$^{131}I/^{123}I$-Metaiodobenzylguanidine (mIBG) Scintigraphy – Procedures Guidelines For Tumour Imaging

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This guideline summarizes the views of the Oncology Committee of the EANM and reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.

The guidelines have been reviewed by the EANM Dosimetry Committee, the EANM Physics Committee and the EANM Radiopharmacy Committee

The guidelines have been brought to the attention of the National Societies of Nuclear Medicine

Key words: $^{131}I/^{123}I$-mIBG scintigraphy - Tumour imaging - Procedure Guidelines - Indications

Aim

The aim of this document is to provide general information about mIBG scintigraphy in cancer patients. This guideline describes the mIBG scintigraphy protocol currently used in the clinical routine, but does not include all existing procedures for neuroendocrine tumours. It should therefore not be taken as exclusive of other nuclear medicine modalities that can be used to obtain comparable results. It is important to remember that the resources and facilities available for patient care may vary from one country to another and from one medical institution to another. The present guideline has been prepared for nuclear medicine physicians and intends to offer assistance in optimising the diagnostic information that can currently be obtained from mIBG scintigraphy. The corresponding guidelines of the Society of Nuclear Medicine (SNM) and the Dosimetry, Therapy and Paediatric Committee of the EANM have been taken into consideration, and partially integrated with this text. The same has been done with the most relevant literature on this topic, and the final result has been discussed within a group of distinguished experts.

Background

^{131}I emits a principal gamma photon of 364 keV (81% abundance) with a physical half-life of 8.04 days. It also emits beta particles with maximum and mean energies of 0.61 MeV and 0.192 MeV, respectively.

^{123}I is a gamma emitting radionuclide with a physical half-life of 13.13 hours. The principal gamma photon is emitted at 159 keV (83 % abundance).

Metaiodobenzylguanidine (mIBG) or Iobenguane a combination of an iodinated benzyl and a guanidine group was developed in the early 1980s to visualise tumours of the adrenal medulla[1]. mIBG enters neuroendocrine cells by an active uptake mechanism via the epipherine transporter and is stored in the neurosecretory granules, resulting in a specific concentration in contrast to cells of other tissues.

mIBG scintigraphy is used to image tumours of neuroendocrine origin, particularly those of the neuro-ectodermal (sympatho-adrenal) system (phaeochromocytomas, paragangliomas and neuroblastomas) [2], although other neuroendocrine tumours (e.g. carcinoids, medullary thyroid carcinoma.) [3,4] can also be visualised. In addition, mIBG can be employed to study disorders of sympathetic innervation, for example in ischemic and not ischemic cardiomyopathy as well as in the differentiation between idiopathic Parkinson's syndrome and multisystem atrophy. mIBG can be labelled with either ^{131}I or ^{123}I. The 159 keV gamma energy of of ^{123}I is more suitable for imaging (especially when using SPECT) than the 360 keV photons of ^{131}I and the difference in

terms of radiation burden permits to inject higher activities of ^{123}I-mIBG. Furthermore, results with ^{123}I-mIBG are usually available within 24 hours whereas with ^{131}I-mIBG delayed images may be required for optimal target to background ratios [5]. Theoretical considerations and clinical experience indicate that the ^{123}I-labelled agent is to be considered the radiopharmaceutical of choice as it has a more favourable dosimetry and provides better image quality allowing an accurate anatomical localisation by the use of SPECT/CT hybrid systems. Nonetheless, ^{131}I-mIBG is widely employed for most routine applications mainly in adult patients because of its, ready availability and the possibility of obtaining delayed scans. Furthermore, ^{131}I-mIBG may be preferred when estimation of tumour uptake and retention measurement is required for mIBG therapy planning.

Clinical Indications

1) Oncological indications

a) Detection, localisation, staging and follow-up of neuroendocrine tumours and their metastases, in particular [6,7,8]:

- phaeochromocytomas
- neuroblastomas
- ganglioneuroblastomas
- ganglioneuromas
- paragangliomas
- carcinoid tumours
- medullary thyroid carcinomas
- Merkel cell tumours
- MEN2 syndromes

b) Study of tumour uptake and residence time in order to decide and plan a treatment with high activities of radiolabelled mIBG. In this case the dosimetric evaluation should be individual and not based on the ICRP Tables, that have only an indicative value limited to diagnostic procedures [9,10,11].

c) Evaluation of tumour response to therapy by measuring the intensity of mIBG uptake and the number of focal mIBG uptake sites [12,13].

d) Confirmation of suspected tumours derived from neuroendocrine tissue.

