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

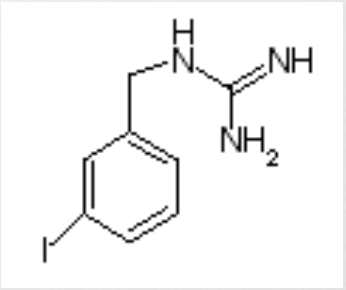
Neuroendocrine cancers Bottom line

- Myriad unique diseases
- Have a lot in common
  - Some surprising shared therapeutic targets

meta-Iodobenzylguanidine (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

I-123 MIBG

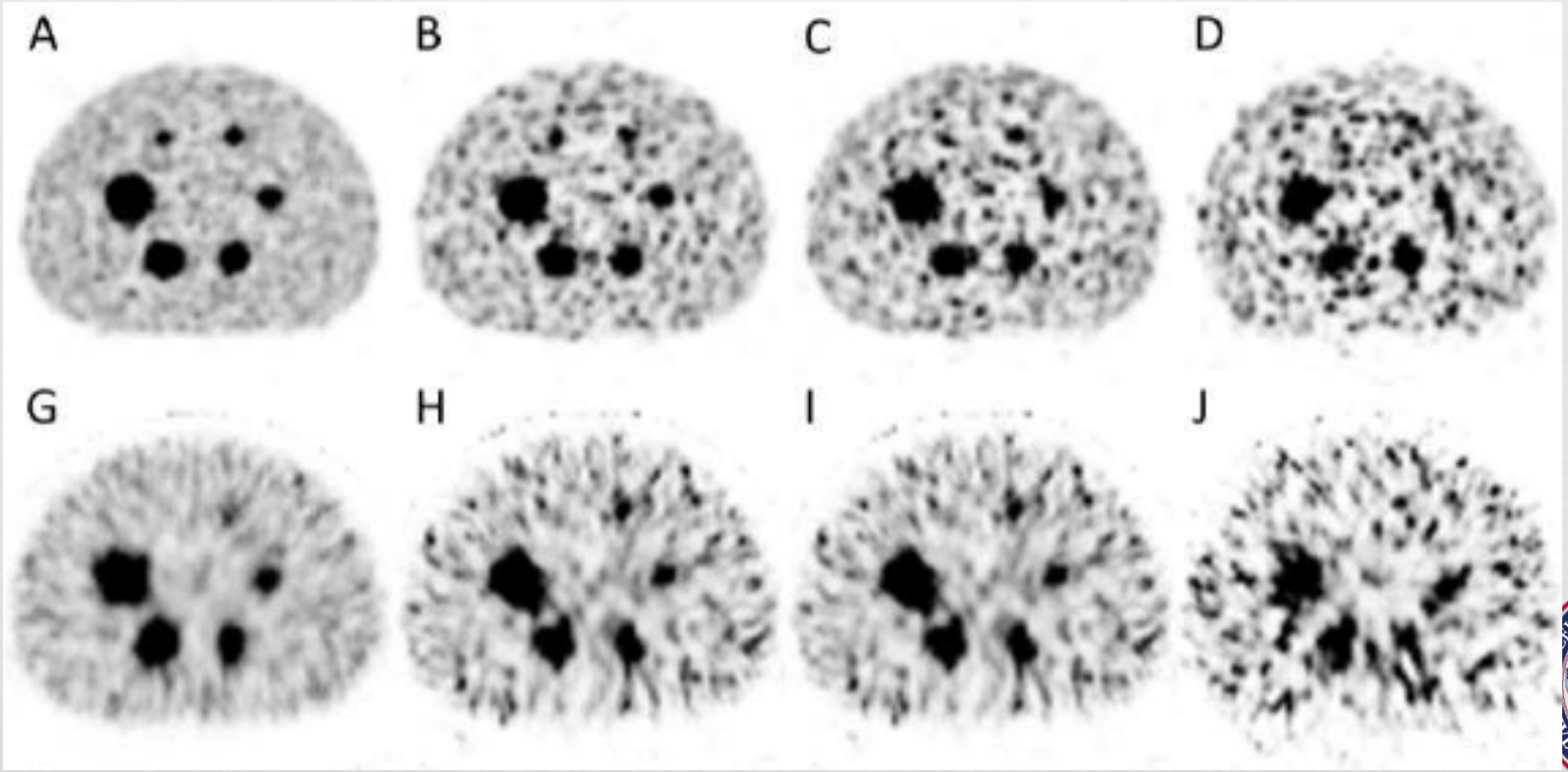
- 13.2 h half life
- 10 mCi dose
- 159 keV photopeak
- Primarily γ
- Limited availability*
- Expensive
- SPECT or SPECT/CT
- Lower thyroid exposure

I-131 MIBG

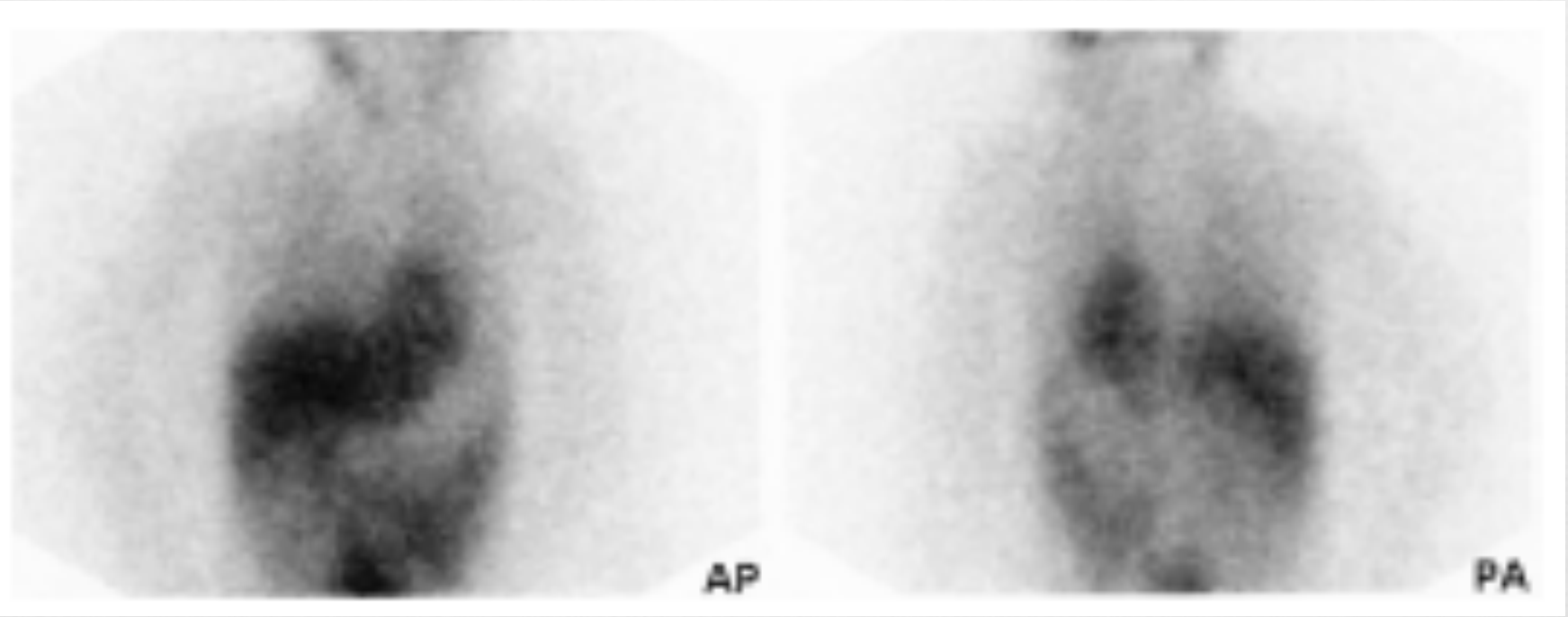
- 8 d half life
- 0.5 mCi dose
- 364 keV photopeak
  - Lower resolution
- γ and β^-
- Widely available
- SPECT impossible (for diagnostic scans)

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[1]

