In a previous December 2012 article published in PAACT’s newsletter I had the opportunity to discuss the preliminary results of our imaging work with Carbon 11 Acetate PET/CT. In this article, I provide an update to our study and give some case examples of patients to help illustrate the utility and options provided by this advanced imaging for prostate cancer recurrence.

The treatment landscape for prostate cancer has been revolutionized by the arrival of multiple novel treatment approaches and agents over the last few years. After initial treatment with surgery or radiation however, up to 40% of patients will unfortunately experience PSA relapse. For these patients, treatment options tend to be limited, usually including salvage radiation and/or hormone therapy. In addition, the PSA relapse can occur in the setting of a negative CT Scan and/or bone scan, leaving patients and physicians guessing about the location of cancer recurrence, and the number and size of metastatic lesions.

Oligometastatic prostate cancer is a relatively new term referring to the detection of a limited number of metastatic sites developing at PSA relapse after primary treatment.
Oligometastasis refers to 1-3 or at most up to 5 lesions in lymph nodes or in bones. The concept emerged in the 1990s from observations that there were some patients with just a few sites of metastases with slowly progressive disease who experienced very favorable long-term outcomes with local therapy (usually radiation) targeted to these few sites. Observations of this sort spawned the hypothesis that there may exist an intermediate stage of cancer between primary disease and widespread metastases that could be treated successfully with limited therapy, delaying or avoiding long-term androgen suppression, or hormone therapy.

Knowing the precise location of a cancer recurrence is therefore important since recurrence in the prostate bed or pelvic lymph nodes may be amenable to additional focal therapy. Finding lesions outside of the pelvis (distant metastases) may require systemic treatment with hormones combined with radiation or other focal treatment, such as radiation.

The primary difficulty is that standard imaging techniques such as technetium (T99) bone scan, CT scans and MRI are usually unable to see small recurrent tumors outside the prostate, or metastases. These studies are therefore very limited in terms of directing focal treatment and so also limit potential treatment options. An accurate global (total body imaging) assessment is needed to identify all locations of metastases. The recent development of whole body imaging with C11-Acetate PET/CT appears to facilitate the identification of early, limited recurrent prostate cancer and appears to provide a tool to help better guide individualized treatment options.

C11-Acetate & C11-Choline

Over-expression of certain enzymes in prostate cancer (fatty acid synthase and choline kinase) results in increased cell membrane lipid production. Tumor cells depend on their ability to produce their own lipids. Different PET tracers, such as Carbon-11-Acetate (C11-Acetate) and Carbon-11-Choline (C11-
Choline) have been developed that take advantage of this metabolic pathway and allows for lipid membrane imaging in prostate cancer. These metabolic agents used in PET/CT imaging provide for direct detection and measurement of the cancerous lesions, and additionally have the advantage of a more comprehensive review of the body – evaluating the lymph nodes, the prostate gland region, other organs such as the lungs, as well as the bone.

At the Phoenix Molecular Imaging Center in Phoenix Arizona, a large scale FDA-approved clinical trial investigation of C11-Acetate PET/CT imaging has continued to demonstrate excellent results and has led to direct benefit to many patients that would not have been achievable with standard imaging techniques.

**In this study, over 560 men with recurrent prostate cancer (as evidenced by a rising PSA) have now been studied using a high resolution PET/CT camera and Carbon 11 Acetate.** This study represents the largest single site prostate cancer PET molecular imaging evaluation conducted in North America. **Our results have demonstrated an overall detection rate for the site of recurrence of 88%. In 59% of these studies locally recurrent or regional lymph nodes were found with no evidence of distant metastases.**

The PSA level is being shown to have an influence on the C11-Acetate detection rate. When the PSA is > 1.0 ng/mL the detection rate increases to 92%. With a PSA of 0 – 0.4ng/mL the rate is 64% and when the PSA is 0.4 – 1.0 ng/mL this is 75%. The PSA doubling time (or rate of PSA rise) also appears to have an influence, such that when the PSA is <1.0 and the PSA doubling time is < 3 months, the detection rate is 95%. To calculate your own PSA doubling time, simply calculate how long it takes a rising PSA to double, or search online for one of the many PSA doubling time calculators.

