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ABOUT SERVICES INTEGRATIVE HEALTH WEEKLY EZINE

CONNECT LOG IN *November 1, 2017*

Overview of PET/CT Imaging in Recurrent Prostate Cancer – Current and Emerging Techniques

Over the last few years, we have seen tremendous activity in the area of molecular imaging for prostate cancer. Just about every day we have colleagues asking about the various PET/CT imaging tests - what is available? How do they compare? What are the parameters for successful imaging?

We are proud to be contributing to this body of knowledge. Our work regarding C11-Acetate PET/CT imaging in the recurrent PCa setting with relationship to PSA kinetics has been recently published. This represents the largest single-site evaluation of a molecular imaging agent. A link to the publication and brief overview PET/CT imaging for Prostate Cancer follow for your review. We hope

you find this information useful.

CONVENTIONAL TYPES OF IMAGING

Ultrasound has a role in doing prostate biopsies and the placement of radioactive seeds in primary prostate cancer. It is also useful for evaluating local recurrence after surgery in patients with an increasing PSA. CT Scans are commonly used for staging men with newly-diagnosed disease, looking for enlarged lymph nodes in the pelvis. However, it is inaccurate for detecting cancer in the lymph nodes. If cancer is present in the nodes, a CT scan only finds it 35% of the time. Prostate MRI is used for staging, biopsy guidance, surgical planning, radiation planning, and restaging after PSA relapse. Multi-parametric MRI is being found to be very helpful for detection and local staging of untreated prostate cancer, to reveal features such as extra-capsular extension or seminal vesicle invasion, thus helping to confirm local (organ confined) disease. Additionally, multi-parametric MRI is emerging as a useful imaging tool for following changes in the prostate gland for men on active surveillance.

TECHNETIUM-MDP

Prostate cancer frequently metastasizes to the bone, therefore the mainstay of imaging for advanced prostate cancer has been technetium-labeled (Tc99) bisphosphonate bone scintigraphy. Tc99 bone scans are used for initial staging of intermediate-to-high-risk disease and for restaging after PSA relapse.

Unfortunately, it is not sensitive enough to detect small skeletal metastases. False positives are common due to interference from non-cancerous arthritic changes and/or prior trauma.

SODIUM FLUORIDE (NAF) PET/CT SCANS

NaF PET/CT is similar to standard bone scans, but uses PET imaging which is significantly more sensitive and specific than standard Tc99 (Technetium) bone scans. In the PCa recurrent setting, bone lesions as small as 2-3 mm with PSA values < 1.0 can be detected. Unlike Tc99m bone scan, arthritic changes and prior trauma are much less problematic with NaF PET/CT. Another advantage of NaF PET is the shorter scan time, typically less than one hour, compared to 4 hours for Tc99.

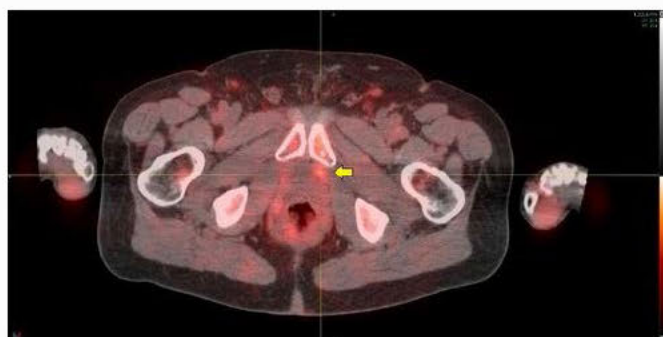
11C CHOLINE AND ACETATE PET/CT SCANS

Prostate cancer cells rely on fatty acid metabolism as their energy source. 11C-choline and 11C-acetate are lipid metabolism PET agents. Both of these agents are useful for detecting recurrent disease after a PSA relapse. 11C-choline has been approved for use at Mayo Clinic. 11C-acetate is available under expanded access clinical trials at multiple institutions. Small direct comparison studies of 11C-acetate and 11C-choline have revealed no clear clinical differences between these agents, although a few studies have suggested a slightly higher detection rate of local recurrences and small pelvic lymph node metastases with 11C-acetate.