2) Other (non-oncological) indications

Functional studies of the adrenal medulla (hyperplasia), sympathetic innervation of the myocardium, salivary glands and lungs, movement disorders [14].

Precautions

- Pregnancy. In the case of a diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure.

- Breastfeeding:
  a) when ^{123}I-mIBG is used, breastfeeding should be discontinued at least 48 h post-injection;
  b) when ^{131}I-mIBG is used, breastfeeding should be terminated.

- Evaluation of the effects of the necessary withdrawal of drugs interfering with mIBG scintigraphy and their replacement in discussion with the referring physician.

Pre-examination procedure

1) Patient preparation

The technologist, nurse or physician should give the patient (or parents if the patient is a child) a thorough explanation of the correct patient preparation and the details of the scintigraphic study[15].

Thyroid blockade

Thyroid uptake of free iodide is prevented using stable iodine per os (tab.1).

The treatment should begin 1 day before the planned mIBG administration and continued for 1-2 days, for ^{123}I-mIBG or 2-3 days for ^{131}I-mIBG.

Potassium perchlorate is generally used the day of the injection, in case of emergency or in patients who are allergic to iodine.

Table 1: Thyroid blockade in adults*

Compound	**Daily dose**
Capsules	
Potassium iodate	170 mg
Potassium iodide (KI)	130 mg
Solution	
Lugol 1%	1 drop/Kg with a maximum of 40

	(20 drops twice a day)
Capsules	
Potassium perchlorate	400 mg

* in children, the dose should be reduced according to EANM Paediatric Committee guidelines

Drug interactions

Many classes of drugs are known (or may be expected) to interfere with the uptake and/or vesicular storage of mIBG. Table 2 includes some of the most important medications that may affect the results of mIBG scintigraphy [16,17].

Care must be taken to ensure that such drugs are discontinued (if possible) for an adequate time prior imaging. Patients with metabolically active catecholamine secreting tumours (i.e. phaechromocytoma, paraganglioma) often receive alpha- or beta-blocking treatment. Therefore, drug interruption should be decided in consultation with the referring physician, who is able to evaluate the patient's condition and may postpone the study, or realise it without changing the medication, although this could impair diagnostic accuracy [18,14,19].

Table 2: Drug interactions with mIBG
(adapted from the Radiopharmacy Protocol of the Nuclear Medicine Department, Queen Elizabeth Hospital, Birmingham, UK)

Drug Group	Approved name	Recommended withdrawal time	Mechanism of interaction *
CARDIOVASCULAR AND SYMPATHOMIMETIC DRUGS			
Anti-arrhythmics for ventricular arrhythmias	Amiodarone	Not practical to withdraw	**1,3**
Combined □,□blocker	Labetalol	72 hours	**1,3**
Adrenergic neurone blockers	Brethylium	48 hours	*2,3*
	Guanethidine	48 hours	*2,3*
	Reserpine	48 hours	2,3
□- blockers	Phenoxybenzamine (IV doses only)	15 days	**5**
Calcium channel blockers	Amlodipine	48 hours	*4,5*
	Diltiazem	24 hours	4,5
	Felodipine	48 hours	*4,5*
	Isradipine	48 hours	*4,5*
	Lacidipine	48 hours	*4,5*
	Lercanidipine	48 hours	*4,5*
	Nicardipine	48 hours	4,5
	Nifedipine	24 hours	4,5
	Nimodipine	24 hours	4,5
	Nisoldipine	48 hours	*4,5*
	Verapamil	48 hours	**4,5**
Inotropic sympatho-mimetics	Dobutamine	24 hours	*3*
	Dopamine	24 hours	*3*
	Dopexamine	24 hours	*3*
Vasoconstrictor sympathomimetics	Ephedrine	24 hours	1
	Metaraminol	24 hours	3
	Norepinephrine	24 hours	3
	Phenylephrine	24 hours	3
□2 stimulants (sympathomimetics)	Salbutamol	24 hours	*3*
	Terbutaline	24 hours	*3*
	Eformoterol	24 hours	*3*
	Bambuterol	24 hours	*3*
	Fenoterol	24 hours	*3*
	Salmeterol	24 hours	*3*

