Theranostics: Prostate cancer

Sanaz Behnia MD
Assistant professor
Department of Radiology
University of Washington
NO DISCLOSURES
• Target Audience:
• ACPE#:
• Activity Type:

(APhA will complete this information.)
• General Objectives:

1. Recognize the important diagnostic and management challenges in prostate cancer and list the challenges and limitations involved in the applications of PET tracers. Assess the issues and limitations of F18 line PET/CT imaging in preoperative staging and of F18 fluoride PET/CT in follow-up management.

2. Describe and compare the pros and cons of Ga68/F18 PSMA radiolabeling, and compare sensitivity and specificity of Ga68/F18 PSMA vs. other prostate tracers. Summarize the advantages of labeled PSMA in primary and biochemical recurrent prostate cancer. Discuss how Ga68/F18 PSMA imaging can change patient management.

3. Define the mechanism of action; provide warnings and precautions, adverse reactions, and potential drug interactions of Lu177 PSMA. Identify the significant outcomes from this novel therapy.

• Description:

Prostate cancer represents the most common cancer in men and accounts for the third most cause for cancer-associated death in men. Early detection and treatment of primary disease and its metastases is highly relevant in terms of prognosis and therapy management. Recently, PET imaging using PSMA-ligands has gained high attention as a promising new radiotracer in patients with prostate cancer and preliminary results, and exceptional patient outcomes, are positioning Lu-177-PSMA as a “game-changer” in the treatment of prostate cancer.
• Prostate cancer is the most common cancer in men and third most common cause of cancer associated death.
• The incidence increases with age.
• It is detected by PSA screening
• Is treated with surgery and/or radiation
• Up to a third of patients develop biochemical recurrence after treatment, which is detected by two consecutive rising PSA values

• Biochemical recurrence of prostate cancer:
  • Post surgical, PSA >0.2 ng/mL
  • Post radiation, PSA >2 ng/mL

• One of the strongest predictors of metastasis and death is the PSA doubling time (PSADT), in months. PSADT >9 months, have a high probability of long-term, metastasis-free survival and overall survival

• Recurrence
  • Local (prostate gland, prostate bed, urethral or bladder anastomosis)
  • Regional (pelvic lymph nodes)
• Distant metastases (lymph nodes, bones, solid organs)
• Nodal/local recurrence has better prognosis compared to distant metastases
• Treatment varies based on site of involvement
  • Salvage lymphadenectomy, radiotherapy, cryotherapy for local recurrences, especially at lower PSA levels
  • Systemic such as anti-hormonal therapy and/or chemo or immunotherapy for distant metastases.
• Treatment of recurrent disease is most effective if started early

• Within 3 years of biochemical recurrence, there is low rate of positive findings on bone scans (9.4%) and CT scans (14%)

• For nodal metastases, specificity of MRI and CT is high at >90%. Sensitivity is higher for MRI (82 vs. 34%; p<0.05).


• Tc-99m MDP has long been used for detection of bone metastases.
• Adding SPECT-CT to bone scan increases diagnostic accuracy.
• BSI (bone scan index) is considered to be predictive of overall survival (hot spots are classified as metastasis versus not metastasis by an artificial neural network. A percentage of the sum of all the hot spots is calculated)
• Bone scan has low sensitivity until PSA rises to 10-20 ng/ml
F-18 Na-F PET-CT is superior to the conventional bone scan:
- Higher affinity of the tracer to areas of new bone formation
- Higher target to background ratio.
- Spatial resolution of PET-CT (3-6 mm) is higher than SPECT-CT (10-15 mm)

• NM imaging of metastatic prostate cancer:
  • Prostascint
  • Choline: cell membrane synthesis. (F-18, C-11)
  • Acetate is an indirect biomarker, fatty acid synthesis. (C-11).
  • Amino acid transport, Fluciclovine (F-18).
  • PSMA receptor expression (Ga-68, F-18)
  • F-18 FDG PET is not commonly used.
• NM imaging of metastatic prostate cancer:
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  • PSMA receptor expression (Ga-68, F-18)
  • F-18 FDG PET is not commonly used.
Prostascint:
• In-111 captomab pendetide
• Monoclonal antibody
• Binds intracellular PSMA
• Delayed images after injection (96 hours)
• Planar as well as SPECT-CT
• Low yield
• Discontinued 2018
-If this scan doesn’t help, please come back and we will try something else.
-Why can’t we try something else right away?
• NM imaging of metastatic prostate cancer:
  • 
  • Prostascint
  • Cell membrane synthesis; F-18 or C-11 choline
  • Fatty acid synthesis; C-11 acetate
  • Amino acid transport; F-18 Fluciclovine
  • PSMA receptor expression; (Ga-68, F-18)
  • Glucose phosphorylation; F-18 FDG (not commonly used).
Positron (β+) Decay

- Unstable parent nucleus with high P/N ratio.
- Proton decays to a neutron.

