SPECT-CT assessment of NETs

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Background

- Neuroendocrine tumors (NET) are rare (2–5/100000 inhabitants)
- Usually slow growing
- NETs poses heterogeneous biology
- Can range from benign lesions to highly aggressive cancers
Background

- NETs have endocrine capability of hormone production
- Similar to nerve cells (have neuroamine uptake mechanisms)
- Overexpress somatostatin receptors on cell membranes, with SSR subtype 2 being predominant
- Other biomarkers such as dopamine receptors are also overexpressed
- These features are the basis of the clinical use of specific radiolabelled ligands for imaging and therapy
Neuroendocrine tumours

NETs are derived from APUD (amine precursor uptake and decarboxylation) system cells

Gastroenteropancreatic tumours (GEP):
- Carcinoids
- Gastrinoma
- Insulinoma
- Glucagonoma
- VIPoma
- Somatostatinoma

Sympathoadrenal system tumours:
- Pheochromocytomas
- Neuroblastomas
- Paragangliomas
- Ganglioneuroblastomas
- Medullary carcinoma of the thyroid
- Small-cell lung cancers
- Merkel cell carcinoma
- Pituitary adenomas
Radiopharmaceuticals

- $^{123/131}$I-MIBG
- PET radiopharmaceuticals like $^{124}$I-MIBG, $^{18}$F-L-DOPA, $^{18}$F-Dopamine
- Somatostatin analogs
  - $^{111}$In-pentetreotide (OctreoScan®)
  - $^{99m}$Tc-labelled (depreotide, tektrotyd, etc.)
  - $^{68}$Ga-labelled (DOTA-TOC, DOTA-NOC, DOTA-TATE)
- $^{18}$F-FDG PET only in tumours with high proliferative activity
MIBG

- Metaiodobenzylguanidine (MIBG) is an analog of noradrenaline and guanethidine
- Was the first radiopharmaceutical used to specifically localize catecholamine-secreting tumours (pheochromocytomas, neuroblastomas, paragangliomas, ganglioneuroblastomas)
- Other neuroendocrine tumours (carcinoids, medullary thyroid carcinoma, Merkel cell tumours, MEN2 syndromes) can also be visualised
$^{123}$I-MIBG

- $^{123}$I emits a gamma photon (159 keV)
- T1/2 - 13.13 hours
- Lower radiation burden permits to inject higher activities of $^{123}$I-MIBG
- Scanning results are usually available within 24 hours
- More suitable for imaging (especially when using SPECT or SPECT-CT)
$^{131}$I-MIBG

- $^{131}$I emits a principal gamma photon of 364 keV and beta particles with mean energies of 1920 keV
- $T_{1/2} = 8.04$ days
- Imaging with $^{131}$I-MIBG usually requires delayed images for optimal target to background ratios
- Ready available
- In spite of not ideal physical characteristics $^{131}$I-MIBG is widely used for most routine applications mainly in adult patients
- $^{131}$I-MIBG may be preferred when planning therapy
Indications

• Detection, localisation, staging and follow-up of neuroendocrine tumours and their metastases

• Study of tumour uptake and residence time in order to decide and plan a treatment with high activities of radiolabelled MIBG

• Evaluation of tumour response to therapy by measuring the intensity of MIBG uptake and the number of focal MIBG uptake sites

• Confirmation of suspected tumours derived from neuroendocrine tissue

• $^{131}$I/$^{123}$I-Metaiodobenzylguanidine (MIBG) Scintigraphy – EANM Procedures Guidelines For Tumour Imaging
Patient preparation

• Withdrawal of drugs interfering with MIBG
• Thyroid blockade 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 iodate 170 mg
  – Potassium iodide (KI) 130 mg
  – Lugol 1% solution 1 drop/kg (max of 20 drops x 2 a day)
  – Potassium perchlorate (400 mg) is generally used in case of emergency or in patients allergic to iodine on the day of the MIBG injection
• In children, the dose should be reduced according to *EANM Paediatric Committee guidelines*
Drugs interfering with MIBG uptake

