Clinical Impact of Somatostatin Receptor Imaging

Ruoh-Fang Yen, MD, PhD
Department of Nuclear Medicine
NTUH, Taipei, Taiwan
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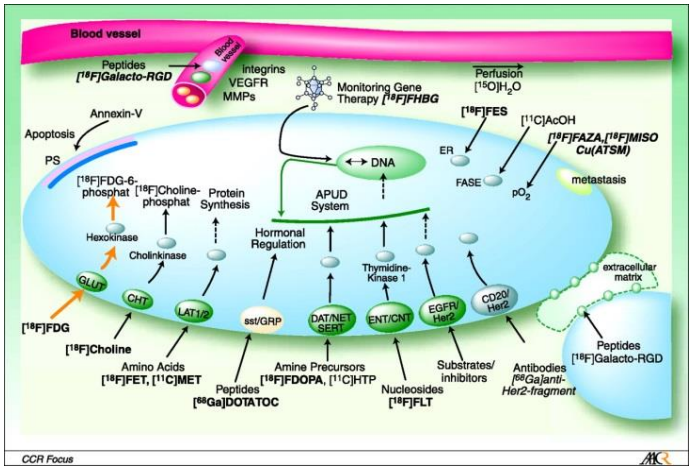
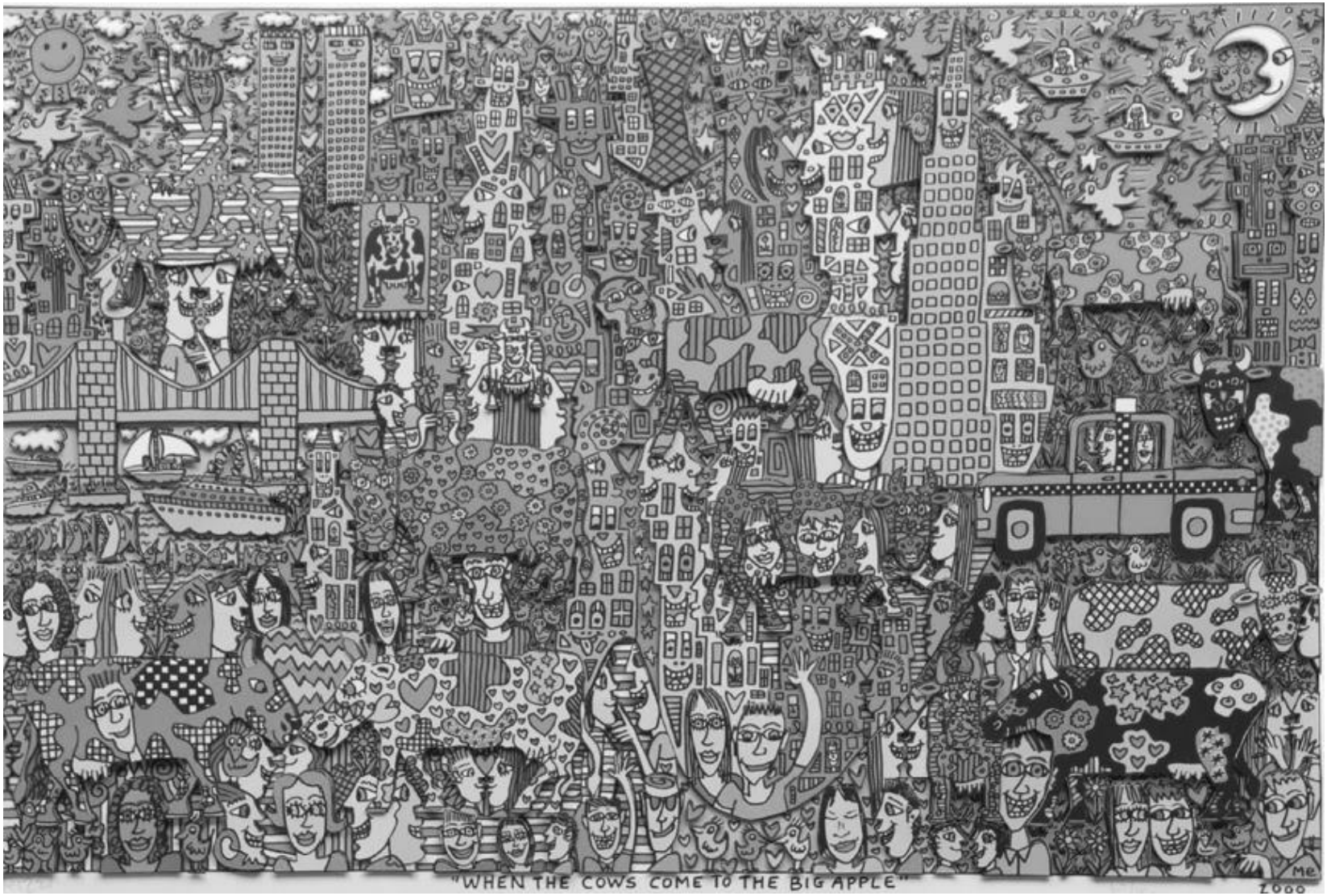
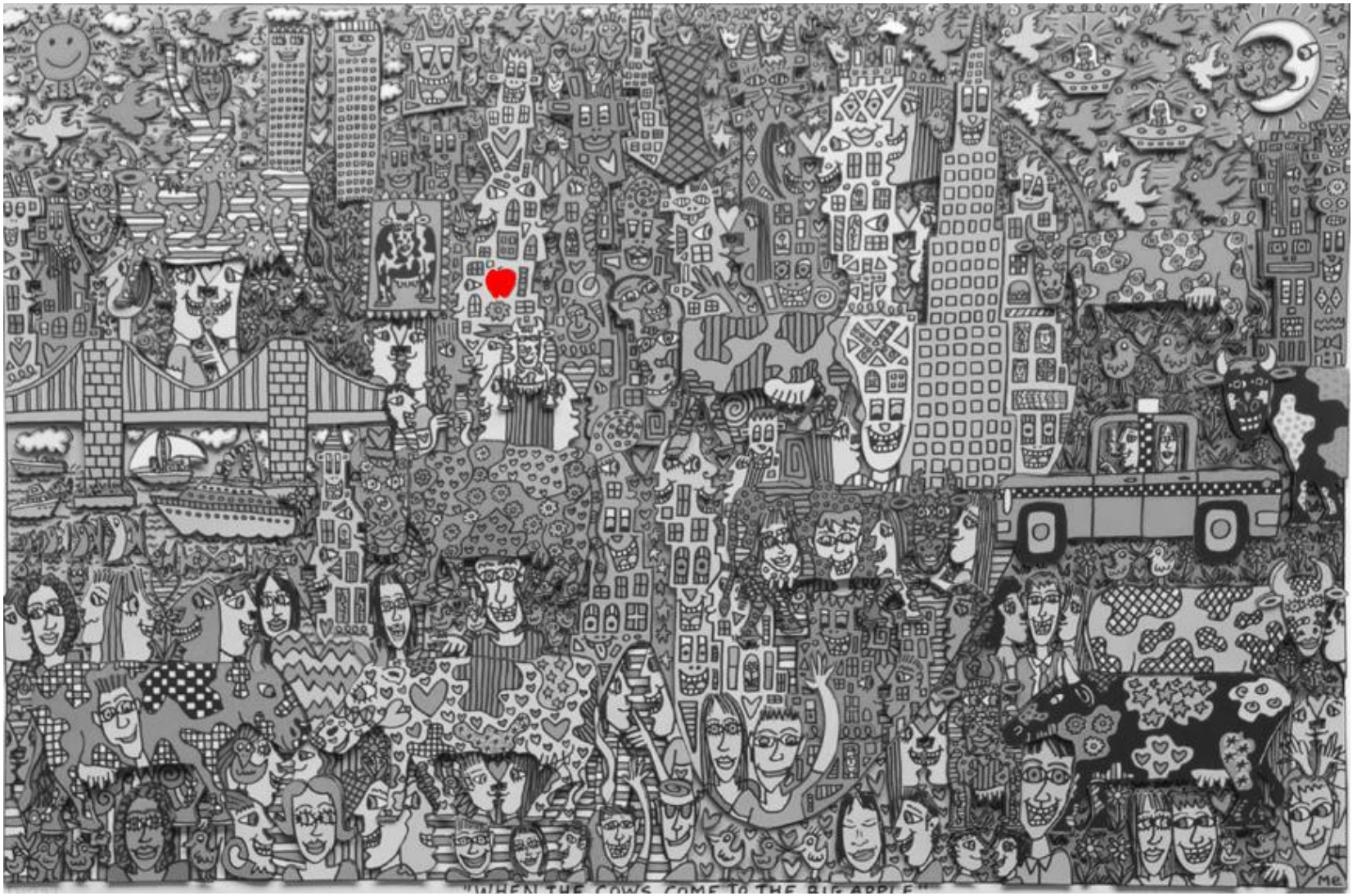
Nuclear Medicine Molecular Imaging

- Visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems
  - **Probes:** Targeting radiopharmaceuticals
  - **Imaging instrumentation**: SPECT and PET
  - **Quantification**: determination of regional concentrations of molecular imaging agents



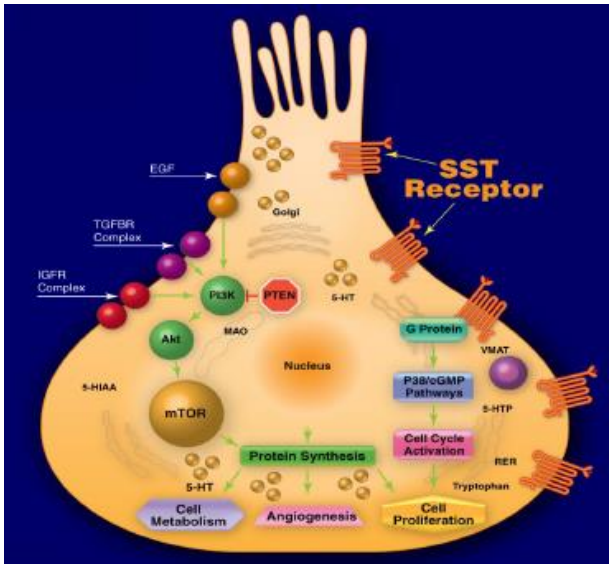
Mankoff DA. J Nucl Med. 2007;48:18N-21N


"WHEN THE COWS COME TO THE BIG APPLE"
2000

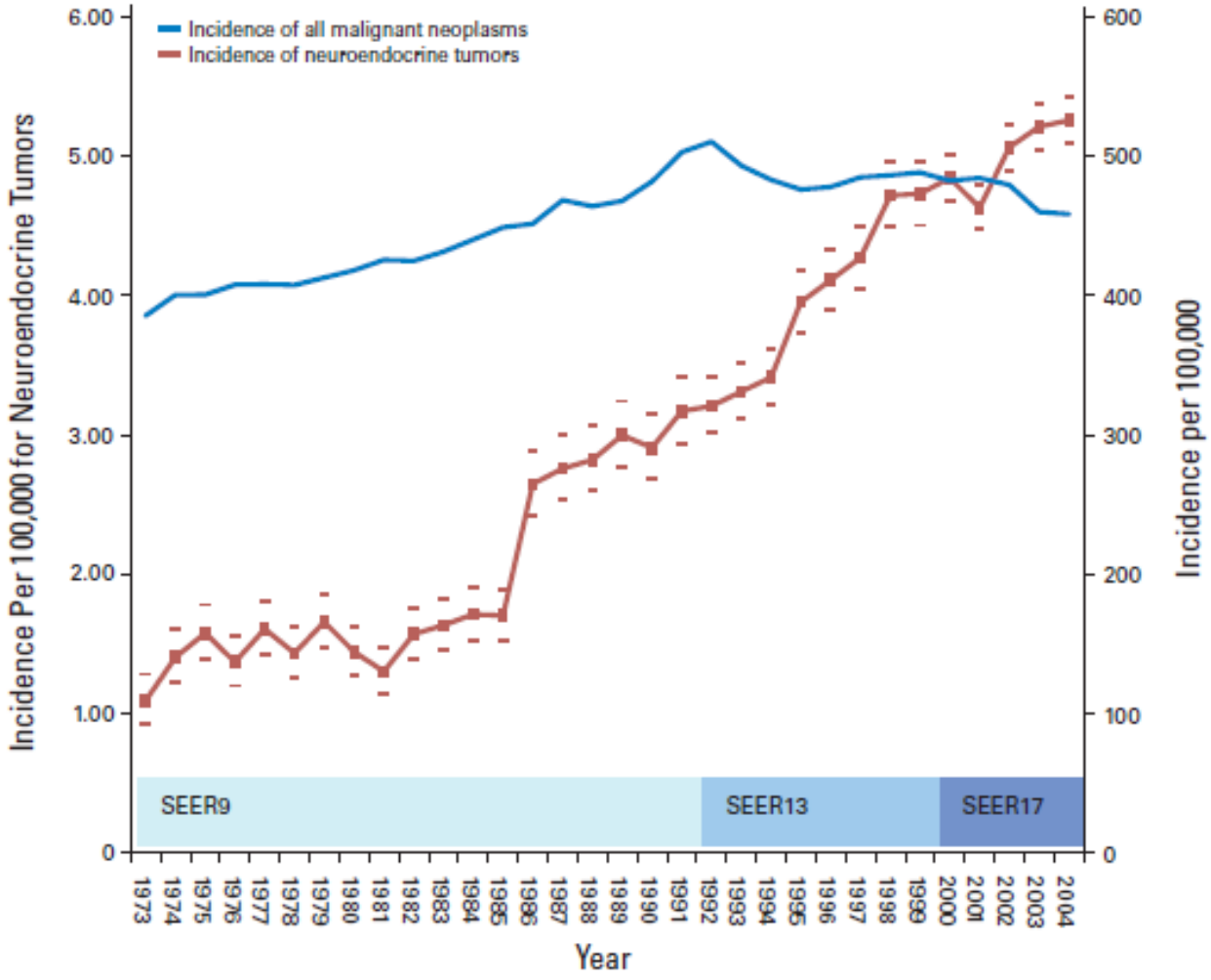

"WHEN THE COWS COME TO THE BIG APPLE"

Neuroendocrine Tumors (NETs)

- Neuroendocrine cells: migrated from the neural crest to the gut endoderm, from multipotent stem cells
- Tumors arising from enterochromaffin cells located in neuroendocrine tissue throughout the body
- NETs present with functional and nonfunctional symptoms and include a heterogeneous group of neoplasms
  - Multiple endocrine neoplasia (MEN)de, type 1 and type 2/medullary thyroid carcinoma
  - Gastroenteropancrtic neuroendocrine tumors (GEP-NETs)
  - Islet cell tumors
  - Pheochromocytoma/paraganglioma
  - Poorly differentiated/small cell/atypical lung carcinoid
  - Small cell carcinoma of the lung
  - Merkel cell carcinoma



Incidence of NETs Increasing



J Clin Oncol 2008;26:3063-3072

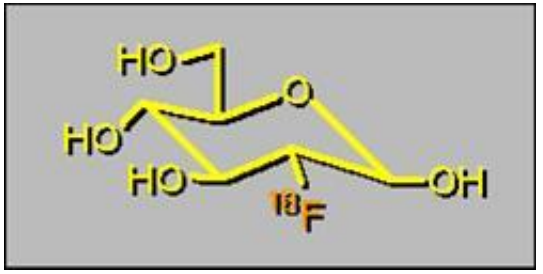
2017 WHO Grading System for Pancreatic NENs

Differentiation	Grade	Mitotic index	Proliferative rate
Well-differentiated NET	G1 (low-grade)	<2 mitoses/10 hpf	<3% Ki-67 index
	G2 (intermediate-grade)	2–20 mitoses/10 hpf	3%–20% Ki-67 index
	G3 (high-grade)	>20 mitoses/10 hpf	>20% Ki-67 index
Poorly differentiated NEC	G3 (high-grade)	>20 mitoses/10 hpf	>20% Ki-67 index
Small cell type			
Large cell type			

NET = neuroendocrine tumor; NEC = neuroendocrine carcinoma; hpf = high-power field.

