AMSER Case of the Month November 2020

75 year-old female with a history of metastatic neuroendocrine tumor and episodic severe pain.

Samuel Orchard, MS3

University of Utah School of Medicine

Dr. Gabriel Fine, MD

Dr. Jeffrey Olpin, MD

University of Utah Health

Department of Radiology

HEALTH
UNIVERSITY OF UTAH

AMSER

Patient Presentation

- HPI
  - 75 year-old woman with a history of metastatic neuroendocrine tumor and recent episodic pain and diarrhea. Presents for tumor progression follow-up and to discuss new treatment options.
- PMH
  - Anemia, arthritis, liver disease, measles, migraine
- Medications
  - Creon 3x daily with meals, Sumatriptan 100 mg as needed, Excedrin
- Oncological History
  - Diagnosed with metastatic small bowel neuroendocrine tumor in 2010, grade 1
  - 2/2010 resection of primary and bulk of her mesenteric disease with debulking of liver mets
  - Started on somatostatin LAR on 04/2010 then switched to lanreotide on 08/2017 and continues now
  - 2/2018 duodenojejunal bypass

What Imaging Should We Order?

Select the applicable ACR Appropriateness Criteria

Variant 4: **Indeterminate, greater than 1 cm liver lesion on initial imaging with CT (noncontrast or single-phase) or noncontrast MRI. Known history of an extrahepatic malignancy.**

Procedure	Appropriateness Category	Relative Radiation Level
MRI abdomen without and with IV contrast	Usually Appropriate	O
CT abdomen with IV contrast multiphase	Usually Appropriate	☢☢☢
FDG-PET/CT skull base to mid-thigh	Usually Appropriate	☢☢☢☢
US abdomen	May Be Appropriate	O
US abdomen with IV contrast	May Be Appropriate	O
Percutaneous image-guided biopsy liver	May Be Appropriate	Varies
CT abdomen without and with IV contrast	May Be Appropriate	☢☢☢☢
DOTATATE PET/CT skull base to mid-thigh	May Be Appropriate	☢☢☢☢
Octreotide scan with SPECT or SPECT/CT chest and abdomen	May Be Appropriate	☢☢☢☢
Liver spleen scan	Usually Not Appropriate	☢☢☢
RBC scan abdomen and pelvis	Usually Not Appropriate	☢☢☢

This imaging modality was ordered by the physician

Comparative Study > J Clin Oncol. 2016 Feb 20;34(6):588-96. doi: 10.1200/JCO.2015.64.0987. Epub 2015 Dec 28.

Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites

Samira M Sadowski [1], Vladimir Neychev [1], Corina Millo [1], Joanna Shih [1], Naris Nilubol [1], Peter Herscovitch [1], Karel Pacak [1], Stephen J Marx [1], Electron Kebebew [2]

Affiliations + expand

PMID: 26712231 PMCID: PMC4872030 DOI: 10.1200/JCO.2015.64.0987

Free PMC article

Special Imaging Considerations

A positron-emitting radioisotope-labeled somatostatin analogue called Ga-68-DOTATATE utilized in PET/CT is designed to image neuroendocrine tumors (NETs). It offers a higher spatial resolution and considerably shorter imaging times compared with In-111 somatostatin receptor or metaiodobenzylguanidine scintigraphy [8].

