Peptide Receptor Radionuclide Therapy (PRRT) of NET

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Relevant Financial Relationship(s)

None

Off Label Usage

None

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Outline

- What is PRRT?
- Patient selection for PRRT
- Treatment protocol
- Side effects
- PRRT outcomes
- Treatment team, current work for a therapy center

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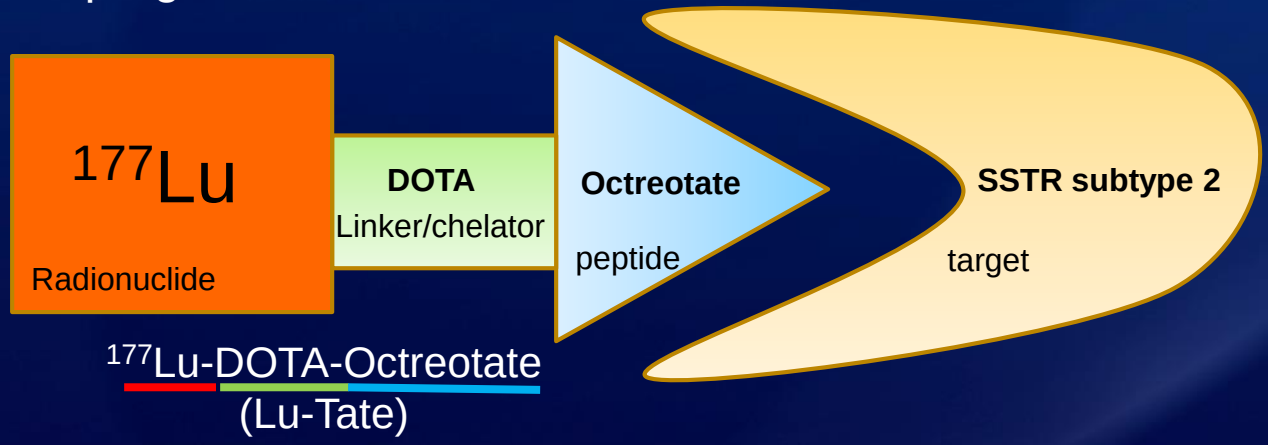
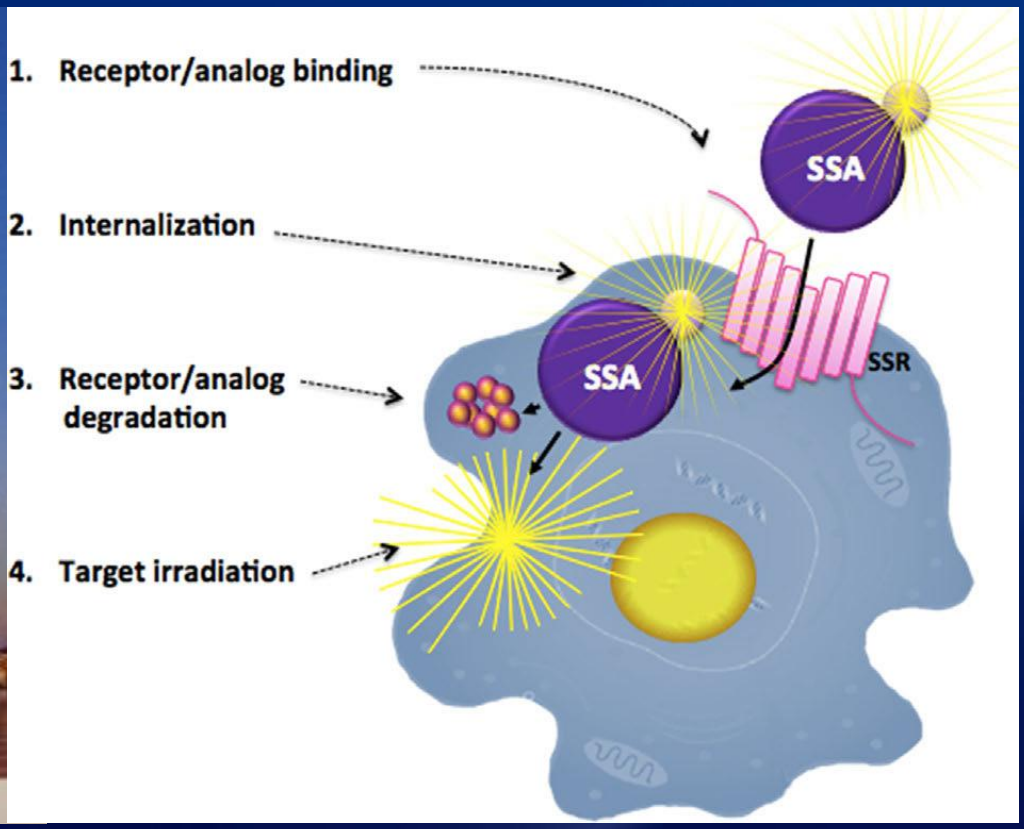
Therapy

- Fact: Majority of NETs have high density of somatostatin receptors compared to other cells
- PRRT targets somatostatin receptors. Lock and key system
- The peptide (Octreotate) and linker (DOTA) are labeled with radioactive isotope that emits radiation and causes DNA damage.
- Objective response rate is between 15-35%. Improves quality of life, overall survival and progression free survival SIGNIFICANTLY!