Example:

\[ ^{18}_9 \text{F} \rightarrow ^{18}_8 \text{O} + \beta^+ + \nu \]

Neutrino (Not relevant to PET)

Positron (think of this as a positively charged electron)

Travels a short distance until kinetic energy lost

- Annihilates with electron
- Mass energy of the β+ and e- (511 keV ea) converted to electromagnetic energy
- Two 511 keV photons emitted at 180 degrees

Courtesy of Tina Tailor M.D
- A ring of detectors surround the patient.
- Detector electronics are linked so two detection events occurring within the same time window are considered “coincident” (determined to have resulted from the same annihilation).

- Coincidence events are stored and reconstructed to show tracer distribution throughout the subject.

- This information is used to mathematically compute the three-dimensional distribution of the PET agent, resulting in a series of tomographic emission images.
• **PET-CT:**

  • **Alignment** of anatomical and Functional images

  • CT scan provides **attenuation correction** information for PET Reconstruction, and helps with accurate localization.
• NM imaging of metastatic prostate cancer:
  • Prostascint
  • Cell membrane synthesis; F-18 or C-11 choline
  • Fatty acid synthesis; C-11 acetate
  • Amino acid transport; F-18 Fluciclovine
  • PSMA receptor expression; (Ga-68, F-18)
  • Glucose phosphorylation; F-18 FDG (not commonly used).
• **Cell membrane synthesis, Choline:**
  - Choline is a component of phosphatidylcholine in cell membrane.
  - Choline kinase activity is upregulated in PC cells, leading to higher uptake of choline.
  - $^{18}$F- or $^{11}$C-Choline PET can be used preoperatively for management planning in patients who are at risk for extracapsular disease.
  - Used in biochemical recurrence of prostate cancer.
  - Normal uptake in urinary tract, liver, pancreas; spleen, bone marrow, salivary glands. Bowel uptake is variable.
  - Sensitivity is low with PSA<2 ng/mL

-Schillaci et al: Nuclear Medicine Communications: January 2010 - Volume 31 - Issue 1 - p 39-45
• NM imaging of metastatic prostate cancer:
  • Prostascint
  • Cell membrane synthesis; F-18 or C-11 choline
  • Fatty acid synthesis; C-11 acetate
  • Amino acid transport; F-18 Fluciclovine
  • PSMA receptor expression; (Ga-68, F-18)
  • Glucose phosphorylation; F-18 FDG (not commonly used).
• **Fatty acid synthesis, Acetate:**
  
  - Prostate cancer exhibits increased lipid metabolism
  - Acetate is actively transported across cell membranes via mono-carboxylate transporters and is converted to acetyl-coA in mitochondria
  - Fatty acid synthase (FAS) facilitates synthesis of fatty acids from acetyl-CoA
  - Cancer cells incorporate lipids in their membrane as phospholipids
  - FAS is overexpressed in many cancers including prostate cancer
  - Detectability is limited in patients with serum PSA levels below 3 ng/ml

• NM imaging of metastatic prostate cancer:
  • Prostascint
  • Cell membrane synthesis; F-18 or C-11 choline
  • Fatty acid synthesis; C-11 acetate
  • Amino acid transport; F-18 Fluciclovine
  • PSMA receptor expression; (Ga-68, F-18)
  • Glucose phosphorylation; F-18 FDG (not commonly used).
• Amino acid transport, Fluciclovine (anti-\([(18)F]FACBC\))

• Synthetic amino acid
• It is taken up by amino acid transporters, specifically ASCT2 and LAT1, which transport glutamine and leucine into cells, where they are used for protein synthesis, cell growth and metabolism.
• These transporters are overexpressed in cancer cells, including prostate
• F-18 Fluciclovine is not metabolized or incorporated into proteins
• It detects prostate cancer metastases in prostate bed, lymph nodes and bones

[14C]Fluciclovine (alias anti-[14C]FACBC) uptake and ASCT2 expression in castration-resistant prostate cancer cells
Ono, Masahiro et al.
Nuclear Medicine and Biology, Volume 42, Issue 11, 887 - 892
Amino acid transporters are up-regulated in prostate cancer.