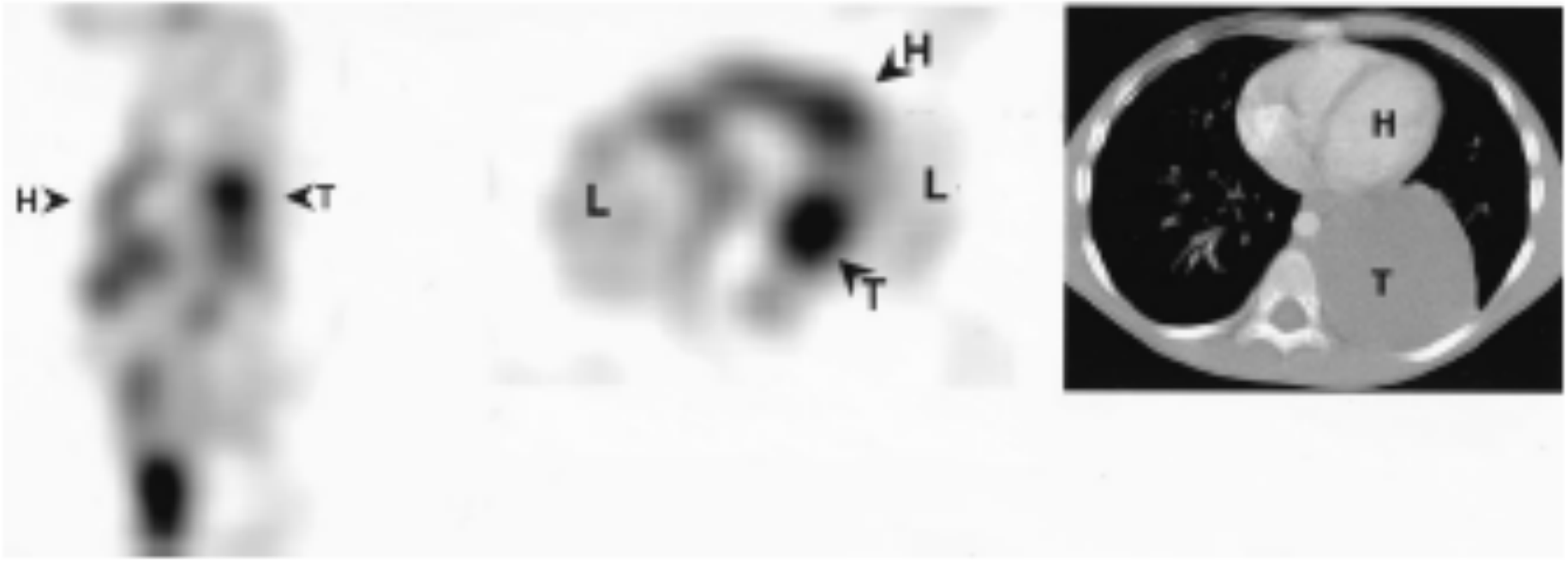


Importance of SPECT



Clin Nucl Med, 30(2) 2005

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

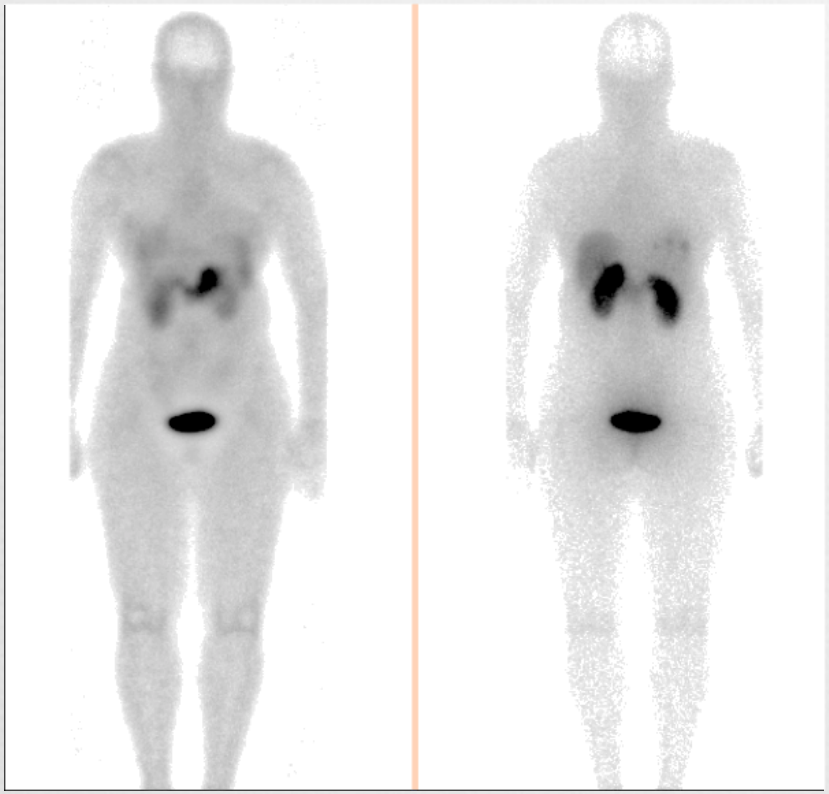
Somatostatin Analogs

- Most neuroendocrine cancers express somatostatin receptors
- Somatostatin has incredibly short half life
- Oligopeptide analogs with longer half lives

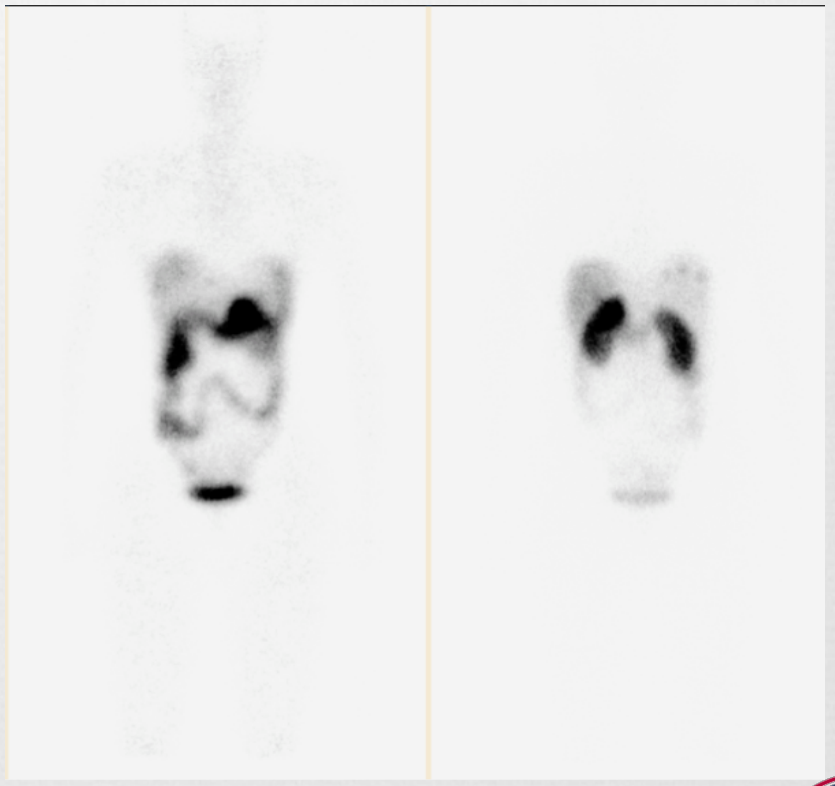
Octreoscan (In-111-pentetreotide)

- Highest affinity for SSTR-2
  - Lesser for SSTR-5 and SSTR-3
- Inject 6 mCi In-111-pentetreotide 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