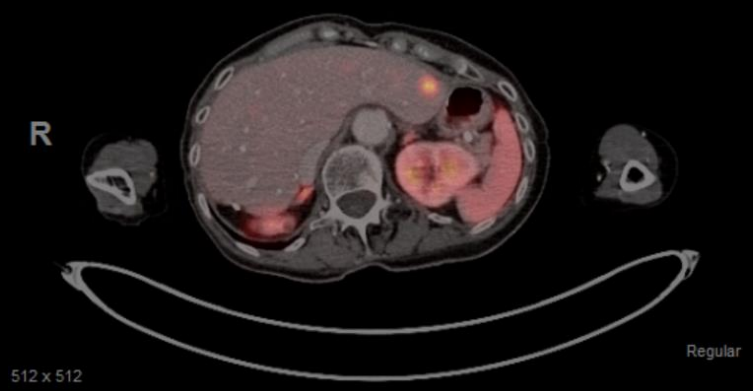
AMSER

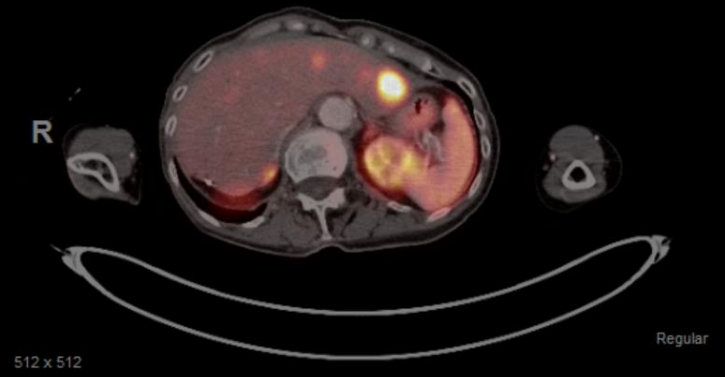
Findings (unlabeled)

