ESMO ADVANCED COURSE ON
Individualising the therapeutic approach in patients with NENs: Role of Nuclear Medicine

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DISCLOSURES

Consulting or Advisory Role | Therasphere, AAA, AML

Speakers’ Bureau | PrimeOncology, Therasphere, AAA, Jansen
Aims- Nuclear Imaging in neuroendocrine neoplasm imaging

- Molecular Imaging tracers in NET
- Why PET CT- evolution in tracer and technology
- Common Pit falls
- Future
NENs | Spectrum of Disease(s)

- **G1**
  - Mitotic activity (Ki-67 or MIB-1) < 2%

- **G2**
  - Increasing grade
  - Site of primary
  - Functional vs. non-functional
  - Anatomical site of origin
  - Progressive vs. stable

- **G3**
  - Mitotic activity (Ki-67 or MIB-1) 20%--70%+

- **Malignant**
Investigating NENs

Why, what and when: Factors that dictate NEN management and imaging

1. Grade
2. Primary
3. Liver only
4. Functional
5. Progressive
6. Therapy options: PRRT?

Management led by specialist NEN MDT
Nuclear Medicine = Molecular Imaging

“Molecular imaging is aimed at the exploitation of specific molecules as the source of image contrast”

Aims:
- Earlier detection and characterization of disease (“molecular signature” prior to irreversible damage)
- Understanding of underlying biology
- Selection of specific treatment option for targeted therapy
- Concept of THERANOSTICS nuclear medicine/molecular imaging ideally set for this dual role
Theranostics- Diagnosis and Therapy

*Theranostics* publishes innovative research articles reflecting the fields of *in vitro* diagnostics and prognostics, *in vivo* molecular imaging, molecular therapeutics, image-guided therapy, biosensors, system biology and translational medicine, personalized medicine and a broad spectrum of biomedical research that can be applied to future theranostic applications.

Simplistically-  ‘if we can see (detect) it we can treat (target) it

Nuclear medicine/molecular imaging ideally set for this dual role
Radionuclide Tracer

Key aspect of nuclear medicine imaging - labelled radiotracers

Octreotide is a somatostatin analogue
If we can see it, we can treat it!
Patient as the image source: Nuclear medicine imaging modalities

SPECT Camera

PET Camera
Hybrid Imaging
Hybrid imaging systems

SPECT/ MDCT

PET/ MDCT
Hybrid Imaging

Hybrid imaging enhances image interpretation and diagnostic accuracy.

[18F]FDG PET/CT
Cervical lymph node metastasis

Anatomical Location
Size
Density

Images

Fusion

Functional Time-course of metabolism
Aims- Nuclear Imaging in neuroendocrine neoplasm imaging

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NET Radionuclide Molecular Imaging

- **Receptors**
  - Annexin V, **Sst 2, 1, 5**
- **Proliferation**
  - FLT
- **Oxygenation**
  - FAZA, ATSM
- **Metabolic activity**
  - FDG, MIBG, FDOPA
- **Angiogenesis**
  - Integrins
- **Genetic mechanisms**
  - FIAU
Somatostatin receptors part of G protein sub group- **Agonist imaging**

- Structurally related membrane glycoproteins- five subtypes of human somatostatin receptors have been cloned.
- Somatostatin analogue octreotide (agonist) binds with high affinity subtypes 2 and 5.
- The expression of somatostatin receptors 2 and 5 is present in 70–90% of carcinoid—especially in **G1 and G2 tumours**
Tumours/disease that may be detected by somatostatin receptor scintigraphy include the following:

Gastroenteropancreatic NET tumors: Carcinoid tumors, gastrinoma, insulinoma, glucagonoma, vasoactive intestinal polypeptide secreting tumor [VIPoma], and nonfunctioning gastroenteropancreatic tumors.

Astrocytomas
Benign and malignant bone tumours
Breast carcinoma
Differentiated thyroid carcinoma
Lymphoma (Hodgkin and non-Hodgkin)
Meningioma
Non-small cell lung carcinoma
Prostate carcinoma
Renal cell carcinoma
Sarcomas
Autoimmune diseases (eg, rheumatoid arthritis, Graves disease, and Graves ophthalmopathy)
Bacterial pneumonia
Cerebrovascular accident
Fibrous dysplasia
Granulomas (eg, tuberculosis and sarcoid)
Radiation pneumonitis

Medullary thyroid carcinoma
Melanoma
Merkel cell tumor of the skin
Paraganglioma/adrenal medullary tumors
Pituitary adenomas
SCLC
### Case 1 - 60 yr male

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>1. Grade</td>
<td>? Grade 1</td>
</tr>
<tr>
<td>2. Primary</td>
<td>SB</td>
</tr>
<tr>
<td>3. Liver only</td>
<td>Not involved</td>
</tr>
<tr>
<td>4. Functional</td>
<td>No</td>
</tr>
<tr>
<td>5. Progressive</td>
<td>No</td>
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<tr>
<td>6. PRRT?</td>
<td>? Future</td>
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Comprehensive staging by DOTATOC: Theranostic option of choice = Radical curative surgery G1 SB NEN
Case 2- 46 yr female

- Grade: Grade 2
- Primary: CUP/SB
- Liver only: No
- Functional: Yes
- Progressive: Yes
- PRRT?: ??