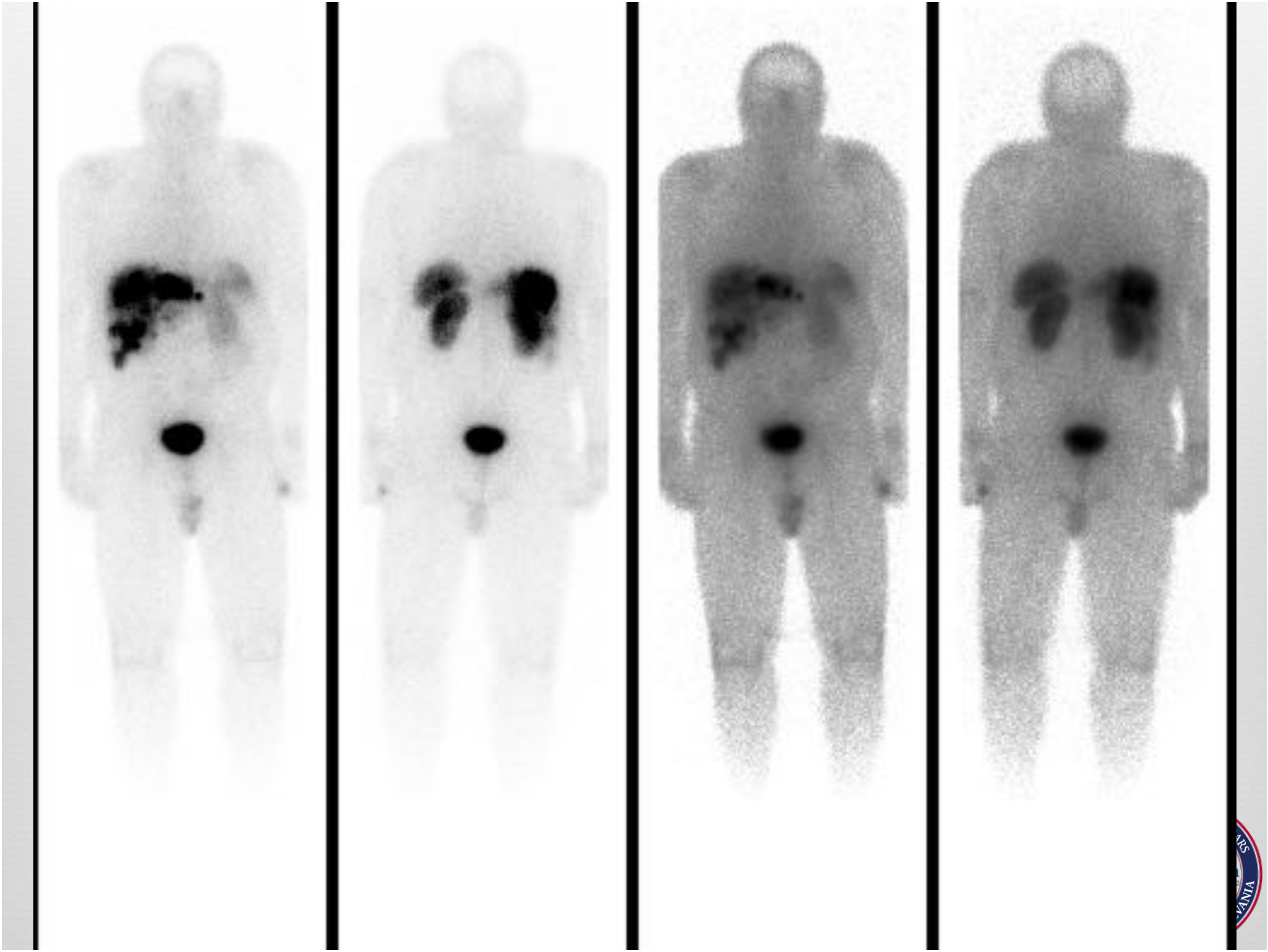
Planar octreoscan

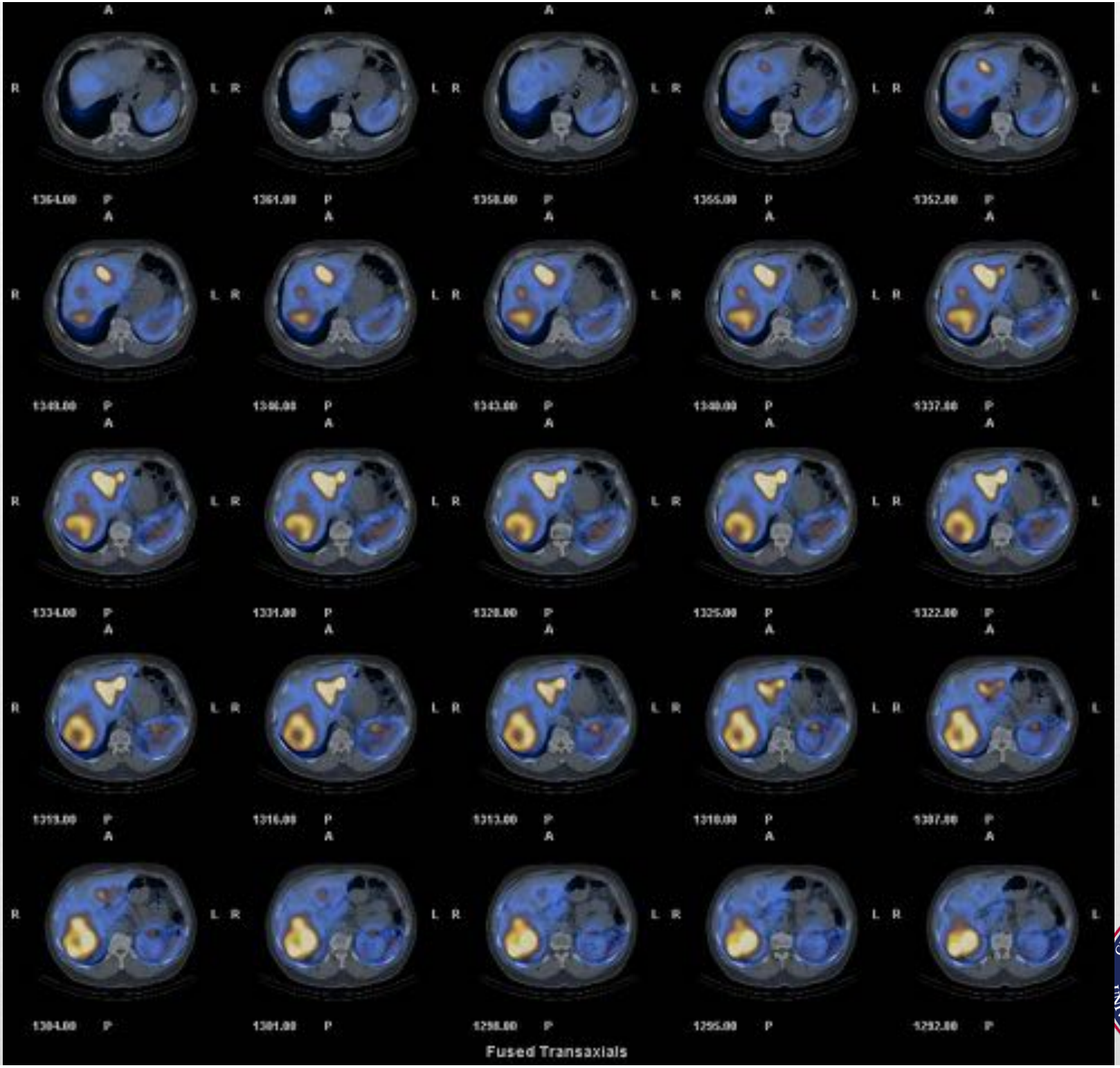


4 hours



24 hours

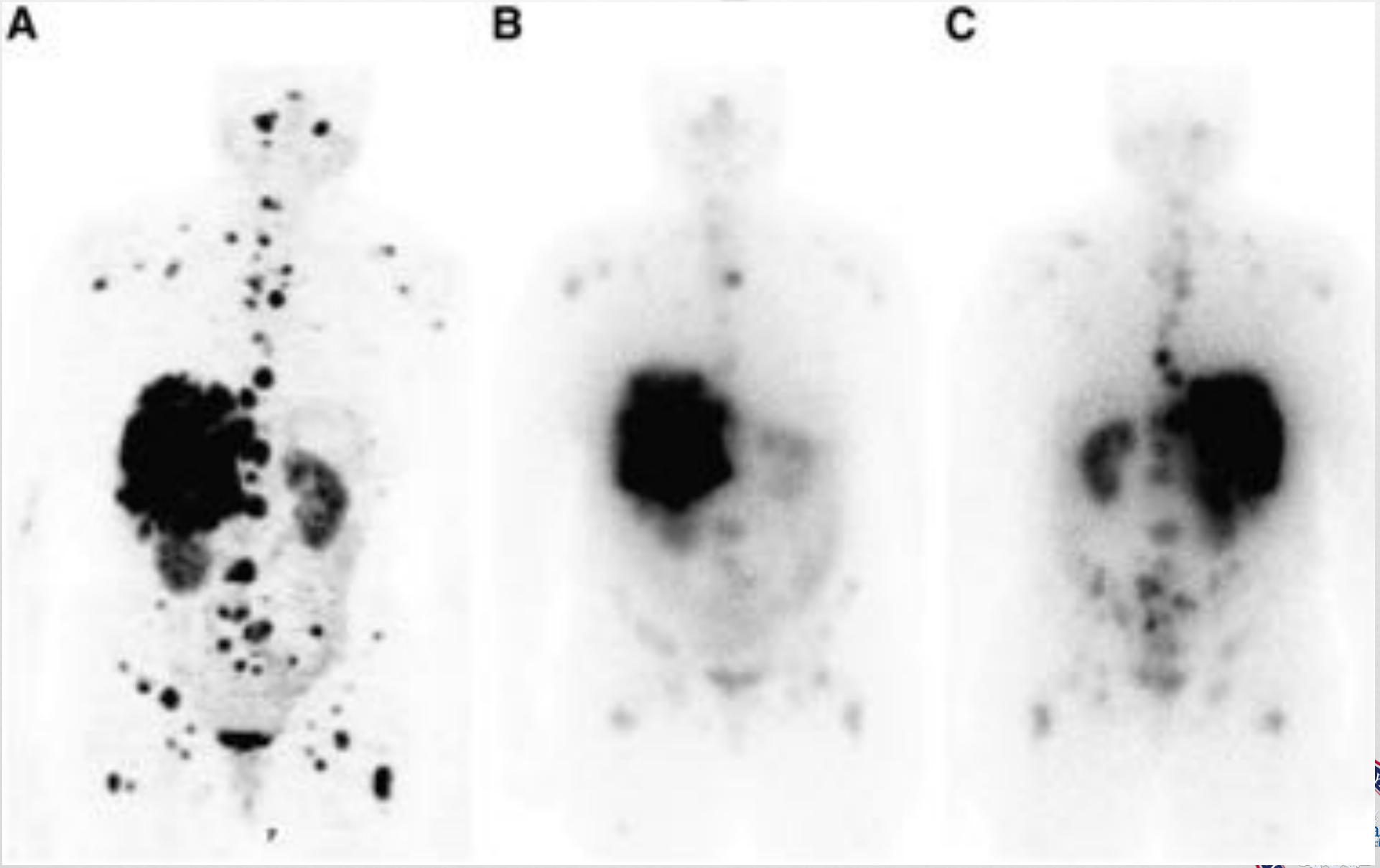




Somatostatin PET imaging

- Ga-68 DOTA-somatostatin analog
  - Recently approved in US
    - Ga-68 DOTATATE (Netspot)
- PET/CT gives:
  - Higher resolution
  - Higher contrast