Normal biodistribution of F-18 fluciclovine:
- Liver (14%)
- Red bone marrow (12%)
- Lungs (7%)
- Myocardium (4%)
- Pancreas (3%)
- First 4 hours post injection: 3% excreted in urine

Normal biodistribution:
FDA News Release

FDA approves new diagnostic imaging agent to detect recurrent prostate cancer

For Immediate Release

May 27, 2016

Release

The U.S. Food and Drug Administration today approved Axumin, a radioactive diagnostic agent for injection. Axumin is indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following prior treatment.

Prostate cancer is the second leading cause of death from cancer in U.S. men. In patients with suspected cancer recurrence after primary treatment, accurate staging is an important objective in improving management and outcomes.

“Imaging tests are not able to determine the location of the recurrent prostate cancer when the PSA is at very low levels,” said Libero Marzella, M.D., Ph.D., director of the Division of Medical Imaging Products in the FDA’s Center for Drug Evaluation and Research. “Axumin is shown to provide another accurate imaging approach for these patients.”
Figure 3: Whole body positivity rate for fluciclovine F-18 and CT in men with biochemically recurrent PCa.
• Primary prostate cancer:

• 79/84 patients (94%) showed focal uptake in prostate

• In 5/84 (6%) Axumin PET-CT was negative

• In 55 patients who had nodal resection, histopathology correlations showed sensitivity, specificity, PPV and NPV of 48%, 84%, 69% and 69% respectively.

Bogsrud TV et al, F-18 Fluciclovine PET/CT scanning in patients with high risk primary prostate carcinoma: SNMMI annual meeting 2016 Oral session SS76 no 520
Prostate, primary:
65-year-old man with a recent diagnosis of prostate cancer.
Focal nodular uptake in left prostate, at the site of known primary.
Left external iliac nodal uptake.
Biochemical recurrence:
Data submitted to FDA included results from prospective studies at Emory University and the University of Bologna and from clinical use at two sites in Norway.

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>Detection rate</th>
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<tbody>
<tr>
<td>0.79 or less</td>
<td>41%</td>
</tr>
<tr>
<td>0.8-2.03</td>
<td>59%</td>
</tr>
<tr>
<td>2.04-6.00</td>
<td>74%</td>
</tr>
<tr>
<td>More than 6.00</td>
<td>86%</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>&lt;0.79</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>PPV (95% CI)</td>
<td>56%</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>58%</td>
</tr>
<tr>
<td>SENSITIVITY (95% CI)</td>
<td>50%</td>
</tr>
<tr>
<td>DETECTION RATE</td>
<td>43%</td>
</tr>
</tbody>
</table>

Detection rate seems to be independent of:
- Gleason score
- PSADT
- Androgen deprivation

Bogsrud TV et al, AUA 2016 Abstract 16-7313
Sletten H Master thesis 2015
• Imaging protocol:
  • At least 4 hour fasting prior to administration
  • Avoid intense exercise for at least one day prior to scan
  • 10 mCi (370 Mbq) intravenous
  • Injection on the PET scanner table, essentially no uptake time, within 3 to 5 minutes post injection.
  • Position the patient supine with arms up
  • Scan time 20-30 minutes
  • It is important to center the prostate gland/prostate bed in the first bed position due to the fact there is rapid urinary excretion of this tracer into the bladder.

