



Multidisciplinary Approaches to Cancer Symposium

NET Theranostics: Transforming the Therapeutic Landscape for Neuroendocrine Tumors — Opportunities and Challenges

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Disclosures

Founder: Site Therapeutics LLC

Intellectual Property for technology generally related to image guided determination of the position and/or orientation of an object using a machine learning algorithm

Additional intellectual property assigned to the University of Utah Research Foundation related to medical image synthesis for motion correction using generative adversarial networks and dynamic frame rate adjustments in digital subtraction angiography

This disclosure is not relevant to my presentation.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

The off-label/investigational use of [^{225}Ac]DOTATATE, [^{212}Pb]DOTAMTATE, SSTR antagonists, [^{177}Lu]DOTATATE, and [^{177}Lu]DOTATOC will be addressed.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.



Outline

- Era of Personalized Medicine/Theranostic Concept
- NET imaging and diagnosis
- Somatostatin receptor imaging and PRRT
- Evidence for [^{177}Lu]DOTATATE
- Emerging agents and future directions
- Cultural and linguistic competency and implicit bias
- Summary and conclusions



Personalized medicine

Medical treatment customized to the individual patient

Theranostic approach allows selection of best treatment based on imaging confirmation that the tumor will accumulate and retain the therapeutic agent



Thera(g)nostic Concept

Combination of **therapeutic** and **diagnostic**

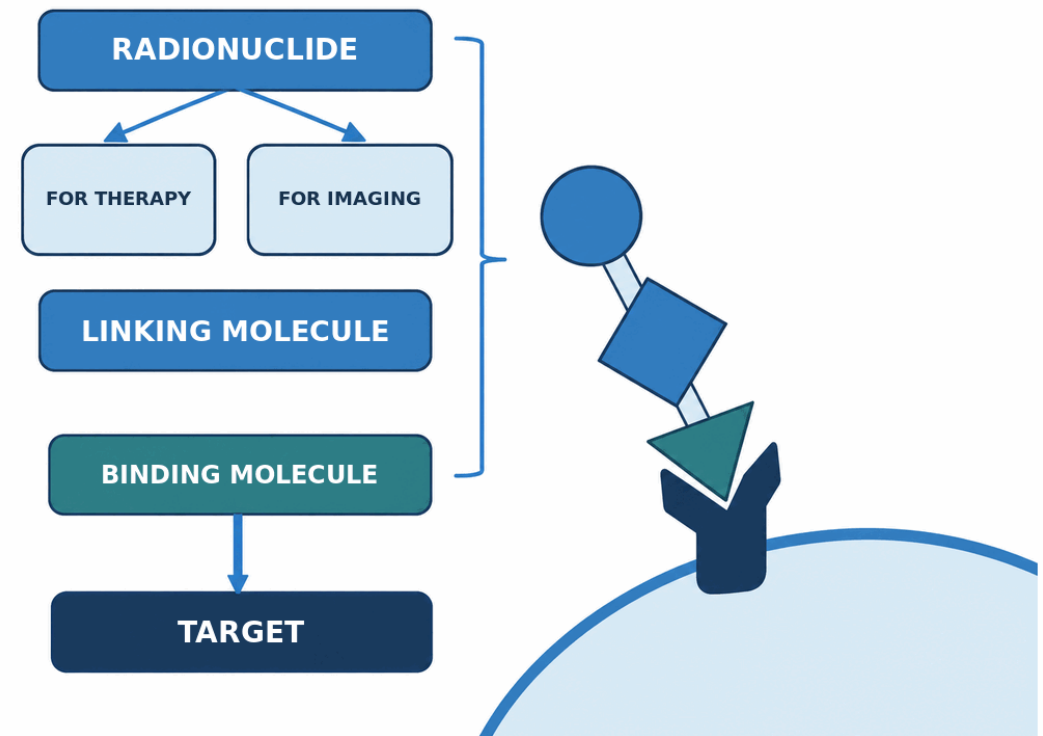
Specific targeting moiety

Attaches to a cell, receptor or other specific biological target

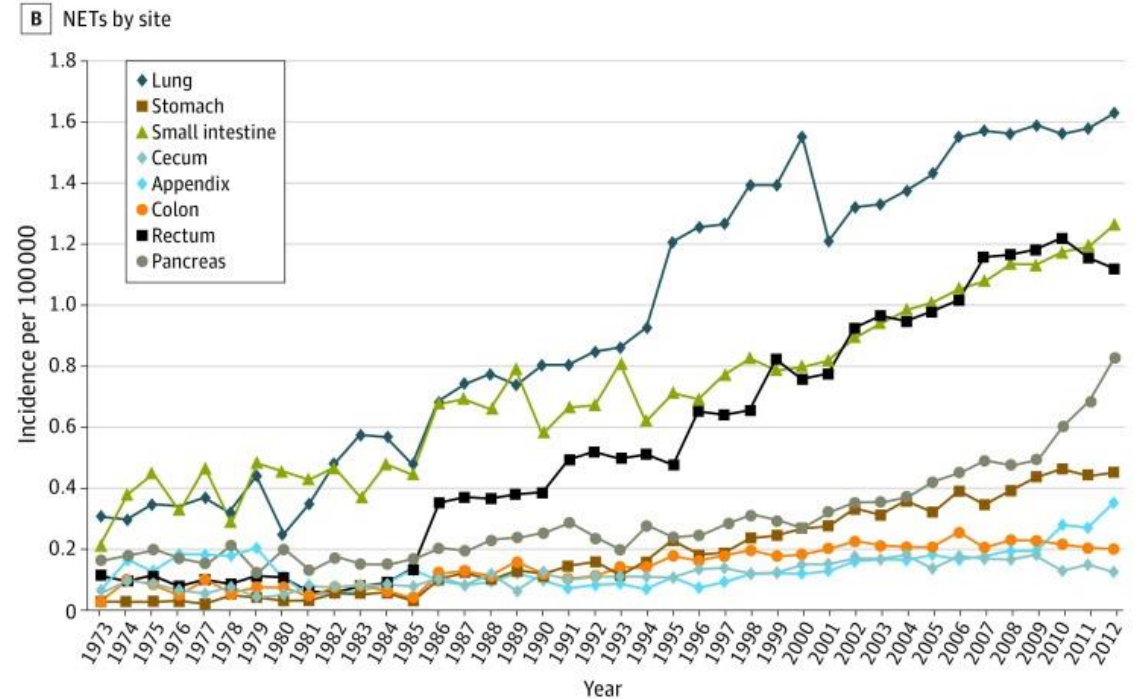
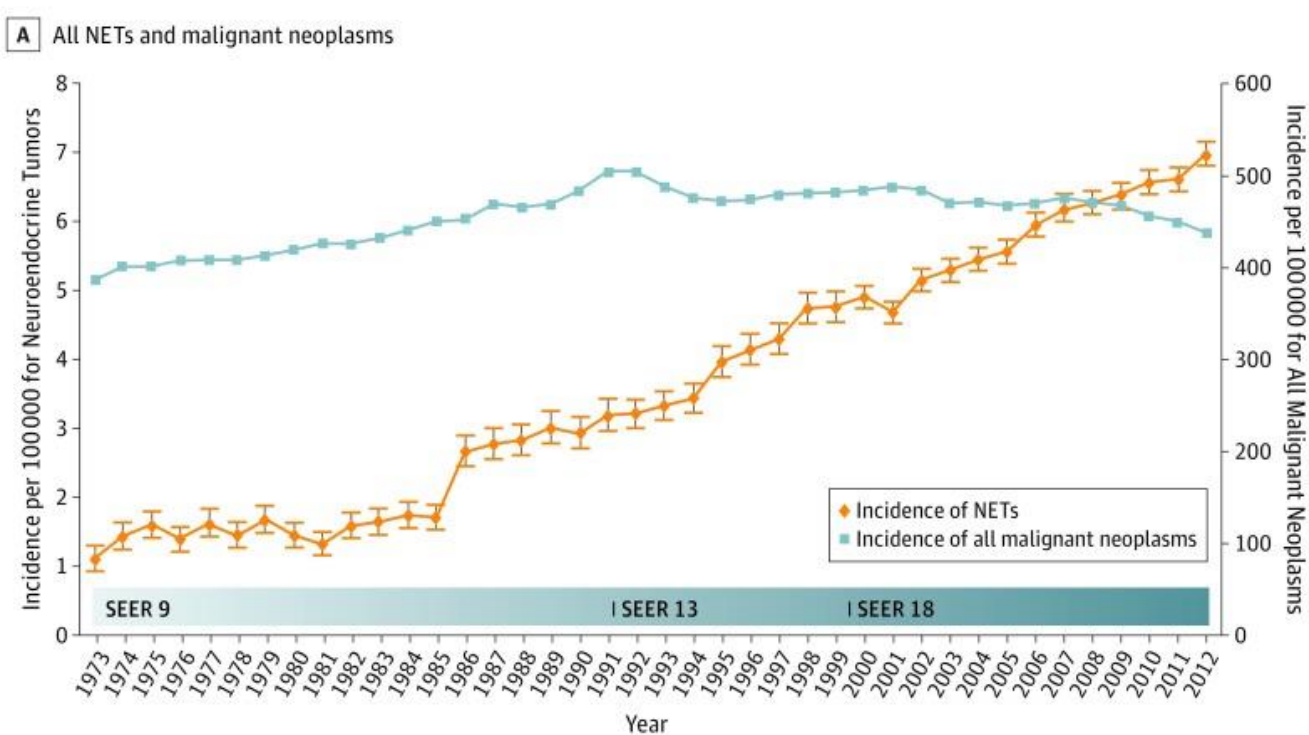
Example: receptor binding peptide, antibody