PET vs planar



Gabriel et al, J Nucl Med 2007

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

ALARA

- Radiopharmaceutical effective dose:

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

Insurance coverage

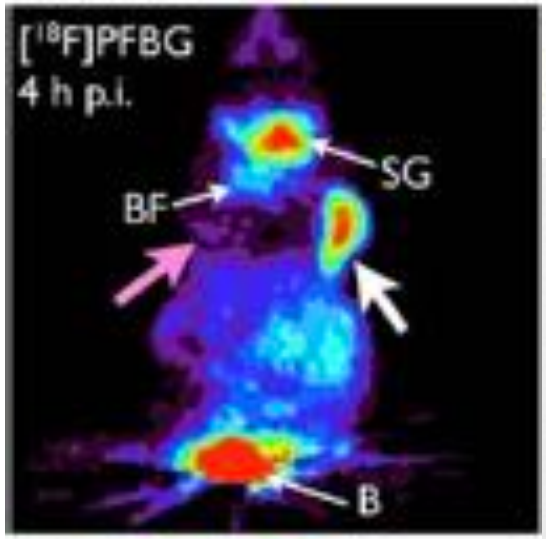
- CMS pass-through drug coverage
- Bill scan and drug separately
- Private insurers/RBMs slowly coming up to speed
  - Thanks Dr. Metz (and others)!

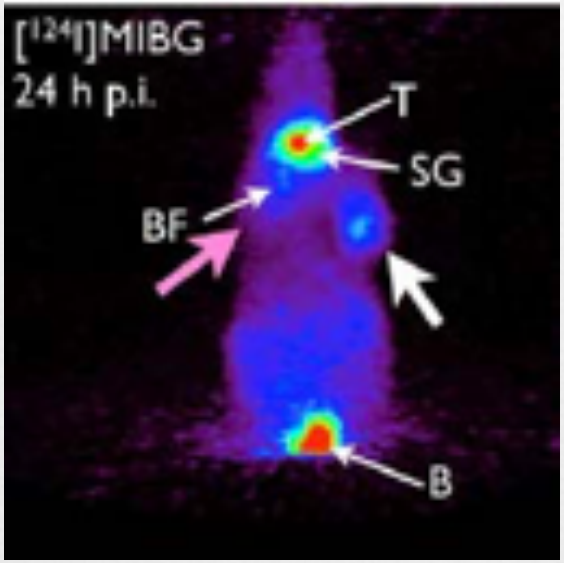
What to use when

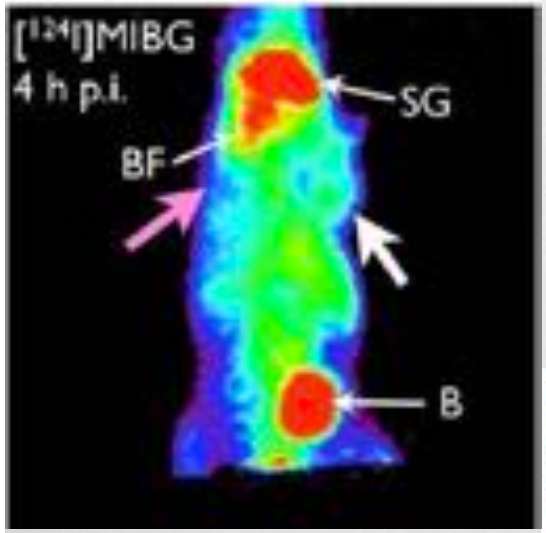
Now and future directions

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

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







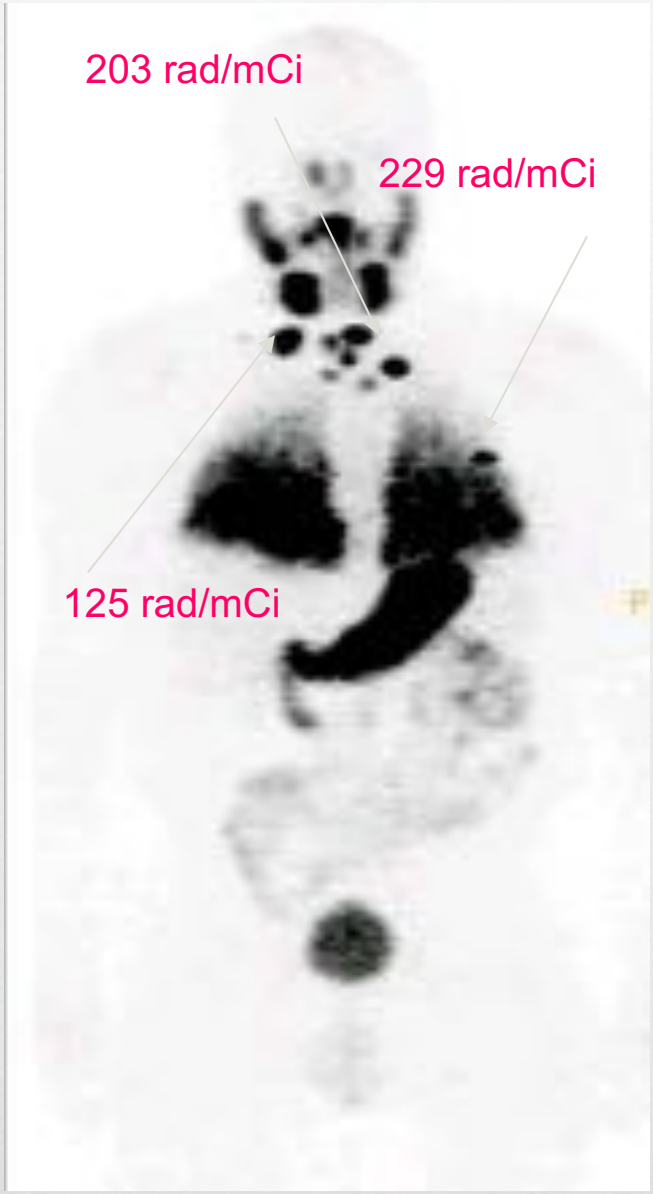
Synthesis and evaluation of 4-[^{18}F] fluoropropoxy-3-iodobenzylguanidine ([^{18}F]FPOIBG): A novel ^{18}F-labeled analogue of MIBG