Theranostic option of choice = PRRT

177Lu DOTATATE
68Ga DOTATOC
NEN Radionuclide Molecular Imaging

- Receptors
  - Annexin V, Sst 2, 1, 5
- Proliferation
  - FLT
- Oxygenation
  - FAZA, ATSM
- **Metabolic activity**
  - FDG, MIBG, FDOPA
- Angiogenesis
  - Integrins
- Genetic mechanisms
  - FIAU
Tumour Glucose (FDG) Metabolism

- Increased glycolysis (Warburg effect (1920)) and increased glucose intake
- Upregulation of Glut-transporters and hexokinase (up to 80%) by hypoxia/HIF-1α
- Upregulation due to oncogenes (src, ras, c-myc, p53) and growth factors, cytokines independent of hypoxia (proliferation-induced)
Conclusion: 18F-FDG PET/CT had no clinical impact on G1 NETs and a moderate impact on G2 NETs. However, in poorly differentiated NETs, 18F-FDG PET/CT plays a significant clinical role in combination with 68Ga-DOTATATE. 68Ga DOTATATE SUVmax relates to grade and Ki-67 and can be used prognostically.
Case 3 - 15 yr female

1. Grade: NEC Grade 3
2. Primary: CUP
3. Liver only: No
4. Functional: No
5. Progressive: Yes
6. PRRT?: ?? Not an option

Theranostic option of choice= Chemotherapy (cis-etop)
Case 4: Unknown primary/possible breast carcinoma

Liver MRI b800 Diffusion images

FDG MIP image

Ga68 DOTATOC MIP image

DOTATOC 24 months later
Uninformed primary/possible breast carcinoma

- Final diagnosis: Recurrent well differentiated typical lung NEN resected 12 years ago presenting with breast mass! Dual tracer imaging can help with the decision making process.
Molecular Imaging in NEN

Role of SST/DOTA SST peptides
- Staging and assessment of receptor status in G1 and G2 NEN (? G3)
- Improves accuracy
  - Detection of primary tumour
  - Nodal disease
  - Skeletal metastases
- VOLUME and EXTENT of disease
- Comprehensive management plan

Role of FDG
- Staging and assessment G3 NEN
- Additional imaging to complement SST DOTA- atypical clinical behaviour
- Improves accuracy
  - Detection of primary tumour
  - Nodal disease
  - Skeletal metastases
- VOLUME and EXTENT of disease
- Comprehensive management plan
Aims- Nuclear Imaging in neuroendocrine neoplasm imaging

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Hybrid Imaging Systems

SPECT/MDCT

PET/MDCT
Evolution of NEN Imaging: PET in NEN

$^{111}$In-Octreotide-SPECT CT

NET PET imaging- PET CT
Evolution towards PET CT in NEN

Octreoscan SPECT CT- Metastatic NET. Ga68 DOTA SSTR PET CT- Primary site, nodal liver and bone metastases
How Do $^{68}$Ga-DOTA Peptides Perform?

- Comparison of 3 imaging modalities:
  - $^{68}$Ga-DOTATOC PET,
  - $^{99m}$Tc-Labeled hydrazinonicotinyl-Tyr3-octreotide SPECT
  - CT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PET, % (n)</th>
<th>SPECT, % (n)</th>
<th>CT, % (n)</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>97 (69/71)</td>
<td>52 (37/71)</td>
<td>61 (41/67)</td>
</tr>
<tr>
<td>Specificity</td>
<td>92 (12/13)</td>
<td>92 (12/13)</td>
<td>71 (12/17)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>96 (81/84)</td>
<td>58 (49/84)</td>
<td>63 (53/84)</td>
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Implications for Patients

Planar/SPECT

48 HOURS

SPECT CT

24 HOURS

PET-CT

90 MINUTES

Clear benefits of $^{68}$Ga-DOTA PET
Results:

- $^{68}$Ga-PET imaging changed management in 36 patients (70.6%), who were subsequently deemed suitable for peptide receptor–targeted therapy

Conclusion:

- In patients with negative or equivocal $^{111}$In-DTPA-octreotide findings, $^{68}$Ga-DOTATATE PET identifies additional lesions and may alter management in most cases


UNTIL 2017 ALL THESE DOTA SST PEPTIDES WERE UNLICENSED PRODUCTS
The first licensed Ga-68 DOTA-peptide: technical aspects and clinical impact in PET-imaging

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Identification of GEP-NETs

Bodei L et al. Neuroendocrinology 2015; 101, 1-17

Clear benefits of PET CT
Aims- Nuclear Imaging in neuroendocrine neoplasm imaging