Schmitt M, Beyder D, Prostate Imaging: A New Frontier for the PET Department: J Nucl Med May 1, 2017 vol. 58 no. supplement 1 782
Local recurrence:
- Focus of increased Axumin uptake in the prostate gland, consistent with recurrence of prostate cancer, biopsy-proven.
Local-regional recurrence: 73 year old s/p brachytherapy, Focal radiotracer uptake in the right seminal vesicle.
Pelvic nodes:
An 80 y/o status post brachytherapy with pelvic external beam radiotherapy for a high risk prostate cancer in 2011, now with rising PSA and enlarging right pelvic lymph node.
15 x 16 mm left external iliac node with increased uptake.
Pelvic nodes:
- 61 year-old with PSA of 0.4 ng/mL after robotic-assisted laparoscopic prostatectomy. Focal uptake in an 8 mm perirectal lymph node.
- Salvage radiation could be difficult because of proximity to the rectum
- Mesorectum is a difficulty for urologists and might not be surgically approached
Distant nodes:
75 year old with history of prostate cancer, status post CyberKnife treatment to lymph nodes, rising PSA, restaging.
5 and 9 mm nodes with increased F-18 Fluciclovine uptake, likely metastasis
Distant nodes: 60 yo s/p radical retropubic prostatectomy 2015 and cyberknife to retroperitoneal nodes in 6/2017. Increased PSA. Increased uptake in a prominent left para-aortic node consistent with metastatic disease.
Distant metastasis:
Focal uptake in a RUL nodule, pathology proven metastasis
Bone Metastases:
73 year old with rising PSA,
(A) F-18 Na F PET, MIP images
(B) F-18 Fluciclovine PET, MIP images
(C) Fused images, F-18 Fluciclovine PET-CT
(D) Attenuation correction CT
• Not specific to prostate cancer, shows increased uptake in other malignancies including but not limited to lymphoma, squamous cell cancer of skin, NSCLC, high grade gliomas.

Anaplastic astrocytoma
Bogsrud et al. SNMMI 2016 Poster 1512

Primary breast cancer
J Nucl Med September 1, 2016 vol. 57 no. 9 1357-1363
71-year-old male with reported history of clinical stage TII A, Gleason 3+4 prostate adenocarcinoma, status post cyber knife. S/P RT on 04/02/2012. Pretreatment PSA levels 7.4 ng/mL. Currently with raising PSA, 0.11 ng/mL (4/16), 0.23 ng/mL (05/2017) and 0.89 ng/mL (12/17).
• NM imaging of metastatic prostate cancer:
  • Prostascint
  • Cell membrane synthesis; F-18 or C-11 choline
  • Fatty acid synthesis; C-11 acetate
  • Amino acid transport; F-18 Fluciclovine
  • PSMA receptor expression; (Ga-68, F-18)
  • Glucose phosphorylation; F-18 FDG (not commonly used).
• Prostate specific membrane antigen (PSMA) is a cell surface protein with increased expression (x1000) in prostate cancer cells compared to benign prostatic tissue.
• PSMA is also expressed in other organs (e.g. kidney, salivary glands).
• Its trans-membrane location and internalization after ligand binding make it a favorable target for imaging and therapy.
PSMA inhibitor target
Ga-68 PSMA
F-18 PSMA

Substrate recognition site
Extracellular luminal surface

Cell membrane
In-11 Capromab Pendetide (ProstScint)

Intracellular cytoplasm
• PSMA is present in all prostatic tissues
• Increased expression is seen in a variety of cancers, most notably in prostate cancer.
• Nearly all adenocarcinomas of the prostate (90%) demonstrate PSMA expression in the majority of primary and metastatic lesions
• Expression increases in dedifferentiated, metastatic, or hormone refractory prostate cancer and it’s level is of prognostic significance.
• Radiolabeled PSMA ligands bind to the extracellular domain of PSMA and become internalized.
• Ga-68 is obtained from a Ge-68/Ga-68 generator system
• Half life is 68 minutes
• Decays with 89% positron emission
• Of Ga-68 PSMA ligands, Ga-68-PSMA-11 has been mostly used and published on
• Appropriateness of use criteria are not yet established
• In cases of biochemical recurrence, it is recommended in patients with PSA values between 0.2 and 10 ng/mL to identify the site of recurrence and to potentially guide salvage therapy.
• Is more sensitive in patients with shorter PSA doubling times and those with higher initial Gleason scores
• Prospective study on 130 patients with high-risk disease (Gleason score >7, PSA >20 ng/mL, clinical stage T2c – 3a)
• Ga-68 PSMA imaging is shown to have higher sensitivity and specificity at initial staging when compared to anatomical imaging (CT and MR)
Examples of LN metastases correctly classified by Ga-68 PSMA in pT2a pN1 M0, Gleason score 4+4=8 and intitial PSA 9.6 ng/mL
Primary tumor with increased uptake in left lobe peripherally. 3 mm perirectal LN, not significant on CT, shows uptake. Proved metastasis by histology.
Effect of ADT on performance of Ga-68 PSMA PET is not understood.

Impact of Staging <sup>68</sup>Ga-PSMA-11 PET Scans on Radiation Treatment Plansin Patients With Prostate Cancer
Urology, 2019
Left external iliac lymph nodes less than 5 mm in short axis with increased uptake on Ga-68 PSMA PET-CT, histologically proven as metastatic.