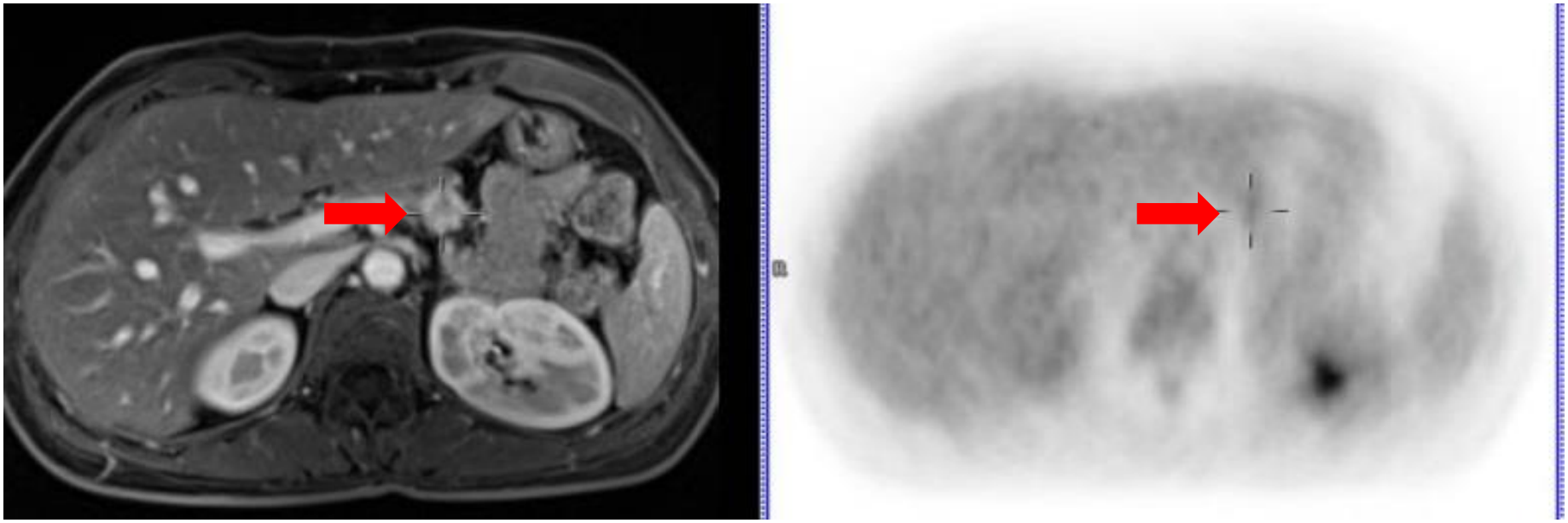
Waseem N et al. J Nucl Med 2019

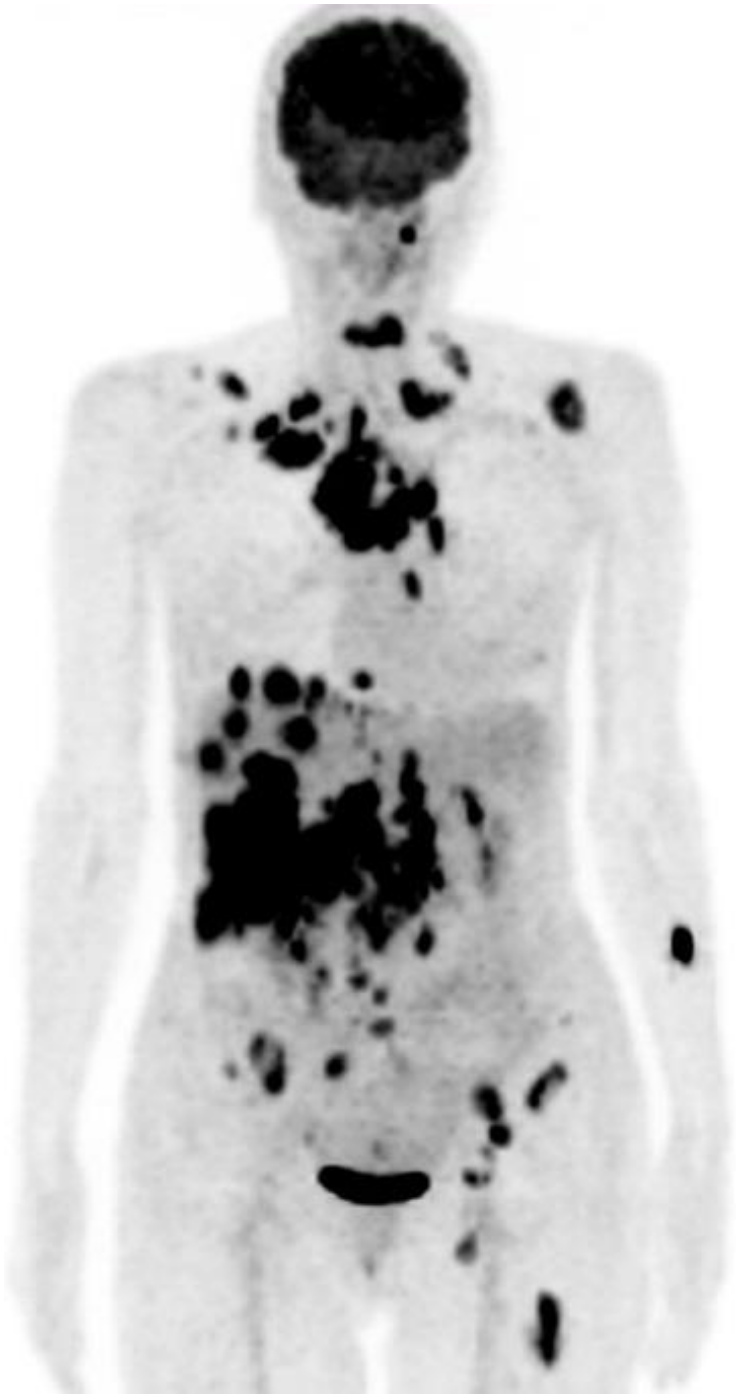
FDG PET



- May be useful for more aggressive, poorly differentiated cases (increased glycolytic rate)
- Preferred tracer for G3 NETs, and some high-grade G2 tumors (in those with ki-67>10%) *(Abgral et al. J Clin Endocrinol Metab 2011)*
- Prognosis *(Binderup T et al. Clin Cancer Res 2010)*
  - High FDG uptake: higher risk of recurrence with worse overall survival
- Identify patients who may benefit from systemic C/T

42F, G1 NET





64F, Duodenal NEC, small cell type

^{68}Ga-DOTA-conjugate peptides

^{111}In-DTPA-octreotide SPECT/CT:

^{111}In —— DTPA — Octreotide SSTR subtype 3-5

DOTATATE (GaTate) PET/CT:

^{68}Ga —— DOTA — Octreotate SSTR subtype 2

Ambrosini et al. PET Clin 2014;
Campana et al. J Nucl Med 2010

Appropriate Use Criteria for Somatostatin Receptor PET in NETs-2017/06

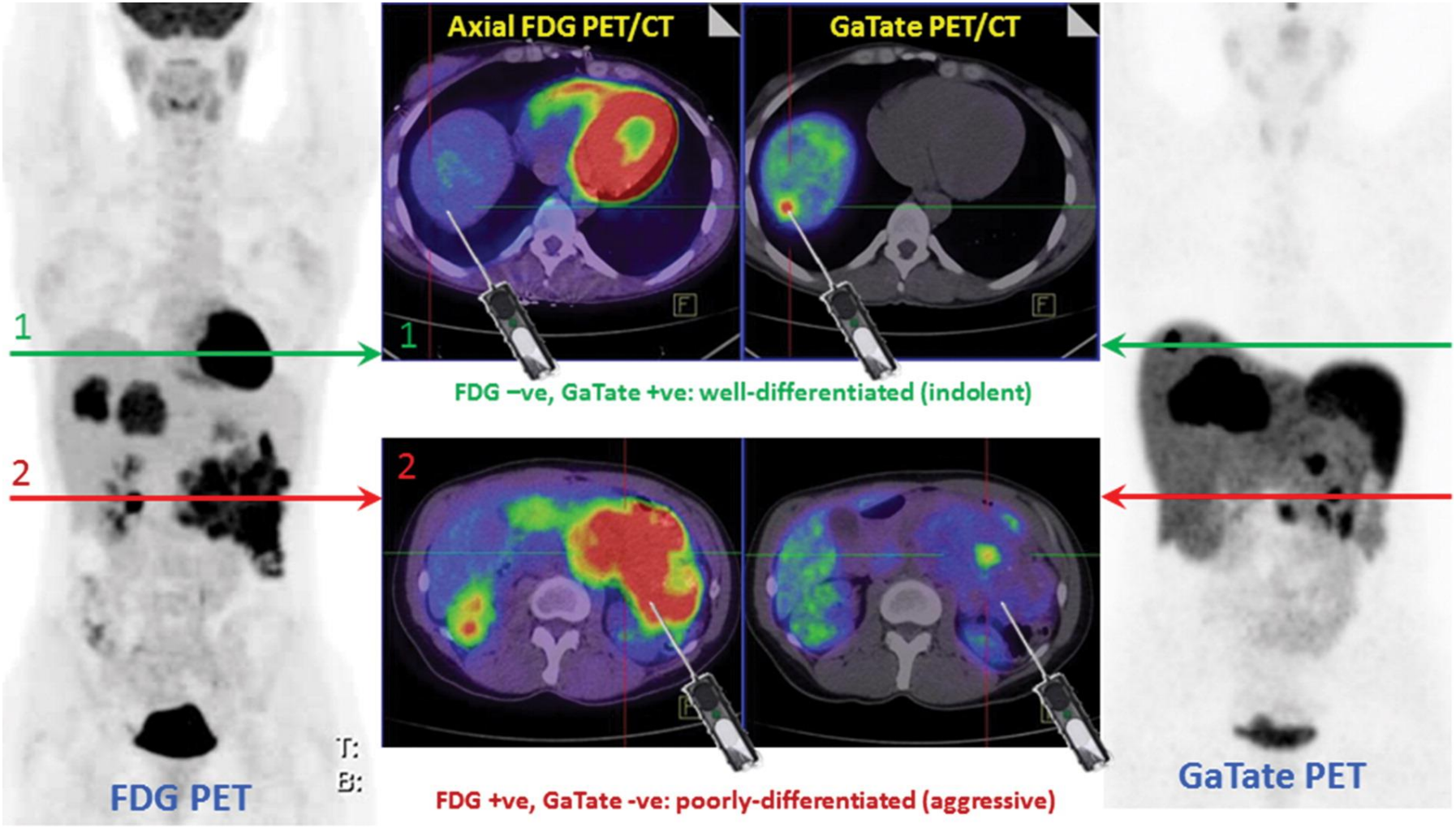
- Improved sensitivity
  - than Octreoscan (14-56%) and FDG (24-75%) for primary and metastatic lesions
  - than CT/MR (12-49%) for identify primary NETs
- 2-hour study, decreased radiation dose, quantify uptake SSTR-PET should replace Octreoscan in all indications in which SSTR scintigraphy is currently being used
- Indications in well-differentiated NETs: 9 appropriate clinical scenarios

TABLE 3
Clinical Scenarios for SSTR-PET

Scenario no.	Description	Appropriateness	Score
1	Initial staging after the histologic diagnosis of NET	Appropriate	9
2	Localization of a primary tumor in patients with known metastatic disease but an unknown primary	Appropriate	9
3	Selection of patients for SSTR-targeted PRRT	Appropriate	9
4	Staging NETs prior to planned surgery	Appropriate	8
5	Evaluation of a mass suggestive of a NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass)	Appropriate	8
6	Monitoring of NETs seen predominantly on SSTR-PET	Appropriate	8

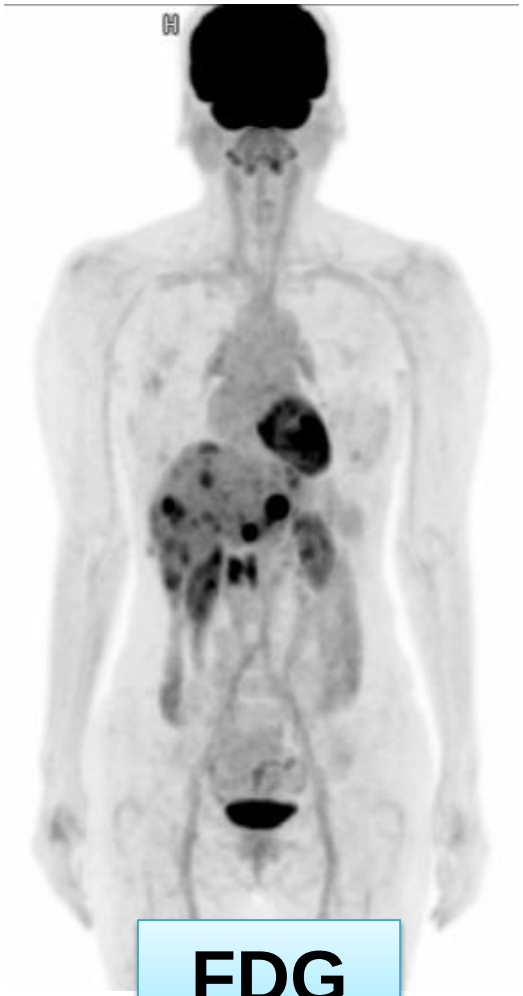
Hope TA et al. J Nucl Med 2017

“Flip-flop” Phenomenon

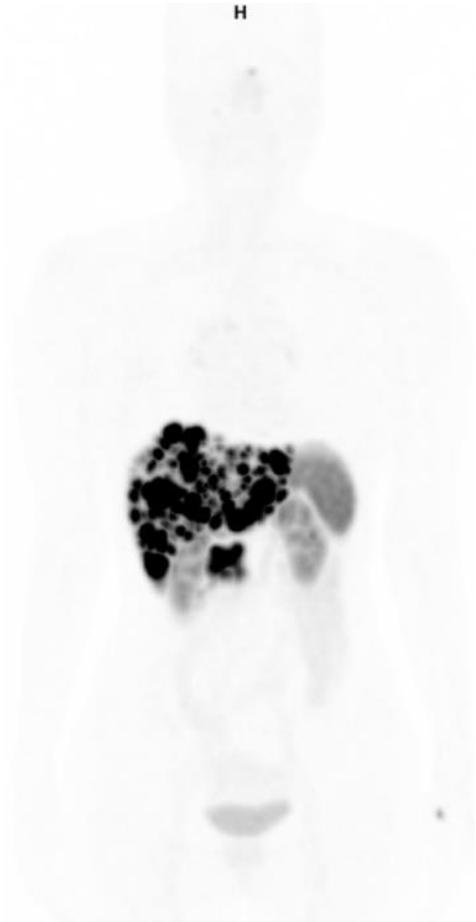


Hofman et al. Radiographics 2015

59F, G2 NET of stomach, Ki-67:18%, with liver metastases, without carcinoid syndrome, long-term control by RAD001 (everolimus), in stable disease (SD) ; 2018/03/23 CgA 207.3 ng/ml (normal range < 36.4 ng/ml)