- Combined alpha/beta adrenergic blocker (Labetalol)
- Adrenergic neurone blockers (Guanethidine, Reserpine)
- Calcium channel blockers (Nicardipine, Nifedipine, etc.)
- Inotropic sympatho-mimetics (Dobutamine)
- Vasoconstrictor sympathomimetics (Ephedrine)
- Sympathomimetics (Salbutamol)
- Systemic and local nasal decongestants, compound cough and cold preparations (Pseudoephedrine, Phenylephrine)
- Sympathomimetics for Glaucoma (Brimonidine)
- Antipsychotics (neuroleptics) (Chlorpromazine)
- Sedating antihistamines (Promethazine)
- Opioid analgesics (Tramadol)
- Tricyclic anti-depressants (Amitriptyline)
- Tricyclic-related anti-depressants (Maprotiline)
- CNS Stimulants (Amphetamines, Cocaine, Caffeine)
Administration of MIBG

• Tracer is administered by slow intravenous injection (at least 5 minutes) in a peripheral vein.

• The activity administered to adults should be:
  – for $^{131}$I-MIBG 40-80 MBq
  – for $^{123}$I-MIBG 400 MBq

• The activity administered to children should be consulted in the *Guidelines for Radioiodinated MIBG Scintigraphy in Children*. 
Administration of MIBG

• Injection via central venous catheters must be avoided if possible (imaging artefacts, potential adverse effects)

• Adverse effects of MIBG (tachycardia, vomiting, abdominal pain) are related to pharmacologic effects of the molecule and are very rare when slow injection is used

• Patients should drink large volumes of fluids following MIBG injection and should void immediately prior the study
Image acquisition

• Single (or multiple) head gamma camera with a large field of view

• Collimator:
  – $^{131}$I-MIBG high energy, parallel hole
  – $^{123}$I-MIBG low energy, high resolution or medium energy

• Matrix: 256x256 or 128x128 with zoom
Scanning protocol with $^{123}$I-MIBG

- Scanning is performed 20-24 h post injection. Selected delayed images (never later than 48 h) may be useful.
- Whole body scan (speed 5 cm/s) or both anterior and posterior limited-field or static spot views of head, neck, chest, abdomen, pelvis (~ 500 kcounts or 10 min acquisition), upper and lower extremities (~ 75-100 kcounts) are acquired.
- In neuroblastoma patients for head imaging both antero-posterior and lateral views are recommended.
- Spot views are preferable in young children.
Scanning protocol with $^{131}$I-MIBG

- Scanning is performed at day 1 and day 2 after injection and can be repeated at day 3 or later
- Whole body scan (speed 4 cm/s) or both anterior and posterior limited-field or static spot views (>150 kcounts) of head, neck, chest, abdomen, pelvis, upper and lower extremities
SPECT & SPECT/CT

Can improve the diagnostic accuracy in case of:

– small lesions (soft tissue metastases and residual tumour uptake)

– in superimposed areas of high physiological (liver, bladder) or pathological (primary tumour) uptake

– distinguishing between soft tissue and skeletal lesions, especially in the spine (fundamental in tumour grading)

– identifying and interpreting the topographic location and the nature of some doubtful lesions
SPECT/CT

• Superimposition, fusion or co-registration of scintigraphic images with CT or MR can be performed

• Whenever possible, SPECT or SPECT/CT should performed, even if in young children sedation may be required

• SPECT (SPECT/CT) should cover pelvis, abdomen and thorax
SPECT acquisition parameters

- 120 projections, in 3-degree steps, 25-35 s per step
- In continuous or step and shoot mode
- 128x128 matrix
- It is possible to reduce acquisition time using 6-degree steps, or a 64x64 matrix with shorter time per frame
- In SPECT/CT imaging the CT image should be taken with high resolution in order to have a better characterization of the anatomical surroundings
Physiological distribution of MIBG

• The uptake of MIBG in different organs depends on catecholamine excretion and/or adrenergic innervation.

• MIBG is normally taken up by the liver, spleen, salivary glands, skeletal muscles and myocardium.

• MIBG may accumulate to a variable degree in nasal mucosa, lungs, gallbladder, colon and uterus.

