Clinical Applications of Theranostics

Mona Natwa MD, Associate Professor Radiology
Chief, Nuclear Medicine and Molecular Imaging
The Ohio State University Wexner Medical Center

Disclosures

None

Role of Nuclear Medicine Physicians in Theranostics

History

- I-131
  - First radiopharmaceutical utilized for radiotherapy
  - Almost 80 years ago
    - Saul Hertz at Mass General for therapy of Hyperthyroidism
    - Jan 1st 1941
- Since then, continued strong use of I-131
  - Hyperthyroidism
  - Thyroid Cancer
  - Lymphoma
  - Pheochromocytomas/Paragangliomas
  - Research use for AML

Growth of Therapeutic Radiopharmaceuticals

- Yt-90
- Sa-153
- St-90

Beta emitters

- Ra-223

Alpha emitter

- Lu-177

Beta emitter (Gamma for imaging)

Ga/Lu Paired utilization

- Benefits to single utilization therapy
- Many more to paired utilization
  - Ability to image exactly what gets treated (front end)
    - Appropriate staging
      - Avid vs. non avid disease
    - Ability to titrate dose via dosimetry
      - Radiation limiting
  - Ability to visualize treated disease (back end)
    - Confirmation of appropriate therapy
- Pulls experience from I-131

Nuclear Medicine Physician Role

- Training in administration of radiopharmaceuticals through residency/fellowship
- NRC guidelines for AU approval
- Team approach
  - Technologist
  - Radiation Safety
  - Medical Physics
  - Nursing

Theranostics and Neuroendocrine Malignancies

Ga-68 Dotatate

Lu-177 Dotatate

Mechanism of Action

Ga-68

- Half life of 68 minutes
- Positron emission

Dotatate

- Binds to somatostatin receptors on the surface membranes of Neuroendocrine tumors, with a preferentially high affinity for type 2 somatostatin receptors.
- Most normal tissue demonstrates low amount of these receptors

Protocol

- Radiopharmaceutical dose of 5 mCi (adult).
- Circulation time of approximately 60 minutes following intravenous injection
- CT and PET images obtained from top of head through mid thigh.