Other adrenoreceptor stimulants	Orciprenaline	24 hours	*3*
Systemic and local nasal decongestants, compound cough and cold preparations	Pseudoephedrine	48 hours	**3**
	Phenylephrine	48 hours	**3**
	Ephedrine	24 hours	**1**
	Xylometazoline	24 hours	**3**
	Oxymetazoline	24 hours	**3**
Sympathomimetics for Glaucoma	Brimonidine	48 hours	*3*
	Dipivefrine	48 hours	*3*
NEUROLOGICAL DRUGS			
Antipsychotics (neuroleptics)	Chlorpromazine	24 hours	*1*
	Benperidol	48 hours	*1*
	Flupentixol	48 hours, or 1 month for depot	*1*
	Fluphenazine	24 hours, or 1 month for depot	*1*
	Haloperidol	48 or 1 month for depot	*1*
	Levomepromazine	72 hours	*1*
	Pericyazine	48 hours	*1*
	Perphenazine	24 hours	*1*
	Pimozide	72 hours	*1*
	Pipotiazine	1 month for depot	*1*
	Prochlorperazine	24 hours	*1*
	Promazine	24 hours	*1*
	Sulpiride	48 hours	*1*
	Thioridazine	24 hours	*1*
	Trifluoperazine	48 hours	*1*
	Zuclopenthixol	48 hours, or 1 month for depot	*1*
	Amisulpride	72 hours	*1*
	Clozapine	7 days	*1*
	Olanzapine	7 – 10 days	*1*
	Quetiapine	48 hours	*1*
	Risperidone	5 days or 1 month for depot	*1*
	Sertindole	15 days	*1*
	Zotepine	5 days	*1*
Sedating antihistamines	Promethazine	24 hours	*1*
Opioid analgesics	Tramadol	24 hours	**1**
Tricyclic anti-depressants	Amitriptyline	48 hours	**1**
	Amoxapine	48 hours	1
	Clomipramine	24 hours	**1**
	Dosulepin (Dothiepin)	24 hours	**1**
	Doxepin	24 hours	1
	Imipramine	24 hours	**1**
	Lofepramine	48 hours	**1**
	Nortriptyline	24 hours	1
	Trimipramine	48 hours	**1**
Tricyclic-related anti-depressants	Maprotiline	48 hours	*1*
	Mianserin	48 hours	*1*
	Trazolone	48 hours	*1*
	Venlaflaxine	48 hours	*1*
	Mirtazepine	8 days	*1*
	Reboxetine	3 days	*1*
CNS Stimulants	Amphetamines eg Dexamfetamine	48 hours	*3*
	Atomoxetine	5 days	*1*
	Methylphenidate	48 hours	*5*
	Modafinil	72 hours	*5*
	Cocaine	24 hours	**1**
	Caffeine	24 hours	*5*

*Mechanisms of interaction

1 Inhibition of sodium-dependent uptake system (i.e. uptake-one inhibition)

2 Transport interference - inhibition of uptake by active transport into vesicles i.e. inhibition of granular uptake, and competition for transport into vesicles i.e. competition for granular uptake

3 Depletion of content from storage vesicles/granules

4 Calcium mediated

5 Other, possible, unknown mechanisms

Patient preparation including children

The patients are encouraged to drink lots of fluids to facilitate excretion of the radiopharmaceutical. As said above it is important that patients, when possible and with the supervision of the referring physician, discontinue all medicaments that could interfere with tumour uptake of radiolabelled mIBG. It is possible that some foods containing vanillin and catecholamine-like compounds (such as chocolate and blue-veined cheeses) can interfere on the uptake of mIBG (depletion of granules).

