Nuclear Medicine Visits
Neuroendocrine Tumors

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Technologists Are The True Representatives of Nuclear Medicine

- Future of NM Technology is very bright
- PET or Single photon work
- FDG –PET : not ideal for well differentiated tumors (Neuroendocrine, prostate)
- FDG-PET does not help to assess whether certain radio nuclide therapy will be useful or not.
40 year old female

- Previously very healthy, jogger
- 5 years ago got separated from her husband
- Started developing multiple fractures
- Ortho in Hawaii referred her to psychiatrist
Bone Scan
OctreoScan

24 hour scan
Mesenchymal Tumor in the Foot

- Tumor Induced Osteomalacia
- 100 or so cases reported so far
- Mesenchymal tumors produce substance (Phosphotonin) that causes phosphorus loss
- After surgery patient’s biochem returned to normal and no more fractures!!!
- Started jogging again.
- Ref: Lancet. 2002 Mar 2;359:761-3
Neuroendocrine tumors

• Patho-physiology
• OctreoScan
  – Patient preparation and technique
• MIBG
  – Patient preparation and technique
• FDG – PET
• Therapy
Neuroendocrine Tumors

- Origin: Neural Crest.
- Amine Precursor Uptake and Decarboxylation (APUD)
- Produce monoamine transmitters.
- Usually well differentiated.
- Express receptors on cell surface.
Expected Location Of Neuroendocrine Cells

- Thyroid (c cells)
- Adrenal Medulla
- Lung
- Skin (melanocytes)
- Nervous System
- GI Tract
- Pancreas
# Cell Types and Tumor Markers

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Cell Type</th>
<th>Tumor Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>C cells</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Chromaffin Cells</td>
<td>VMA(urine)</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Islet A cells</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Islet B cells</td>
<td>Insulin</td>
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<tr>
<td>Gastrinoma</td>
<td>Non B islet cells</td>
<td>Gastrin</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>Enterochromaffin cells</td>
<td>Serotonin</td>
</tr>
</tbody>
</table>
Other APUDOMAs

- Small Cell lung Ca.
- Merckel cell.
- Pituitary adenoma.
- Parathyroid adenoma.
- Melanoma.
Diagnosis and Treatment

- Diagnosis is on biochemical basis.
- Resection is the definitive management.
Why Image?

- Surgical removal is the treatment
- Primarily for localization.
- Pre and post treatment assessment.
- Radioactive ablative treatment options.
Imaging Options

Octreotide vs. MIBG

When to use FDG-PET?

Tc-99m (V) DMSA: only in Europe

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Octreotide

Octreotide (Sandostatin)

Human Somatostatin

111 In-Pentetreotide (Octreoscan)

I-131 Tyr3-Octreotide

1 Mallinckrodt Medical, St. Louis, MO

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Somatostatin

• 14 Amino acid peptide synthesized in the hypothalamus.
• Suppresses metabolic activity.
  – Inhibits the release of a number of different amine and peptide neurotransmitters and hormones.
• Primary target is cells originating from the neural crest.
Somatostatin Receptors

• Membrane glycoproteins.
• Occur:
  – Anterior pituitary
  – Pancreatic islet cells
  – Thyroid C cells
  – Almost all Neuroendocrine cells
  – Activated lymphocytes
  – Vasa recta of the kidney
OctreoScan

- It is imaging of the receptors on neuroendocrine tumors
- Peptide: and hence clears rapidly from the plasma via urine
- Significant gut uptake and biliary excretion is noted
Protocol or Principle

- Practice makes perfect - but knowledge is better.
Patient Preparation for OctreoScan

- Stop Sandostatin treatment for 3 days
- If on Depot treatment may need to wait for 6-8 weeks
- No other preparation
- In cases of Insulinoma give 5% dextrose while injecting In-111 octreotide
Technique

- 10 micrograms of Pentetreotide labeled with 3-6 mCi In-111
- Unit doses are obtained and administered IV
- Image at 4 and 24 hrs.
- +/- Bowel Prep.
Imaging Protocol (by the manufacturer)

- Collimator: medium energy
- Window: 20% at 174 KeV and 247 KeV
- Planar Images:
  - Whole body scan or Spots of whole body? at 4 and 24 hours
- SPECT images at 24 hours of the area of interest
  - 128x128 x60STOPS
Where to SPECT?