PRRT works like a Trojan horse!



Bodei et al. Semin Nucl Med, 2016

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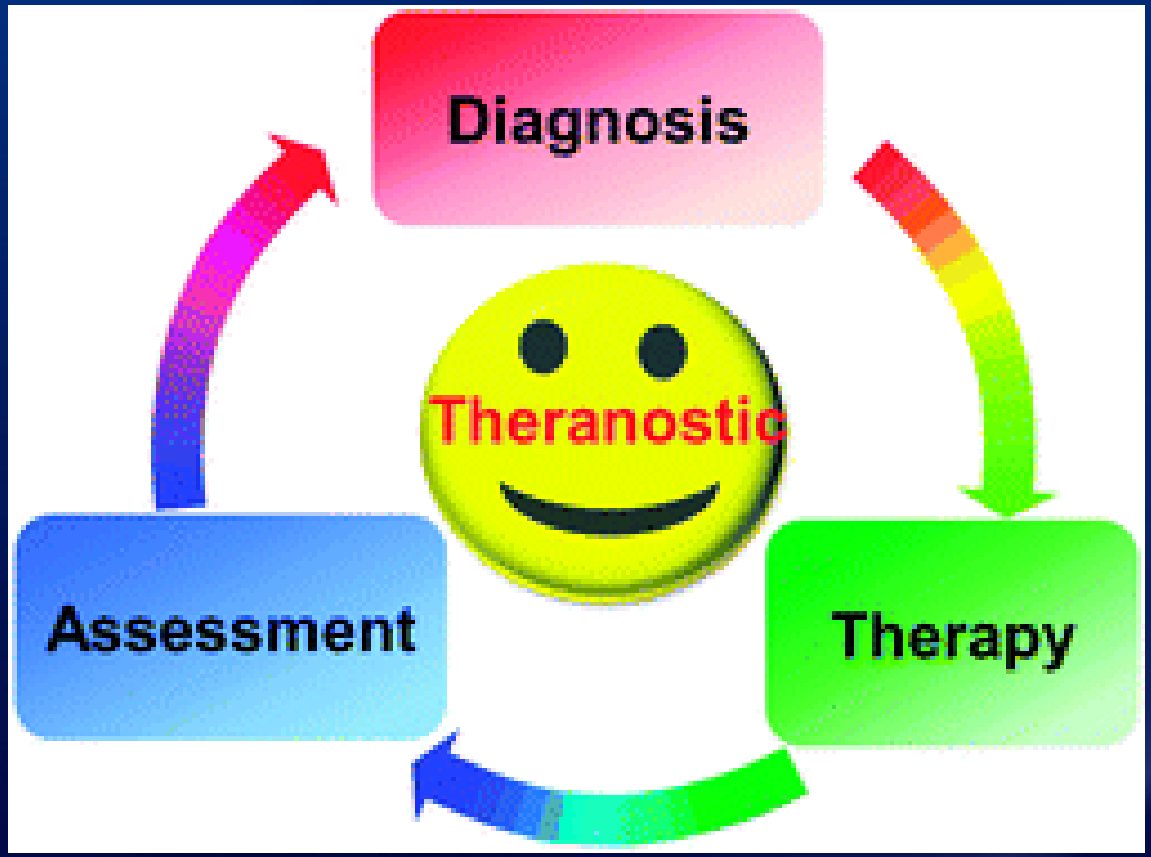
Theranostics (from imaging to therapy)

If you can see it, you can treat it



Kim JS, Chemical Society Reviews, 2015

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Grading of pathologic uptake

Krenning Scoring System

Visual grading of pathologic uptake
Initially developed for Octreotide, but can be use for 68Ga-Dotatate PET/CT