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Case 1: Staging of suspected SB NET
1. Small bowel NET, mesenteric nodal and thyroid metastasis, inflammatory tonsillar uptake

2. Unknown primary NET, serosal small bowel, nodal and thyroid metastases, inflammatory tonsillar uptake

3. Small bowel NET, mesenteric nodal metastasis, synchronous primary thyroid cancer, lymphoma Waldeyer’s ring

4. Small bowel NET, mesenteric nodal metastasis, benign thyroid adenomatoid nodule, inflammatory tonsillar uptake
1. Small bowel NET, mesenteric nodal and thyroid metastasis, inflammatory tonsillar uptake

2. Unknown primary NET, serosal small bowel, nodal and thyroid metastases, inflammatory tonsillar uptake

3. Small bowel NET, mesenteric nodal metastasis, synchronous primary thyroid cancer, lymphoma Waldeyer’s ring

4. Small bowel NET, mesenteric nodal metastasis, benign thyroid adenomatoid nodule, inflammatory tonsillar uptake
Case 2: Known hypervascular pancreatic head tumour
The most likely diagnosis is:

1. Renal Cell Carcinoma
2. Renal NET metastasis
3. Renal lymphoma
4. Calyceal diverticulum
1. Renal Cell Carcinoma
2. Renal NET metastasis
3. Renal lymphoma
4. Calyceal diverticulum
Case 3 – resected pulmonary NET- restaging scan
The most likely diagnosis is:

A. Pancreatic metastasis
B. Splenic hilum splenunculus
C. Intrapancreatic splenunculus
D. Pancreatic primary tumour
The most likely diagnosis is:

A. Pancreatic metastasis
B. Splenic hilum splenunculus
C. Intrapancreatic splenunculus
D. Pancreatic primary tumour
Lesions observed in accessory spleens of 311 patients.

HALPERT B, GYORKEY F.

In a study 3000 autopsies, splenunculus rate 12%
Most <1cm size at splenic hilum or near pancreatic tail
Intrapancreatic accessory spleens rare

Intrapancreatic accessory spleen: A case report and review of the literature

Niroshan Sothilingam, a Toni Leedahl, b Stefan Kriegler, c Rani Kanthan, b and Michael A.J. Moser d, e
- Thyroid carcinoma
- Small cell lung carcinoma
- Lymphoma (Hodgkin’s and non-Hodgkin’s)
Pitfalls

As with FDG, somatostatin receptor PET-CT is non-specific.

Neuroendocrine tumours are a complex tumour group.

Keep an open mind!
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Somatostatin receptors part of G protein sub group- **Antagonist tracers**

**Somatostatin Receptor Antagonists for Imaging and Therapy**
Summary

- Theranostic utilises molecular imaging as a biomarker signal to manage patients.
- Specialist pathology / imaging assessment guides the entire management pathway - G1, G2, G3.
- Molecular Imaging then guides targeted decision making.
- In the vast majority of cases SST PET CT with IV contrast is the imaging modality of choice in G1 and G2 NET (? G3).
- FDG has a limited role but is useful in G3.
- Sequential imaging and MDT review is key to optimising treatment options throughout the patient journey.
- If in doubt utilise both tracers.
- NEN therapy choices especially PRRT is driven by Theranostic principles.
NET Spectrum of Disease(s): Take home message

- **Neuroendocrine tumours**

  - **Benign**
  - **G1**
  - **G2**
  - **G3**
  - **Malignant**

  - Increasing grade
    - <2%-----------------20%-------------------70%+

- **Functional vs. non-functional**
  - Ga DOTA PET
  - (FDG PET)

- **Mitotic activity**
  - (Ki-67 or MIB-1)
Imaging NET

- CT: Lung > MRI > SRS and liver
- MRI: Liver > CT > SRS
- Offers the highest diagnostic potential for assessment of lung and liver involvement in patients with NET
- Not sure if the above statement is entirely true anymore in light of IV contrast enhanced $^{68}$Ga-DOTA (TATE, TOC, NOC) PET-CT: Imaging modality of choice at our centre
Acknowledgements

The Christie

Nuclear Medicine/ CMPE department

Department of Radiology

ENETs NET team
Thank You
The Era of Molecular Imaging and Therapy
NET Radionuclide Molecular Imaging

- Receptors
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- Angiogenesis
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[\textsuperscript{18}F]fluoro-L-DOPA PET in detecting Phaeochromocytomas

14 patients, 17 lesions

18F DOPA PET 100% sensitivity 100% specificity
123 I MIBG 71% sensitivity 100% specificity

18F-FDOPA in NEN

18F-FDOPA most accurate detecting skeletal lesions sensitivity, 100%; specificity, 91%

Becherer et al. 18F-FDOPA PET for neuroendocrine tumors • J Nucl Med 2004; 45:1161–1167