• 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 and in up to 75% of cases if using $^{123}$I-MIBG.
Physiological distribution of MIBG

- Free iodine may cause some uptake in the digestive system and in the thyroid (if not properly blocked)
- Quite symmetric uptake might be seen, along the edge of the trapezius muscles, over the top of each lung, and along either side of the spine to the level of the diaphragm
- MIBG excreted in the urine, so the bladder and urinary tract show intense activity
- No skeletal uptake should be seen
Physiological $^{131}$I-MIBG distribution
Pathologic uptake of MIBG

- 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
Neuroblastoma
Neuroblastoma
NETs
Medullary thyroid carcinoma
Pheochromocitoma
Malignant pheochromocitoma
Sources of error

- Insufficient knowledge of physiological MIBG biodistribution and kinetics
- Small lesions, below the resolution power of scintigraphy
- Incorrect patient preparation
- Lesions close to the areas of high physiological or pathological uptake
- Tumour lesions that do not uptake MIBG (changes in differentiation, necrosis, interfering drugs, etc.)
Sources of error

• 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)
Somatostatin receptor scintigraphy

- Current guidelines recommend somatostatin receptor scintigraphy (SRS) with $^{111}$In-diethylenetriaminepentaacetic acid-octreotide (Octreoscan) for evaluation of the extent of NET.

- Routine use of SPECT and particularly SPECT/CT has significantly improved localisation of tumour sites and evaluation of somatostatin receptor (SSTR) expression, which is important for predicting the likelihood of response to somatostatin analogs (SSA).
Mechanism of $^{111}$In-DTPA octreotide uptake

• After injection, $^{111}$In-octreotide follows receptor-mediated internalization and degradation to the final metabolite in lysosomes.

• This metabolite is not capable of passing through cell membranes and, therefore, stays in the lysosomes, causing the long intracellular retention time of $^{111}$In.

• This internalization process and appropriate distribution profile in humans of $^{111}$In-octreotide is essential for successful SRS and radionuclide therapy.
Indications

• Localise primary tumours and detect sites of metastatic disease (staging)
• Follow up patients with known disease to detect residual, recurrent or progressive disease (re-staging)
• Monitor the effects of therapy (surgery, radiotherapy, chemotherapy or somatostatin analogue therapy)
• Select patients for peptide receptor radionuclide therapy
• Obtain a prognostic parameter for the response of subsequent therapy

\textit{111 In-pentetreotide scintigraphy: EANM procedure guidelines for tumour imaging}
Patient preparation

- Discontinue “cold” octreotide therapy (?)
- Laxative prior to test and between 24 and 48 h post injection
- Good hydration before and after injection
- The recommended activity of $^{111}$In-pentetreotide is $111\text{--}222$ MBq
- For SPECT or SPECT/CT acquisitions $\geq 200$ MBq
Image acquisition

- A large field of view gamma camera
- Collimator: medium-energy, parallel hole
- Energy window: $^{111}$In photopeaks (172 and 245 keV)
- Images should be acquired at 4 & 24 h or 24 & 48 h post-injection (the same protocol)
- It is important to acquire two sets of images, with at least one SPECT acquisition
- Planar images: both anterior and posterior of head, neck, chest, abdomen, pelvis and lower extremities (15 min per view)
- Whole body scan (speed 3 cm/min) in anterior and posterior projections
SPECT acquisition

- 120 projections, in 3-degree steps, 45 s per step
- In continuous or step and shoot mode
- 64×64 matrix
- SPECT studies are preferably performed 24 h after injection of the radiopharmaceutical
- Co-registered CT can be used for attenuation correction and may improve the localisation of somatostatin receptor expressing lesions
Physiological $^{111}\text{In}$-octreotide distribution

- The visualization of the liver, spleen, pituitary, thyroid and kidneys occurs because of receptor binding.
- Stimulated adrenal glands may be faintly visualised.
- Slight symmetrical tracer uptake in the breast region.
- Other organs are shown at different times as a result of the clearance of $^{111}\text{In}$-octreotide: gall bladder, bowel, renal collecting system, ureters and bladder.
Physiological $^{111}$In-pentetreotide distribution
Sources of error

- Physiological colon activity may be interpreted as intestinal lesions
- Normal gall bladder activity may be confused with liver metastases
- Diffuse pulmonary or pleural accumulation can be observed after radiation therapy to the thoracic area or following bleomycin therapy
- The tracer may accumulate in areas of recent surgery and at colostomy sites
Sources of error