C11-Acetate appears superior to C11-Choline. The overall detection rate for cancer recurrence or metastatic
disease with C11-Acetate (88%) has been 14% higher than that reported for C11-Choline (74% – as reported by Mitchell et.al [J Urol 189(4): 1308-1313]). Lesions detected at lower PSA levels (<1.0ng/mL) are of particular clinical interest. It is at this low range where many treatment decisions are made, such as otherwise “blind” radiation to the prostate bed or the initiation of hormone therapy. C11-Choline performance in this range is poor, with a detection rate of only 44%. C11-Choline is therefore generally not recommended when the PSA is less than 1.5-2.0 ng/mL. C11-Acetate performance in this low PSA range on the other hand is significantly higher with a detection rate of 75%. Additionally, when performed in the context of a low doubling time (<3 months), the detection rate for C11-Acetate in this low PSA range is excellent, at 95%. This higher performance in the low PSA range makes C11-Acetate better suited for earlier detection for recurrence.

Case Example 1
Mr. V is 76 years old and was diagnosed with Prostate Adenocarcinoma (PCa) in 2000. His Gleason score was 8 (4+4) and his PSA was 4.0. He underwent a prostatectomy in 2001 and his PSA remained <0.1 for several years. His PSA then began to rise and by 2011 his PSA was 3.3 ng/mL and PSA doubling at a rate of 10.9 months.

A C11-Acetate PET/CT imaging study was performed which showed a small recurrence of the cancer in the prostate bed (yellow arrow on image). No involved lymph nodes were detected and no lesions were seen on the C11 study to suggest distant metastatic disease. Based on the results of the C11-Acetate
imaging study, Mr. V proceeded with Intensity Modulated Radiation Therapy (IMRT) to the prostate bed. The radiation therapy plan was modified from the typical “blind” application of radiation to this region. Instead, the area of recurrent cancer identified on the imaging study was targeted by the radiation and less radiation was then given to the surrounding areas, including the urinary bladder and rectum.

How has he done?
After his radiation treatment, the PSA fell to 1.1 ng/mL and has remained stable at that level for 3 years. He experienced no side effects from the radiation treatment and no other treatment has thus far been necessary. He is pleased that he has not yet needed to start hormone therapy.

Case Example 2
Mr. S is 69 years old and was diagnosed with PCa in 2010. His Gleason score was 8 (4+4) and his PSA was 4.8ng/mL. He underwent a prostatectomy at which time extracapsular extension was found. After surgery his PSA was initially undetectable, but it began to rise a few months later and within a year his PSA had risen to 0.5 ng/mL, with a PSA doubling time of 3.18 months.

Mr. S’s urologist told him it was most likely that the cancer had metastasized, and probably involved the bone given how quickly his PSA was rising. A technetium bone scan was performed, which was negative for bone metastasis. Even so, he was advised by his urologist to begin hormone therapy as his only option.

Mr. S was not ready to start hormone therapy based on the above information...

A C11-Acetate PET/CT imaging study was performed which showed a small focus of increased metabolism in the right seminal vesicle bed (yellow arrow on image below). This indicated
locally residual cancer left behind after surgery which was now growing. There were no involved lymph nodes on the scan and no lesions were seen on the C11 study to suggest distant metastatic disease to the bone or elsewhere. In other words, he had no known metastatic disease.

Based on the C11-Acetate imaging study, Mr. S underwent IMRT. The radiation therapy was performed to the entire prostate bed region but also with a radiation “boost” targeted to the area of cancer noted on the imaging study.

How has he done?
After his radiation treatment, his PSA fell to <0.1 ng/mL and has remained stable at that level for 1.5 years so far. He experienced no side effects from the radiation treatment and has not yet had to start any hormone therapy.

Case Example 3
Mr. W is 72 years old and was diagnosed with PCa in 2006. His Gleason score was 9 (5+4) and his PSA was 10.8. He underwent a prostatectomy and his PSA remained <0.1 ng/mL for 7 years. His PSA then began to rise, and by 2013 it was 0.63 ng/mL with a PSA doubling time of 9.3 months. An abdominal and pelvic CT scan as well as technetium bone were negative. A C11-Acetate PET/CT imaging study was performed which showed a small metabolic 9 mm lymph node to the right of and next to the rectum (yellow arrow on image below). A small 5 mm metabolic node was also seen higher up in the left pelvis (not shown). No metabolic lesions were seen in the prostate bed and no lesions were seen on the C11 study to
suggest distant metastatic disease.