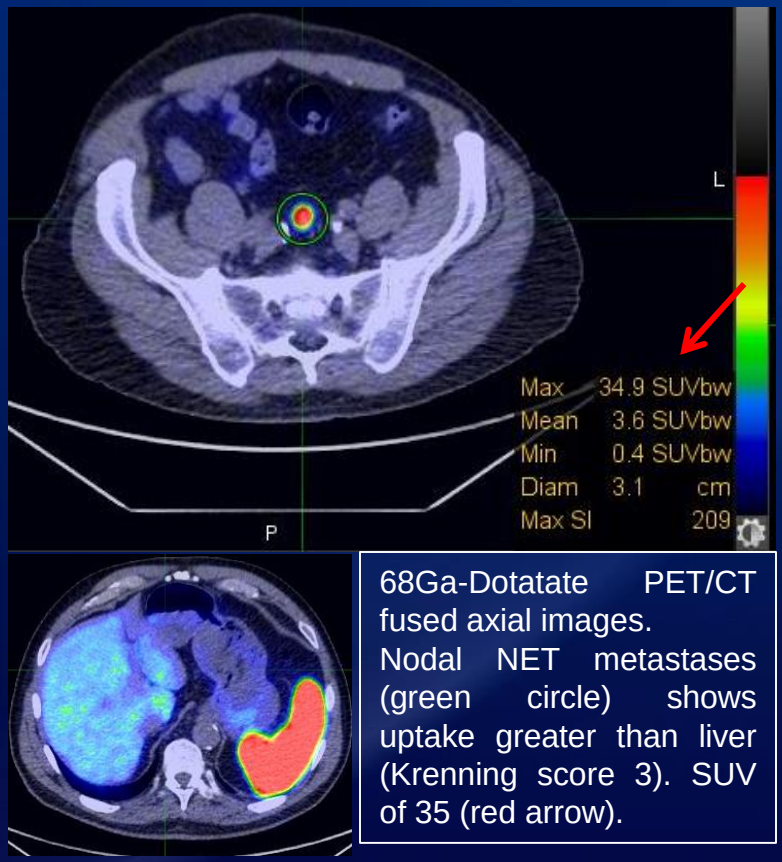
0 No uptake

1 very low

2 less than or equal to that of liver

3 greater than that of liver

4 grater than that of spleen



68Ga-Dotatate PET/CT fused axial images.
Nodal NET metastases (green circle) shows uptake greater than liver (Krenning score 3). SUV of 35 (red arrow).

Susceptible for treatment with peptide receptor radionuclide therapy (PRRT)

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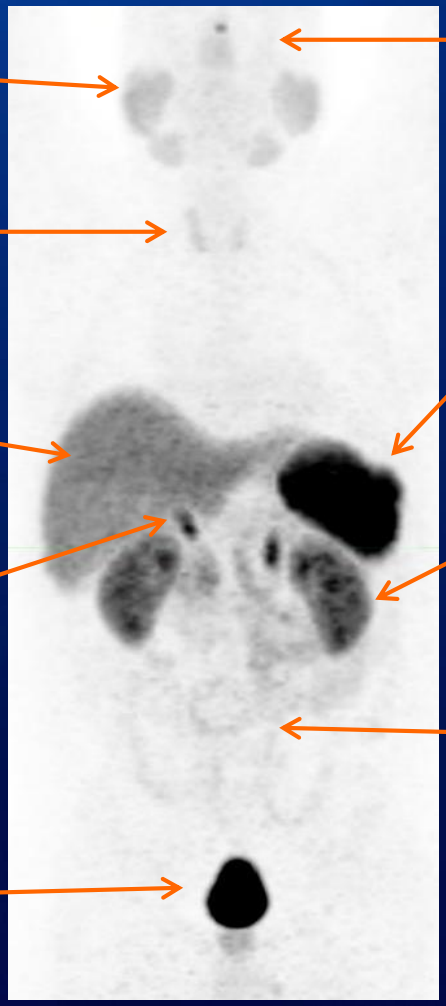
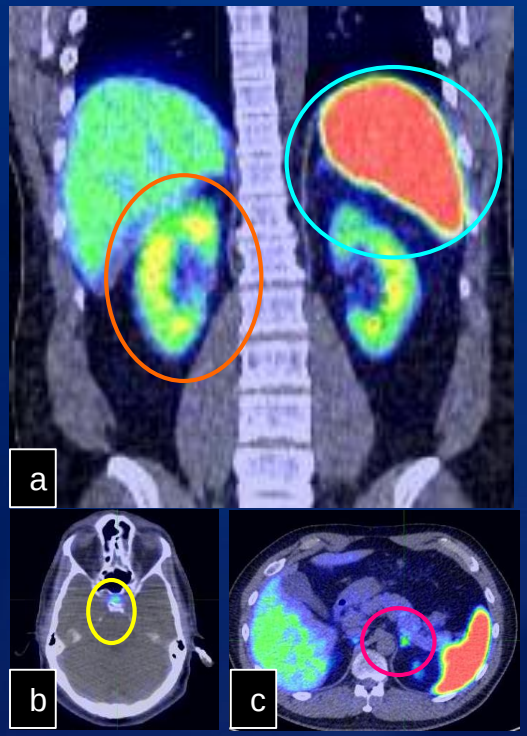
Physiologic distribution



Coronal MIP 68Ga-Dotatate PET/CT image showing normal distribution of the radiotracer.