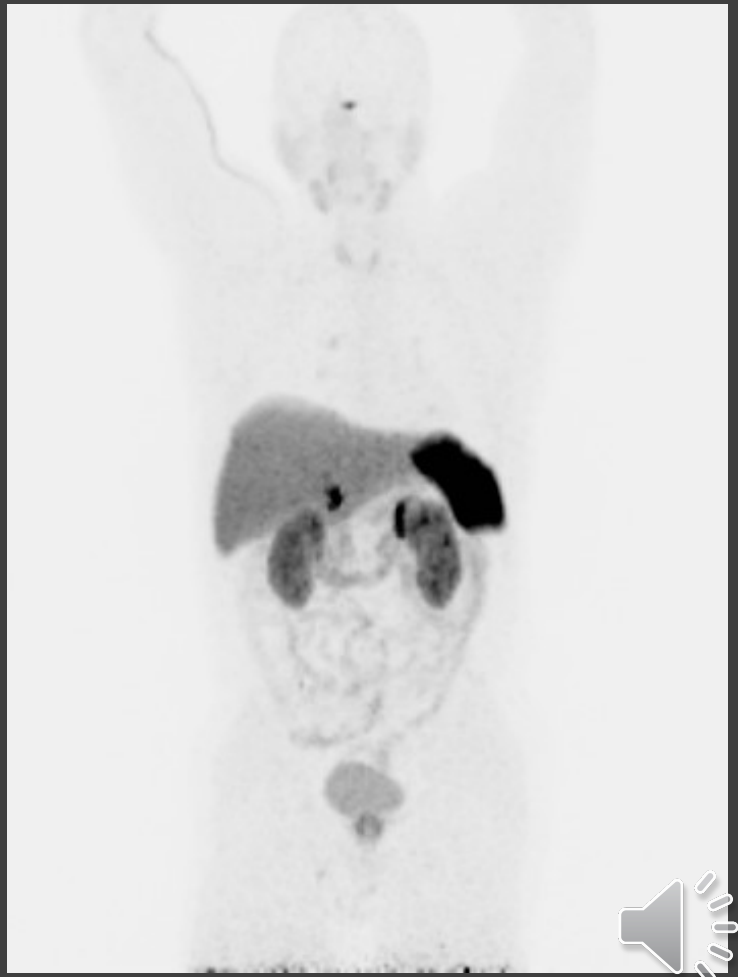
Biodistribution

- Intense
  - Spleen
  - Adrenal Glands
  - Pituitary Gland
- Moderate/variable
  - Pancreas
  - Liver
  - Thyroid
  - Kidneys
  - Salivary Glands

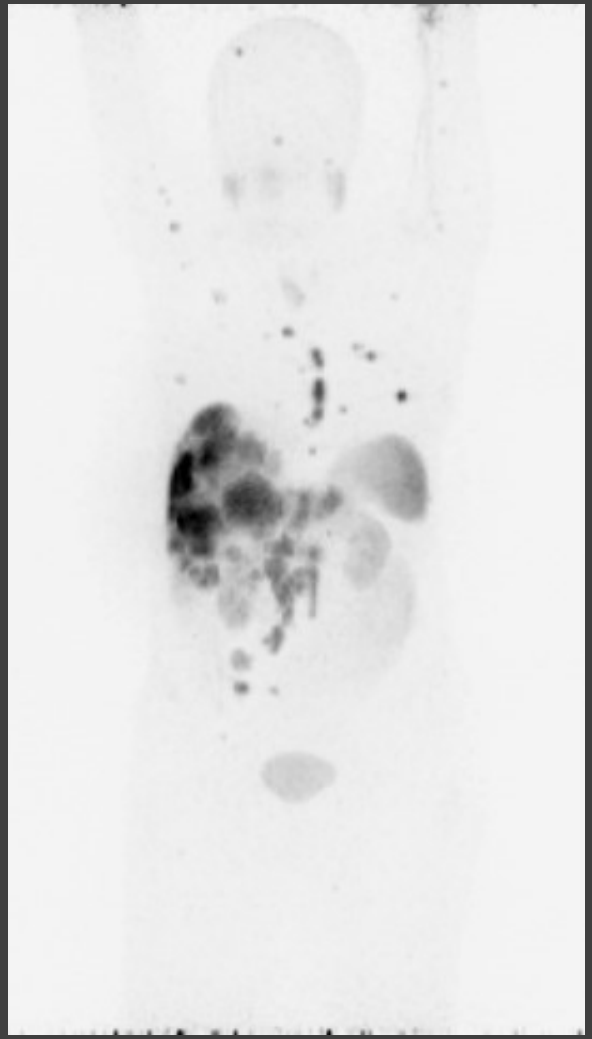
Interpretation

- Uptake is a sign of somatostatin receptor presence, NOT presence of malignancy
  - Negative exam may still have significant disease burden
- Most useful application of this exam is to assess appropriateness of therapy with Lu-177
- Generally qualitative analysis
  - Not overly concerned with SUV values
- Due to intense variable uptake, different windows utilized
  - Liver
  - Spleen/Adrenal Glands

Ga-68 Dotatate PET/CT Scan



Ga-68 Dotatate PET/CT



Lu-177 Dotatate

- Targeted therapy for somatostatin receptor positive malignancies
  - Needs screening exam with diagnostic agent that targets somatostatin receptors
  - Ideally PET
  - Alternatively planar and SPECT with In-111 pentetreotide
- Up to 4 cycles
  - Two month gap between cycles

Dose Modification

- Dose Reduction (100 mCi)
  - Thrombocytopenia
  - Anemia
  - Neutropenia
- Dose cancellation
  - Renal toxicity
  - Hepatic Toxicity

Preparation

- Discontinue long acting somatostatin analogs for a minimum of 4 weeks prior to Lutathera
- Short acting somatostatin analogs should be held for at least 24 hours prior to therapy
- 30 mg long acting octreotide administered shortly following each therapeutic administration (between 4 and 24 hours)
  - Also administered following completion of therapy every 4 weeks for 18 months or until progression.