In a large-scale study of 11C-acetate PET/CT imaging in 887 patients with relapsing PSA (at Phoenix Molecular Imaging), the overall detection rate of recurrent prostate cancer was 88% with a PPV of 91%. A PSA threshold of 1.09 ng/mL was established for optimal imaging. However, if the PSA was less than 1.0 ng/mL and the PSA doubling rate was brisk (less than 3 months), the detection

rate was better than 90%. (Am J Nucl Med Mol Imaging 2017;7(1):1-11) The reported detection rate for ^{11}C -choline generally ranges from 42-82% with a PSA threshold of 2.0 recommended for optimal imaging. At least one study in 102 patients has also demonstrated a significant influence of the PSA doubling time on ^{11}C -choline with a 93% detection rate noted in a PSA range of 0.67-1.1 ng/mL if the PSA doubling rate was under seven months.

^{11}C has a short half-life of 20 minutes, so ^{11}C -Acetate and Choline are available only at sites with cyclotrons capable of producing this agent alongside of the imaging facility. This does limit its availability to specialized centers.



^{11}C -Acetate PET/CT in a 66 y/o with Gleason 3+4=7 disease. Prostatectomy two years previously and now with a rising PSA of 0.3 ng/mL.



Imaging shows a small metabolic focus in the left prostate bed (top image) and a small positive left external iliac node (lower image). The results of the scan changed treatment

plans. Salvage radiation treatment was performed and with the treatment field extended to include the pelvic lymph nodes.

AXUMIN PET/CT SCANNING (18F-FACBC)

Amino acids, such as leucine, methionine, and glutamine, are absorbed into the cancer cells because of the increased metabolic demands of the growing cancer cells. The FDA recently approved Axumin (Fluciclovine or 18F-FACBC), which is a fluorine-18 radiolabeled synthetic leucine amino acid.

CLINICAL TRIALS OF AXUMIN

Scans were performed in 105 patients. The results were checked for accuracy with biopsy or surgery after the scan. Three independent reviewers analyzed the scan results. For men who had biopsy confirmation of cancer in the prostate bed, the true-positive rate ranged from 49-58%. The false positive rates ranged from 16-30%. For patients who had positive biopsies outside of the prostate bed, the results were much better, with a true-positive rate of 88-93% and a false-positive rate of only 7-8%. Optimal detection rates were seen when the PSA was above

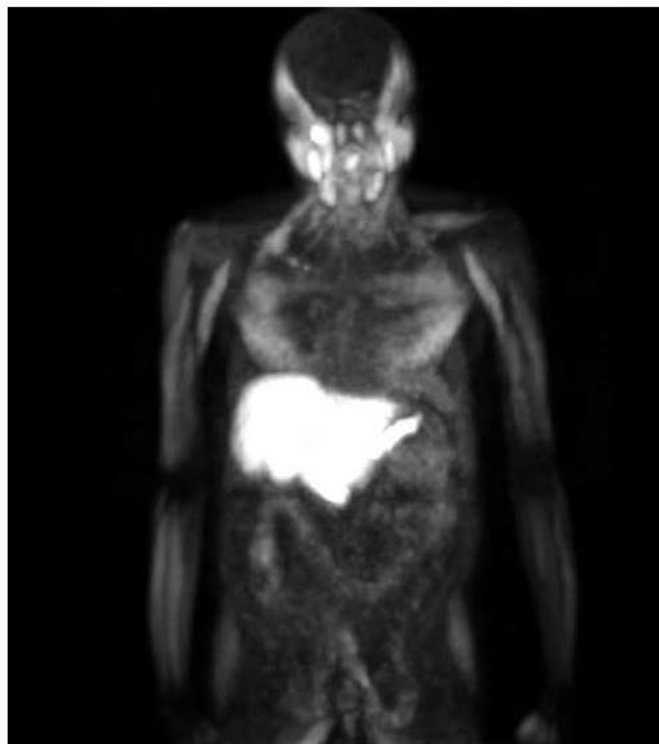
1.78 ng/mL.