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

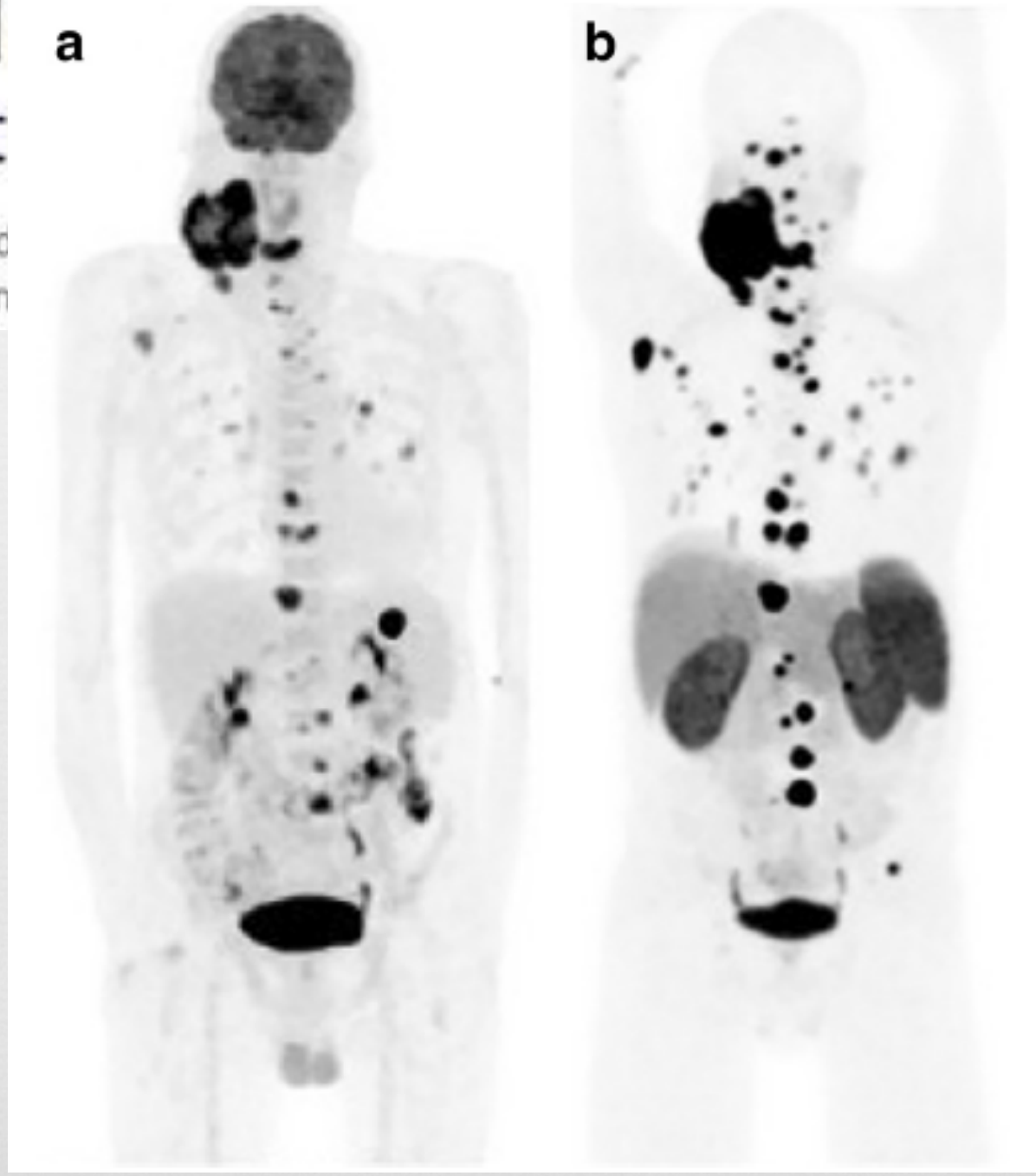
Lesional dosimetry



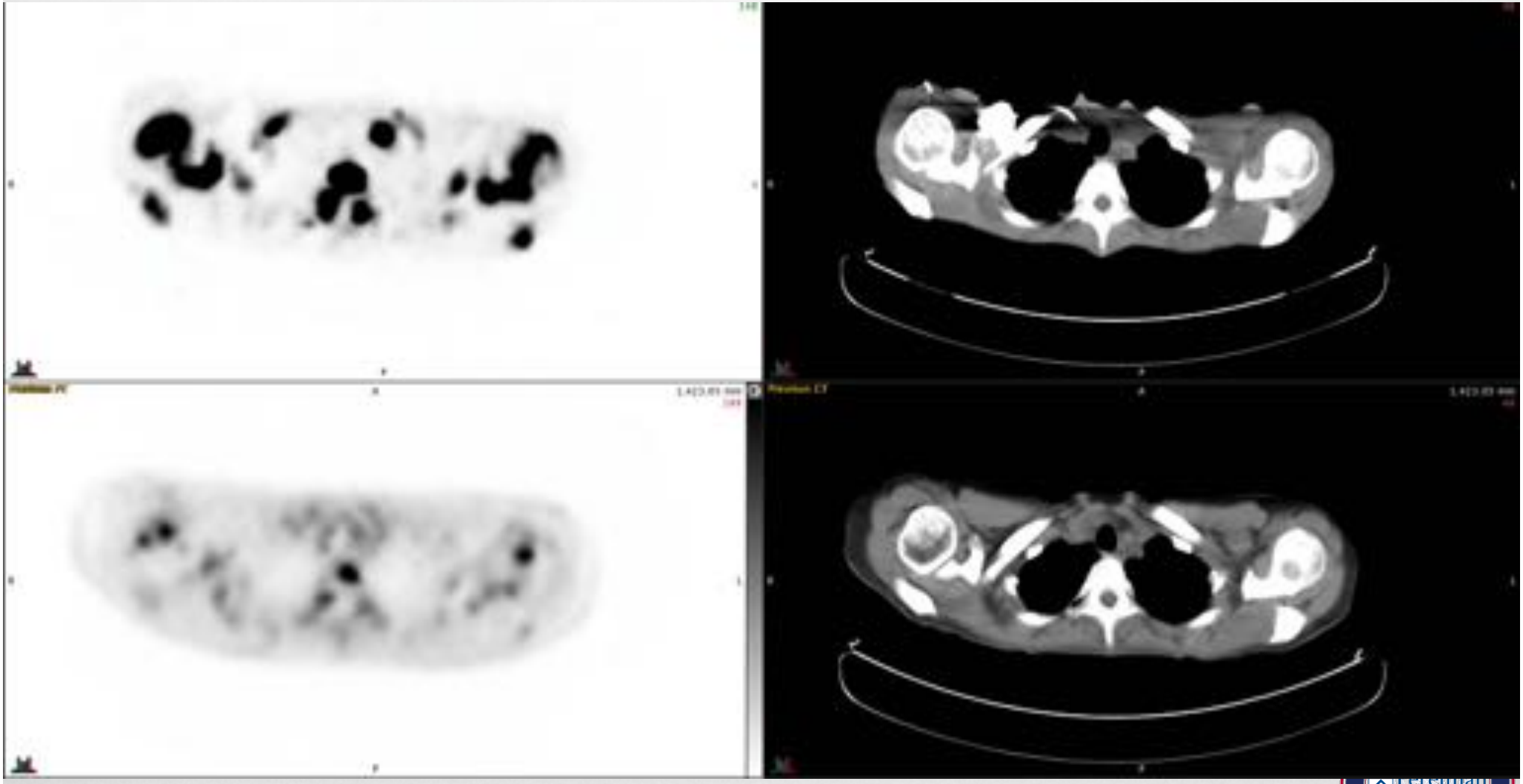
Courtesy of John Humm, PhD

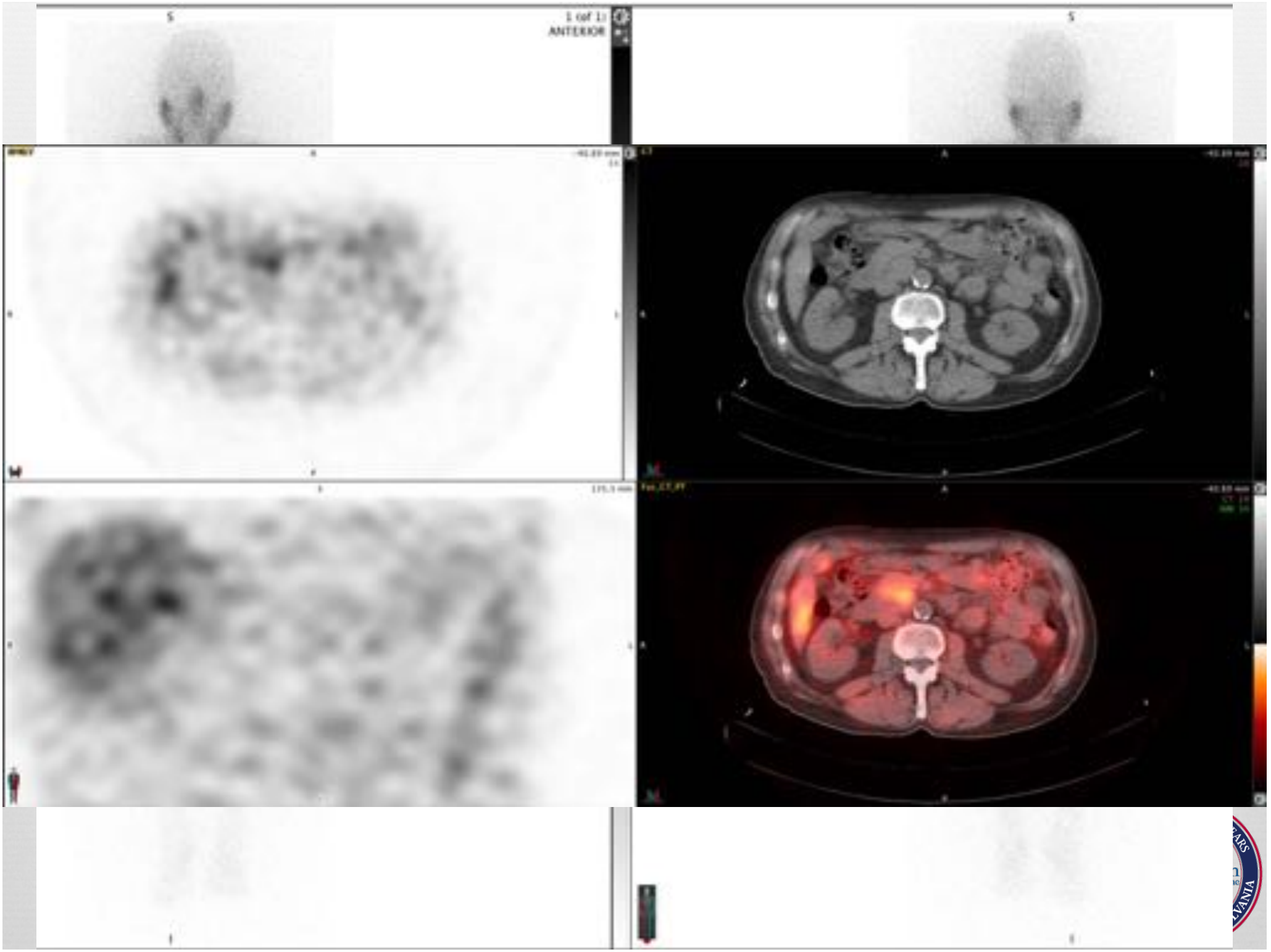
^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in Paragangl ma: utility, pat