Linker (connection to targeting moiety)

Attached to linker is a pharmacophore
Diagnostic or therapeutic construct with similar biodistribution



Neuroendocrine Tumor (NET) Trends



Dasari A, Shen C, Halperin D, et al. JAMA Oncol. 2017;3:1335–1342.

NET Imaging Diagnosis

Colonoscopy

Capsule endoscopy

CT

MRI

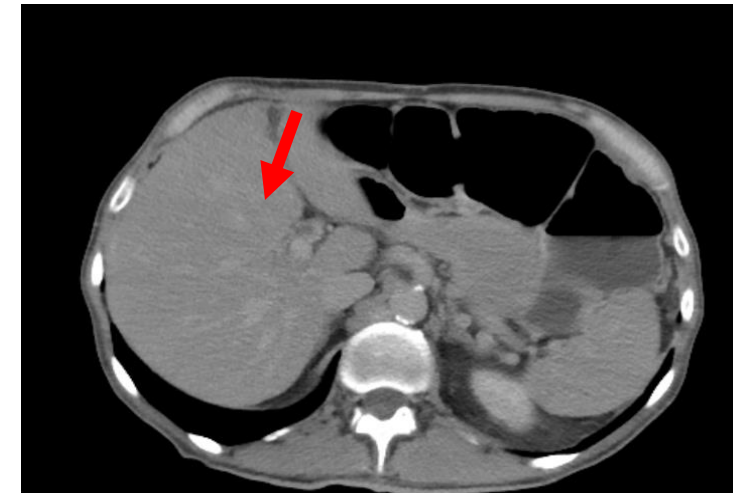
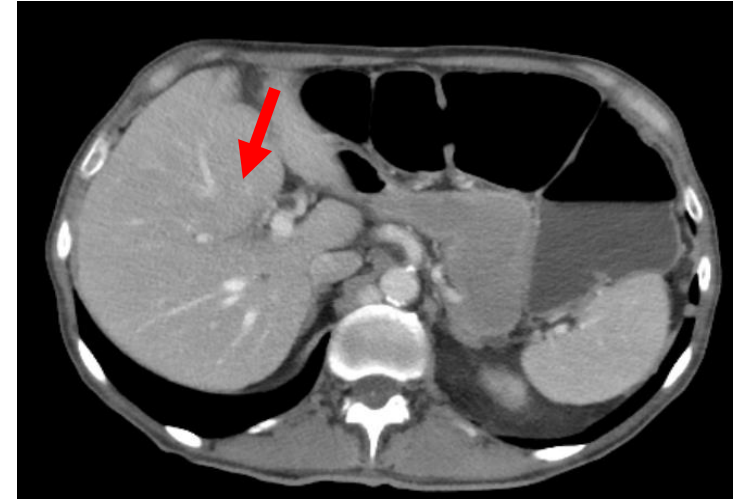
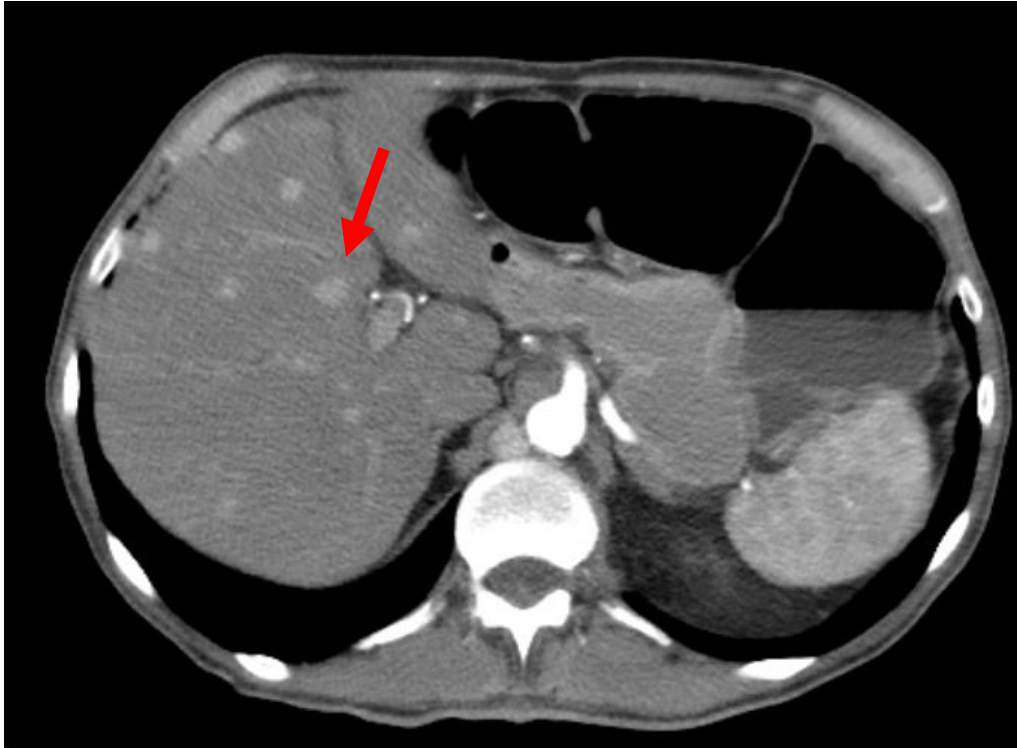
Nuclear Medicine