Side Effects

- Renal failure
- Hepatic Failure
- Bowel Obstruction
- Carcinoid Crisis
- Nausea/Vomiting
  - Amino Acids

Radiation Exposure Considerations

- Found minimal exposure to others after 24 hours
- Patients told to limit prolonged contact with others for 24 hours, then to go back to normal activity
- Pregnancy restrictions for up to 7 months following final therapy

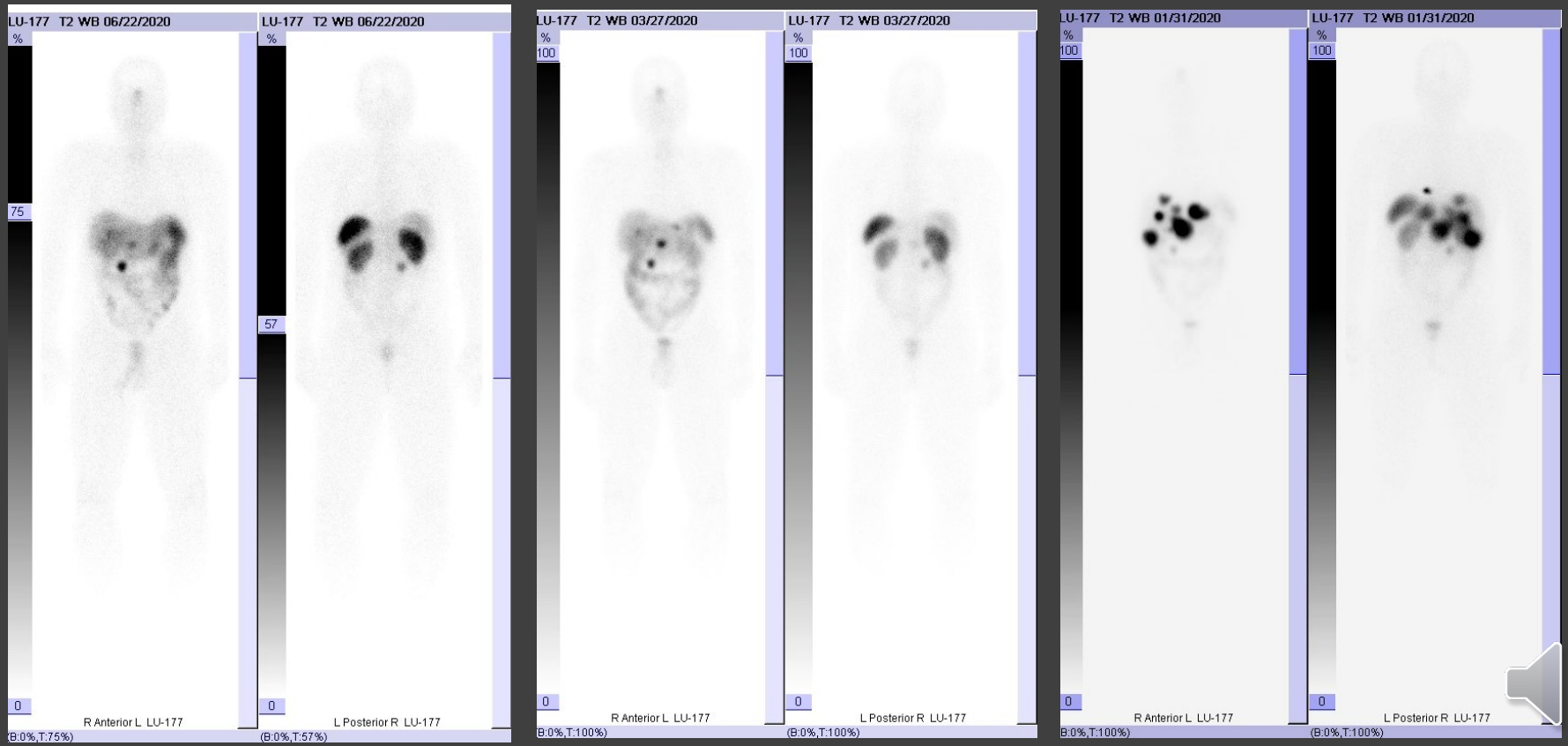
Logistical Considerations

- Amino acids started 30 minutes prior to therapy and continued for 4 hours
- Lutathera administered over 21 minutes
- Method of IV administration
  - Syringe Pump
  - Gravity Method

Post-therapy imaging

- Assess adequacy of therapy
- Can be compared to pre-therapy imaging

Lu-177 Dotatate Post-Therapy Scan



Efficacy of Lu-177 Dotatate

- Associated with an approximately 80% reduction in mortality or tumor progression.
- Reduction in deterioration of global health status
- Improvement in progression free survival when large lesion or elevated alk phos seen at baseline

Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, Baum RP, Kunz P, Hobday T, Hendifar A, Oberg K, Sierra ML, Thevenet T, Margalet I, Ruszniewski P, Krenning E; NETTER-1 Study Group. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With (177)Lu-Dotatate in the Phase III NETTER-1 Trial. J Clin Oncol. 2018 Sep 1;36(25):2578-2584. doi: 10.1200/JCO.2018.78.5865. Epub 2018 Jun 7.