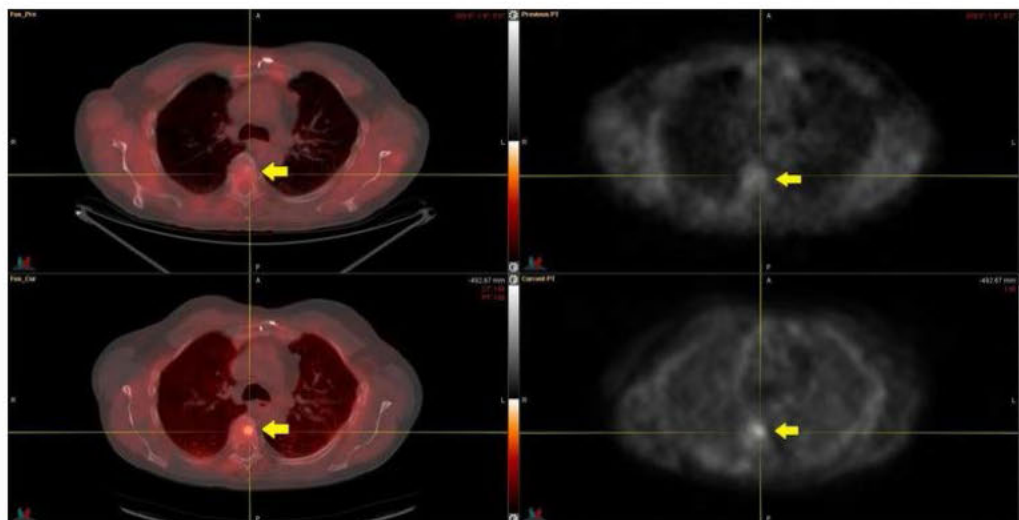
In another clinical trial of 96 patients, a comparison was made between Axumin and ¹¹C-choline PET. The scans showed equivalent findings 61-77% of the time. However, this study did not include biopsy confirmation. In a third study performed in Italy, 89 patients with a rising PSA were studied. The overall cancer detection rate was 37%. In those patients with a PSA of less than 1.0 ng/mL, the detection rate was 21%, with a PSA of 1.0-2.0 ng/mL detection was 29%, and when the PSA was higher than 3.0 the detection rate was 59%. In a more recent multi-center study of Axumin in 596 patients, the overall detection rate was 68% with a true positive rate of 62% and false positive rate of 38% ([http://www.jurology.com/article/S0022-5347\(16\)31518-X/pdf](http://www.jurology.com/article/S0022-5347(16)31518-X/pdf)).

We and others have observed that with Axumin, there is typically much higher muscle and bone marrow background activity than that seen with ¹¹C-Acetate or Choline. This makes small lesions in the prostate bed and bone difficult to detect (see examples below). In some patients, the muscle uptake of Axumin may be so high as to render the study non-diagnostic, despite having properly abstained from physical activity prior to the scan. Additionally, in a small but significant number of patients, interfering urinary excretion is seen. These factors likely help explain the apparent lower performance of this agent compared to ¹¹C-Acetate and Choline.

Axumin study showing high
physiologic muscle background

uptake, rendering the study suboptimal for evaluation of suspected sites of metastasis.





Detection of a⁸
 bony metastasis.
 Top row shows a
 Axumin study in
 a patient with
 Gleason 4+4=8
 disease, post
 prostatectomy
 and salvage radiation

two years previously. PSA now rising, 1.1 ng/mL. Fused Axumin PET/CT on the top left and axial Axumin PET on the top right. The Axumin study is negative.

Bottom row of same patient after ¹¹C-Acetate PET/CT imaging clearly shows a metastasis in the body of T5.

PSMA PET/CT SCANS

The prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that occurs much more commonly in prostate cancer cells compared to benign prostate tissue. The clinically approved imaging method using PSMA was ProstaScint. ProstaScint, however, has several limitations. The technique uses an intact antibody which targets the internal portion of the cell membrane glycoprotein (PSMA) which requires long circulating times. There is prolonged blood-pool retention leading to high background signals, low detection rates, and much lower spatial resolution compared to PET.

Better agents for detecting PSMA have been developed, such as 68gallium-PSMA-11. Several retrospective studies have indicated a higher diagnostic efficiency of 68Ga-PSMA PET/CT compared to 11C-choline PET. In one study, for example, with 319 patients with PSA relapse, an overall 82.8% detection rate was seen. As might be expected, the probability of detecting lesions was correlated with PSA level. A 50% detection was seen when the PSA was 0.2-0.5, 58.3% detection with a PSA of 0.5-1.0, 71.8% detection with a PSA of 1.0-2.0, and 93% detection when the PSA was over 2.0.

