The evolving role of PET/CT for neuroendocrine tumor imaging

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Neuroendocrine cancers

- Diverse group of neoplasms of various behaviors and origins
  - All originate from cells that share common elements with nerve cells
    - Neuron specific enolase
    - Chromogranin A
    - APUD: Amine Precursor Uptake and Decarboxylase
  - Often, but not always, secrete hormones
Carcinoid

- 5,000 new cases per year in the U.S.
- ~75% from GI tract
- ~25% bronchial
- Often presents with carcinoid syndrome
  - Diarrhea
  - Flushing
  - Abdominal pain
- Second most prevalent GI cancer
Pancreatic NETs

- Estimates of incidence vary, probably ~3,000 new cases per year in U.S.
  - 1-2% of clinically significant pancreatic neoplasms

- Various cells of origin result in various symptoms
  - Gastrinoma, insulinoma, VIPoma, glucagonoma, somatostatinoma
Other NETs

- Gastroenteropancreatic neuroendocrine tumors (GEPNETS)
  - Umbrella category
- Bronchial carcinoid
- Unknown primaries
Pheochromocytoma/Paraganglioma

- Rule of 10s:
  - ~10% of cases are bilateral
  - ~10% of cases are extraadrenal
  - ~10% of cases are malignant
  - ~10% of cases are genetically predisposed
Paraganglioma

Name pheochromocytoma describes location of origin

Paraganglioma arises outside the adrenal
Parasympathetic paraganglioma

- More often head and neck origin
- Almost always benign
- Usually non-functioning
- SDHC
  - Lesser extent SDHD
Sympathetic paraganglioma

- Often abdominal
  - Organ of Zuckerkandl
  - Retroperitoneal
- Much higher malignancy rate (up to 1/3?)
- Often functioning
- SDHB
  - Also VHL, NF1, MEN-2
Neuroblastoma

Most common extracranial solid tumor of childhood

- Most common malignancy in first year of life

- ~600 new cases annually in US

- <10% of new cases in patients > 5 years old
Neuroblastoma

- Originate from neural crest cells
  - Most common primary site is retroperitoneum
  - Primaries can be found in neck, posterior mediastinum and pelvis
- ~60% have metastatic disease at presentation
  - Bone, nodes and liver most common
- Prognosis is dismal
Neuroendocrine cancers
Bottom line

- Myriad unique diseases
- Have a lot in common
  - Some surprising shared therapeutic targets
meta-Iodobenzylguanididine (MIBG)

- Described by Wieland et al in 1979 at University of Michigan
- Iodination in the meta position
- Not a norepinephrine analog
- Substrate for NET
# I-123 versus I-131 MIBG

Both FDA approved

<table>
<thead>
<tr>
<th>I-123 MIBG</th>
<th>I-131 MIBG</th>
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</thead>
<tbody>
<tr>
<td>13.2 h half life</td>
<td>8 d half life</td>
</tr>
<tr>
<td>10 mCi dose</td>
<td>0.5 mCi dose</td>
</tr>
<tr>
<td>159 keV photopeak</td>
<td>364 keV photopeak</td>
</tr>
<tr>
<td>Primarily $\gamma$</td>
<td>Lower resolution</td>
</tr>
<tr>
<td>Limited availability*</td>
<td>$\gamma$ and $\beta^-$</td>
</tr>
<tr>
<td>Expensive</td>
<td>Widely available</td>
</tr>
<tr>
<td>SPECT or SPECT/CT</td>
<td>SPECT impossible (for diagnostic scans)</td>
</tr>
<tr>
<td>Lower thyroid exposure</td>
<td></td>
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</tbody>
</table>

*Limited availability indicates that I-123 MIBG may not be available in all regions due to regulatory and supply issues.
A phantom study: should $^{124}$I-mIBG PET/CT replace $^{123}$I-mIBG SPECT/CT?

Casper Beijst$^{1,2}$, Bart de Keizer$^1$, Marnix G.E.H. Lam$^1$, Geert O. Janssens$^3$, Godelieve A.M. Tytgat$^4$, Hugo W.A.M. de Jong$^3$
Importance of SPECT
Importance of SPECT

Clin Nucl Med, 30(2) 2005
Somatostatin receptor

- 5 known subtypes
- 7 transmembrane domains
- Highly expressed in GI tract
- Generally inhibitory function
- Expressed on huge number of cancers
  - Not limited to neuroendocrine cancers
- SSTR-2 most commonly expressed on cancers
Somatostatin Analogs

- Most neuroendocrine cancers express somatostatin receptors
- Somatostatin has incredibly short half life
- Oligopeptide analogs with longer half lives
Octreoscan (In-111-pentetretotide)

- Highest affinity for SSTR-2
- Lesser for SSTR-5 and SSTR-3
- Inject 6 mCi In-111-pentetretotide intravenously
- Planar whole body images at 4 and 24 hours
- SPECT(/CT) of abdomen at 4 hours
- SPECT(/CT) of chest at 24 hours
- Some sites image at 48 hours and beyond
- Lots of bowel activity
Planar octreoscan