Chian A. Chang[1], David ², Rodney J. Hicks[1,2] and Michael S. Hofman

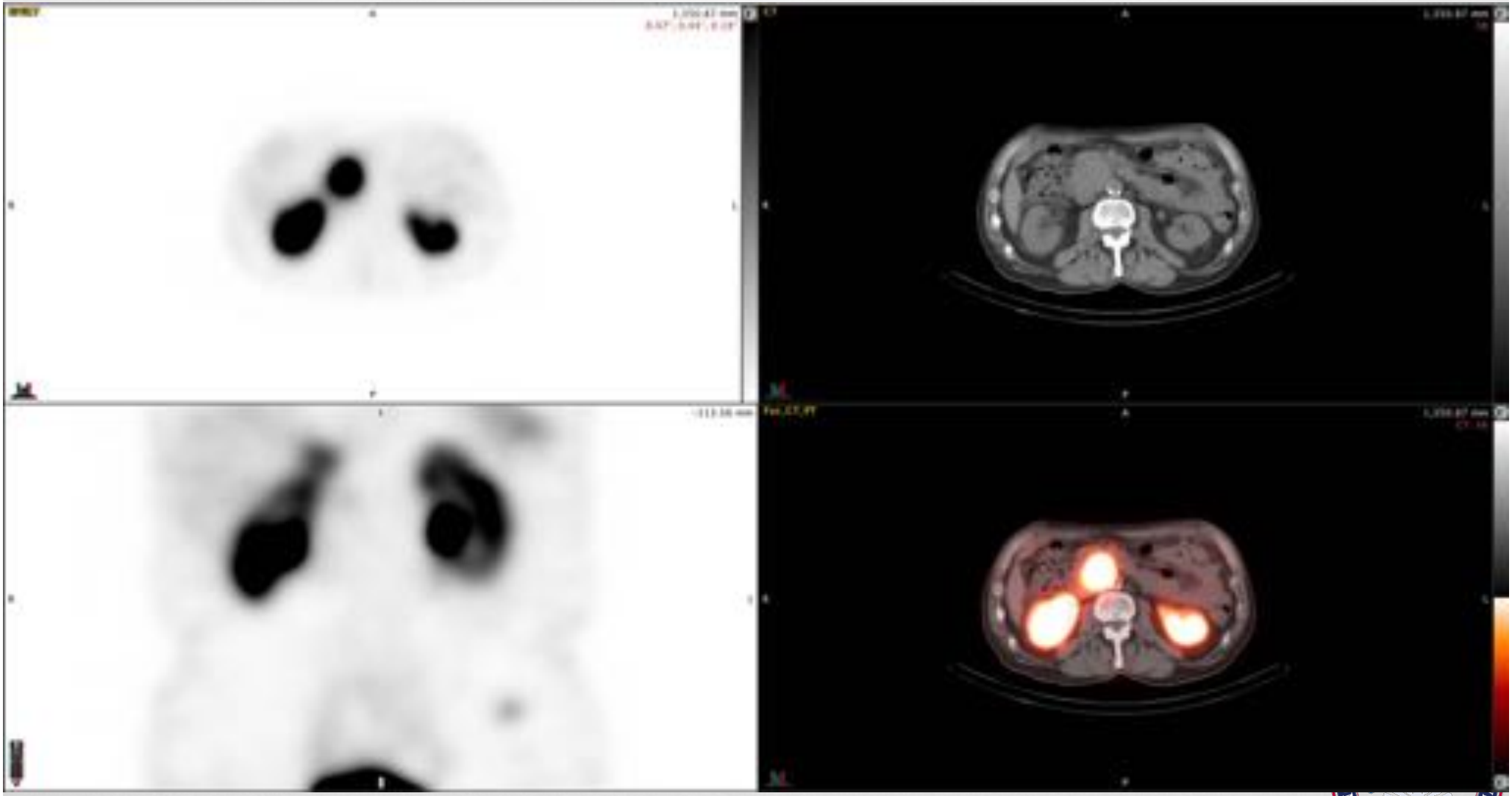


Metastatic paraganglioma

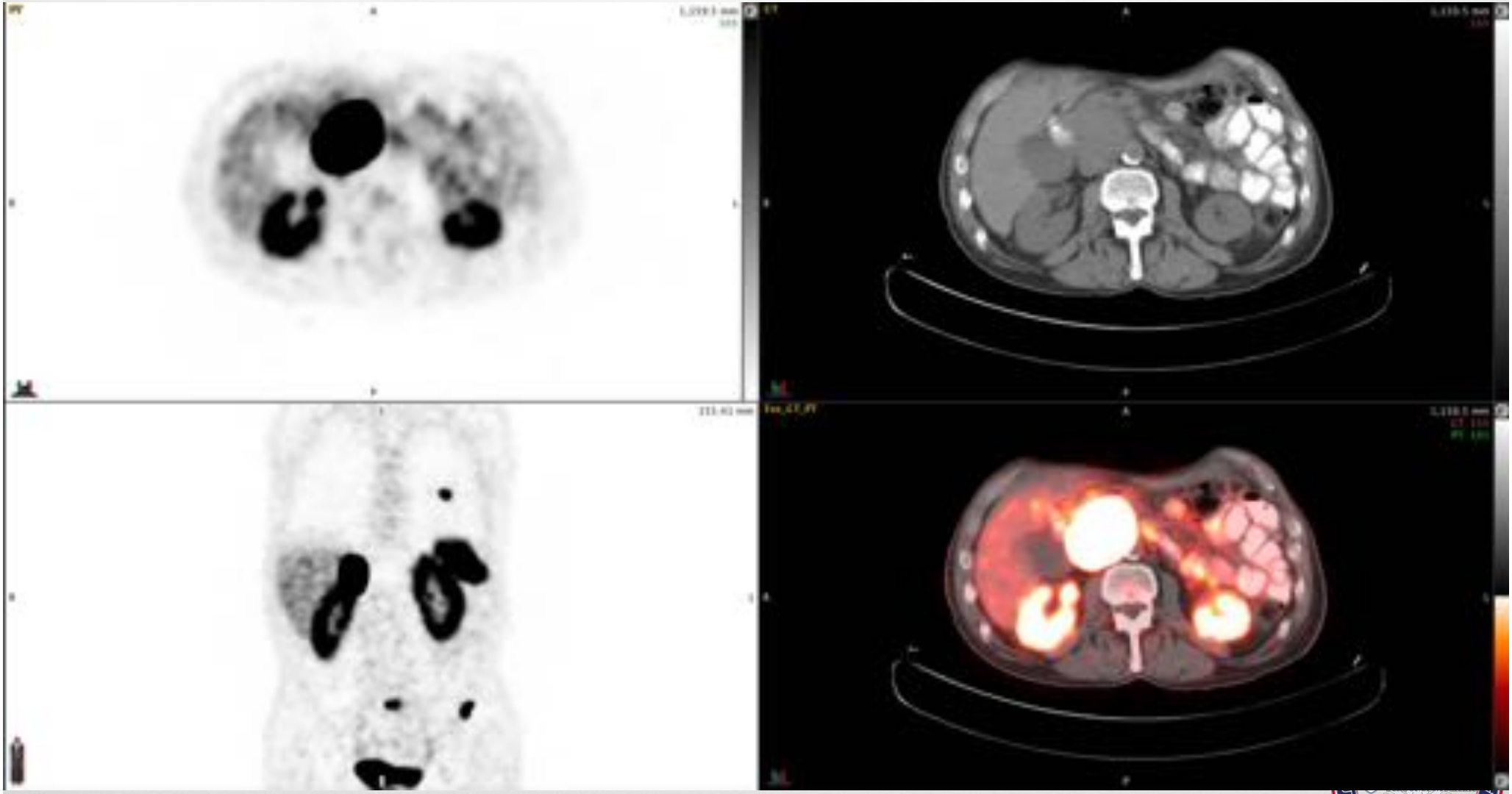


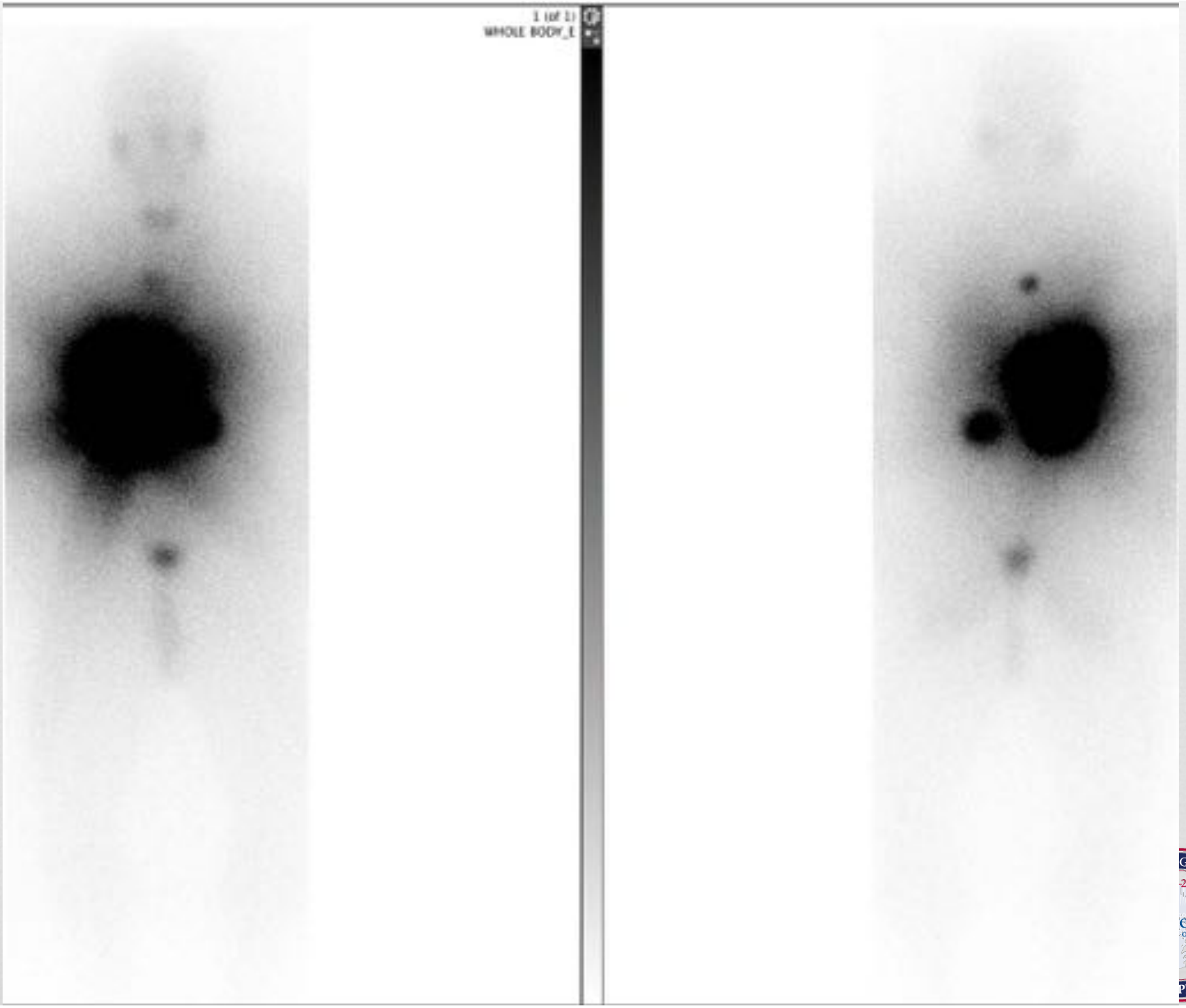

1 of 1
ANTERIOR

Metastatic paraganglioma



Metastatic paraganglioma