Theranostics and Prostate Cancer

Ga-68 PSMA

Lu-177 PSMA

Mechanism of Action

Ga-68

- Half life of 68 minutes
- Positron emission

PSMA

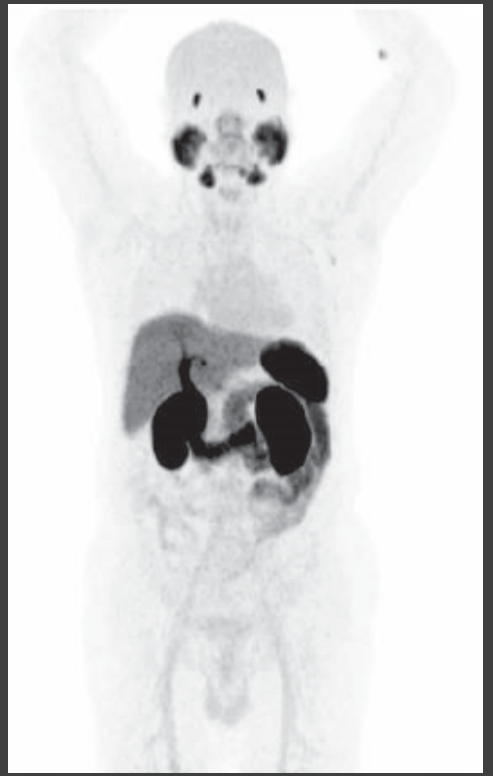
- Transmembrane protein primarily present in all prostatic tissues.
- Seen amongst various malignancies, but most notably in prostate cancer
- Increased expression in de-differentiated, metastatic, or hormone refractory disease
- Also can be used as a prognosticator for disease outcome

Ga-68 PSMA-11

- Several low molecular weight ligands for human PSMA (linked with a chelator for Ga-68) currently available for imaging purposes with PET/CT
- PSMA-11 available on public access
- High affinity for most to human PSMA with internalization into prostate cancer cells
- Biodistribution correlates well to cellular expression of PSMA
- No direct head to head comparison of different ligands

Biodistribution

- Lacrimal and salivary glands
- Liver
- Spleen
- Small and large bowel
- Kidney
  - Tracer predominantly cleared through renal system
  - Small amount through hepatobiliary system