2018

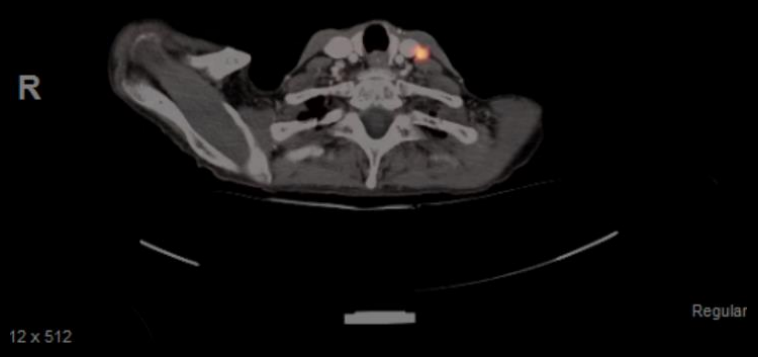
2020

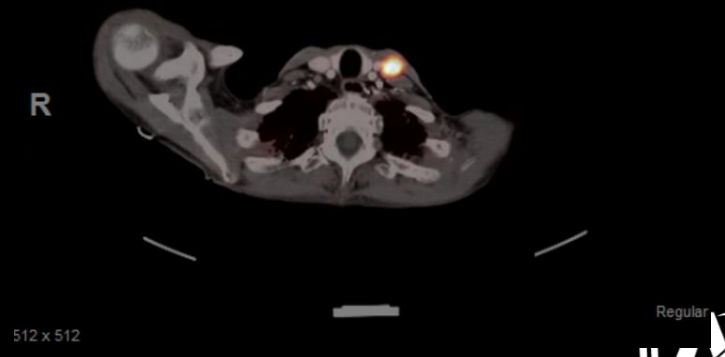
Dotatate PET/CT





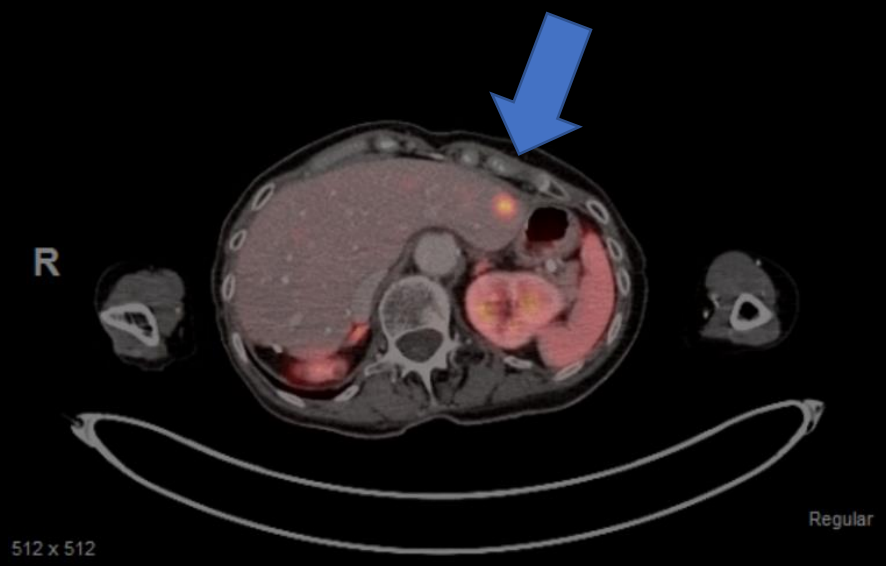
Dotatate PET/CT



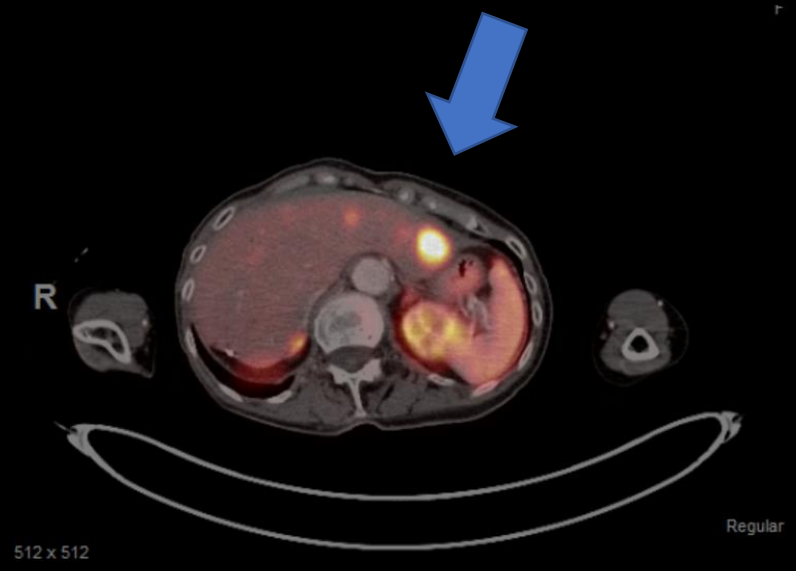


Findings: (labled)

2018



2020
2.4 x 2.2 cm, 43.8 SUV max

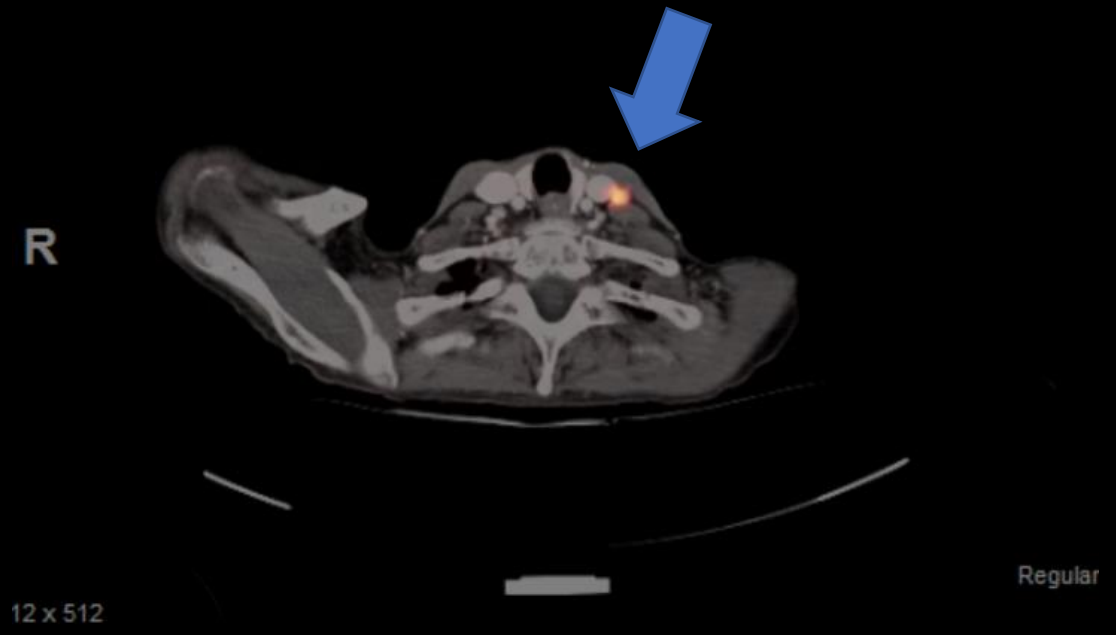


Progressive disease with at least one new hepatic lesion with increased size and avidity associated with multiple hepatic metastatic lesions.

