Med* 1997; **38**: 1389–92.
44. Matthay KK, Shulkin B, Ladenstein R, Michon J, Giammarile F, Lewington V, et al. Criteria for evaluation of disease extent by 123I-metaiodobenzylguanidine scans in neuroblastoma: a report for the International Neuroblastoma Risk Group (INRG) Task Force. *Br J Cancer* 2010; **102**: 1319–26. doi: https://doi.org/10.1038/sj.bjc.6605621
45. Sharp SE, Shulkin BL, Gelfand MJ, Salisbury S, Furman WL. 123I-MIBG scintigraphy and 18F-FDG PET in neuroblastoma. *J Nucl Med* 2009; **50**: 1237–43. doi: https://doi.org/10.2967/jnumed.108.060467
46. Ady N, Zucker J-M, Asselain B, Edeline V, Bonnin F, Michon J, et al. A new 123I-MIBG whole body scan scoring method—Application to the prediction of the response of metastases to induction chemotherapy in stage IV neuroblastoma. *Eur J Cancer* 1995; **31**: 256–61. doi: https://doi.org/10.1016/0959-8049(94)00509-4
47. Suc A, Lumbroso J, Rubie H, Hattchouel JM, Boneu A, Rodary C, et al. Metastatic neuroblastoma in children older than one year: prognostic significance of the initial metaiodobenzylguanidine scan and proposal for a scoring system. *Cancer* 1996; **77**: 805–11. doi: https://doi.org/10.1002/(SICI)1097-0142(19960215)77:4<805::AID-CNCR29>3.0.CO;2-3
48. Decarolis B, Schneider C, Hero B, Simon T, Volland R, Roels F, et al. Iodine-123 metaiodobenzylguanidine scintigraphy scoring allows prediction of outcome in patients with stage 4 neuroblastoma: results of the Cologne interscore comparison study. *J Clin Oncol* 2013; **31**: 944–51. doi: https://doi.org/10.1200/JCO.2012.45.8794
49. Yanik GA, Naranjo A, Parisi MT.etal. *A Children's Oncology Group (COG) and INRC metastatic imaging committee report: validation of post-induction curie scores in high-risk neuroblastoma*. Chicago, IL: American Society of Clinical Oncology (ASCO); 2014.
50. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13- *cis* -retinoic acid. Children's Cancer Group. *N Engl J Med Overseas Ed* 1999; **341**: 1165–73. doi: https://doi.org/10.1056/NEJM199910143411601
51. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med* 2010; **363**: 1324–34. doi: https://doi.org/10.1056/NEJMoa0911123
52. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng S-C, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. *J Clin Oncol* 2007; **25**: 1054–60. doi: https://doi.org/10.1200/JCO.2006.09.3484
53. Howard JP, Maris JM, Kersun LS, Huberty JP, Cheng S-C, Hawkins RA, et al. Tumor response and toxicity with multiple infusions of high dose131I-MIBG for refractory neuroblastoma. *Pediatr Blood Cancer* 2005; **44**: 232–9. doi: https://doi.org/10.1002/pbc.20240
54. Vik TA, Pfluger T, Kadota R, Castel V, Tulchinsky M, Farto JCA, et al. ^{123} I- *m* IBG scintigraphy in patients with known or suspected neuroblastoma: Results fro*m* a prospective multicenter trial. *Pediatr Blood Cancer* 2009; **52**: 784–90. doi: https://doi.org/10.1002/pbc.21932
55. Hoefnagel CA, de Kraker J, Voûte PA, Valdés Olmos RA. Preoperative [131I] metaiodobenzylguanidine therapy of neuroblastoma at diagnosis ("MIBG de novo"). *J Nucl Biol Med* 1991; **35**: 248–51.