Protocol

- No specific preparation prior to injection of radiopharmaceutical
- Aggressive hydration during uptake time =/- Lasix administration
- 60 minute injection to scan time
  - Increased detection of small lesions with delayed uptake up to 3-4 hours following injection
  - Decay of radiopharmaceutical
- Voiding recommended immediately prior to acquisition of imaging
  - False positives from ureteral uptake
  - False negatives from halo effects
- Scanning performed caudal-cranial to reduce effects of tracer excretion

Current Experience

- Localization of tumor in recurrent prostate cancer
  - PSA between .2 and 10 ng/mL
  - Higher sensitivities in shorter PSA doubling times when compared to higher initial Gleason scores
- Primary staging in high risk malignancy prior to therapy
  - Used for potential visualization of radiologically occult lymph node metastases
  - Potential higher accuracy in detecting bone metastases

Emerging Indications

- Staging prior to and through PSMA radiotherapy
  - Degree of uptake indicates appropriateness of therapy
- Targeted biopsy following previous negative biopsy with high suspicion of malignancy
- Monitoring of systemic treatment in metastatic prostate cancer
  - Awaiting comparison studies to bone scans and other traditional forms of imaging

Correlation with intensity of uptake with Gleason Score

- 141 patients with known prostate cancer s/p prostatectomy
- Evaluation of max SUV of prostate, with care taken to exclude the bladder
- Mean Max SUV significantly higher for grade 3 + 4 + 5 (18.9) versus 1+2 (7.2)
- Could potentially be utilized in the future to target sites of biopsy in appropriate patients

Demirci E, Kabasakal L, Şahin OE, et al. Can SUVmax values of Ga-68-PSMA PET/CT scan predict the clinically significant prostate cancer?. *Nucl Med Commun*. 2019;40(1):86–91. doi:10.1097/MNM.0000000000000942

Limitations

- Hepatic activity
- False positives in a variety of non-prostate malignancies
  - Colon
  - Esophageal
  - Thyroid
  - Lung
  - Renal cell
  - Brain
- Celiac ganglia of autonomic nervous system
  - Retroperitoneal lymph nodes

Lu-177 PSMA

- Currently not approved by the FDA outside of clinical trial purposes
- Can be considered within the constructs of a trial
  - Patients with metastatic castrate resistant prostate cancer as late line therapy
  - PSMA expression at tumor sites must be confirmed
    - PSMA tagged PET agent (also not currently FDA approved)
      - F-18
      - Ga-68

Radiation Dose and Stability

- Highest radiation dose to parotid glands, kidneys, and bone marrow
- Bone marrow was the lowest of three doses
- Dose is stable in saline for up to 48 hours and remains stable in blood, with predominant renal excretion (over 50%), without degradation

Conditions prior to therapy

- Bone marrow reserve
- Appropriate renal function
- Appropriate hepatic function
- Discontinuation of potentially myelosuppressive therapy for over 6 weeks

Rahbar K, Afshar-Oromieh A, Jadvar H, Ahmadzadehfar H. PSMA Theranostics: Current Status and Future Directions. *Mol Imaging*. 2018;17:15360121187760 68. doi:10.1177/1536012118776068

Protocol

- 4-6 cycles administered in trials without adverse renal effects or greater than grade 2 salivary effects
  - Still significant xerostomia
  - Symptomatic and significant oral intake alteration (eg, copious water, other lubricants, diet limited to purees and/or soft moist foods)
- 8-12 weeks between cycles
  - Allows adequate evaluation of potential bone marrow suppression
  - CBC every 2-4 weeks between cycles
  - Majority of side effect reported related to hematologic adverse events