$[^{68}\text{Ga}]$ DOTATATE / $[^{64}\text{Cu}]$ DOTATATE PET

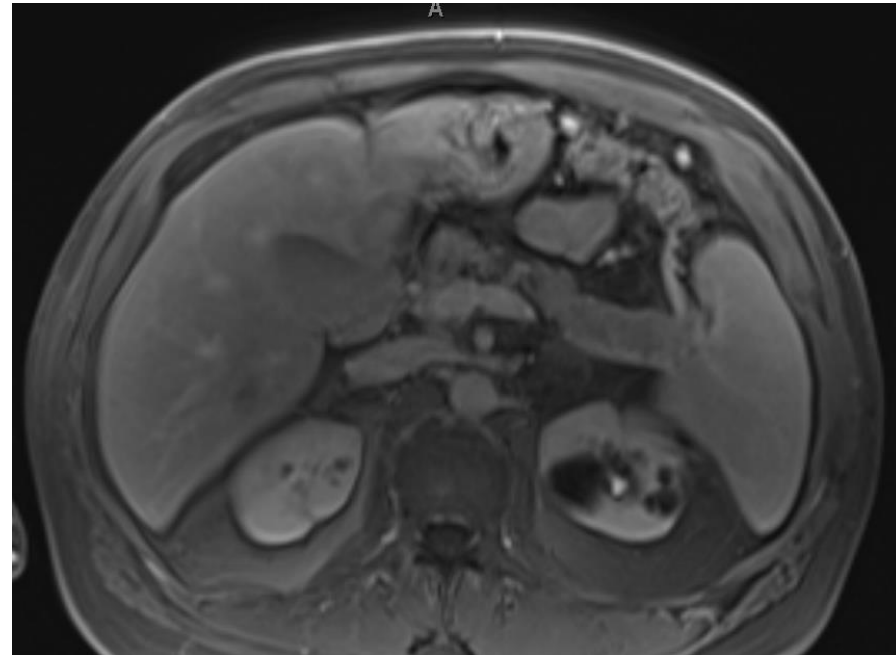
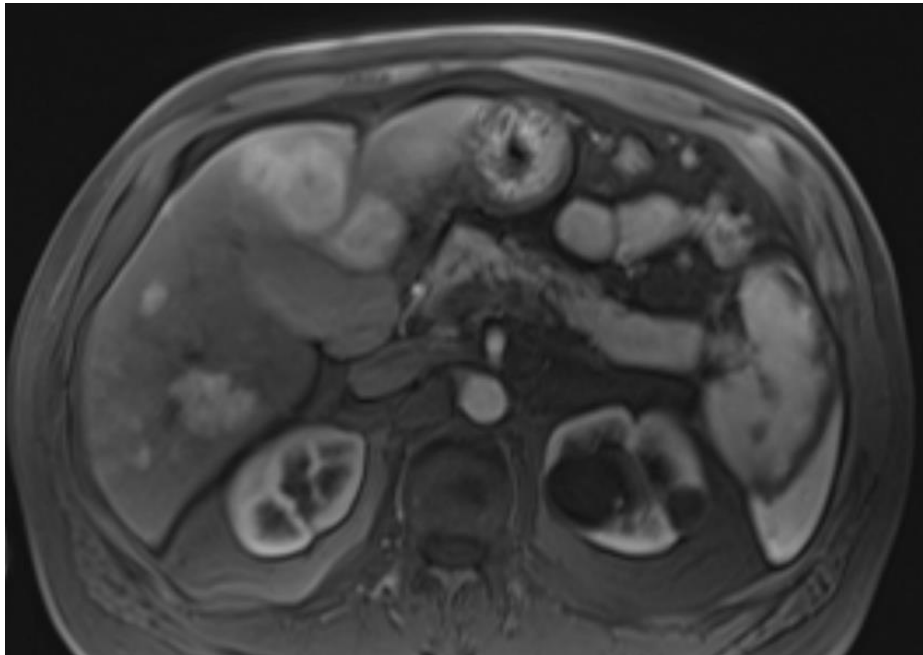
$[^{18}\text{F}]$ FDG PET

$[^{111}\text{In}]$ In—pentetreotide SPECT

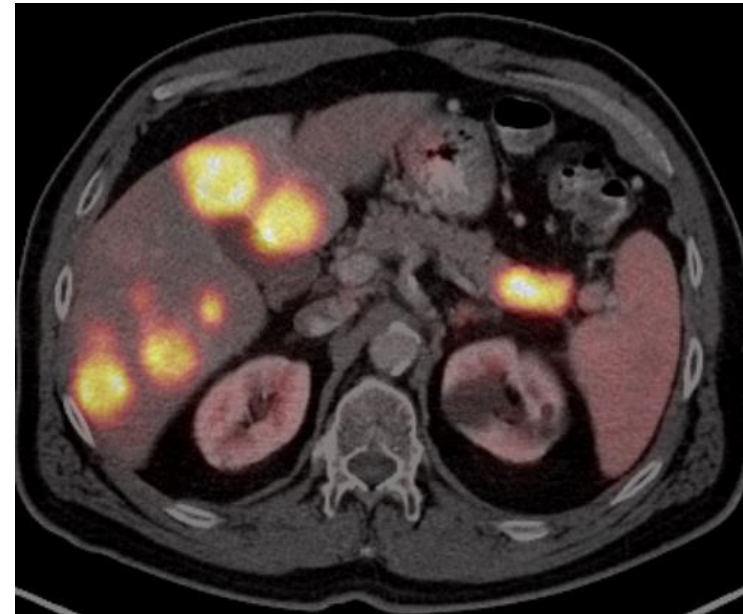
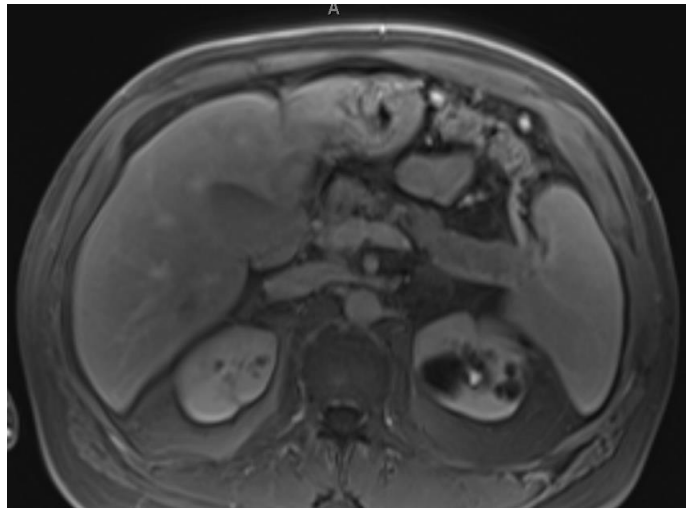
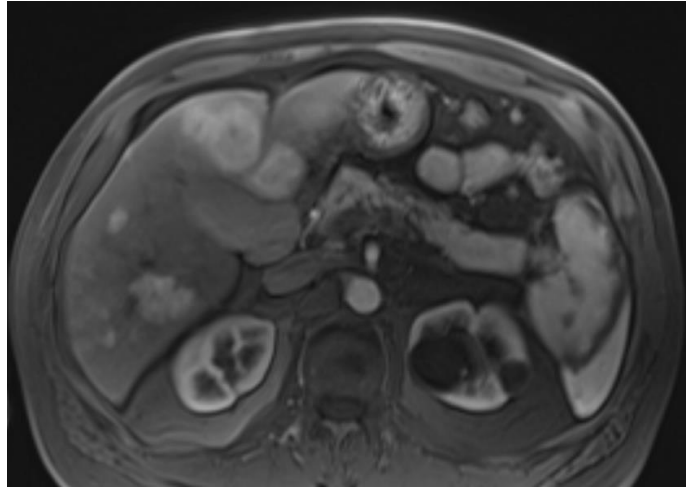
CT Imaging