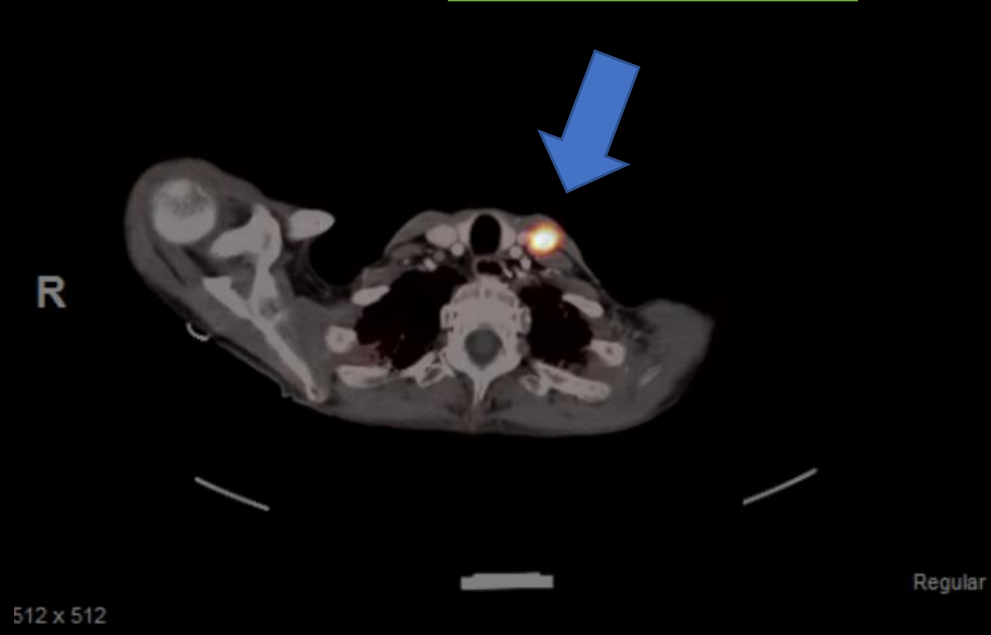
AMSER

Findings: (labled)

2018
1.2 x 0.8 cm,
9.3 SUV max



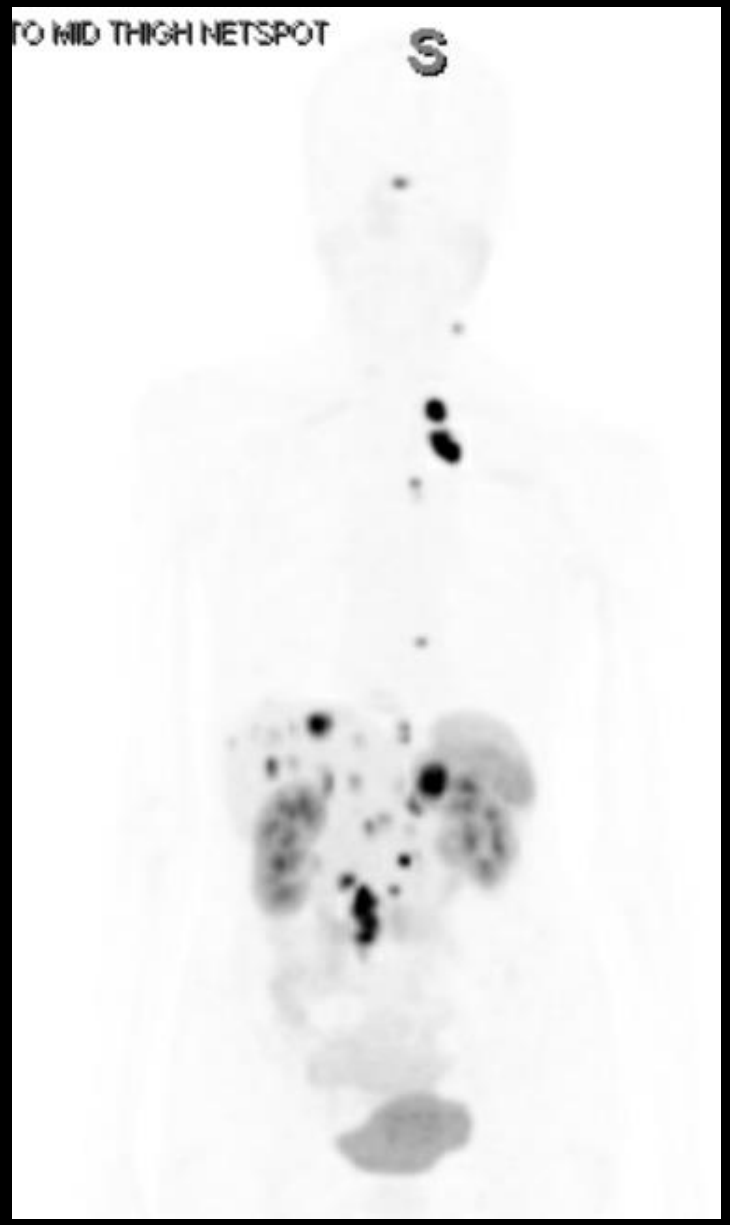
2020
1.3 x 1.5 cm, 68.7
SUV max



Progressive disease with increased size and avidity associated with left level IV cervical node