Evaluation of 71 resected LNs in 34 patients:

<table>
<thead>
<tr>
<th></th>
<th>HP Positive</th>
<th>HP Negative</th>
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<tbody>
<tr>
<td>N=34</td>
<td>n=22</td>
<td>n=12</td>
</tr>
<tr>
<td>PET positive</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>PET negative</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91%</td>
<td>Specificity</td>
</tr>
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</tbody>
</table>

• Detection of bone metastases:
  • Retrospective study of 126 patients with prostate cancer, Ga-68 PSMA and bone scan obtained within 3 months of each other:
  • Region based analysis revealed a sensitivity and specificity of 98.8% and 99% for PET versus 91.6% and 97.9% for bone scan.
  • 72 metastases were identified only by PET (17.6%).

• Patient preparation for Ga-68 PSMA PET:
  • Hydration before and during the study
  • Fasting is not required
  • Patients can take their medications
  • Voiding prior to acquisition, image bladder up
  • Lasix (20 mg) can be considered
  • Dose of (0.049–0.060 mCi) per kilogram bodyweight (4-5 mCi in an 80 kg patient) of tracer, intravenous, followed by saline flush

• Uptake time 60 minutes (50-100 minutes)
• Acquisition of mid body, arms up (base of skull to mid thigh). Can alter if desired.
Normal biodistribution

- Increased PSMA expression is not specific to prostate cancer and can also be seen in colon cancer, esophageal cancer, thyroid cancer, lung cancer, renal cell carcinoma, and brain tumors
- PSMA uptake in the celiac ganglia of the autonomous system is common and can be mistaken for retroperitoneal nodal metastasis
- Increased uptake is seen in Paget’s disease

• NM imaging of metastatic prostate cancer:
  • Prostascint
  • Cell membrane synthesis; F-18 or C-11 choline
  • Fatty acid synthesis; C-11 acetate
  • Amino acid transport; F-18 Fluciclovine
  • PSMA receptor expression; (Ga-68, F-18)
  • Glucose phosphorylation; F-18 FDG (not commonly used).
5–10% of prostate cancers do not express PSMA.
This case is a 72 yo man with metastatic castrate-resistant prostate cancer (mCRPC) who had failed conventional therapy options. He has intensely FDG avid metastatic prostate cancer throughout his bones, with a negative 68Ga-PSMA scan. His lack of PSMA activity precluded Lu PSMA as therapeutic option for him. Up to 20% of men with mCRPC will not be eligible for Lu PSMA due to inadequate expression of PSMA.

69 year old gentleman with prostate cancer s/p brachytherapy
A,B: FDG PET MIP images show uptake in prostate and right sacrum
C,D: Fused images
“We’ve found a mass. The good news is we have weapons of mass destruction.”
Ionizing radiation is used to kill cancer cells and shrink tumors by damaging the cells’ DNA, thereby stopping these cells from continuing to grow and divide.
• Radioactive decay:
  • Radioactive nuclei are unstable due to excess or deficiency of neutrons.
  • Such nuclei have excess internal energy compared with a stable arrangement of neutrons and protons.
  • They achieve stability by transforming to a more stable nucleus, the process is called radioactive decay
  • These events are accompanied by the emission of energy, including particulate and electromagnetic radiations.
  • Most radionuclides decay in one or more of the following ways: (a) alpha decay, (b) beta minus emission, (c) beta-plus (positron) emission, (d) electron capture, or (e) isomeric transition.
• **Alpha decay:**
  • Usually occurs with heaviest nuclides and results in emission of alpha particles (two protons and two neutrons, identical to helium nucleus).
  • Mass number (A) reduces by 4, atomic number (Z) reduces by two.
  • Alpha particles are high energy and limited range. The range of a 4 MeV alpha particle is about 14 microns in tissue.
• Beta⁻⁻ decay:
  • Also called negatron decay, characteristically occurs with radionuclides that have an excess number of neutrons compared with the number of protons (high N/Z ratio).
  • A neutron is converted to a proton and the process creates an electron and an antineutrino.
  • Mass number (A) is unchanged, atomic number (Z) is increased by one.
Advantages of radionuclide therapy:

- Non-invasive to minimally invasive.
- Duration of treatment is shorter compared to chemotherapy and external beam radiation therapy.
- Selectively delivers a highly concentrated dose of radiation to the target while sparing the surrounding normal tissues.
- Side effects are less in comparison with conventional treatment methods.
• Palliative beta emitters for bone metastases:
  • $^{89}$Strontium ($^{89}$Sr), calcium analogue, half life of 50 days
  • $^{32}$Phosphorus ($^{32}$P), half life 14 days, targeted to bone through inorganic phosphate pathways.
  • $^{153}$Samarium ($^{153}$Sm), rapid blood pool and urinary clearance. 1.9 days half life. 10-20 fold affinity to areas of new bone formation. 70-80% of patients experience some relief in bone pain within one week.