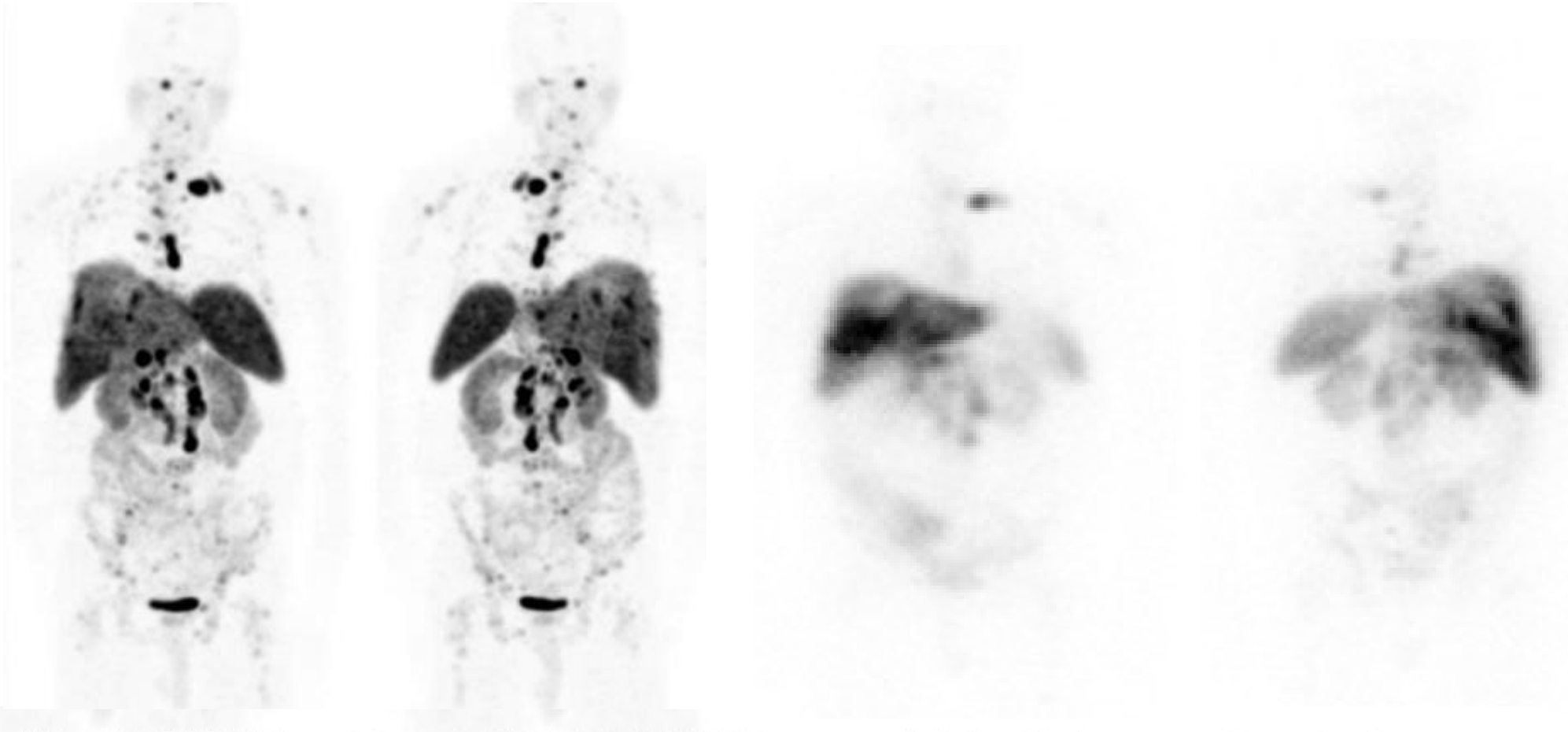
MRI Imaging



MRI versus DOTATATE PET/CT Imaging



[⁶⁸Ga]DOTATATE PET/CT vs. OCTREOSCAN



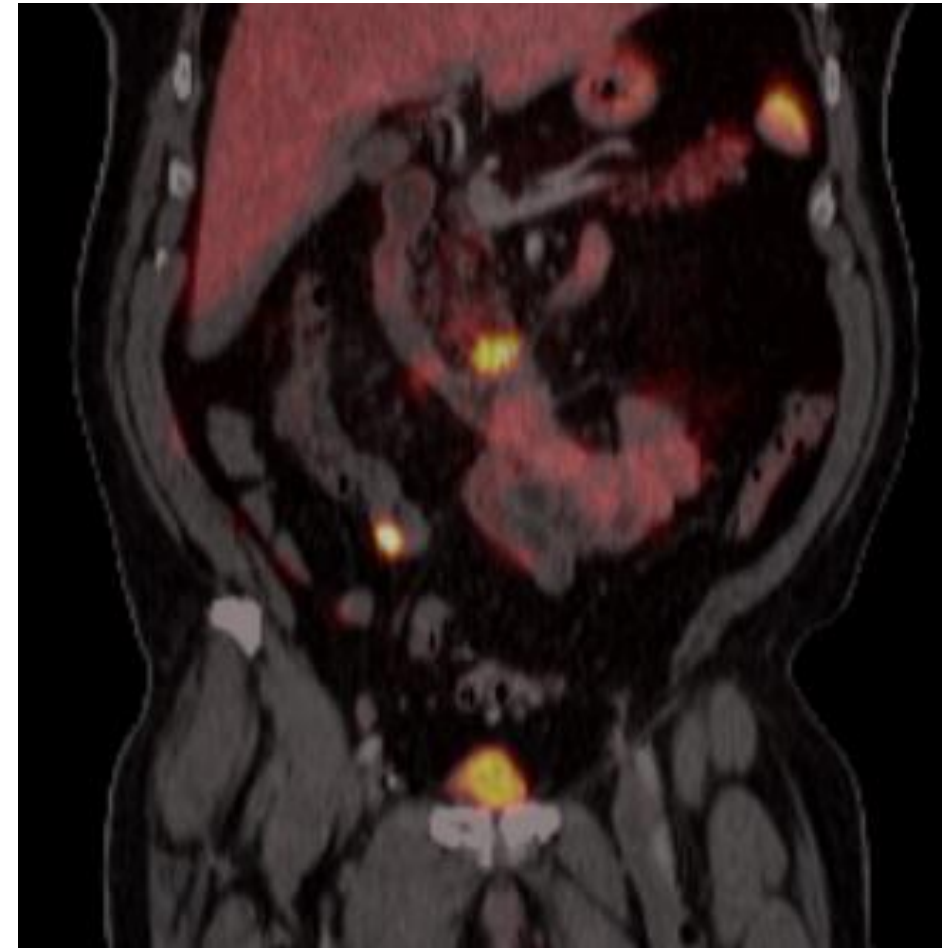
Anterior ⁶⁸Ga-DOTATATE

Posterior ⁶⁸Ga-DOTATATE

Anterior Octreoscan Posterior Octreoscan

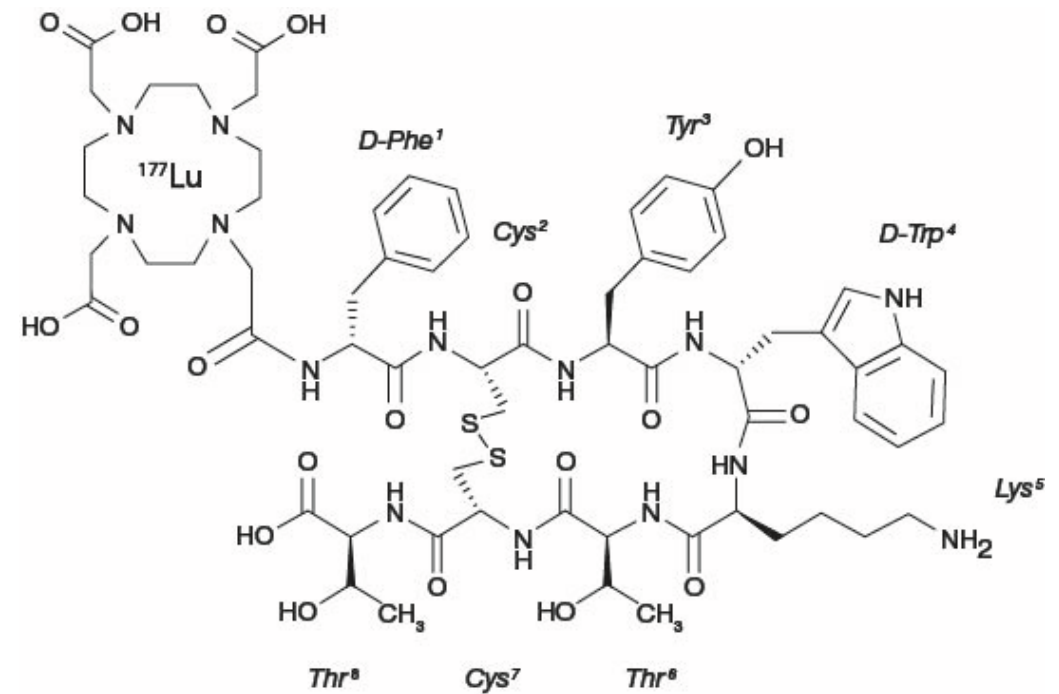
Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. Am J Nucl Med Mol Imaging. 2014;4(5):426–434.