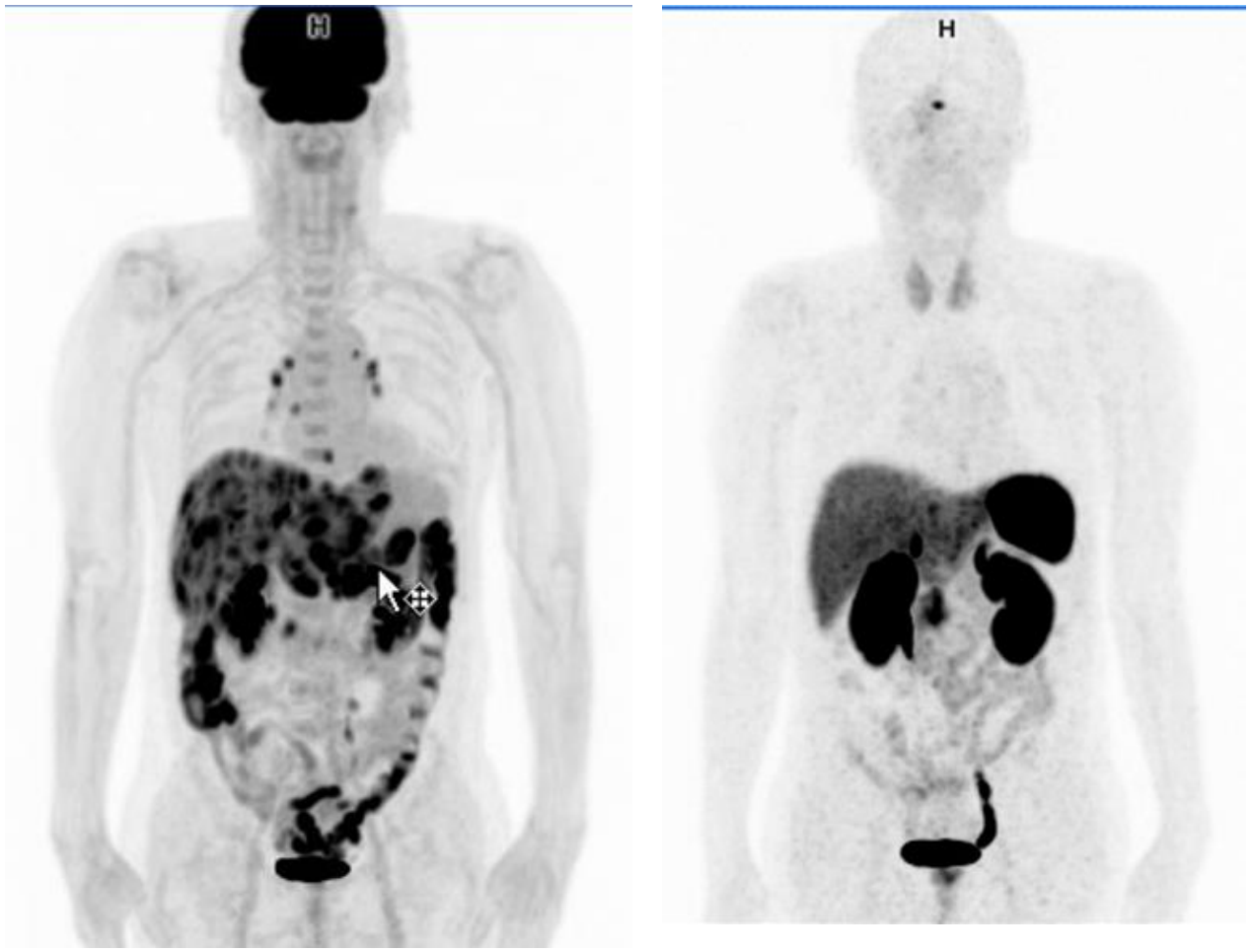


FDG



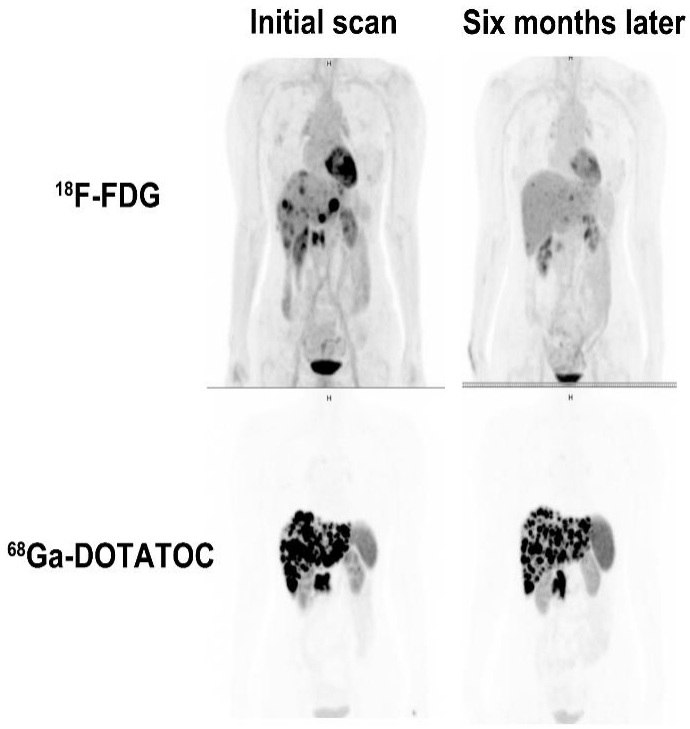
DOTATOC

62M, PB G2 NET, Ki-67: 15%, with liver metastases



Therapy Response Monitoring

- A patient with G2 NET of stomach (Ki-67 proliferation index of 18.0%).
- serum CgA level was noted in the past six months (latest: 207.3 ng/mL).
- Patient underwent transarterial chemoembolization for the hepatic tumors and five courses of chemotherapy.
- Follow-up PET/CT images revealed only slight resolution in the DOTATOC-avid tumors, but partial resolution found in the FDG-avid lesions.