4 hours

24 hours
Somatostatin PET imaging

- Ga-68 DOTA-somatostatin analog
  - Recently approved in US
  - Ga-68 DOTATATE (Netspot)

- PET/CT gives:
  - Higher resolution
  - Higher contrast
PET vs planar

Permutations

- Octreotide
  - DTPA - pentetreotide
  - DOTA – DOTATOC
    - DOTANOC
- Octreotate
  - DOTA – DOTATATE
- Antagonists
  - In-111
  - Ga-68
  - Lu-177
  - Y-90
  - Etc.
Ga-68 DOTATATE PET/CT Imaging protocol

- Minimal patient prep
  - Encourage hydration
  - Schedule as far from somatostatin analog as possible
- Inject 0.054 mCi/kg up to 5.4 mCi
- Image at 45-60 minutes post injection
  - Some image later
- Oral, IV contrast optional
  - Patients predisposed to diarrhea
- Patient in and out in under 2 hours
Ga-68

- Generator produced
  - Ge-68 parent, 271 d half-life
  - Ga-68 daughter, 68 minute half-life
- Can elute ~3x/working day
- 3 doses per day
- Timing is critical
Radiopharmaceutical effective dose:

- Ga-68 DOTATATE 3.15 mSv
- In-111 Octreoscan 26 mSv
Insurance coverage

- CMS pass-through drug coverage
- Bill scan and drug separately
- Private insurers/RBM's slowly coming up to speed
  - Thanks Dr. Metz (and others)!
What to use when

Now and future directions
Synthesis and evaluation of $^{18}$F-labeled benzylguanidine analogs for targeting the human norepinephrine transporter

Hanwen Zhang · Ruimin Huang · NagaVaraKishore Pillarsetty · Daniel L. J. Thorek · Ganesan Vaidyanathan · Inna Serganova · Ronald G. Blasberg · Jason S. Lewis

Synthesis and evaluation of 4-[$^{18}$F]fluoropropoxy-3-iodobenzylguanidine ([$^{18}$F]FPOIBG): A novel $^{18}$F-labeled analogue of MIBG

Ganesan Vaidyanathan *, Darryl McDougald, Eftychia Koumarianou, Jaeyeon Choi, Marc Hens, Michael R. Zalutsky
Imaging intentions

- Not always disease detection
- Theranostics/companion diagnostics
  - Assess suitability for therapy
  - Measure kinetics
  - Evaluate response
Lesional dosimetry

203 rad/mCi

229 rad/mCi

125 rad/mCi

Courtesy of John Humm, PhD
$^{68}$Ga-DOTATATE and $^{18}$F-FDG PET/CT in Paraganglioma: Utility, Pattern of Spread, and Correlation with Tumor Blood Flow.
Metastatic paraganglioma
Metastatic paraganglioma
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Metastatic paraganglioma
Metastatic paraganglioma
Feasibility and advantage of adding $^{131}$I-MIBG to $^{90}$Y-DOTATOC for treatment of patients with advanced stage neuroendocrine tumors

David L. Bushnell$^{1,2}$, Mark T Madsen$^3$, Thomas O’codirisio$^3$, Yusuf Menda$^1$, Saima Muzahir$^1$, Randi Ryan$^4$ and M Sue O’dorisio$^5$

<table>
<thead>
<tr>
<th>Organ dose limits</th>
<th>Maximum activity (GBq) $^{90}$Y-DOTA alone (given over multiple cycles)</th>
<th>Optimum percentage of maximum $^{90}$Y activity to be given when adding MIBG</th>
<th>Activity (GBq) of $^{131}$I-MIBG that can be added without exceeding limits</th>
<th>Tumor dose (cGy): $^{90}$Y-DOTA given alone</th>
<th>Tumor dose (cGy): $^{90}$Y + $^{131}$I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>2,300</td>
<td>4.9</td>
<td>75</td>
<td>33.3</td>
<td>1,006</td>
</tr>
<tr>
<td>Marrow</td>
<td>300</td>
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Meta-analysis of 42/2,479 publications

Attempt to estimate sensitivity/specificity of PET vs SPECT

Considerable statistical and data quality limitations

PET sensitivity ~91%, specificity 91%

Probably superior to SPECT
Mesenteric adenopathy
SPECT/CT vs PET/CT
Liver mass, unknown primary
Conclusions

- PET/CT improves signal-noise
  - Better contrast, lesion detectability

- Ga-68 DOTATATE excellent diagnostic quality
  - Broad spectrum of neuroendocrine cancers
  - Short half-life
    - Causes logistical urgencies
    - Limits utility as companion diagnostic

- Multiple other potential agents in development
  - Therapeutics to match coming soon!
Thank you