During administration

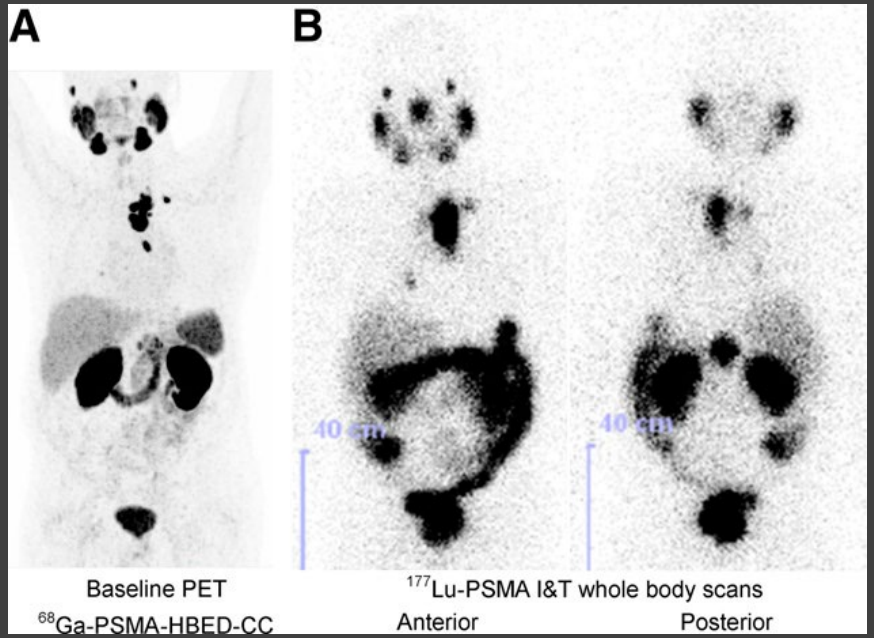
- Icepacks to salivary glands for 30 min prior to 4 hours following Lu-177 PSMA administration
- +/- antiemetics
- +/- corticosteroids
- Foley for 48 hours for radiation safety
- Dose 6-7.4 GBq Lu-177 PSMA
  - Slow bolus over 30 seconds
  - 1000mL NaCl or Ringers
- Can be administered in an outpatient area

Following administration

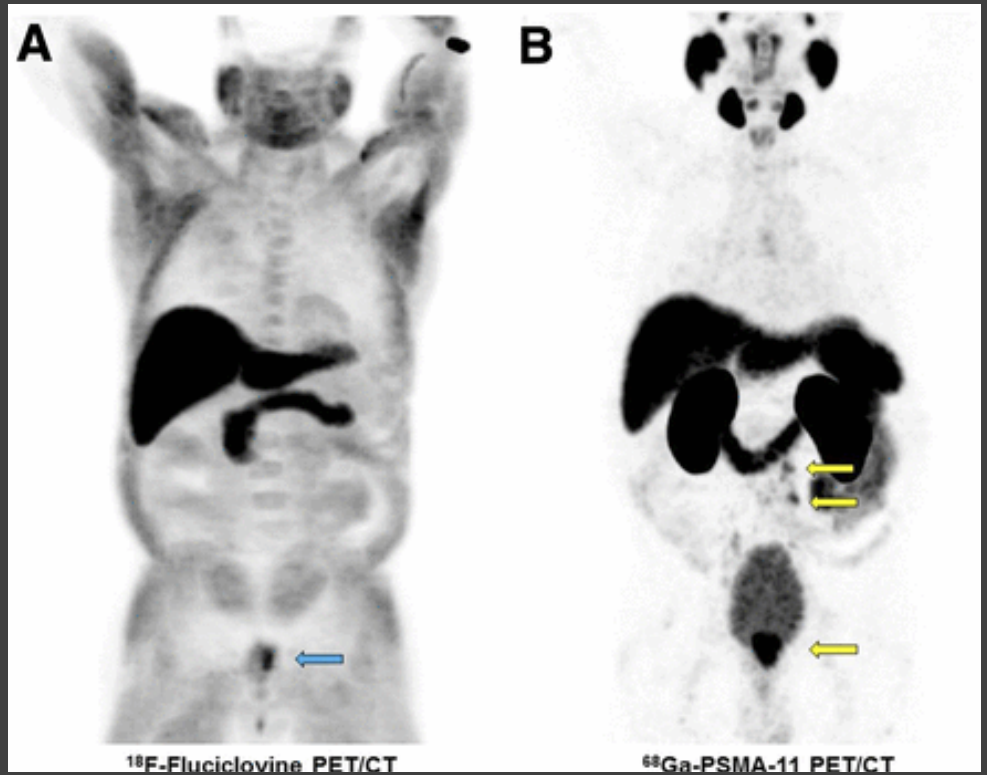
- Within 6 hours dose rate to public decreases significantly
- Can be administered in an outpatient area
- Foley should stay in for 48 hours following administration of dose for radiation precautions
- Imaging to demonstrate appropriate deposition of therapeutic dose