56. Klingebiel T, Bader P, Bares R, Beck J, Hero B, Jürgens H, et al. Treatment of neuroblastoma stage 4 with 131I-meta-iodobenzylguanidine, high-dose chemotherapy and immunotherapy. A pilot study. *Eur J Cancer* 1998; **34**: 1398–402. doi: https://doi.org/10.1016/S0959-8049(98)00130-0
57. Wilson JS, Gains JE, Moroz V, Wheatley K, Gaze MN. A systematic review of 131I-meta iodobenzylguanidine molecular radiotherapy for neuroblastoma. *Eur J Cancer* 2014; **50**: 801–15. doi: https://doi.org/10.1016/j.ejca.2013.11.016
58. Matthay KK, DeSantes K, Hasegawa B, Huberty J, Hattner RS, Ablin A, et al. Phase I dose escalation of 131I-metaiodobenzylguanidine with autologous bone marrow support in refractory neuroblastoma. *J Clin Oncol* 1998; **16**: 229–36. doi: https://doi.org/10.1200/JCO.1998.16.1.229
59. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng S-C, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. *J Clin Oncol* 2007; **25**: 1054–60. doi: https://doi.org/10.1200/JCO.2006.09.3484
60. Matthay KK, Quach A, Huberty J, Franc BL, Hawkins RA, Jackson H, et al. Iodine-131–metaiodobenzylguanidine double infusion with autologous stem-cell rescue for neuroblastoma: a new approach to neuroblastoma therapy phase I study. *J Clin Oncol* 2009; **27**: 1020–5. doi: https://doi.org/10.1200/JCO.2007.15.7628
61. Mastrangelo R, Tornesello A, Riccardi R, Lasorella A, Mastrangelo S, Mancini A, et al. A new approach in the treatment of stage IV neuroblastoma using a combination of [131I]meta-iodobenzylguanidine (MIBG) and cisplatin. *Eur J Cancer* 1995; **31**: 606–11. doi: https://doi.org/10.1016/0959-8049(95)00048-N
62. Mastrangelo R, Tornesello A, Lasorella A, Iavarone A, Mastrangelo S, Riccardi R, et al. Optimal use of the 131-I-metaiodobenzylguanidine and cisplatin combination in advanced neuroblastoma. *J Neurooncol* 1997; **31**(1/2): 153–8. doi: https://doi.org/10.1023/A:1005770405844
63. Mastrangelo S, Tornesello A, Diociaiuti L, Pession A, Prete A, Rufini V, et al. Treatment of advanced neuroblastoma: feasibility and therapeutic potential of a novel approach combining 131-I-MIBG and multiple drug chemotherapy. *Br J Cancer* 2001; **84**: 460–4. doi: https://doi.org/10.1054/bjoc.2000.1645
64. Gaze MN, Chang Yen-Ch'ing, Flux GD, Mairs RJ, Saran FH, Meller ST. Feasibility of dosimetry-based high-dose 131I I-meta-iodobenzylguanidine with topotecan as a radiosensitizer in children with metastatic neuroblastoma. *Cancer Biother Radiopharm* 2005; **20**: 195–9. doi: https://doi.org/10.1089/cbr.2005.20.195
65. Vöö S, Bucerius J, Mottaghy FM. I-131-MIBG therapies. *Methods* 2011; **55**: 238–45. doi: https://doi.org/10.1016/j.ymeth.2011.10.006
66. Armour A, Cunningham SH, Gaze MN, Wheldon TE, Mairs RJ. The effect of cisplatin pretreatment on the accumulation of MIBG by neuroblastoma cells in vitro. *Br J Cancer* 1997; **75**: 470–6. doi: https://doi.org/10.1038/bjc.1997.82
67. Meco D, Lasorella A, Riccardi A, Servidei T, Mastrangelo R, Riccardi R. Influence of cisplatin and doxorubicin on 125 I-meta-iodobenzylguanidine uptake in human neuroblastoma cell lines. *Eur J Cancer* 1999; **35**: 1227–34. doi: https://doi.org/10.1016/S0959-8049(99)00078-7

68. Yeo H, Roman S. Pheochromocytoma and functional paraganglioma. *Curr Opin Oncol* 2005; **17**: 13–18. doi: https://doi.org/10.1097/01.cco.0000147900.12325.d9
69. Ilias I, Pacak K. A clinical overview of pheochromocytomas/paragangliomas and carcinoid tumors. *Nucl Med Biol* 2008; **35**(Suppl 1): S27–S34. doi: https://doi.org/10.1016/j.nucmedbio.2008.04.007
70. Plouin P-F, Fitzgerald P, Rich T, Ayala-Ramirez M, Perrier N, Baudin E, et al. Metastatic Pheochromocytoma and paraganglioma: focus on therapeutics. *Horm Metab Res* 2012; **44**: 390–9. doi: https://doi.org/10.1055/s-0031-1299707
71. Jimenez C, Rohren E, Habra MA, Rich T, Jimenez P, Ayala-Ramirez M, et al. Current and future treatments for malignant Pheochromocytoma and sympathetic paraganglioma. *Curr Oncol Rep* 2013; **15**: 356–71. doi: https://doi.org/10.1007/s11912-013-0320-x
72. Koopmans KP, Jager PL, Kema IP, Kerstens MN, Albers F, . 111In-octreotide is superior to 123I- metaiodobenzylguanidine for scintigraphic detection of head and neck paragangliomas. *J Nucl Nuclear Medicine* 2008; **49**: 1232–7. doi: https://doi.org/10.2967/jnumed.107.047738
73. Chen CC, Carrasquillo JA. Molecular imaging of adrenal neoplasms. *J Surg Oncol* 2012; **106**: 532–42. doi: https://doi.org/10.1002/jso.23162
74. Martucci VL, Pacak K. Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. *Curr Probl Cancer* 2014; ; **38**: 7–41Jan-Feb. doi: https://doi.org/10.1016/j.currproblcancer.2014.01.001
75. Ilias I, Pacak K. A clinical overview of pheochromocytomas/paragangliomas and carcinoid tumors. *Nucl Med Biol* 2008; **35**(Suppl 1): S27–S34. doi: https://doi.org/10.1016/j.nucmedbio.2008.04.007
76. Jacques AET, Sahdev A, Sandrasagara M, Goldstein R, Berney D, Rockall AG, et al. Adrenal phaeochromocytoma: correlation of MRI appearances with histology and function. *Eur Radiol* 2008; **18**: 2885–92. doi: https://doi.org/10.1007/s00330-008-1073-z
77. Mittendorf EA, Evans DB, Lee JE, Perrier ND. Pheochromocytoma: advances in genetics, diagnosis, localization, and treatment. *Hematol Oncol Clin North Am* 2007; **21**: 509–25. doi: https://doi.org/10.1016/j.hoc.2007.04.012
78. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab* 2004; **89**: 479–91. doi: https://doi.org/10.1210/jc.2003-031091
79. Sisson JC. Shulkin BL: Nuclear medicine imaging of Pheochromocytoma and neuroblastoma. *Q J Nucl Med* 1999; **43**: 217–23.