Comparison of contrast enhanced CT TO DOTATATE PET/CT



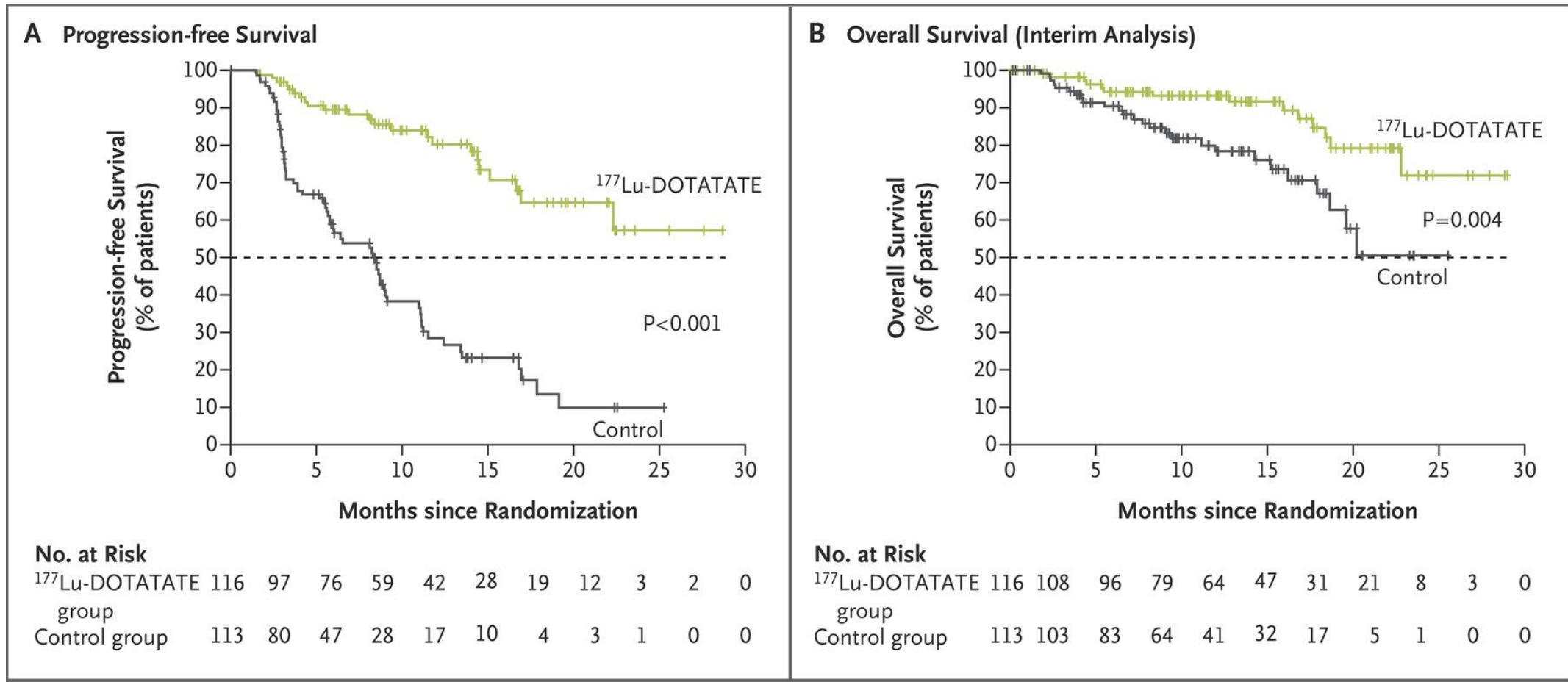
PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

- ^{177}Lu -DOTATATE– Lutetium radionuclide chelated to a peptide (somatostatin analogue)
- Used to treat gastro-enteropancreatic neuroendocrine tumors (GEP-NETs)
- Lutetium emits high energy electrons (B) and gamma (imaging)
- Peptide targets SSTR with high binding affinity (**SSTR2**)



LUTATHERA (lutetium Lu 177 dotatate)

NETTER 1: [^{177}Lu]DOTATATE Phase III clinical trial



Strosberg J, et al. *N Engl J Med*. 2017;376(2):125–135.



[¹⁷⁷Lu]DOTATATE Phase III clinical trial

- 200 mCi (7.4 GBq) q 8 weeks x 4 cycles
- 79% reduced risk for progression free survival
- PFS(not reached vs 8.5 months, $p<0.0001$)
- ORR (13% vs 3%, $p=0.0008$)
- Increased OS improvement in median OS of 11.7 months (48 months versus 36.3 months)
- Favorable safety profile and quality of life improvements
- PFS was 8.4 months with Octreotide, 28-29 months with [¹⁷⁷Lu]DOTATATE