Children need particular preparation, an adapted environment and an adequate staff of operators who are expert and well trained in paediatric procedures. Parents should be involved in child preparation and during the scintigraphic study (assistance, sedation, etc.). For paediatric patients see *Guidelines for Radioiodinated MIBG Scintigraphy in Children*, which was published under the auspices of the EANM Paediatric Committee

1) Pre-injection

Clinical evaluation by the nuclear medicine physician

The nuclear medicine physician should consider any information that could be useful for the interpretation of scintigraphic images:

- relevant history of suspected or known primary tumour
- intake of possibly interfering drugs
- absence or presence of symptoms
- laboratory test results (plasma and urinary catecholamine dosage, CEA, 5-HIAA, NSE, chromogranin A, calcitonin, etc.)
- results of any other imaging studies (CT, MRI, US, X-rays)
- history of recent biopsy, surgery, chemotherapy, hormone therapy, radiation therapy.

2) Tracer injection, dosage and injected activity

mIBG, diluted in compliance with manufacturer's instructions, is administered by slow intravenous injection (at least 5 minutes) in a peripheral vein. The preparation should have a high specific activity.

The activity of radiopharmaceutical to be administered should be determined taking into account the Diagnostic Reference Levels (DRL) for radiopharmaceuticals; these are defined as *levels of activity for groups of standard-sized patients and for broadly defined types of equipment.* It is expected that these levels will not be exceeded for standard procedures when good and normal

practice regarding diagnostic and technical performance is applied. For the aforementioned reasons the following activities for mIBG should be considered only as a general indication, based on the data of the literature and the current experience. However, it should be noted that in each country nuclear medicine physicians should respect the DRLs and the rules stated by the local law. The injection of activities greater than local DRLs must be justified.

The activity administered to adults should be: for ^{131}I-mIBG: 40-80 MBq (1.2 - 2.2 mCi); for ^{123}I-mIBG: 400 MBq (10.8 mCi). The activity administered to children should be calculated on the basis of a reference dose for an adult, scaled to body weight according to the schedule proposed by the EANM Paediatric Task Group. For minimum and maximum recommended activities in children one should consult the above mentioned *Guidelines for Radioiodinated MIBG Scintigraphy in Children* (minimum activity 20 MBq for ^{123}I-mIBG and 35 MBq for ^{131}I-mIBG; maximum activity 400 MBq for ^{123}I-mIBG and 80 MBq for ^{131}I-mIBG).

4) Post-injection

Patients should be encouraged to drink large volumes of fluids following mIBG injection and should void immediately prior the study.

5) Side-effects

Adverse effects of mIBG (tachycardia, pallor, vomiting, abdominal pain), that are not related to allergy but to pharmacologic effects of the molecule, are very rare when slow injection is used. Injection via central venous catheters must be avoided if possible (imaging artefacts, potential adverse effects).

Radiation dosimetry

The estimated radiation absorbed dose to various organs in healthy subjects following administration of ^{123}I mIBG and ^{131}I mIBG is given in the following tables. The data for ^{123}I mIBG are quoted from ICRP 80 and for ^{131}I mIBG are calculated with approximation from ICRP 53 by considering weighting factors (wt) from ICRP 60 [9,11].

Absorbed doses: ^{123}I mIBG

	Absorbed dose per unit activity administered (mGy/MBq)		
Organ	Adult	15 years	5 years
Adrenals	0.017	0,022	0.045
Bladder	0.048	0.061	0.084
Bone surfaces	0.011	0.014	0.034

Brain	0.0047	0.0060	0.016
Breast	0.0053	0.0068	0.017
Gall bladder	0.021	0.025	0.054
Stomach	0.0084	0.011	0.030
Small Intestine	0.0084	0.011	0.030
Colon	0.0086	0.011	0.029
Heart	0.018	0.024	0.055
Kidneys	0.014	0.017	0.036
Liver	0.067	0.087	0.18
Lungs	0.016	0.023	0.049
Muscles	0.0066	0.0084	0.020
Oesophagus	0.0068	0.0088	0.021
Ovaries	0.0082	0.011	0.025
Pancreas	0.013	0.017	0.042
Red marrow	0.0064	0.0079	0.018
Skin	0.0042	0.0051	0.013
Spleen	0.020	0.028	0.066
Testes	0.0057	0.0075	0.018
Thymus	0.0068	0.0088	0.021
Thyroid	0.0056	0.0073	0.019
Uterus	0.010	0.013	0.029
Remaining organs	0.0067	0.0085	0.020
Effective dose (mSv/MBq)	**0.013**	**0.017**	**0.037**