AMSER

MIP



Final Dx:

Metastatic, well-differentiated, grade 1, small bowel neuroendocrine tumor

Neuroendocrine Tumors

- Incidence
  - 7.8 per 100,000/yr
- Prevalence
  - 35 per 100,000
- Grading
  - Based on mitotic index and Ki-67 index determined by pathologist
- Presentation
  - Carcinoid symptoms – diarrhea, flushing
  - Tumor growth symptoms – SBO, early satiety, RUQ pain, hepatomegaly

Grade	Lung and Thymus (WHO)[34]	GEP-NETs (ENETS, WHO)[3,28,29]	Lung and Thymus (Moran et al)[23]	Pancreas (Hochwald et al)[14]
Low grade	<2 mitoses / 10 hpf AND no necrosis	<2 mitoses / 10 hpf AND <3% Ki67 index	≤3 mitoses / 10 hpf AND no necrosis	<2 mitoses / 50 hpf AND no necrosis
Intermediate grade	2–10 mitoses / 10 hpf OR foci of necrosis	2–20 mitoses / 10 hpf OR 3%–20% Ki67 index	4–10 mitoses / 10 hpf OR foci of necrosis	2–50 mitoses / 50 hpf OR foci of necrosis
High grade	>10 mitoses / 10 hpf	>20 mitoses / 10 hpf OR >20% Ki67 index	>10 mitoses / 10 hpf, Necrosis present	>50 mitoses / 50 hpf

In the pathology report, the actual proliferative rate (mitotic count and/or Ki67 index) should be specified, and a grade should be provided, with the specific grading system used to be specified in the report.

Source

The Pathologic Classification of Neuroendocrine Tumors: A Review of Nomenclature, Grading, and Staging Systems

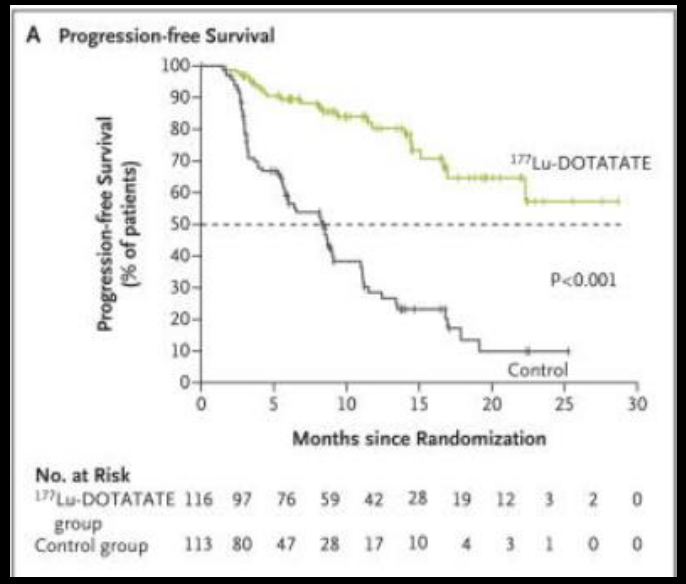
Pancreas39(6):707-712, August 2010.

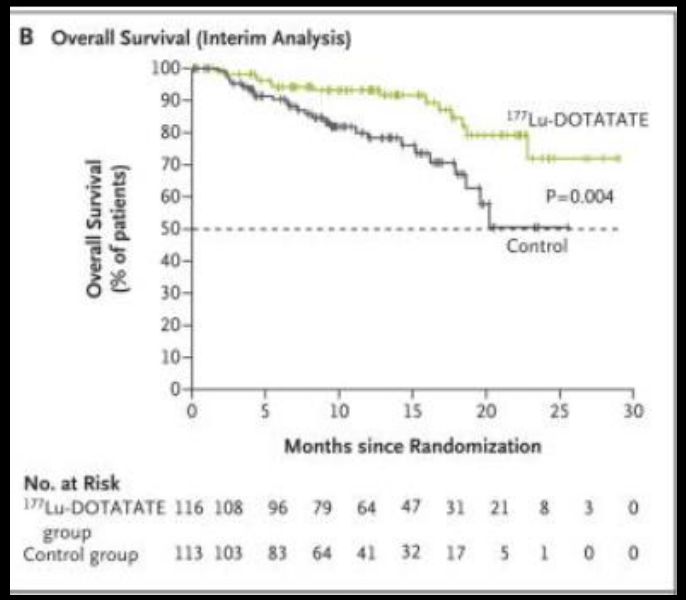
Detecting Neuroendocrine Tumors: Gallium-68 Dotatate PET/CT