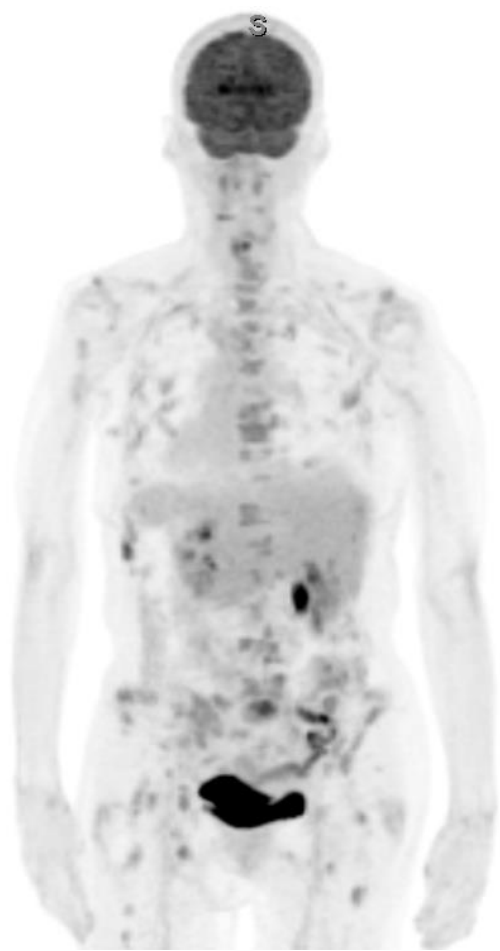


Intense Uptake on DOTATATE PET/CT/Low Uptake on FDG PET/CT

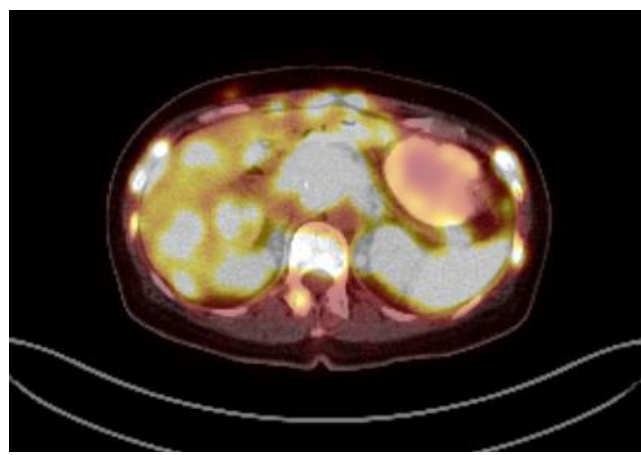
DOTATATE PET/CT



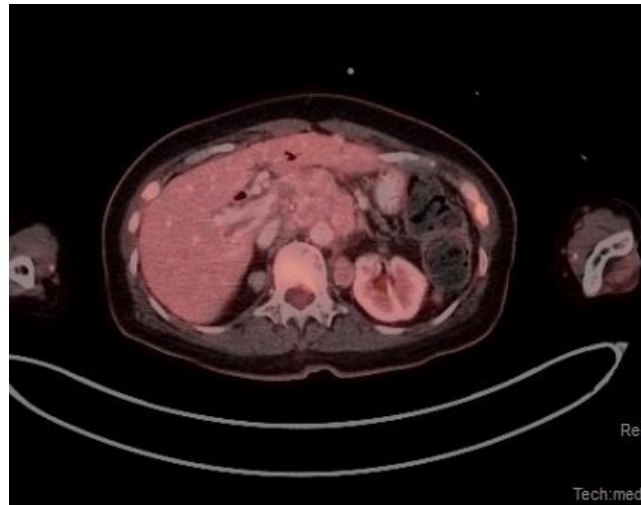
FDG PET/CT



DOTATATE PET/CT

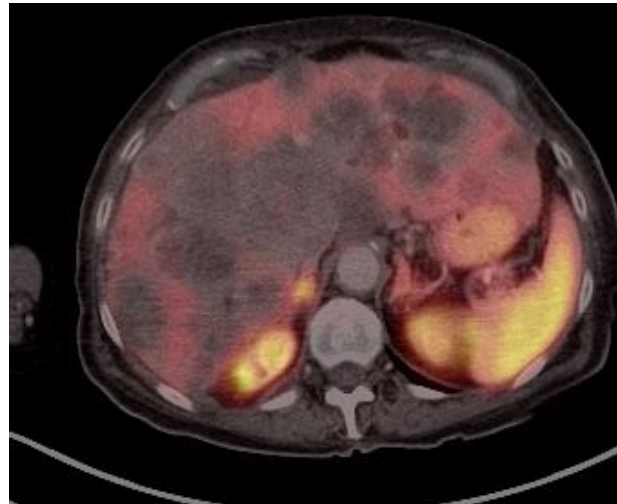
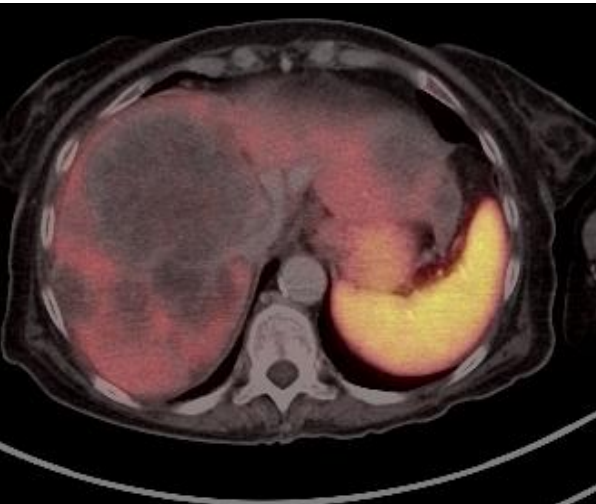
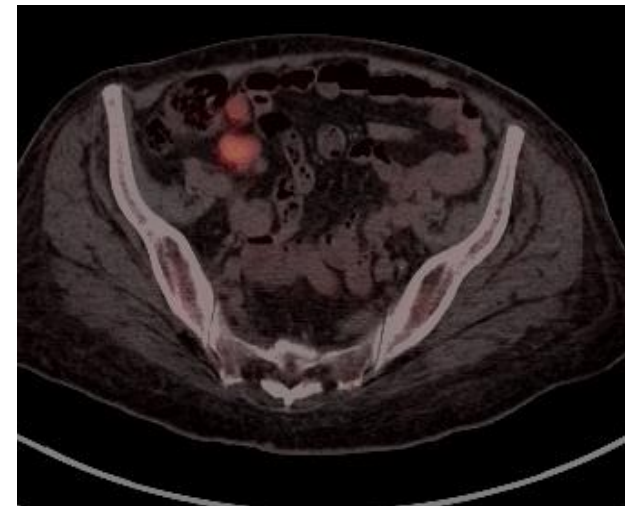
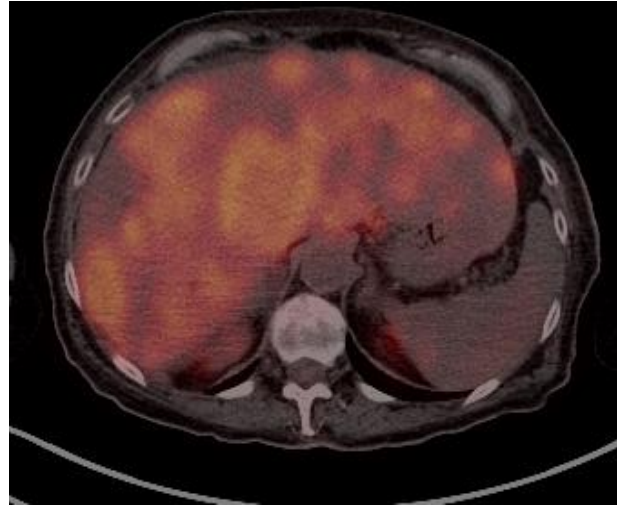
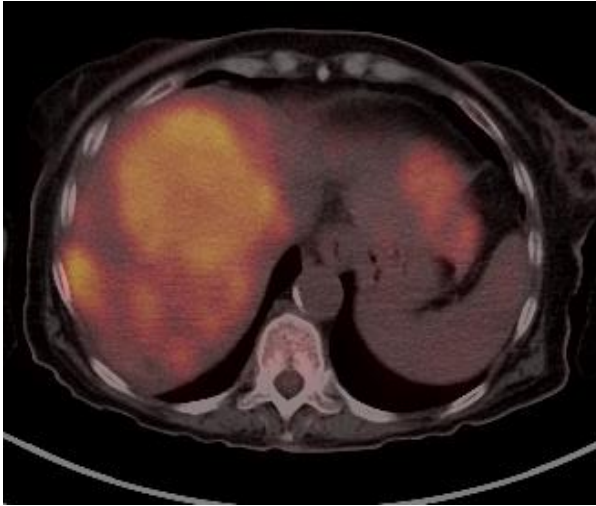


FDG PET/CT



Intense Uptake on FDG PET/CT/Low Uptake on DOTATATE PET/CT

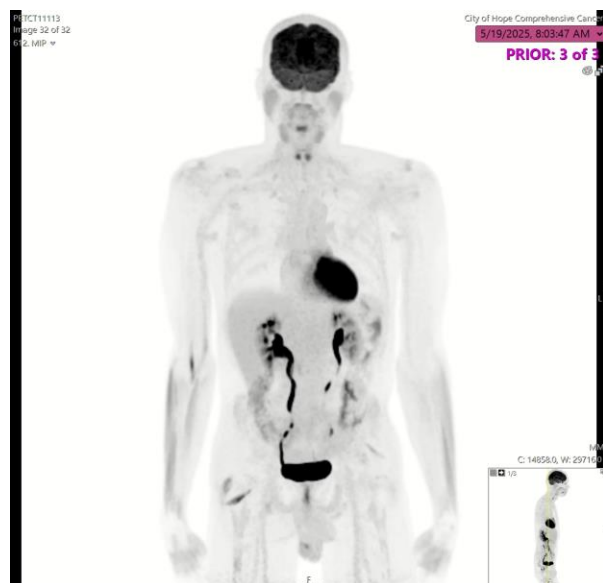
^{18}F FDG



^{68}Ga DOTATATE

Example Recently Treated Patient: City of Hope

FDG PET/CT 5/19/2025



[¹⁷⁷Lu]DOTATATE:

7/3/2025

8/28/2025

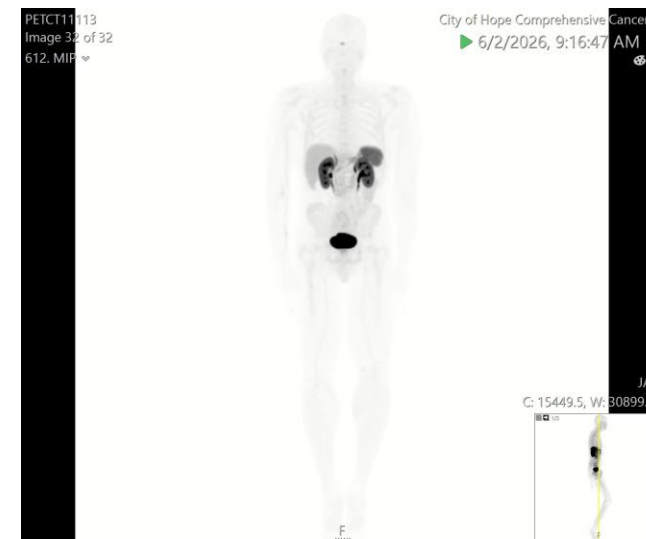
10/22/2025

12/17/2025

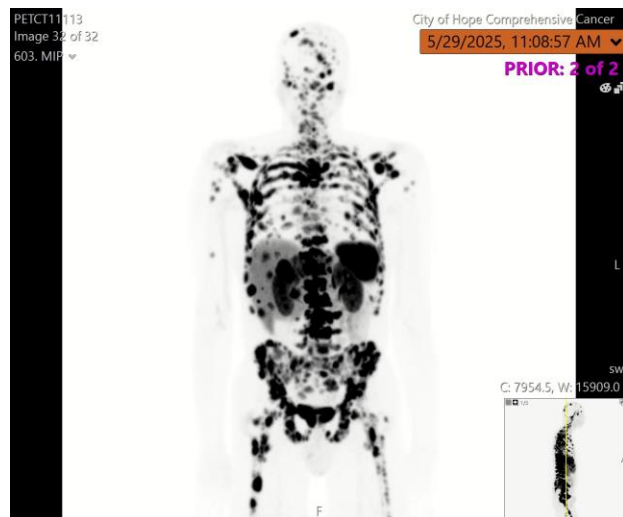
DOTATATE PET/CT 1/15/2026



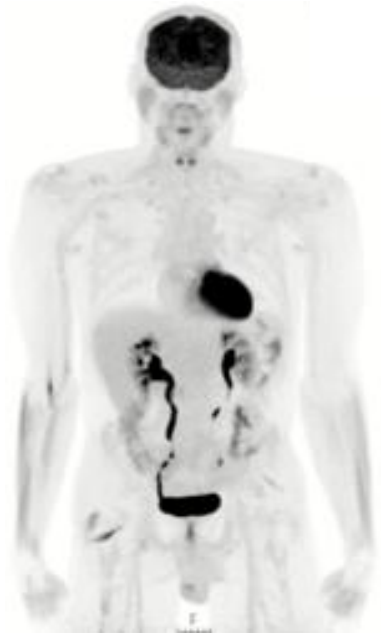
DOTATATE PET/CT 6/2/2026



DOTATATE PET/CT 5/29/2025



Example Recently Treated Patient: City of Hope



FDG PET/CT 5/19/2025



DOTATATE PET/CT 5/29/2025

[¹⁷⁷Lu]DOTATATE:

7/3/2025

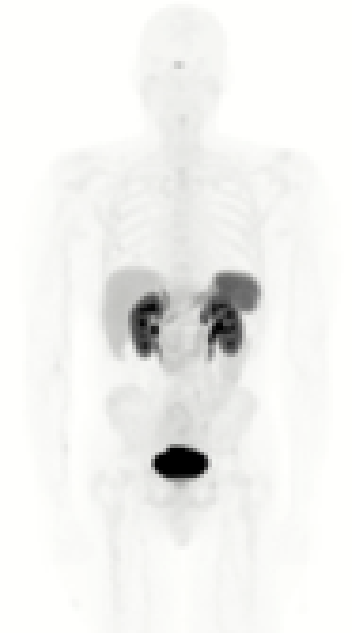
8/28/2025

10/22/2025

12/17/2025



DOTATATE PET/CT 1/15/2026



DOTATATE PET/CT 6/2/2026

NETTER-2: PRRT moves into first-line treatment

- Phase III trial in newly diagnosed, advanced, well-differentiated, grade 2 or 3 SSTR-positive GEP-NETs
- Compared first-line [^{177}Lu]DOTATATE plus octreotide LAR with high-dose octreotide LAR
- Median progression-free survival: 22.8 vs. 8.5 months**
- Hazard ratio for progression or death: 0.28**
- Objective response rate: 43% vs. 9.3%**
- Establishes PRRT as a potential earlier-line treatment rather than solely a later-line option

References: Strosberg J, et al. N Engl J Med. 2017;376(2):125–135. Singh S, et al. Lancet. 2024;403(10446):2807–2817.



COMPETE: ¹⁷⁷Lu-edotreotide versus everolimus

Why it matters: randomized phase III evidence directly compares PRRT with an established targeted systemic therapy

- 309 patients with progressive, SSTR-positive, grade 1 or 2 GEP-NETs after somatostatin analog therapy
- Edotreotide uses DOTATOC, a different SSTR2-targeting peptide from DOTATATE. COMPETE did not compare the two PRRT constructs.
- **Median progression-free survival: 23.9 vs. 14.1 months, HR 0.67**
- **Objective response rate: 22% vs. 4%**
- **Grade 3 or 4 treatment-related adverse events: 18% vs. 40%**

Clinical impact: supports considering PRRT before everolimus after somatostatin analog progression. It does not establish comparative efficacy versus [¹⁷⁷Lu]DOTATATE .

Regulatory context: ¹⁷⁷Lu-edotreotide remains investigational in the United States.



Targeted alpha therapy

Alpha particles deliver high-energy radiation over a short tissue range

Potential advantage

DNA damage with limited particle range may improve tumor-cell killing while reducing irradiation of adjacent normal tissue.

Agents in development

[²²⁵Ac]DOTATATE is under prospective study after prior ¹⁷⁷Lu-based PRRT.
[²¹²Pb]DOTAMTATE has shown early response signals in phase I and phase II development.