Absorbed doses: ^{131}I- mIBG

	Absorbed dose per unit activity administered (mGy/MBq)		
Organ	Adult	15 years	5 years
Adrenals	0,17	0.23	0.45
Bladder	0.59	0.73	1.70
Bone surfaces	0.061	0.072	0.18
Breast	0.069	0.069	0.18
Small intestine	0.074	0.091	0.24
Stomach	0.077	0.093	0.25
ULI wall	0.080	0.096	0.26
LLI wall	0.068	0.081	0.21
Heart	0.072	0.091	0.20
Kidneys	0.12	0.14	0.30
Liver	0.83	1.10	2.40
Lungs	0.19	0.28	0.60
Salivary glands	0.23	0.28	0.51
Ovaries	0.066	0.088	0.23
Pancreas	0.10	0.13	0.32

Red marrow	0.067	0.083	0.19
Spleen	0.49	0.69	1.70
Testes	0.059	0.070	0.19
Thyroid	0.050	0.065	0.18
Uterus	0.080	0.10	0.26
Other tissues	0.062	0.075	0.19
Effective dose (mSv/MBq)	**0.14 mSv/MBq**	**0.19 mSV/MBq**	**0.43 mSv/MBq**

Radiopharmaceutical meta-[$^{123/131}$ I] iodobenzylguanidine (mIBG)

mIBG is an analog of noradrenaline and guanethidine

Preparation

Radioactive mIBG is usually a ready for use licensed radiopharmaceutical which is sold by companies. The compound is radioiodinated by isotope exchange and distributed to nuclear medicine centres where no additional preparation is required

Quality control

Extensive quality control should normally be performed on the preparation by the producer before shipping. Departments receiving mIBG should assay the product with a calibrated ionisation chamber.

Gamma camera quality control

A strict quality control programme should be routinely performed according to the rules of each country, as stated in EANM guidelines on quality control [20].

Image acquisition

1) Instrumentation

Gamma camera: a single (or multiple) head gamma camera with a large field of view is necessary to acquire planar and/or tomographic (SPECT) images. Fusion images with SPET/CT hybrid systems can improve diagnostic accuracy. The use of modern SPECT/CT systems is highly recommended.
Collimator: ^{131}I-mIBG: high energy, parallel hole. ^{123}I-mIBG: low energy, high resolution.
However, ^{123}I decay includes a small fraction (less than 3%) of high-energy photons (346,440,505,529,539 keV) that can scatter in the collimator or experience septal penetration, both

phenomena that degrade image quality when acquisition is performed with low energy collimators. Medium energy collimators may thus improve image quality, by reducing scatter while preserving acceptable sensitivity (i.e. without increasing acquisition time).
Given the variability in collimator characteristics and design from different manufacturers, the choice of the collimator providing best image quality for ^{123}I-mIBG imaging should therefore be left to each Nuclear Medicine department.

2) Acquisition modality
Timing of imaging: scanning with ^{131}I-mIBG is performed 1 and 2 days after injection and can be repeated at day 3 or later. Scanning with 123I-mIBG is performed between 20 and 24 h. Selected delayed images (never later than day 2) may be useful in case of equivocal findings at day 1.The patient should be placed in the supine position. Views: whole body imaging with additional limited-field images or spot images. Limited-field or spot images are recommended especially in paediatric patients.
Imaging field:
^{131}I-mIBG: total body scan (speed 4 cm/sec) or both anterior and posterior limited-field or static spot views (>150 kcounts) of head, neck, chest, abdomen, pelvis, upper and lower extremities.
^{123}I-mIBG: total body scan (speed 5 cm/sec) or both anterior and posterior limited-field or static spot views (about 500 kcounts or 10 minutes acquisition) of head, neck, chest, abdomen, pelvis, upper and lower extremities. In neuroblastoma patients for head imaging both antero-posterior and lateral views are recommended.
In order to reduce acquisition time, for upper and lower limbs, spot views, 75-100 kcounts could be sufficient for ^{123}I-mIBG.
Spot views are often superior to whole body scans in contrast and resolution, especially in low count regions, and are therefore preferable in young children (who may also better bear this exam, longer in total time, but with interruptions in between). However, the relative uptake intensity in organs and lesions is more accurately depicted in whole body images.
Cooperative patients should be encouraged to void prior to imaging. It is recommended to start the exam with abdomen/pelvis spot views when performing multiple spot views of the body.
Image parameters
A pixel size of about 2mm requires a 256x256 matrix or 128x128 matrix with zoom.
For quantification: different levels of approximation can be adopted to correct for attenuation. The basic method of geometric mean between conjugate views can be improved using a standard source-phantom based method.