Molecular Radiotheranostics-
Peptide Receptor Radionuclide Therapy (PRRT)

- Image-and-Treat
  - Imaging
    - Positron emission: ^{68}Gallium
  - Therapy
    - beta: ^{90}Yttrium (11mm, $T_{1/2}$= 64 h), ^{177}Lutetium (2mm, $T_{1/2}$=6.7 d), ^{131}I
    - alpha: ^{213}Bismuth, ^{223}Ra

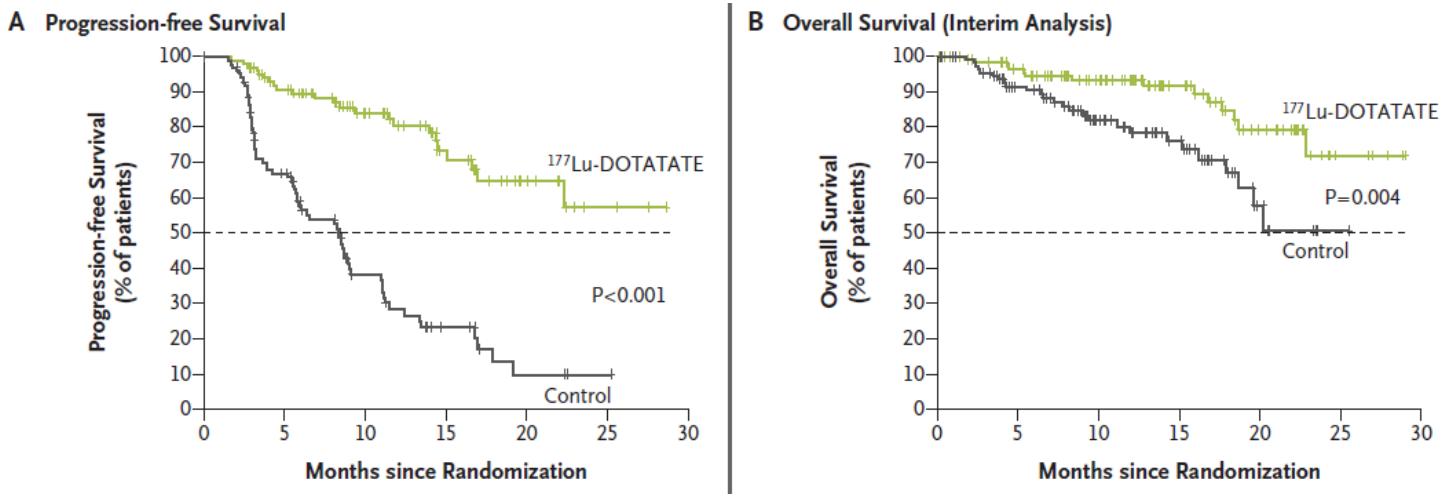
Netter-1 study (2012/9-2015/7)

- Phase III multicenter trial (1st RCT in PRRT)
  - 41 centers in 8 countries (sites: 27 Europe, 14 USA)
- 229 patients with inoperable, progressive, SSR+, midgut NETs
  - ^{177}Lu-Dotatate group (n=116): 4 doses of 7.4 GBq every 8 weeks (plus 30mg LAR every 4 weeks for symptom control)
  - Octreotide LAR group (n=113): 60 mg every 4 weeks

Strosberg J et al. N Engl J Med 2017;376:125-135

Results

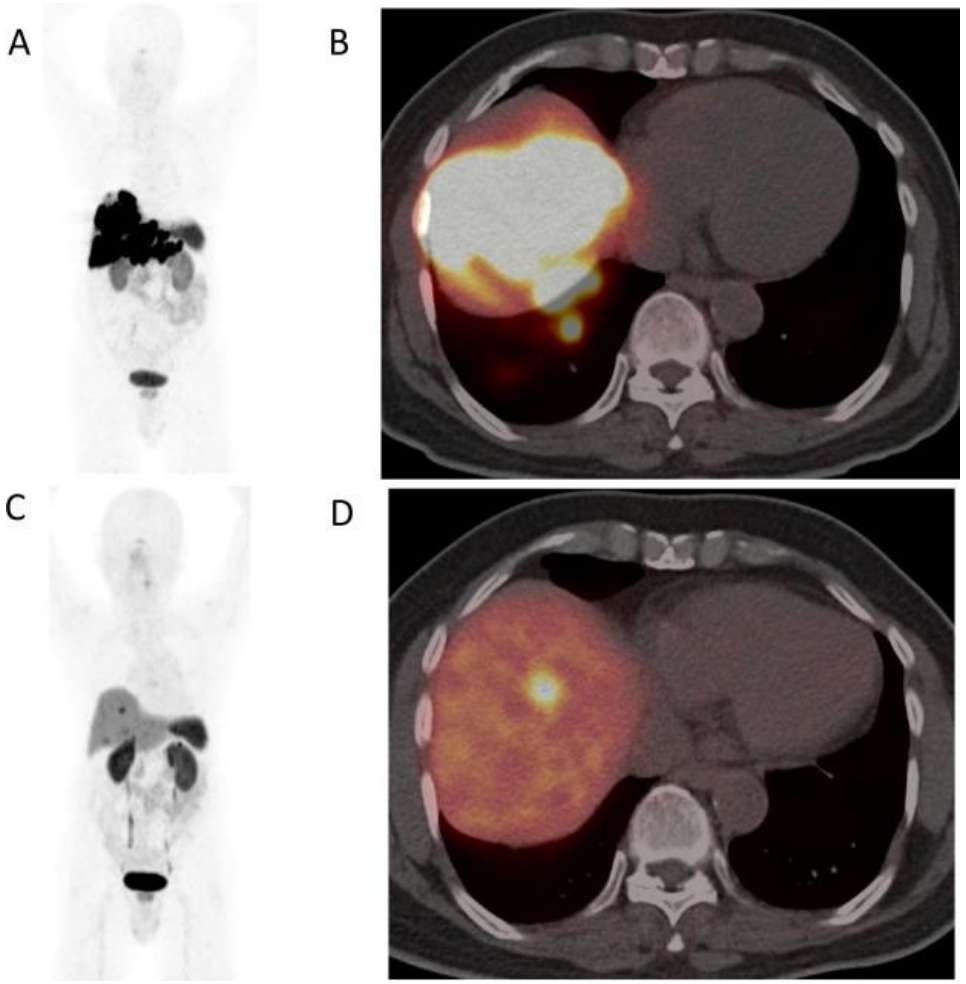
- The estimated rate of progression-free survival at 20-month: 65.25% *vs.*10.8%
- Overall survival: HR, 0.52; 95% CI, 0.32-0.84;
- The response rate: 18% vs 3%
- 44% lymphopenia, 20% ↑GGT, 7% vomiting, 5% nausea, 5% ↑GOT