• Know the biochemical marker:
  – Calcitonin = medullary cancer thyroid = SPECT of neck and chest
  – ACTH like substance = Bronchial carcinoid = SPECT chest
  – Increased urinary 5-HIAA = mid gut carcinoid = SPECT abdomen and pelvis.
Indications

• Localize disease.
• Assess metastatic extent.
• Evaluate pre and post treatment.
• Assess for presence of somatostatin receptors for Sandostatin therapy.
Normal Distribution of Octreotide

- Pituitary
- Thyroid
- Spleen
- Liver
- Kidney
- Bladder
- Gallbladder
- Colon

4 hr

24 hr

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Normal OctreoScan distribution with Gallbladder uptake

4 hr

24 hr

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Carcinoid
Vipoma

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Pheochromocytoma
45 yo m with Cushing’s

- Pituitary imaging normal.
- Adrenal hyperplasia on CT/MRI.
Chest CT and MRI
Bronchial Carcinoid
Cushing’s syndrome: ? Ectopic ACTH production
MRI – ?Ectopic ACTH
Bone mets?
In-111 OctreoScan
In-111 OctreoScan SPECT
Paraganglioma with bone mets
Paraganglinoma – primary and mets
50 year old male developed osteomalacia

Pathologic fractures
Phosphate losing.
Sensitivity

- Varies with tumor type due to expression of different subclasses of the somatostatin receptor.
  - Carcinoid  96%.
  - Gastrinoma  100%.
  - Pheochromocytoma 86%.
  - Paraganglioma 100%.
  - Glucagonoma 100%.
  - Decreased sensitivity seen with Insulinoma (60%), neuroblastoma, and medullary thyroid ca.

Pitfalls and Other Positives

- Granulomas (Sarcoid, TB, Wegeners).
- Lymphoma.
- Non small cell lung cancer.
- Breast cancer.
- Meningioma.
- Astrocytoma.
- Nasal and hilar uptake associated with viral URI’s.
Sarcoid
FDG PET
Patient with Cushingoid features
Ectopic ACTH producing tumor?
OctreoScan imaged with SPECT/CT Hawkeye
Function and Anatomy Fusion

• SPECT and CT
• Low end CT versus High end CT
• Low MA 140 KeV and 1.0Cm thick slices do pose problems
• Attenuation correction helps beware of transmission and emission mis-registrations
Wedge resection: Nocardia

- FDG uptake: Infection has higher glucose metabolic rate
- OctreoScan uptake: activated lymphocytes have increased somatostatin receptors
How to Simplify OctreoScan without Compromising Quality

- In-111 Octreotide has excellent plasma clearance at 4 hours
- The Gut uptake increases at 24 hours making interpretation of abdominal findings difficult at 24 hours
Comparison of 4 and 24 Hour SPECT
$^{111}$In-DTPA-Octreotide Scintigraphy in the Detection of Neuroendocrine Tumors

F. Esteves, B. Yaban, R. Halkar, A. Taylor and N. Alazraki

Nuclear Medicine Department
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111In-DTPA-Octreotide Scintigraphy
(4h vs. 24h SPECT)

MIP Images - Anterior abdomen/pelvis

4 hours

24 hours

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\[ ^{111}\text{In-DTPA-Octreotide Scintigraphy} \]
(4h vs. 24h Planar)

Anterior and Posterior Planar Images

4 hours

24 hours

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$^{111}$In-DTPA-Octreotide Scintigraphy
(4h vs. 24h SPECT)

MIP images - Anterior chest/abdomen

Bronchial Carcinoid Metastases

4-hours 24-hours

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MIBG
Meta-iodobenzylguanidine (MIBG)

- Structurally resembles nor epinephrine and Guanethidine (a neurosecretory granule depleting agent).
- Localizes to storage granules in adrenergic tissue of neural crest origin.
- Uptake via active transport Type I amine uptake mechanism.
- Uptake is proportional to the number of neurosecretory granules within the tumor.
MIBG Labeling

- **I-123**
  - 3-10 mCi
  - Image at 6-24 hrs
  - Normal adrenals more often visualized (30%)
  - Improved spatial resolution.

- **I-131**
  - 500 micro Ci
  - Image at 3-7 days.
  - Adrenals less often visualized (faintly seen in 10-20%).
  - Option for Ablative treatment dose.

• Block thyroid uptake with SSKI or Lugol’s solution. Continued for 5-6 days to block uptake of free iodine.
Indications

- Pheochromocytoma (Paraganglioma)
- Neuroblastoma
- Carcinoid and other APUD tumors uptake MIBG less frequently.
- Ablative treatment with I-131
Pheochromocytoma

- Sensitivity 86% and Specificity 95-99% if biochemically positive for disease.\(^1\)
- CT and MRI more accurate for adrenal lesions.
- MIBG superior for extra-adrenal lesions (10%).\(^2\)
- MIBG superior for assessment of metastatic disease.