- What is Gallium 68 Dotatate?
  - Radioactive analog of the hormone somatostatin
  - Preferred imaging technique for NET by the North American Neuroendocrine Tumor society
- Other options?
  - (111)In-pentetreotide SPECT/CT and anatomic imaging (Multiphasic CT and/or MRI)
  - G68 Dotatate found to have a much higher detection rate
    - G68 Dotatate – 95.1%
    - (111)In-pentetreotide SPECT/CT – 30.9%
    - Anatomic imaging – 45.3%

Management

- Local, small tumor
  - Resection
  - Most small tumors (<2 cm) won't metastasize, but up to 30% of large tumors have already metastasized at diagnosis
- Metastatic disease
  - Somatostatin analogs (octreotide, lanreotide) – effective at treating carcinoid syndrome as well as controlling tumor growth
  - Molecular targeted therapy i.e. anti-VEGF
  - Peptide receptor radioligand therapy
    - Lutetium Lu-177 dotatate

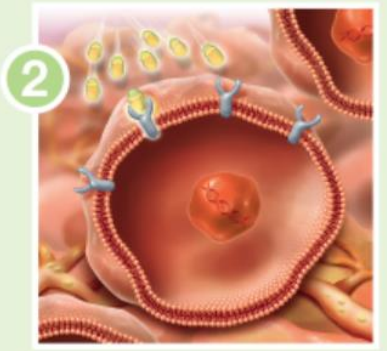




Mechanism of action of LUTATHERA[1]

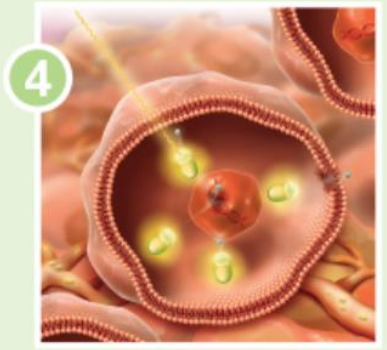
LUTATHERA binds to somatostatin receptors, with highest affinity for subtype 2 receptors, that are expressed on the surface of GEP-NET cells.[1,3] Upon binding to somatostatin receptor-expressing cells, LUTATHERA is internalized.[1] The beta emission from LUTATHERA induces cellular damage by formation of free radicals in somatostatin receptor-positive cells and in neighboring cells.[1]

LUTATHERA is infused into the bloodstream.

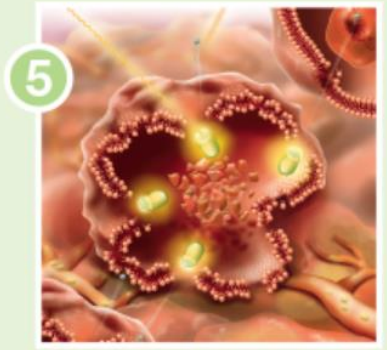


LUTATHERA binds to cells expressing somatostatin receptors, including GEP-NET cells.

LUTATHERA is internalized into somatostatin receptor-bearing cells...



...where it delivers beta radiation.



The radiation causes damage in somatostatin receptor-positive cells and neighboring cells.

Image: Lutathera.com

References:

1. Sadowski, S. M., Neychev, V., Millo, C., Shih, J., Nilubol, N., Herscovitch, P., . . . Kebebew, E. (2016). Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. *Journal of Clinical Oncology, 34*(6), 588-596. doi:10.1200/jco.2015.64.0987
2. Klimstra, D. S., Modlin, I. R., Coppola, D., Lloyd, R. V., & Suster, S. (2010). The Pathologic Classification of Neuroendocrine Tumors. *Pancreas, 39*(6), 707-712. doi:10.1097/mpa.0b013e3181ec124e
3. Oberg, K. (2010). Faculty Opinions recommendation of Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group. *Faculty Opinions – Post-Publication Peer Review of the Biomedical Literature*. doi:10.3410/f.1343956.1391054
4. 177Lu-Dotatate for Midgut Neuroendocrine Tumors. (2017). *New England Journal of Medicine, 376*(14), 1390-1392. doi:10.1056/nejmc1701616