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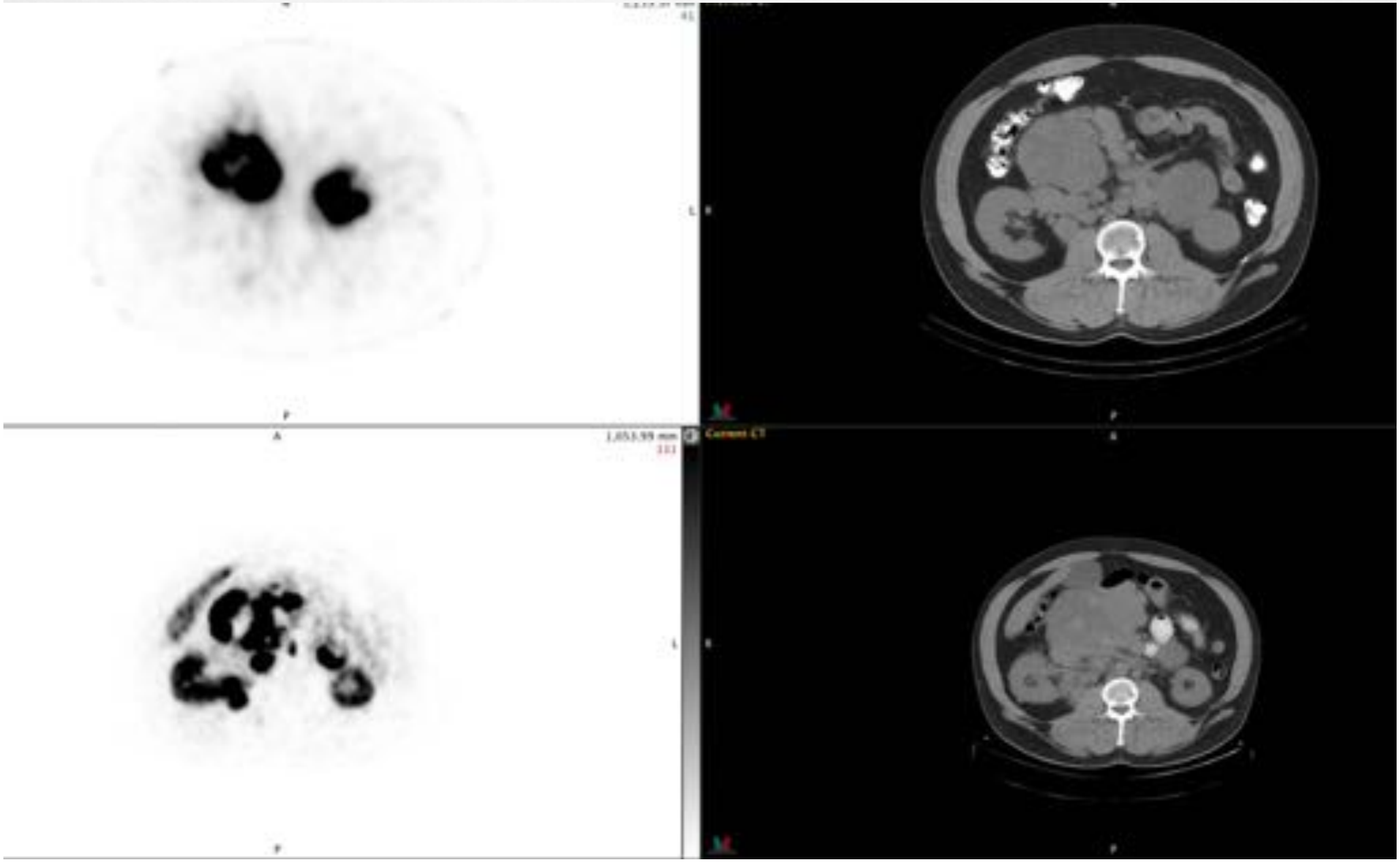
WHOLE BODY_1

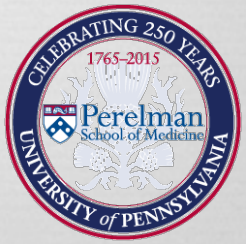
Metastatic paraganglioma



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[1], Thomas O'cdorisio[3], Yusuf Menda[1], Saima Muzahir[1], Randi Ryan[4] and M Sue O'dorisio[5]