No PSMA PET agents are yet commercially available, with 68Ga-PSMA-11 under clinical trial investigation in multiple U.S. institutions (e.g. UCSF, UCLA, and Stanford University). “PSMA” is not one agent however. In addition to 68Ga-PSMA-11, there are many different PSMA-targeting agents in current development – somewhat of a dizzying array. Each has a different molecular configuration, requiring study to understand how well they work and how they are different from each other. Competition for the “best” PSMA agent is likely to be fierce. Below is a list of some of the agents currently under investigation:

68Ga-PSMA-11

68Ga-PSMA-617

68Ga-PSMA-I&T

68Ga-PSMA-R2

68Ga-PSMA-SR6

68Ga-NODAGA

68Ga-P16-093

64Cu-PSMA-617

64Cu-NODAGA

99mTc-MIP-1404

99mTc-HYNIC-PSMA

99mTc-J591

99mTc-EC0652

123I-MIP-1972

123I-MIP-1095

18F-DCFPyl

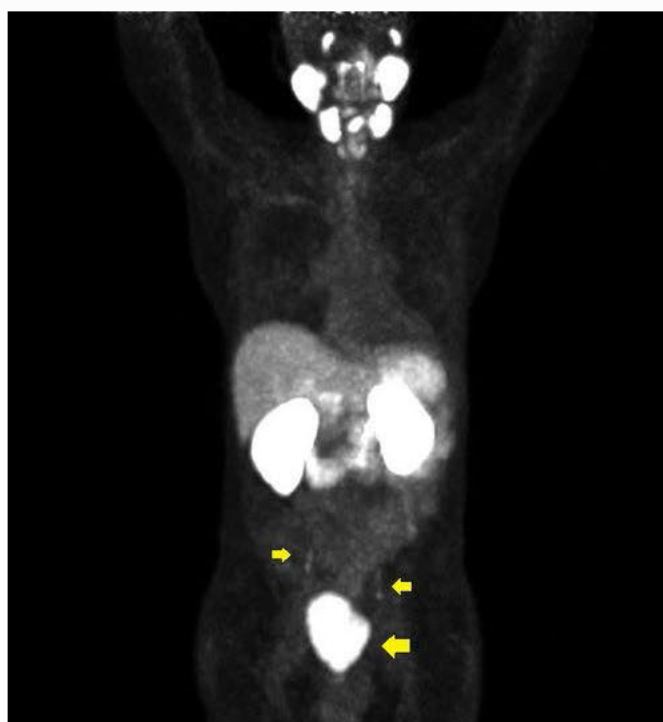
18F-DCFBC

18F-CTT1057

18F-PSMA-1007

A few limitations of PSMA-targeting agents are important to understand. Not all prostate cancers exhibit PSMA overexpression. In one study, about 8% of patients with prostate cancer did not show PSMA overexpression. Another study showed that there can be up to a 25% heterogeneity in expression in PSMA in an individual, thus in one person some of the cancer will be positive while other cancer deposits will be missed. Additionally, PSMA ligands are not completely specific for prostate cancer and several benign lesions such as thyroid adenoma, Paget's disease, schwannoma, adrenal adenomas, and several types of vascular tumors (colon, breast, renal, liver, thyroid) may also exhibit increased PSMA expression. False positive celiac ganglia activity frequently has been noted in the upper abdomen. Finally, most PSMA-targeting agents to date are significantly excreted in the urinary tract and urinary bladder. This is a huge issue as this which

obscures the prostate bed, making detection of locally recurrent lesions and lymph nodes in the lower pelvis challenging if not impossible to find – see the example below. When we consider that in up to 30% of men with recurrence their cancer is located in these regions, false negative PSMAAs may have significant negative impact on their care. ^{18}F -PSMA-1007 is one of the more recent additions to the long list of PSMA agents and is in the early pre-clinical study phase. This agent shows less prominent urinary excretion and may have a potential advantage compared to other PSMA agents in addressing this issue.