Optional images

Single photon emission tomography (SPECT) can improve the diagnostic accuracy. SPECT is useful mainly in cases where uncertainty exists regarding the localisation and interpretation of the tracer uptake:

-SPECT can improve characterization of small lesions (soft tissue metastases and residual tumour uptake), that may not be evident on planar images, especially in case of superimposed areas of high physiological (i.e. liver, bladder) or pathological (i.e. primary tumour) uptake;

-SPECT can help distinguishing between soft tissue and skeletal lesions, especially in the spine (that is fundamental in tumour grading);

SPECT can also facilitate the comparison with anatomical imaging: the integration of anatomical and scintigraphic imaging is essential in clinical practice in order to interpret and identify the topographic location and the nature of some doubtful lesions. For these reasons the superimposition, fusion or co-registration of nuclear medicine with CT or MR anatomical images have a significant impact on the diagnostic accuracy.

This is particularly true in the context of growing availability of hybrid SPECT-CT modality[20]. Thus, whenever possible, SPECT should performed, even if in young children sedation may be required.

Acquisition parameters depend on the equipment available and the radioisotope used.

Ideally, SPECT should cover pelvis, abdomen and thorax.

Generally, SPECT protocol consists in 120 projections, in 3-degree steps, in continuous or step and shoot mode, 25-35 seconds per step. Data are acquired on a 128x128 matrix. In case of non-cooperative patients, it is possible to reduce acquisition time using 6 degree steps, or a 64x64 matrix with shorter time per frame[22,23]. In SPECT/CT imaging the CT image should be taken with high resolution in order to have a better characterization of the anatomical surroundings. These images are also important for dosimetry calculations (uptake and size of the tumour).

Image processing

No particular processing procedure is needed for planar images.

In case of SPECT one should take into account the different types of gamma camera and software available. Careful choice of processing parameters should be adopted in order to optimize image quality.

Iterative reconstruction with a low pass post-filter often provides better images than filtered back projection. Any reporting should clearly state the methodology adopted for image processing and quantification

Interpretation criteria

To evaluate mIBG scintigraphy the following items should be taken into account:

- clinical issue raised in the request for mIBG scintigraphy
- clinical history of the patient
- presence of symptoms or syndrome
- topographical localisation of the uptake according to other imaging data
- uptake in non-physiological areas (this is suspicious for a neuroendocrine tumour or metastatic localisations)
- intensity and features of the tracer uptake (mIBG uptake may be observed both in benign and malignant tumours)
- clinical correlation with any other data from previous clinical, biochemical and morphological examinations
- causes of false negative results (lesion size, tumour biology, physiological uptakes masking cancer lesions, pharmaceutical interference, etc.)
- causes of false positive results (artefacts, uptake due to physiological processes, benign uptakes, etc.).

Physiological distribution of mIBG

The uptake of radiolabelled mIBG in different organs depends on catecholamine excretion and/or adrenergic innervation. After intravenous injection approximately 50% of the administered radioactivity appears in the urine by 24 h, and 70–90% of the residual activity is recovered within 48 h. Since mIBG is excreted in the urine, the bladder and urinary tract show intense activity. mIBG is normally taken up mainly by the liver; smaller uptake is described in spleen, lungs, salivary glands, skeletal muscles and myocardium. Normal adrenal glands are usually not seen, but faint uptake may be visible 48–72 h after injection in up to 15% of cases when using ^{131}I-mIBG. However normal adrenals can be visualized in up to 75% of cases if using ^{123}I-mIBG (ref). mIBG may accumulate to a variable degree in nasal mucosa, lungs, gallbladder, colon and uterus. Free iodine in the bloodstream may cause some uptake in the digestive system and in the thyroid (if not properly blocked). No skeletal uptake should be seen. Extremities show only slight muscular activity.