68Ga-Dotatate PET/CT.
(a) Coronal and (b,c) axial fused images showing highest sites of physiological uptake.

The highest physiologic uptake of 68Ga-Dotatate is in the spleen, followed by the adrenal gland, kidney and pituitary gland.

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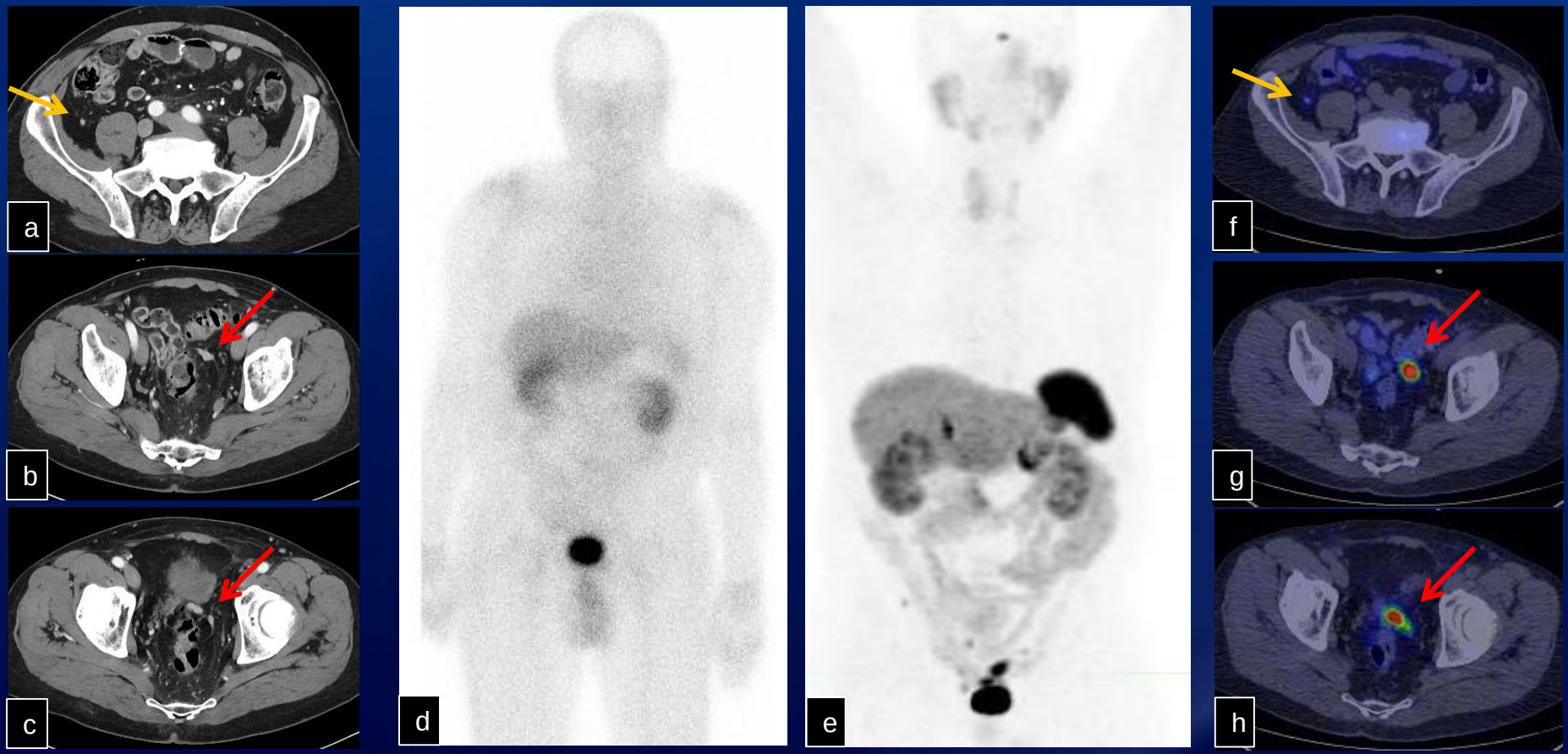
Biochemical evidence of NET with negative 111In-Octreotide imaging

CT

Octreoscan

^{68}Ga-DOTATATE PET/CT



70 yo Male. Resected node-positive small bowel G2 NET 2 years ago. Slightly elevated urinary HIAA.