• Ra-223 dichloride (Xofigo)
  • 95.3% Alpha emitter 3.6% Beta, 1.1% Gamma
  • Alpha particles have high LET over a short distance
  • Half life of 11.4 days
  • Calcium mimic
  • Elimination is via feces with only minimal renal clearance.
• Dose: body weight (kg) x 1.49 (uCi)
• One intravenous injection every four weeks, a total of six injections.
• FDA approved (2013) for treatment of bone metastases in CRPC
• Increases the overall survival by 3-4 months
• Delays first skeletal-related event.
• **Lu-177**
  • Reactor produced radio-metal
  • Beta emitter (490 keV), max energy of 0.5 MeV, max tissue penetration 1.5 mm which provides better radiation of smaller lesions (Y-90 12mm)
  • Also emits gamma rays at 208 and 113 keV (10% and 6% abundance) which allows imaging
  • Half life is 6.73 days
  • Overexpression of PSMA in prostate cancer allows treatment with Lu-PSMA radio-ligands
Lu PSMA is administered by a slow intravenous injection (30–60 sec) in a volume of 5 mL (diluted with 0.9% sterile sodium chloride solution), followed by a saline flush.

Patients are hydrated pre- and post-administration of 177Lu PSMA with 1–1.5 L of water and encouraged to void as frequently as possible.

Injected doses range from 3 to 8 GBq per injection with up to six injections, minimum of 6 week intervals.

Dose calculation has not been standardized. Calculations have been based on a combination of disease burden, patient weight and renal function.

• Renal excretion of Lu-177 occurs in the first 48 hours.
• Radiation safety instructions focus on managing potential radioactive spills.
• Patients are required to remain in the department for 2–4 h for observation and for measured radiation levels to decrease.
• In the currently published literature, 30-70% of treated patients will experience a >50% reduction in serum PSA level. This compares well to the PSA response rates achieved by chemotherapy agents used in mCRPC (Cabazitaxel and Docetaxel)
Waterfall plot showing percentage PSA change from baseline at 8 weeks after the first cycle in 23 patients (one patient with multiple liver metastases died ten weeks after the first cycle)

(A) SPECT CT whole body imaging 24 h post-Dose 1. 8.0 Gbq Lu PSMA Images demonstrate Lu PSMA uptake in multiple metastatic foci throughout the axial and appendicular skeleton. Serial time point imaging of the associated gamma emissions allows estimation of tumor dose delivered with each injection. 

(B) SPECT CT whole body imaging 24 h post-Dose 2. 8.0 Gbq Lu PSMA SPECT CT images show a marked reduction in the intensity and number of Lu PSMA avid metastatic foci, which concords with the marked reduction in serum PSA in this patient.

75 year old patient with local recurrence as well as diffuse bone and lymph nodes metastases (left MIP image). History of chemotherapy and therapy with abiraterone, PSA elevation under enzalutamide. The patient underwent PSMA therapy as the last possible option. Continuing PSA decline and partial response in Ga-PSMA PET images after the first (middle MIP image) and second cycles (right MIP image).

• Side effects of Lu-177 PSMA:
  • Overall, low grade
  • Dry mouth in up to 30%
  • Fatigue in up to 25%
  • Nausea up to 10%, particularly in the 24–48 h after injection.
  • No report of renal toxicity, although it is likely that this will be a longer term complication if it is to occur.
Table 3
Toxicity in patients undergoing Lu PSMA therapy