	Organ dose limits	Maximum activity (GBq) ^{90}Y-DOTA alone (given over multiple cycles)	Optimum percentage of maximum ^{90}Y activity to be given when adding MIBG	Acivity (GBq) of ^{131}I-MIBG that can be added without exceeding limits	Tumor dose (cGy): ^{90}Y-DOTA given alone	Tumor dose (cGy): ^{90}Y + ^{131}I
Kidney	2,300	4.9	75	33.3	1,006	2,499
Marrow	300					

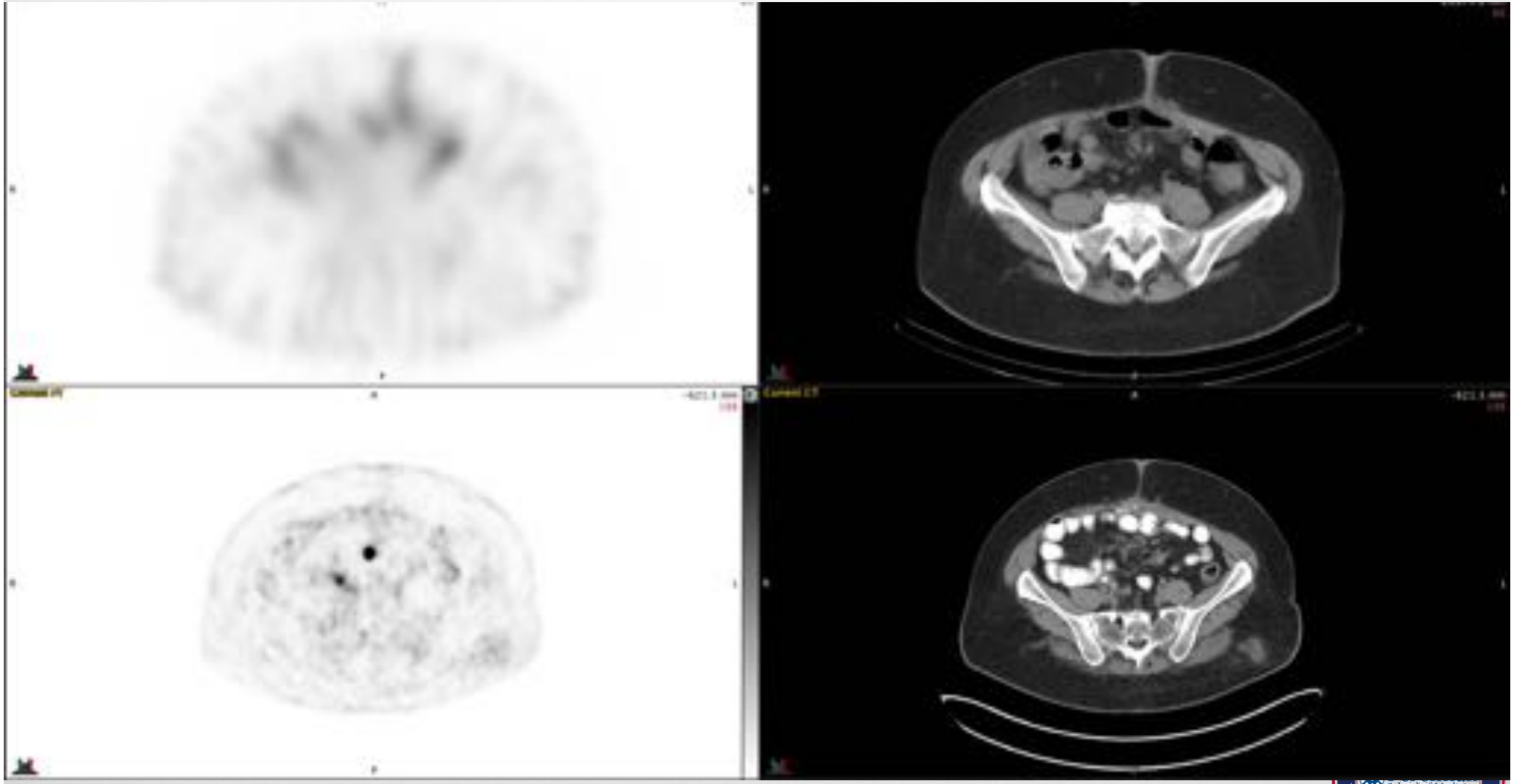


^{68}Ga-DOTATATE Compared with ^{111}In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis

Stephen A. Deppen[1–3], Jeffrey Blume[4], Adam J. Bobbey[5], Chirayu Shah[1,6], Michael M. Graham[7], Patricia Lee[8], Dominique Delbeke[3,6], and Ronald C. Walker[1,3,5,6]

- 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



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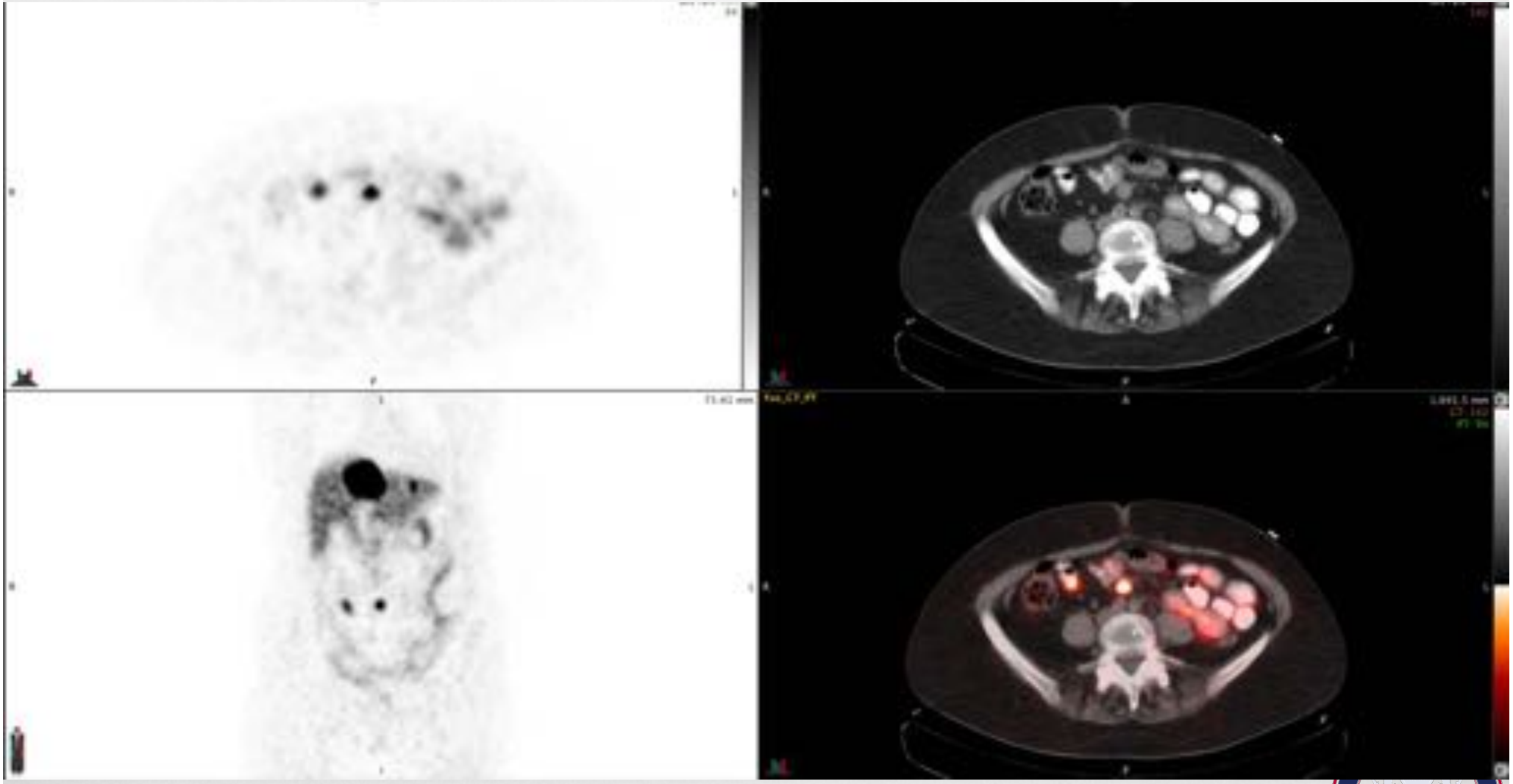
Liver mass, unknown primary



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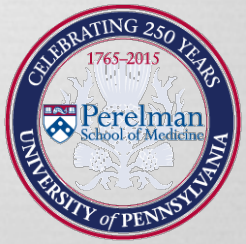
Conclusions

- 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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