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Patient selection

- Inoperable/metastatic well-differentiated (grade 1/2) NET (Ki-67 less than 20))
- Well-differentiated grade 3 NET may be considered
- Sufficient bone marrow reserves
- Creatinine clearance >50 mL/min, Cr<1.7
- Karnofsky Performance Status >50
- Expected survival >3 months
- Signed informed consent

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Exclusion criteria

- Pregnancy, breast feeding
- Renal or severe liver impairment
- Abnormal blood work (very low Platelets, WBCs, Hb)
- Recent myelotoxic chemo or extended radiation
- Heart failure (advanced stage)

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Initial consultation

- Review of imaging, indications, potential side effects
- Any acute illness, any psychiatric condition
- Uncontrolled heart failure? (Carcinoid heart)
- ECOG performance status less than 2
- Consent

- Long acting SSAs should be off for 4-6 weeks and short acting should be off for 1 day

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Day of therapy

- About 8 hour stay, Eisenberg 7-2 (we have 4 rooms)
- Patients report to admission desk at Methodist at 8 am
- Nuc med visit
- IV team visit

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Day of therapy

- Adm of nausea medicine both oral and IV
- Aa solution starts first, lasts for 4 hours
- About 30 minutes after Aa started, Lutetium is administered for about 1 hr)
- Dismissal 30 minutes after completion of aa administration and measurements performed by RSO

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After therapy

- 4 x cycles of therapy about 8 weeks apart
- Post treatment scans and consultations
- Maintain clinical follow up with your oncologist
- Radiation safety instructions

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Brief review of Rad Safety Instructions

- Contact: For first 1 day avoid close contact from everyone (3 ft).
- For 1 week, avoid contact from pregnant women and children younger than 10 years of age (3 ft).
- Hygiene: wash hands, shower daily, drink fluids, flush toilet twice, keep trash separate
- Travel: If air travel to home is required, you can fly safely provided no one flight of the trip is longer than 20 hours. Once home, no flights for 3 days.

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Side effects (early)

- Usually mild
- Nausea/vomiting, fatigue, mild abdominal pain, diarrhea (likely from administered amino-acid, occurs within first 24 hours after therapy)
- Exacerbation of hormonal symptoms (less than 1%) (Patients treated for VIPoma or bronchial carcinoids are most at risk).

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Side effects (late)

- Kidneys and bone marrow
- Hematological toxicity: most common are thrombocytopenia and lymphopenia (without any clinical consequence) (grade ¾ toxicity is less than 10%, around 3-4%), MDS in 1%.
- No significant renal toxicity (median decline of Cr clearance 3.8% per year). Severe renal failure is very rare, only a few sporadic cases reported
- Mild hair loss (about 60% of patients, no balding)

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Is it effective?

- Dr.Kwekkeboom first described PRRT with Lutetium in 2003 and reported first results in 2005 for 131 patients
- CR: 2% of the patients, PR in 26% and minor response (MR) in 19%.
- Same group at 2008, 310 GEP NET patients:
- CR:2%, PR: 28% and MR in 16%
- Kim et al at 2015, 479 patients, Disease control reported as 81%