1 Semin Nucl Med, July 95, p.247
2 JNM, 1993;34 173-79
Normal Distribution (MIBG)

- Salivary Glands
- Thyroid
- Lung
- Myocardium
- Liver
- Spleen
- Adrenal
- Colon
- Bladder
- Uterine and neck muscle uptake
- Upper thorax in children.
Pheochromocytoma

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Metastatic Pheochromocytoma
Metastatic Carcinoid

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Drugs that interfere with MIBG uptake:

- **Cocaine**
- **Tricyclic antidepressants. D/c 6 weeks prior to test.**
  - Amitriptyline, Desipramine, Doxepin, Imipramine, Trazodone.
- **Nasal Decongestants**
  - pseudoephedrine HCL (Sudafed), Phenylpropanolamine HCL (Sucrets), Phenylephrine HCL,
- **Catecholamine agonists.**
  - Amphetamines, Benzphetamine, Chlorphentermine, Chlortermine, Dextroamphetamine,
    Diethylpropion, Mazindal, Methamphetamine, Methylphenidate (Ritalin), Phendimetrazine,
    Phenmetrazine, Phentermine.
- **Antipsychotics**
  - Phenothiazines, Chlorpromazine, Fluphenazine, Mesoridazine, Perphenazine, Piperacteazine,
    Prochlorperzaine, Promazine, Thioridazine, Triflupromazine, Reserpine, Haloperidol, Thiothixene.
- **Calcium channel blockers**
- **Adrenergic blockers. D/c 3 wks prior to test.**
  - Lebetalol, Bretylium.
- **"Diet Control Pills"**
  - Phenylpropanolamine, (anorexiant) Diadex, Resolution II Half Strength, Prolamine,
- **Some foods containing vanillinn and catecholamine-like compounds.**
  - Chocolate, Blue-veined cheeses.

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What about PET?

- FDG-PET is less sensitive and specific in most neuroendocrine tumors
- Undifferentiated tumors show more FDG uptake
- Only when OctreoScan and MIBG fail to localize use FDG-PET
Neuroendocrine Tumors That do not Concentrate OctreoScan and MIBG

- Parathyroid adenoma
  - Dual isotope or Dual phase Tc-99m MIBI imaging
- Adrenal cortical tumors
When PET helps?

- 45 year old female with hypertensive crisis
- Urinary VMA high
- Catacholamines high
- MRI: T1 and T2 image findings favored pheochromocytoma
OctreoScan

A

B

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FDG-PET

A

B

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Surgical Removal and Histology Showed Adrenal Cyst
Therapy

• In USA: only I-131 MIBG is approved
• In 111 OctreoScan
• Y-90 Analogues IND use
I-131 MIBG Ablative Rx

• Any tumor that takes up MIBG
• 250-300 mCi
• Primarily useful for decreasing symptoms of metastatic disease.
• Increases quality of life.
• Curative use has yet to be demonstrated

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Metastatic Pheochromocytoma

I-123 MIBG

I-131 1 wk post

I-123 1 yr post I-131

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Metastatic Carcinoid

- 49 yo F with carcinoid mets to liver.
- Worsening on Sandostatin therapy
- Treated with I-131 MIBG
- Off Sandostatin x 6 months.
- Recurred and retreated with similar results.
Therapy with Somatostatin analogues

- Non radio labeled Somatostatin
- In-111 DTPA Octreotide
- Yo-90-DOTA -Tyr
Octreotide therapy

- Sandostatin reduces side effects and slows tumor progression.
- Clinical trials with OctreoTher*
  - Tyr-3-Octreotide coupled with yttrium-90 (Beta emitter)

Novartis
Smith et al. Digestion 2000;62 sup 1:69-72

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Non radiolabeled Octreotide

• Indications:
  – Graves exophthalmopathy
  – Pituitary secreting adenoma
  – Other neuro-endocrine tumors

• Dosage and Route of administration:
  – 25 microgram s/c TID

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In-111Octreotide for Therapy

• 100-200mCi IV  8-14 applications every 15 days
• Auger and conversion electrons
• Toxic to bone marrow
Y-90 labeled Analogues

• 2.7 days half life
• Pure Beta emitter
• D-lysine to decrease renal uptake is being tried
MIBG vs Octreotide

- First have a biochemical proof of disease.
- Current medicines.
- Sensitivity not significantly different.
- Consider target to background ratio.
  - MIBG background higher in lung
  - Renal background higher with octreotide

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Neuroendocrine Tumors are Rare

• Patient “I have a politically incorrect disease”
• If you are in a small practice send the patient to a University Hospital-they are always in red and they don’t mind.
Summary

• Patho-physiology
• OctreoScan
• MIBG
• FDG-PET
• Therapy