In children, brown fat uptake is usually quite symmetric, along the edge of the trapezius muscles[26]. However, it is seen also over the top of each lung, and along either side of the spine to the level of the diaphragm, in children and in adults [1]

Pathology

mIBG soft tissue uptake is observed in primary tumour and in metastatic sites including lymph nodes, liver, bone and bone marrow. Increased uptake in the skeleton (focal or diffuse) is indicative of bone marrow involvement and/or skeletal metastases.

Sources of error [27,28]

- clinical and biochemical findings that are unknown or have not been considered
- insufficient knowledge of physiological mIBG biodistribution and kinetics
- small lesions, below the resolution power of scintigraphy
- incorrect patient preparation (e.g. pelvic views cannot be correctly interpreted if the patient has not voided before the acquisition)
- lesions close to the areas of high physiological or pathological uptake
- tumour lesions that do not uptake mIBG (e.g. changes in differentiation, necrosis, interfering drugs, etc.)
- patient motion (mainly in children)
- increased diffuse physiological uptake (hyperplastic adrenal gland after contralateral adrenalectomy)
- increased focal physiological uptakes (mainly in the urinary tract or bowel)
- thyroid activity (if no adequate thyroid blockade is performed)
- urine contamination or any other external contamination (salivary secretion).

Reporting

The nuclear medicine physician should record all information regarding the patient, type of examination, date, radiopharmaceutical (administered activity and route), concise patient history, all correlated data from previous diagnostic studies, and the clinical question.

The report to the referring physician should describe:

- whether the distribution of mIBG is physiological or not;
- all abnormal areas of uptake (intensity, number and site; if necessary, retention of mIBG over time);
- comparative analysis: the findings should be related to any previous information or results from other clinical or instrumental examinations;
- interpretation: a clear diagnosis of malignant lesion should be made if possible, accompanied by a differential diagnosis when appropriate;
- comments on factors that may limit the accuracy of scintigraphy are sometimes important (lesion size, artefacts, interfering drugs, etc.).

Should gaining of definitive diagnosis require additional diagnostic examination or an adequate follow-up, this must be recommended.

Standardised form

In order to evaluate the prognosis at diagnosis and to quantify treatment response in neuroblastoma, different scoring systems have been proposed [29, 30,31,32].

Issues requiring further clarification

- Radiolabelled mIBG and pentetreotide can be used to visualise different neuroendocrine tumours. In some of these tumours both modalities show a high diagnostic accuracy. Further investigations are needed to accurately define the clinical indications of the single studies. This evaluation should be based on diagnostic efficacy, costs, and clinical impact on patient management [33,34].

Other imaging modalities

FDG-PET visualizes some neuroendoendocrine tumours. However the FDG uptake is satisfactory only in cancer with high metabolic and proliferative rate. Several false negative results are described in well-differentiated neoplasms [35]. In neuroblastoma, FDG-PET has been studied in comparison with ^{123}I-mIBG. ^{123}I-mIBG was more sensitive for bone localizations, whereas FDG-PET seemed to be more reliable for soft tissue lesions. [36]. These approaches showed a poor concordance, therefore the two techniques could be used as complementary, although no definitive data are available [36-39].

Some studies reported experience, in tumors known to be mIBG avid, with PET radiopharmaceuticals like ^{124}I-mIBG, ^{18}F-L-DOPA, ^{18}F-Dopamine [40,41] and ^{68}Ga-DOTA-peptides. Reported data are too limited to draw any obvious conclusion on their possible use,

although there is a strong rationale to forecast a future role of these radiopharmaceuticals in the clinical practice.

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The European Association has written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These general recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialised practice setting may be different than the spectrum usually seen in a more general setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, resource available for patient care may vary greatly from one European country or one medical facility to another. For these reasons, guidelines cannot be rigidly applied.