- Variable tumour differentiation and heterogeneous expression of somatostatin receptor subtypes may influence tumour detectability.
- Liver metastases from neuroendocrine tumours are sometimes difficult to detect.
- Positive scintigraphy with $^{111}$In-octreotide reflects the presence of an increased density of somatostatin receptors rather than malignant disease.
- Positive scintigraphic results require further evaluation.
Diseases expressing somatostatin receptors

Tumours with low expression of receptors:

- Breast carcinoma
- Melanoma
- Lymphomas
- Prostate carcinoma
- Non-small cell lung cancer
- Sarcomas
- Renal cell carcinoma
- Differentiated thyroid carcinoma
- Astrocytoma
- Meningioma

Non-neoplastic diseases:

- Autoimmune diseases
- Granulomas
- Thyroid-associated ophthalmopathy
- Post-radiation inflammatory disease
- Bacterial infections
NETs
$^{99m}$Tc-depreotide

- $^{99m}$Tc-depreotide (NeoTect®) was designed for identification of somatostatin receptor-bearing pulmonary masses in patients without underlying malignancy presenting with pulmonary lesions on CT and/or chest x-ray which are highly suspicious for malignancy.

- $^{99m}$Tc-depreotide sensitivity (93%) and specificity (88%) in the detection of non-small cell cancer in patients with solitary pulmonary nodules is favourably comparable with that of $^{18}$F-FDG PET.
\( {^{99m}}\text{Tc-depreotide} \)

- \( {^{99m}}\text{Tc-depreotide} \) preferentially binds to SSTR 2, SSTR 3 and SSTR 5
- Although, affinity to SSTR 2 is less pronounced than that of \( {^{111}}\text{In-octreotid} \)
- Compared with \( {^{111}}\text{In-ctreotid} \) scintigraphy \( {^{99m}}\text{Tc-depreotid} \) shows a significantly higher non-specific uptake in lungs, liver and bone marrow
Imaging with $^{99m}$Tc-depreotide

- Imaging is performed 1 and 4 hours after injection of 700-750 MBq of $^{99m}$Tc-depreotide
- Whole body scan in anterior and posterior projections
- SPECT or SPECT-CT of the chest or region of interest
Physiological $^{99m}$Tc-depreotide distribution
Bronchogenic carcinoid
Papillary thyroid carcinoma, rising Tg, negative iodine scan
$^{99\text{m}}$Tc-tektrotyd

- $^{99\text{m}}$Tc-tektrotyd ($^{99\text{m}}$Tc-EDDA-HYNIC-TOC)
- Binds to SSTR 2 with high affinity, SSTR 3 and SSTR 5 with low affinity
Imaging parameters

• Light diet on the day before the study, fasting prior to injection
• Imaging is performed 1 and 4 hours after injection of 700-950 MBq of $^{99m}$Tc-tektrotyd
• Whole body scan in anterior and posterior projections
• SPECT or SPECT-CT of the region of interest
Physiological $^{99m}$Tc-tektrotyd distribution
Metastatic carcinoid
Accidental finding
Physiological $^{68}\text{Ga}$-DOTA-TATE distribution
Paraganglioma
Metastatic carcinoid
Take home message

SPECT & SPECT/CT can improve the diagnostic accuracy in case of:

– small lesions (soft tissue metastases and residual tumour uptake)

– in superimposed areas of high physiological (liver, bladder) or pathological (primary tumour) uptake

– distinguishing between soft tissue and skeletal lesions, especially in the spine (fundamental in tumour grading)

– identifying and interpreting the topographic location and the nature of some doubtful lesions
Summary

- NETs are very heterogenic group of tumours
- NETs have capability of hormone production, overexpress various receptors on their cell membranes, have neuroamine uptake mechanisms
- On these features the imaging with various specific radiolabelled ligands is based
- One of main goals of this imaging is selection of the most suitable radiopharmaceutical for radionuclide therapy
67-y-old female with NET

111In-octreotide

99mTc-depreotide

Post therapy scan

90Y-DOTA-octreotate
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