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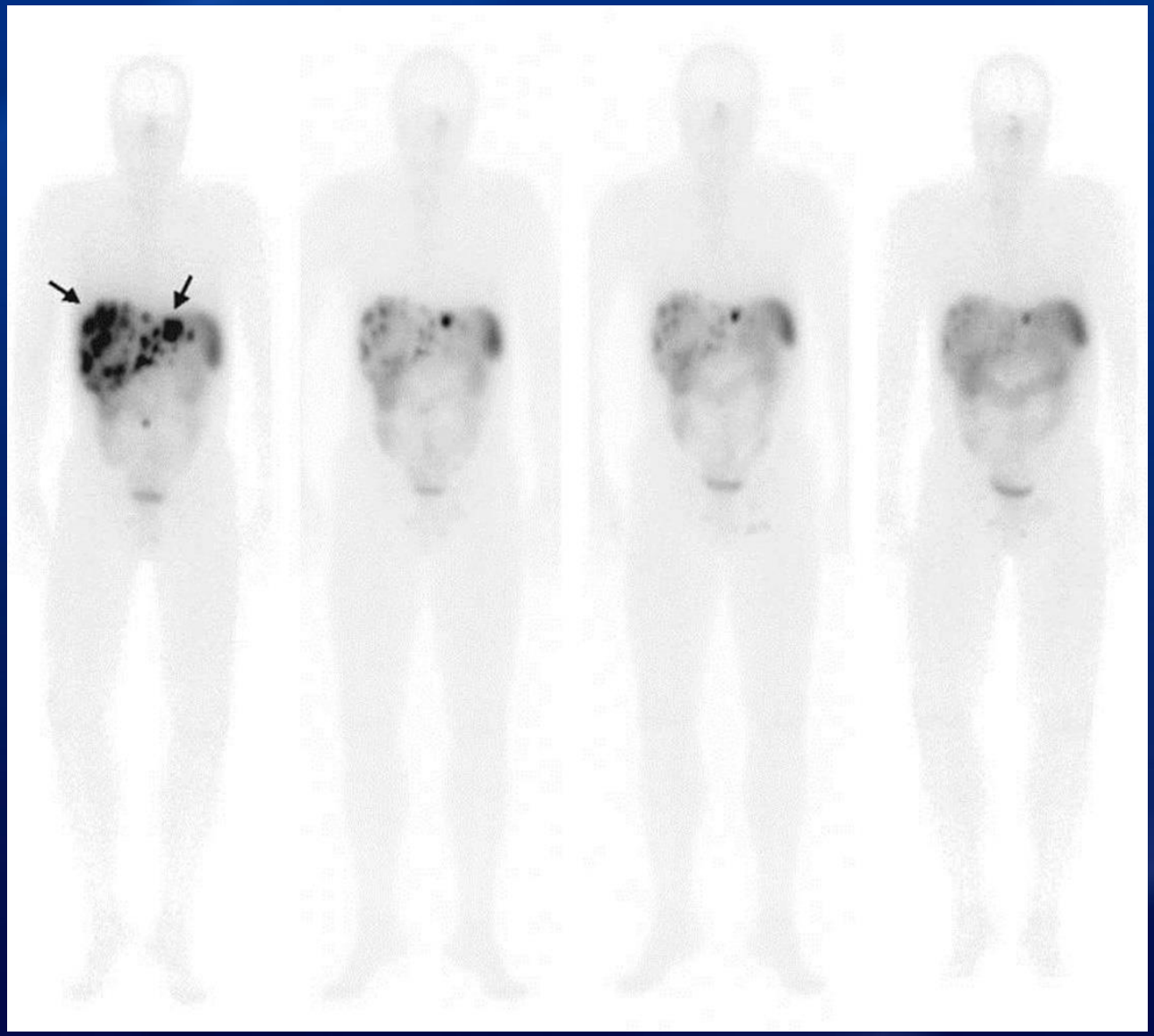

Krenning et al. Hematol Oncol Clin NA 2016

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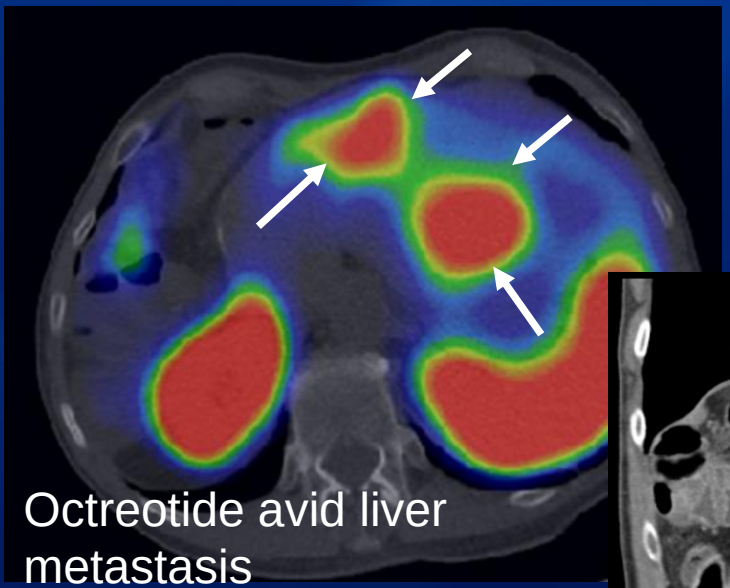
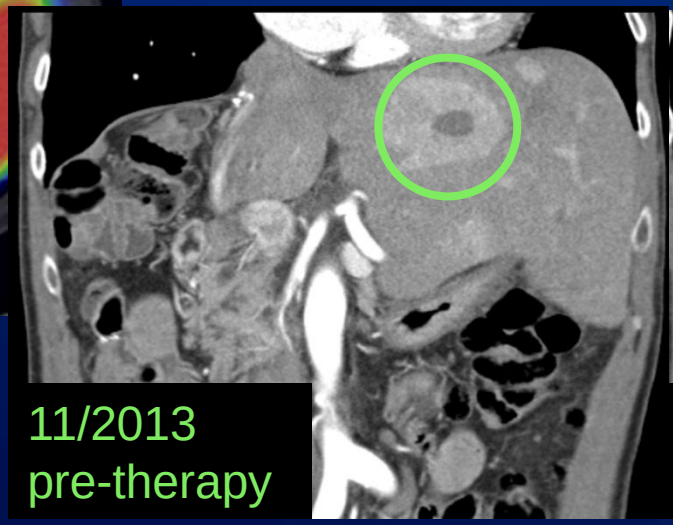
Prior Experience- Netter 1 Trial