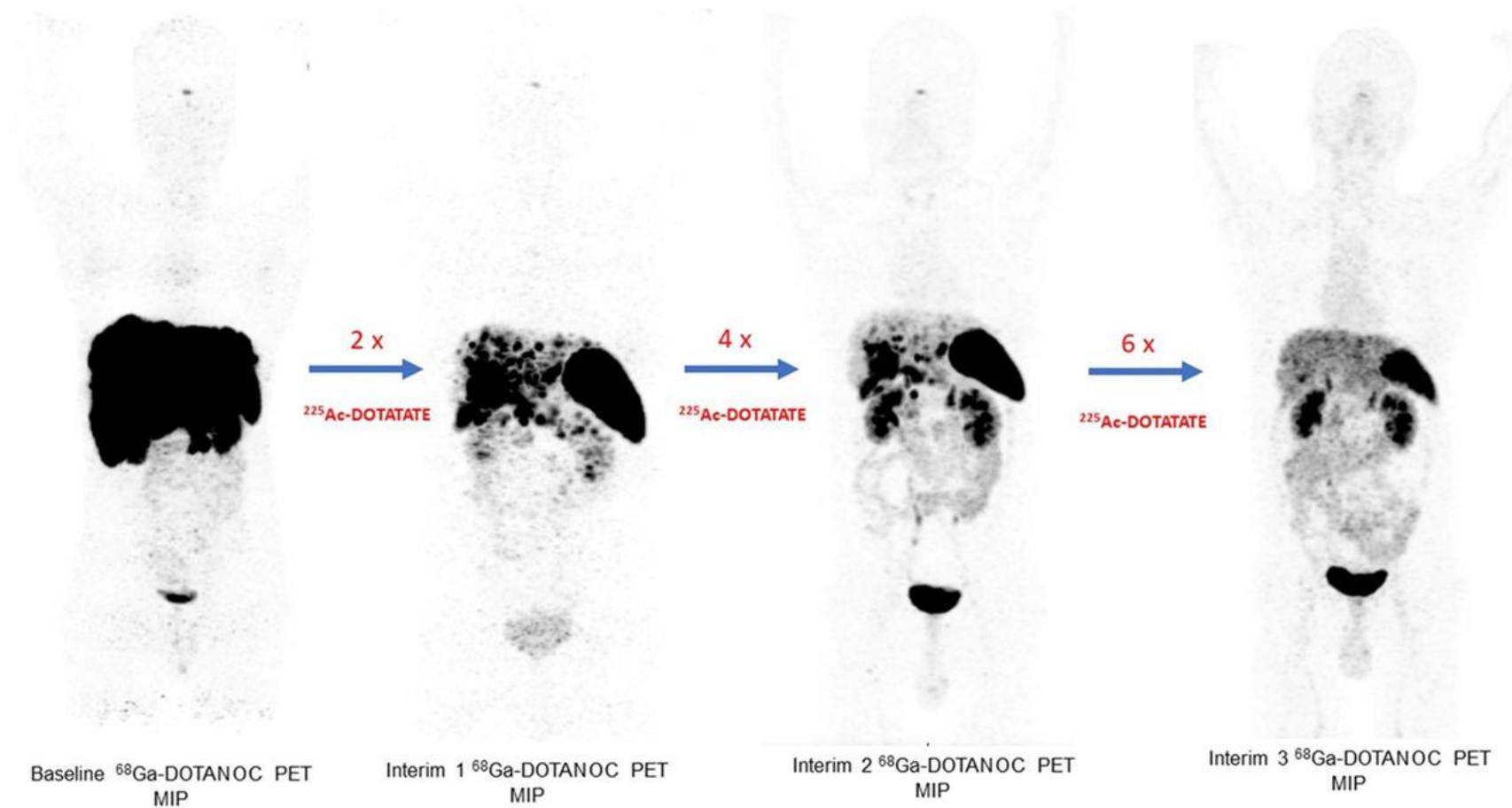
Questions still open

Comparative efficacy, patient selection, dosimetry, isotope supply, organ toxicity, and long-term marrow risk require further study.

Neither agent is FDA approved for NET treatment.



225 Ac-DOTATATE for -Targeted α -Radiation Therapy



2022 SNMMI Abstract of the Year Excellent sustained response in a 34-year-old male with pancreatic neuroendocrine tumor. Society of Nuclear Medicine J Nucl Med 2022;63:9N

NET theranostics landscape in 2026

Approach	Current status	Opportunity	Important limitation
Initial ¹⁷⁷Lu-DOTATATE product	FDA approved	Established PRRT	Sequencing and long-term toxicity
Additional ¹⁷⁷Lu-DOTATATE product	FDA approved, Sept. 2026	Supply backup and procurement flexibility	No demonstrated efficacy advantage
¹⁷⁷Lu-edotreotide	Positive phase III	Alternative ¹⁷⁷ Lu construct	U.S. Complete Response Letter
²²⁵Ac-DOTATATE	Clinical development	Treatment after ¹⁷⁷ Lu PRRT	Randomized efficacy pending
²¹²Pb-DOTAMTATE	Phase I and II development	Short-lived alpha emitter	Complete phase II publication pending
SSTR antagonists	Phase I and II development	High tumor uptake	Hematologic toxicity
Personalized dosimetry	Prospective development	Individualized treatment intensity	Workflow and validation

References: Singh S, et al. Lancet. 2024;403(10446):2807–2817. ClinicalTrials.gov NCT03049189, NCT05477576, NCT05153772, NCT02592707.



Challenges in NET theranostics

Clinical challenges

- Tumor grade, primary site, receptor expression, and growth rate complicate patient selection
- The optimal sequence with systemic and liver-directed treatments remains uncertain
- Long-term marrow and renal risks require extended follow-up

Access and implementation

- Isotope supply, manufacturing capacity, treatment slots, and radiation-safety requirements limit scale
- Travel, repeated visits, language barriers, and caregiver burden can delay treatment
- Coverage and referral patterns can widen geographic and socioeconomic disparities



Equity across the NET theranostics pathway

Where disparities can arise

- Symptoms may be dismissed or attributed to more common conditions
- Distance, referral networks, and insurance can delay specialist evaluation
- Language, transportation, work schedules, and caregiving affect treatment feasibility

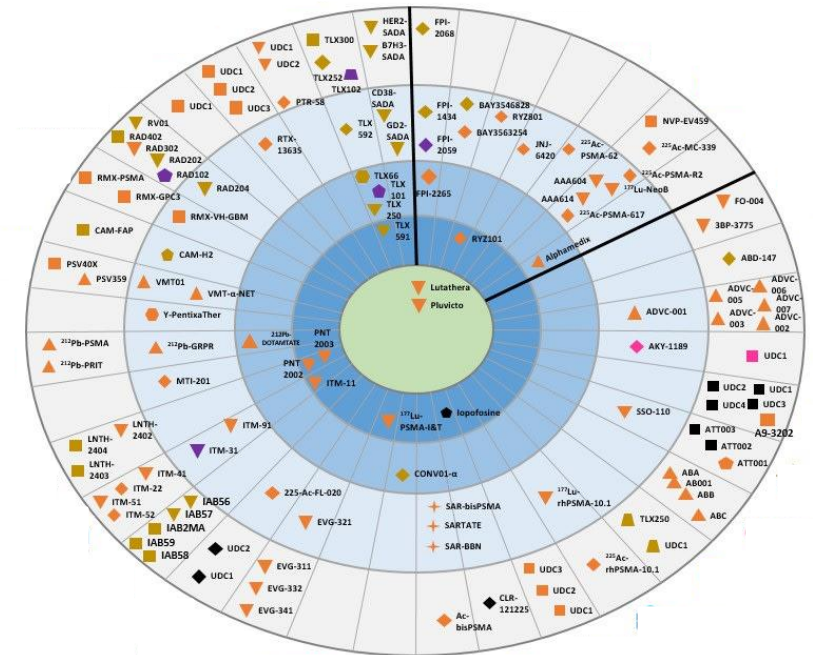
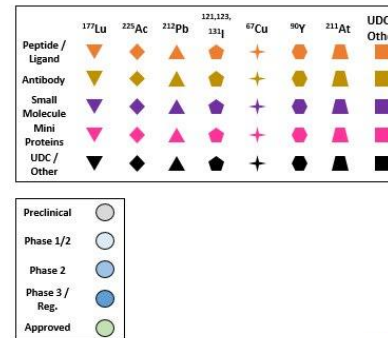
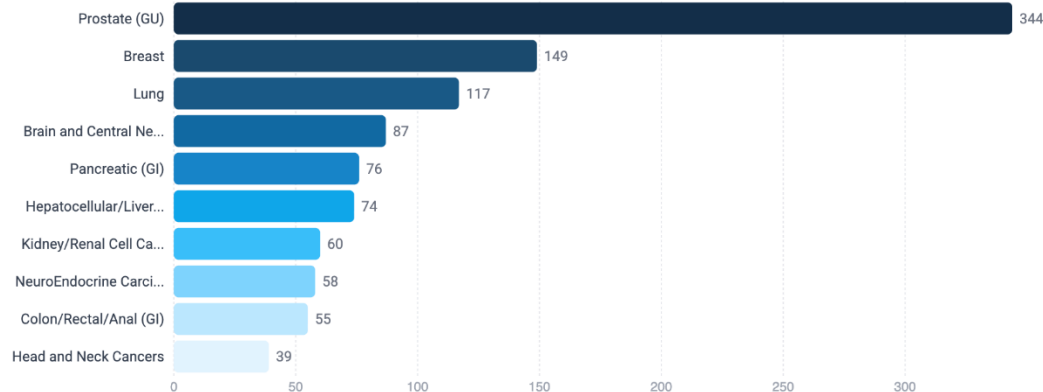
Clinical safeguards

- Use consistent criteria for SSTR imaging, treatment selection, and follow-up
- Document interpreter needs, transportation barriers, and financial concerns early
- Track referral-to-treatment time and missed or delayed cycles by patient population

Disparities can compound before a patient reaches the theranostics clinic.



Clinical Trials



<https://www.theranostictrials.org/>



Summary and Conclusion

Theranostics combines molecular imaging with targeted radionuclide therapy to personalize care for patients with NETs.

[¹⁷⁷Lu]DOTATATE has established PRRT as an effective treatment, with evidence supporting its use earlier in the disease course.

New targets and radionuclides may expand treatment beyond current SSTR-directed approaches.

Theranostics is likely to play an increasingly prominent role in cancer care in NETs and many other malignancies

Selected references

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 12. Chen DW, et al. J Natl Compr Canc Netw. 2023;21:951–959.e1. doi:10.6004/jnccn.2023.7037.
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Thank You

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