80. Nielsen JT, Nielsen BV, Rehling M. Location of adrenal medullary pheochromocytoma by I-123-metaiodobenzylguanidine SPECT. *Clin Nucl Med* 1996; **21**: 695–9. doi: https://doi.org/10.1097/00003072-199609000-00005
81. Wiseman GA, Pacak K, O'Dorisio MS, Neumann DR, Waxman AD, Mankoff DA, et al. Usefulness of 123I-MIBG scintigraphy in the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma: results from a prospective multicenter trial. *J Nucl Med* 2009; **50**: 1448–54. doi: https://doi.org/10.2967/jnumed.108.058701
82. Wong KK, Chondrogiannis S, Fuster D, Ruiz C, Marzola MC, Giammarile F, et al. Additional value of hybrid SPECT/CT systems in neuroendocrine tumors, adrenal tumors, pheochromocytomas and paragangliomas. *Rev Esp Med Nucl Imagen Mol* 2017; ; **36**: 103–9Mar - Apr.
83. Timmers HJLM, Chen CC, Carrasquillo JA, Whatley M, Ling A, Havekes B, et al. Comparison of $18F^{18}$-fluoro-L-DOPA, $18F^{18}$-fluoro-deoxyglucose, and $18F^{18}$-fluorodopamine PET and 123I I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* 2009; **94**: 4757–67. doi: https://doi.org/10.1210/jc.2009-1248
84. Kaji P, Carrasquillo JA, Linehan WM, Chen CC, Eisenhofer G, Pinto PA, et al. The role of 6-[18F]fluorodopamine positron emission tomography in the localization of adrenal pheochromocytoma associated with von Hippel-Lindau syndrome. *Eur J Endocrinol* 2007; **15693**: 483–7. doi: https://doi.org/10.1530/EJE-06-0712
85. Fonte JS, Robles JF, Chen CC, Reynolds J, Whatley M, Ling A, et al. False-negative 123I-MIBG SPECT is most commonly found in SDHB-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease. *Endocr Relat Cancer* 2012; **19**: 83–93. doi: https://doi.org/10.1530/ERC-11-0243
86. Timmers HJLM, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, et al. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. *J Clin Oncol* 2007; **25**: 2262–9. doi: https://doi.org/10.1200/JCO.2006.09.6297
87. Fanti S, Ambrosini V, Tomassetti P, Castellucci P, Montini G, Allegri V, et al. Evaluation of unusual neuroendocrine tumours by means of 68Ga-DOTA-NOC PET. *Biomed Pharmacother* 2008; **62**: 667–71. doi: https://doi.org/10.1016/j.biopha.2008.01.010
88. Maurice JB, Troke R, Win Z, Ramachandran R, Al-Nahhas A, Naji M, et al. A comparison of the performance of 68Ga-DOTATATE PET/CT and 123I-MIBG SPECT in the diagnosis and follow-up of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging* 2012; **39**: 1266–70. doi: https://doi.org/10.1007/s00259-012-2119-7
89. Michałowska I, Ćwikła JB, Pęczkowska M, Furmanek MI, Buscombe JR, Michalski W, et al. Usefulness of somatostatin receptor scintigraphy (Tc-[HYNIC, Tyr3]-Octreotide) and 123I-metaiodobenzylguanidine scintigraphy in patients with SDHx gene-related pheochromocytomas and paragangliomas detected by computed tomography. *Neuroendocrinology* 2015; **101**: 321–30.