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

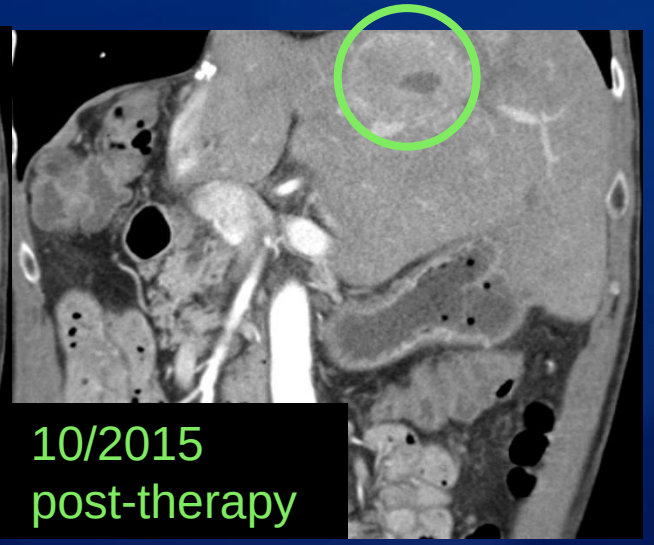
J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*



Octreotide avid liver metastasis



11/2013 pre-therapy



10/2015 post-therapy

66y/o male with carcinoid received Lutathera 11/2013. Continues to have partial response/stable disease without progression.

Table 2. Objective Tumor Response.*

Response Category	^{177}Lu-Dotatate Group (N=101)	Control Group (N=100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

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Factors predicting the response

- High tumor uptake at Somatostatin receptor imaging
- Limited liver involvement

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PRRT improves quality of life

- 265 patients, Quality of life questionnaire
- Significantly improved in 36%
- Specific symptoms including diarrhea, appetite loss and insomnia improved in 44-77%
- Improved bone pain

Khan et al, J Nucl Med 2011 52:1361-68

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Progress Continues
Early Access

- Prior experience from NETTER-1
- Patient care
  - Eisenberg 7-2 nurses
  - Med 10 team
- Treated 10/10 expanded access patients
- Passed site visit to be a sight in the multi-center Lu-DOTATATOC therapy trial

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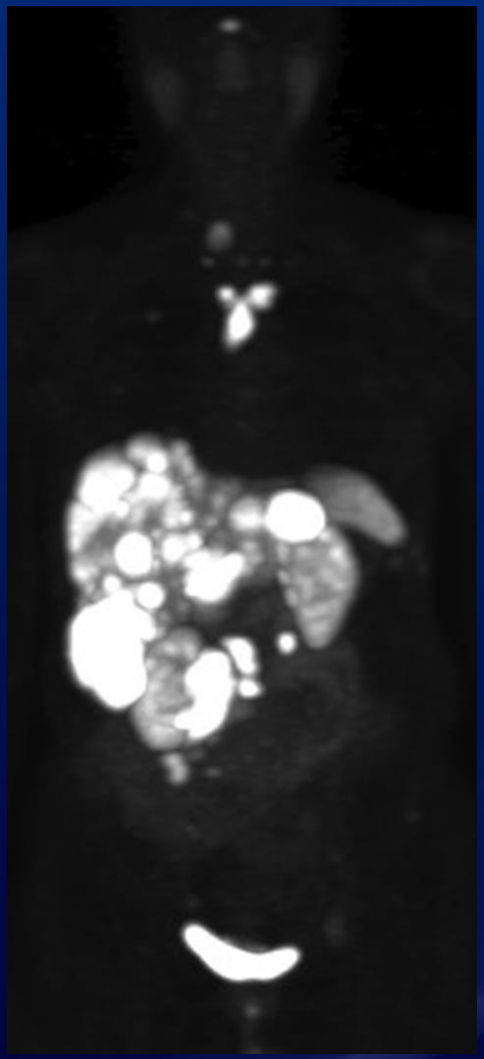
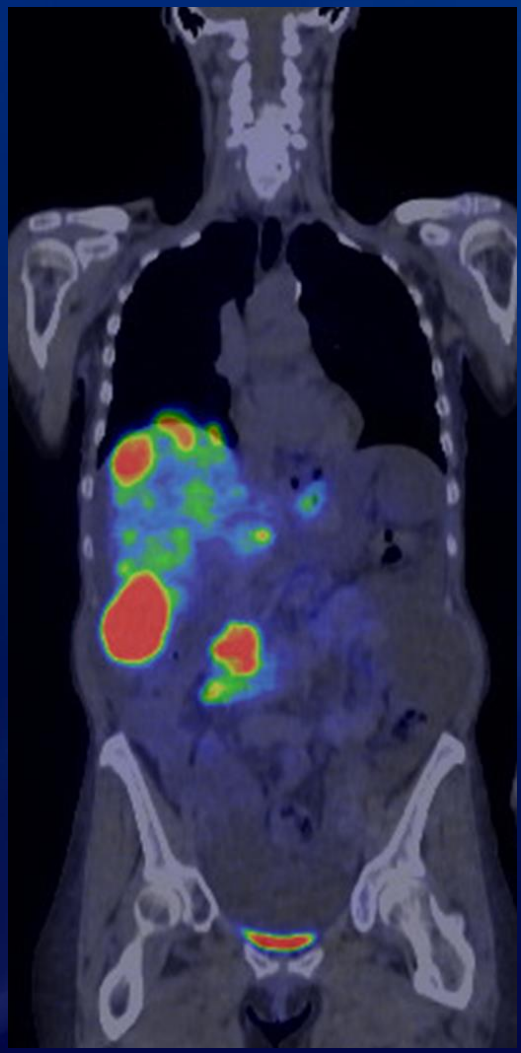
Current Practice
Expanded Access