Theranostic Pair with PSMA

Clinical Investigations:
Martina Weineisen et al, 68Ga- and 177Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies ,J Nucl Med 2015 56:1169-1176 published ahead of print June 18, 2015 (10.2967/jnumed.115.158550).

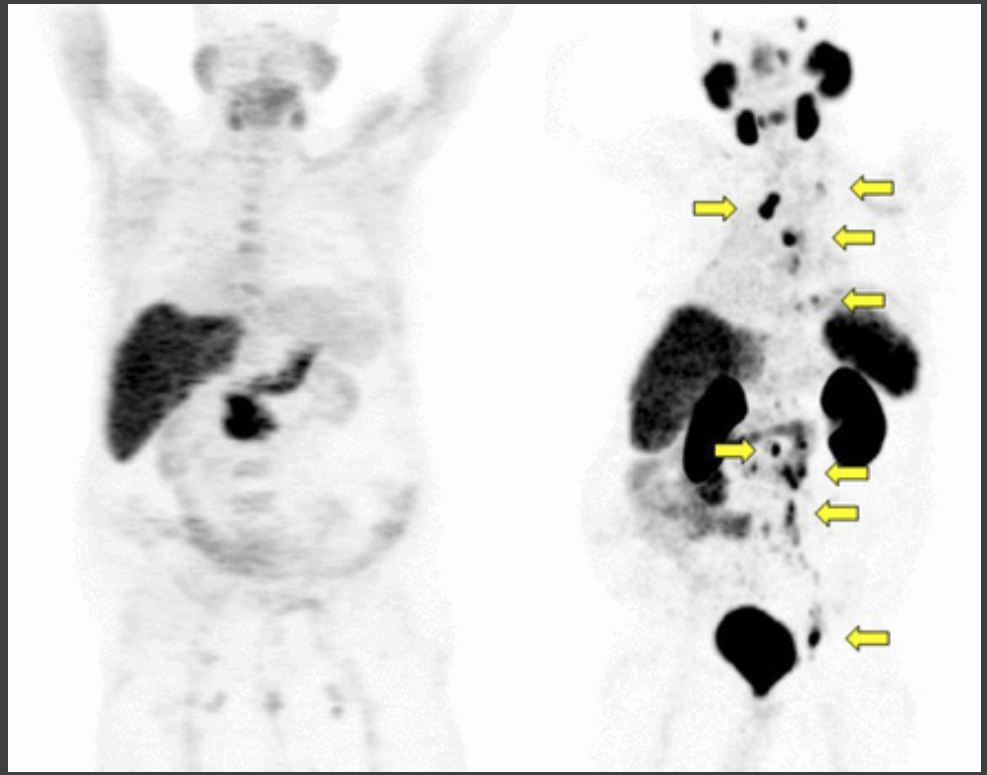


Increased degree of activity within the prostate as well as additional visualization of abdominal nodes in Ga-68 PSMA when compared to F-18 Fluciclovine



Maximum-intensity-projection 18F-fluciclovine PET (A) and 68Ga-PSMA-11 PET (B) in patient 9. Jeremie Calais et al. J Nucl Med 2018;59:789-794

Multifocal lymph node activity seen on Ga-68 PSMA when compared to F-18 Fluciclovine



Maximum-intensity-projection 18F-fluciclovine PET (A) and 68Ga-PSMA-11 PET (B) in patient 9. Jeremie Calais et al. J Nucl Med 2018;59:789-794

The End

Thank You!