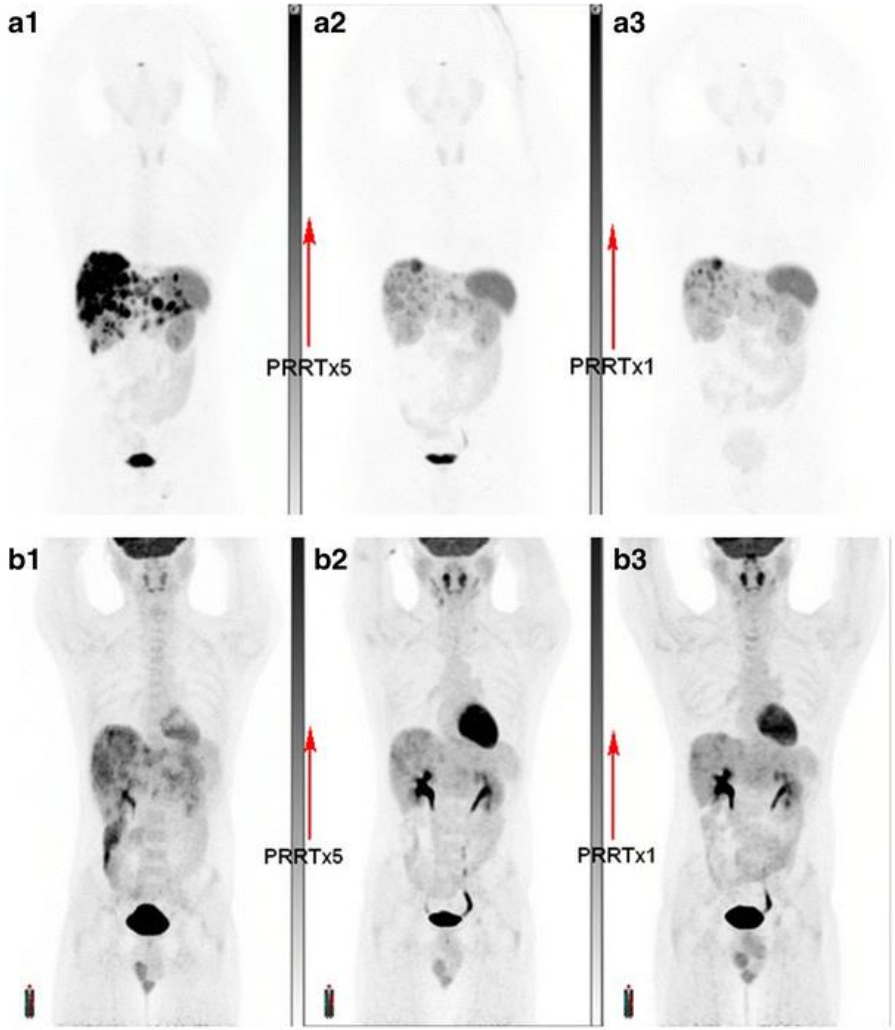


SSTR Treatment

Before Lu-177 DOTATATE

After Lu-177 DOTATATE





68Ga-DOTATATE

18F-FDG

Thang SP, et al. Eur J Nucl Med Mol Imaging 2018

GAINED APPROVAL FROM EUROPEAN MARKETING AUTHORISATION (ma)

PRESS RELEASE

Advanced Accelerator Applications Announces European Approval of Lutetium (^{177}Lu) Oxodotreotide (Lutathera®) for Gastroenteropancreatic Neuroendocrine (GEP-NET) Tumors

Completes First Theragnostic Radiopharmaceutical Pairing in Oncology

September 29, 2017, Saint-Genis-Pouilly, France - Advanced Accelerator Applications S.A. (NASDAQ:AAAP) (AAA or the Company), an international specialist in Molecular Nuclear Medicine (MNM), today announced that the European Commission (EC) has approved the marketing authorization of lutetium (^{177}Lu) oxodotreotide* (Lutathera®) for "the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults." This approval allows for the marketing of lutetium (^{177}Lu) oxodotreotide* (Lutathera®) in all 28 European Union member states, as well as Iceland, Norway and Liechtenstein.

January 26, 2018

Advanced Accelerator Applications Receives FDA Approval for Lutathera® for Treatment of Gastroenteropancreatic Neuroendocrine Tumors

Patient Selection for PRRT

- SRS imaging positive (theranostic principle)
- Inoperable
- Metastatic well-differentiated NETs progressed with cold somatostatin therapy
- Sufficient bone marrow reserve
  - >75,000/μL for ^{177}Lu
- No significant renal impairment
- G3 tumors?

Summary

- Underline biological expression/characteristics
  - ^{18}F-FDG PET
    - Increased GLUT transporter expression; more often in dedifferentiated NETs
  - ^{68}Ga-DOTATOC PET
    - Increased expression of SSTRs
- Theranostics:
  - ^{68}Ga-DOTATATE/^{177}Lu-DOTATATE

Advantages of NM Theranostics

- Confirm targeting
  - –Few futile therapies
- Measure kinetics
  - –Personalized dosing
- Learn about biology
  - –Vast tumor heterogeneity

Thank you for your attention!

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