In most cases such as this, IMRT radiation treatment to the prostate bed with radiation extending to the pelvic lymph nodes has been the recommended course of action, with good results. Mr. W’s case was however more complicated. He has a history of ulcerative colitis and recently had a bout of this requiring treatment with steroids. In this scenario, standard radiation would be problematic as it would likely make his bowel inflammation much worse. Radiation was essentially considered contraindicated for him. His urologist suggested hormone treatment, but Mr. W is a working professional and felt that this would interfere significantly with his work and travel.

Mr. W opted to undergo a different form of radiation treatment – Protons – with the newest (Intensity Modulated) generation of this technique (available at Scripps in San Diego California) having the ability to be conformal in a similar way to IMRT, but offering a level of precision not possible with standard radiation with IMRT. The proton therapy was performed only to the pelvic lymph nodes detected on the C11 Acetate imaging study and with the C11 Acetate PET/CT imaging electronically integrated into the treatment plan to help guide the proton therapy. The image below shows the targeting of the proton beam treatment (color areas), which is narrow and avoids the intestine.
How has he done?
Nine months after his proton radiation treatment, his PSA has decreased to 0.1 ng/mL. He experienced no side effects from the radiation treatment and most importantly, has not had any exacerbation of his ulcerative colitis. He will continue to follow his PSA.

Case Example 4
Mr. G was 48 when he was diagnosed with prostate cancer in 1995 with Gleason 7 (4+3) disease and a PSA of 58. He had a prostatectomy at that time. His PSA rose in 2001 for which he subsequently had radiation treatment to the prostate bed. In 2013 his PSA was again rising. A CT scan showed enlarged nodes in the pelvis and abdomen. These were treated with additional radiation and he was started on hormone therapy.

He completed Provenge treatment in 2014. The PSA continued to rise to a level of 2.96 ng/mL with a PSA doubling time of 1.25 months. Bone metastasis were suspected by his doctor but could not be seen on standard imaging.
A C11-Acetate PET/CT imaging study was performed which showed a small but focally metabolic lesion involving the right
seminal vesicle bed region (yellow arrow on image below). No metabolic lesions were seen in the prostate bed and no lesions were seen on the C11 study to suggest active distant metastatic disease.

Mr. G’s prostate cancer appears resistant to hormone therapy (castrate resistant) and a second line hormonal treatment (Xtandi) was recommended by his oncologists. He starting this medication. Finding only a single active area of cancer in the pelvis however also prompted the addition of focal IMRT re-irradiation to the right seminal vesicle region. With the ability to focally identify the recurrent cancer region, the application of radiation to an area previously radiated is now being performed by many radiation oncologists with good results and low side effects. Only with the information from the C11-Acetate scan could this have been possible.

How has he done?
After completing the radiation treatment, his PSA has decreased to 0.2 ng/mL. He experienced no side effects from the radiation treatment and he will continue to follow his PSA.

Summary
C11-Acetate PET/CT imaging appears highly useful in men with recurrent prostate cancer and can help provide treatment options that otherwise would not be available. It has a high detection rate even at very low PSA levels, and in many cases identifies areas of recurrent or regionally metastatic disease that can be treated with radiation or other focal therapy. Treatment with hormone therapy may be avoided or significantly delayed. In other cases, C11-Acetate may show evidence of distant metastatic disease not seen by other techniques, thereby helping to better identify situations where systemic/hormone therapy may be the most appropriate course of action. Case example #4 also shows that C11-Acetate may reveal areas of resistant disease in the context hormone treatment and various other treatments, which may also benefit from
additional focal treatment.

For more information about C11-Acetate imaging you can visit our web site www.phxmi.com, the clinicaltrial.gov web site https://clinicaltrials.gov/ct2/show/NCT01304485. You can also call our office in Arizona at 602.368.3055, open 8:00 am – 5:00 pm Mountain Time.