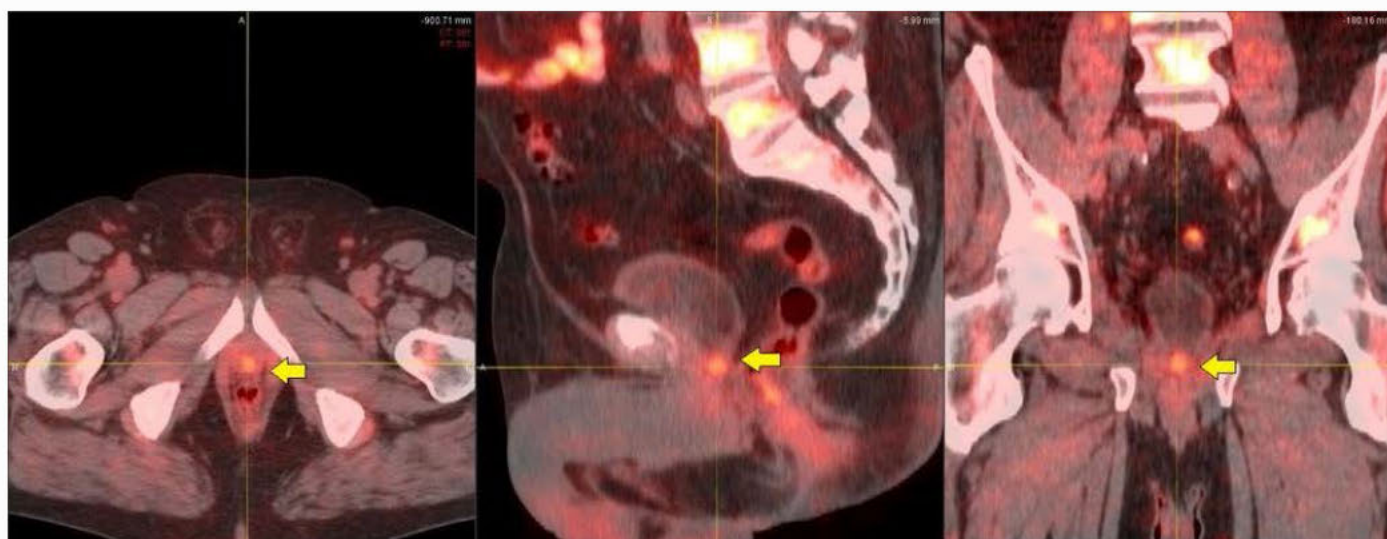


Ga68-PSMA-11 PET image in a patient with Gleason 4+5=9 disease, post prostatectomy and with a rising PSA of 1.1 ng/mL.

The PSMA study is negative. Prominent urinary bladder and ureteral tracer activity is present (arrows) which interfere with assessment of the prostate bed and pelvic lymph nodes.

This study was performed after use of diuretics, which unfortunately was of little help in clearing the urinary activity.

The image below shows a ^{11}C -Acetate PET/CT imaging in the same patient as the above PSMA example showing axial, sagittal and coronal views from left to right. A metabolic focus can be seen in the prostate bed at the anastomosis site (arrows). The lack of urinary tracer excretion of ^{11}C -Acetate allows visualization of small and subtle lesions in this region, not typically possible with PSMA based agents.



IN SUMMARY

The excitement surrounding the current and emerging PET agents is appropriately exuberant. Radical breakthroughs are occurring in the area of imaging, however a fair amount of confusion exists and further research is needed. There is still no “perfect” imaging methodology with 100% accuracy, with each of the current agents demonstrating some pros and cons.

Our experience at Phoenix Molecular Imaging has shown ¹¹C-Acetate PET to be a valuable and accurate tool, providing a better understanding of the location and extent of local recurrences and distant disease - often leading to changes in treatment plans.

The recent FDA approval of Axumin is exciting as its ¹⁸F tag makes it more readily available than ¹¹C tagged agents. So far Axumin (detection rate 68%, 38% false positive) however it does not appear to perform nearly as well as Acetate or Choline (88-90% detection rate and <10% false positive rate). Given the predilection for bony metastasis in prostate cancer, the routine addition of NaF PET/CT studies with Axumin appears prudent in order help mitigate its much lower detection rate of bony lesions. Acetate or Choline remain overall much better choices for imaging.

PSMA-targeted imaging appears to be promising and may provide higher sensitivity and specificity than other imaging agents to date. There are some important and practical limitations with PSMA however, as detailed above - lack of PSMA expression in some cancers, false positives in benign vascular lesions and inability to fully assess the lower pelvis due to high urinary excretion.

Research is ongoing on PSMA agents to understand how well and accurately they perform.

Fabio Almeida, MD is the Medical Director of Phoenix Molecular Imaging and Yuma Regional Cancer Center PET/CT providing his extensive clinical expertise in PET/CT imaging. He is a board certified nuclear medicine/oncology imaging physician, internist and integrative medicine physician. Hi research is focused on applied medical informatics with emphasis on imaging and networking systems, optimization of fusion technology and volumetric tumor assessment for radiation therapy planning. He is one of the pioneers in the development and implementation of cross modality fusion for cancer imaging (SPECT, PET, CT and MRI) and PET/CT. He has authored and participated in several publications in radiology, oncology and information science.

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PREVIOUS

Lutetium-PSMA (Lu-
PSMA) Prostate Cancer
Trial

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