90. Cheah WK, Clark OH, Horn JK, Siperstein AE, Duh Q-Y. Laparoscopic adrenalectomy for pheochromocytoma. *World J Surg* 2002; **26**: 1048–51. doi: https://doi.org/10.1007/s00268-002-6669-x
91. Carrasquillo JA, Pandit-Taskar N, Chen CC. Radionuclide therapy of adrenal tumors. *J Surg Oncol* 2012; **106**: 632–42. doi: https://doi.org/10.1002/jso.23196
92. Loh K-C, Fitzgerald PA, Matthay KK, Yeo PPB, Price DC. The treatment of malignant pheochromocytoma with Iodine-131 metaiodobenzylguanidine (131I-MIBG): a comprehensive review of 116 reported patients. *J Endocrinol Invest* 1997; **20**: 648–58. doi: https://doi.org/10.1007/BF03348026
93. van Hulsteijn LT, Niemeijer ND, Dekkers OM, Corssmit EPM. ^{131} I-MIBG therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. *Clin Endocrinol* 2014; **80**: 487–501. doi: https://doi.org/10.1111/cen.12341
94. Kam BLR, Teunissen JJM, Krenning EP, de Herder WW, Khan S, van Vliet EI, et al. Lutetium-labelled peptides for therapy of neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2012; **39**(Suppl 1): 103–12. doi: https://doi.org/10.1007/s00259-011-2039-y
95. Castellani MR, Seregni E, Maccauro M, Chiesa C, Aliberti G, Orunesu E, et al. MIBG for diagnosis and therapy of medullary thyroid carcinoma: is there still a role? *Q J Nucl Med Mol Imaging* 2008; **52**: 430–40Review.

96. Roman S, Lin R, Sosa JA. Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. *Cancer* 2006; **107**: 2134–42.
97. Rufini V, Salvatori M, Garganese MC, Di Giuda D, Lodovica Maussier M, Troncone L. Role of nuclear medicine in the diagnosis and therapy of medullary thyroid carcinoma. *Rays* 2000; ; **25**: 273–82Apr-Jun.
98. Baulieu J-L, Guilloteau D, Delisle M-J, Perdrisot R, Gardet P, Delépine N, et al. Radioiodinated meta-iodobenzylguanidine uptake in medullary thyroid cancer: A French cooperative study. *Cancer* 1987; **60**: 2189–94. doi: https://doi.org/10.1002/1097-0142(19871101)60:9<2189::AID-CNCR2820600913>3.0.CO;2-C
99. Castellani MR, Alessi A, Savelli G, Bombardieri E. The role of radionuclide therapy in medullary thyroid cancer. *Tumori* 2003; **89**: 560–2. doi: https://doi.org/10.1177/030089160308900523
100. Hoefnagel CA. MIBG and radiolabeled octreotide in neuroendocrine tumors. *Q J Nucl Med* 1995; **39**(4 Suppl 1): 137–9.
101. Taal BG, Hoefnagel CA, Valdés Olmos RA, Boot H. Combined diagnostic imaging with 131I-metaiodobenzylguanidine and 111In-pentetreotide in carcinoid tumours. *Eur J Cancer* 1996; **32A**: 1924–32. doi: https://doi.org/10.1016/0959-8049(96)00241-9
102. 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. doi: https://doi.org/10.1210/jcem.86.2.7194
103. Nocaudie-Calzada M, Huglo D, Carnaille B, Proye C, Marchandise X. Comparison of somatostatin analogue and metaiodobenzylguanidine scintigraphy for the detection of carcinoid tumours. *Eur J Nucl Med* 1996; **23**: 1448–54. doi: https://doi.org/10.1007/BF01254466
104. Rufini V, Salvatori M, Saletnich I, Valenza V, Maussier ML, Martino G, et al. Radiolabeled somatostatin analog scintigraphy in medullary thyroid carcinoma and carcinoid tumor. *Q J Nucl Med* 1995; **39**: 140–44 .
105. Bomanji J, Mather S, Moyes J, Ellison D, Grossman A, Britton KE, et al. A scintigraphic comparison of iodine-123-metaiodobenzylguanidine and an iodine-labeled somatostatin analog (tyr-3-octreotide) in metastatic carcinoid tumors. *J Nucl Med* 1994; **33**: 1121–4.
106. Ezziddin S, Sabet A, Logvinski T, Alkawaldeh K, Yong-Hing CJ, Ahmadzadehfar H, et al. Long-term outcome and toxicity after dose-intensified treatment with 131I-MIBG for advanced metastatic carcinoid tumors. *J Nucl Med* 2013; **54**: 2032–8. doi: https://doi.org/10.2967/jnumed.112.119313