54y/o male with carcinoid received Lutathera 10/18/2017

>300 Ga-DOTATATE PET/CTs performed

Anticipated FDA approval of Lutathera on 1/28/2018





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Future directions

- Combination of PRRT with chemotherapy
- Antagonist imaging and therapy
- Alpha emitters, such as Bismuth

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PRRT is a team work
requires dedicated multidisciplinary team

- Medical oncology
- Hematology
- GI oncology
- Radiology/Nuclear Radiology
- Surgery
- Interventional radiology

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Therapy Center team

Physicians

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Therapy Center team

Nuclear Pharmacy

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Therapy Center team

Nursing

Therapy Center team

Nuclear Medicine Technologists

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Therapy Center team

Finance/Admin

Therapy Center team

Radiation Safety

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Therapy Center team

Program Support

THANK YOU

No two zebra's stripes are same, no two NET patients are same

Don't think only horses when you hear hoof beats, but zebras as well

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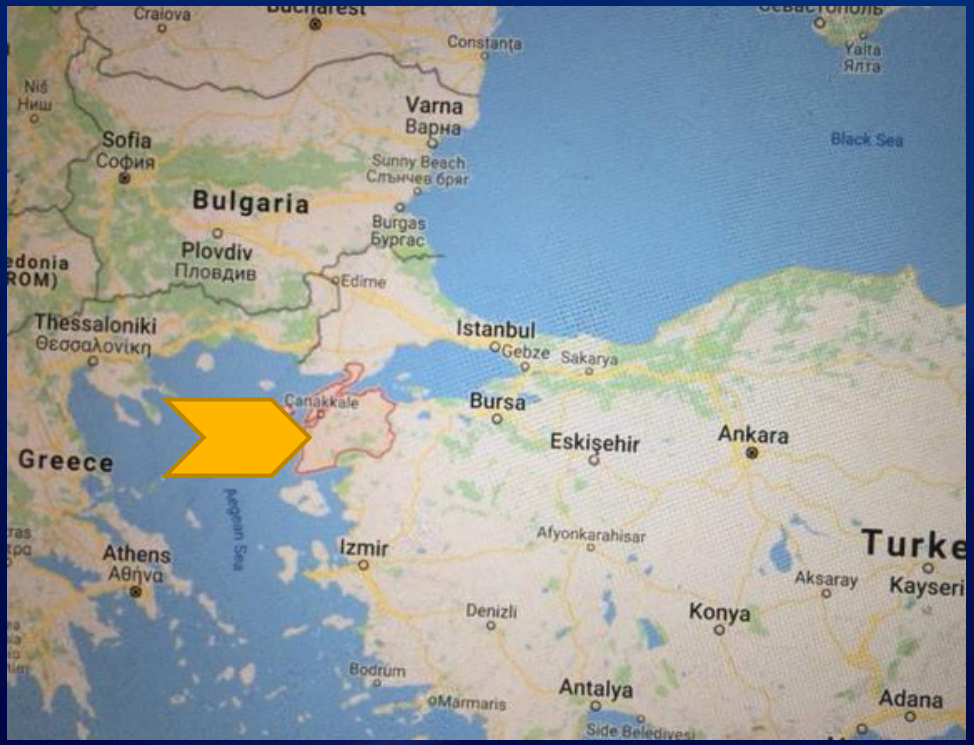
QUESTIONS?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Niš
Ниш
Varna
Варна
Sofia
София
Black Sea
Sunny Beach
Слънчев бряг
Bulgaria
Burgas
Бургас
Plovdiv
Пловдив
Edirne
Thessaloniki
Θεσσαλονίκη
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