<table>
<thead>
<tr>
<th>Haematological toxicity (G2-3)</th>
<th>Non-haematological toxicity</th>
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<tbody>
<tr>
<td></td>
<td>Hb</td>
</tr>
<tr>
<td>Zechmann 2014 et al.</td>
<td>Below ‘normal range’ 75%</td>
</tr>
<tr>
<td>Ahmadzadehfar 2015 et al.</td>
<td>10%</td>
</tr>
<tr>
<td>Ahmadzadehfar 2016 et al.</td>
<td>25%</td>
</tr>
<tr>
<td>Kratochwil 2016 et al.</td>
<td>10%</td>
</tr>
<tr>
<td>Baum 2016 et al.</td>
<td>5%</td>
</tr>
<tr>
<td>Rahbar 2016 et al.</td>
<td>15% N/S changes</td>
</tr>
<tr>
<td>Rahbar 2016 et al.²</td>
<td>9–20%²</td>
</tr>
<tr>
<td>Heck 2016 et al.</td>
<td>32% (G1-2)</td>
</tr>
<tr>
<td>Yadav 2016 et al.</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Fatigue and dry mouth appear most commonly. Haematological problems occur and can be significant in the group of men with borderline marrow function due to extensive bone metastases.
• A recent study of 40 patients identified platelet level and pain as the most significant predictor of poor response to 177LU-PSMA (possibly due to burden of metastatic bone disease).

• Other studies have commented that bone metastases appear to respond less well than visceral or lymph nodal disease to treatment with Lu PSMA.
The ideal candidate has intense GaPSMA activity at all sites of metastatic prostate cancer, ensuring a high radiation dose delivered uniformly. This case demonstrates intense Ga PSMA activity compared to minimal FDG activity in metastatic prostate cancer.

• Not all patients with mCRPC will have a good treatment response to 177Lu PSMA.

• Up to a third show progressive disease despite treatment. It is not known whether the tumor cells uniformly express a high density of the PSMA receptor.

• Heterogeneity of PSMA receptor activity within the tumor population may mean that some sites will not respond to treatment with 177Lu PSMA, leading to disease progression and rising PSA.

• Currently PSMA expression is measured by assessing intensity of activity on a 68Ga-PSMA staging PET/CT and is a requirement for treatment in all currently published studies.
Good Start
But you've still got a ways to go
1. Which one of these imaging agents can not be used for evaluation of prostate cancer:

A. F-18 PSMA
B. Ga-68 DOTATATE
C. F-18 Na-F
D. Tc-99m MDP
2. Which of these statements is correct?

A. Ra-223 is used as palliative treatment for bone pain in metastatic prostate cancer but does not affect the overall survival

B. Lu-177 is useful for treatment of all patients with metastatic prostate cancer

C. Samarium-153 is used as palliative treatment for bone pain in metastatic prostate cancer but does not affect the overall survival

D. F-18 FDG is never used for staging of prostate cancer
Which of these statements is correct?

A. Ra-223 is used as palliative treatment for bone pain in metastatic prostate cancer but does not affect the overall survival. Incorrect. Overall survival is improved.

B. Lu-177 is useful for treatment of all patients with metastatic prostate cancer. Incorrect. Not all patients with prostate cancer will respond to Lu-17.

C. Samarium-153 is used as palliative treatment for bone pain in metastatic prostate cancer but does not affect the overall survival. Correct.

D. F-18 FDG is never used for staging of prostate cancer. Incorrect. FDG PET will be positive in a minority of patients.
2. Which statement is correct.
   A. Lu-177 is made by a generator
   B. Lu-177 is made by a cyclotron
   C. Ga-68 is made by a cyclotron
   D. Ga-68 is made by a generator
Which statement is correct.

A. Lu-177 is made by a generator. Reactor is correct.
B. Lu-177 is made by a cyclotron. Reactor is correct.
C. Ga-68 is made by a cyclotron. Generator is correct.
D. Ga-68 is made by a generator. Correct.
2. Question

A. Answer
B. Answer
C. Answer
D. Answer

Your questions need to reflect each learning objectives approved for your program. Please avoid True/False questions. Also avoid questions with “all of the above,” “none of the above,” “more than one correct answer” for an answer choice.
3. Question

A. Answer
B. Answer
C. Answer
D. Answer

Your questions need to reflect each learning objectives approved for your program. Please avoid True/False questions. Also avoid questions with “all of the above,” “none of the above,” “more than one correct answer” for an answer choice.
4. Question
   A. Answer
   B. Answer
   C. Answer
   D. Answer

Your questions need to reflect each learning objectives approved for your program. Please avoid True/False questions. Also avoid questions with “all of the above,” “none of the above,” “more than one correct answer” for an answer choice.