

Carbon-11-Acetate PET/CT Imaging in Prostate Cancer

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PET imaging of cancer metabolism is commonly performed with F18 fluorodeoxyglucose (FDG), and has become one of the primary tools in the evaluation of cancer patients [1]. This is based on the well-established understanding that many cancers are highly glycolytic, or have increased metabolism of glucose [2].

Although FDG may accumulate in aggressive and undifferentiated tumors, most prostate cancers demonstrate poor uptake of FDG, probably because most of these are well-differentiated tumors. Additionally, FDG is secreted into the urinary system, often interfering with pelvic pathologic findings and therefore significantly limiting its usefulness.

PET imaging of other metabolic pathways, such as amino acid or lipid metabolism, has now been explored in cancer. Fatty Acid Synthase (FAS) participates in controlling the lipid composition of cell membranes, and is over-expressed in many human cancers, particularly prostate cancer [5,7]. The degree of its over-expression appears to be correlated with tumor aggressiveness [6]. Among the different PET tracers that have been specifically evaluated for lipid metabolism imaging, Carbon-11-Acetate (C11-Acetate) demonstrates utility for detecting recurrent prostate cancer.

Recurrent & Metastatic Prostate Cancer

Unfortunately, recurrence of prostate cancer after treatment is frequent, occurring within 10 years in 20–50% of patients after radical prostatectomy (RP), and in 30–40% of patients after external-beam radiation therapy (EBRT).

Tumor recurrence is commonly assessed by a progressive increase of serum prostate-specific antigen (PSA) that typically precedes the clinically detectable recurrence. After RP, a PSA level of greater than 0.2 ng/mL, confirmed by two consecutive measures, can be associated with either residual or recurrent disease. After radiation therapy (RT), a PSA value of 2.0 ng/mL above the nadir represents persistent or recurrent disease.

Management of recurrent prostate cancer depends strongly on whether recurrence is confined to the prostatic bed (local failure), the regional lymph nodes in the pelvis or if distant spread has occurred. Although a trend of increasing PSA has been proposed as a way of predicting local recurrence versus distant recurrence, only imaging procedures are capable of discriminating between these scenarios [3,4].

Therapeutic options in recurrent and advanced prostate cancer are rapidly expanding. Thus, there is a need to develop imaging approaches that will a) allow for detection of and discrimination between local recurrence and distant metastatic disease, and b) permit the monitoring of tumor responses to these new therapeutic approaches.

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Standard imaging methods, including computed tomography (CT), magnetic resonance imaging (MRI), and bone scans (BS) are currently used, but none of these are very effective at detecting recurrences early enough to help select patients for salvage therapy with a curative intent. Additionally, these may limit the potential use of novel therapies by their inability to detect recurrences.

Several small studies have evaluated the relationship between serum PSA levels and detection of prostate cancer recurrence with C11-Acetate PET. In a study of 25 patients by Fricke et al, the degree of C11-acetate uptake was correlated with serum PSA levels [8].

Kotzerke et al evaluated a series of patients with suspected recurrence based on serum PSA measurements [9]. Trans-rectal ultrasound followed by biopsy served as the gold standard for C11-acetate PET imaging findings. C11-Acetate was true positive for disease recurrence in 15/18 patients with biopsy proven recurrence and was true negative in all 13 patients without recurrent disease by biopsy. Sensitivity was 83% and specificity 100%. Additionally, 4 of 5 patients with biopsy proven cancer and positive C11-Acetate PET imaging findings had serum PSA levels of less than 2.0 ng/mL.

Sandblom et al evaluated 20 patients with elevated PSA levels ranging from 0.5 to 8.1 ng/mL after radical prostatectomy [10].

C11-Acetate PET identified disease sites in 75% of the patients. In this study, all PET-positive patients had serum PSA levels of greater than 2.0 ng/mL. “False positive” findings were reported in 3 patients. One patient exhibited tracer uptake in the chest, which was subsequently confirmed to represent non-small cell lung cancer, while two other patients had inflammatory changes, one in the esophagus and the other in the mediastinum. As expected, this study suggested that C11-Acetate uptake is not cancer-specific, but rather, a probe of lipid metabolism which may also be altered in inflammatory disease.

Comparative Studies

A few groups have compared the diagnostic performance of C11-Acetate with that of other metabolic PET imaging probes in patients with prostate cancer. In a small study, Kotzerke et al evaluated 12 patients with prostate cancer [11]. C11-Acetate and C11-Choline, a substrate of choline kinase that is also incorporated into membrane lipids, were compared in patients after initial diagnosis, at the time of biochemical recurrence or after radical prostatectomy. The study found that C11-Acetate was not excreted into the bladder while urinary excretion was variable for C11-Choline. In terms of overall biodistribution and tumor uptake, the diagnostic performance of both imaging probes was found to be comparable.

In our own institution, we compared lesion detectability using FDG and C11-Acetate imaging

in a small group of prostate cancer patients with recurrent or metastatic disease [12]. Eighteen patients were imaged with both FDG and C11-Acetate PET with a PSA ranging from 0.32 – 13 ng/mL (mean 5.0ng/mL). C11-Acetate PET detected tumor in 14 (78%) of patients, whereas FDG PET detected lesions in only 2 (14%) of the imaged patients. In the two FDG PET positive patients, the PSA was relatively higher than in the other patients, with values of 7.8 and 11.15 ng/mL, respectively. C11-acetate PET was also positive in these two patients, detecting more disease with a significantly higher tumor to background uptake ratio. C11-acetate PET detected recurrence in the intact prostate or prostate bed in 5 patients, lymph node involvement in 6, bone in 4 and liver in 1. In 3 of 5 patients with lesions detected on C11-acetate, the PSA was < 1.0 ng/mL.

These studies suggest that C11-choline and C11-acetate appear to have a comparable accuracy for detecting local recurrence and metastatic disease in early PSA recurrence, while FDG PET does not seem to provide significant diagnostic value in this context.

Preliminary Results from the Arizona Molecular Imaging Center

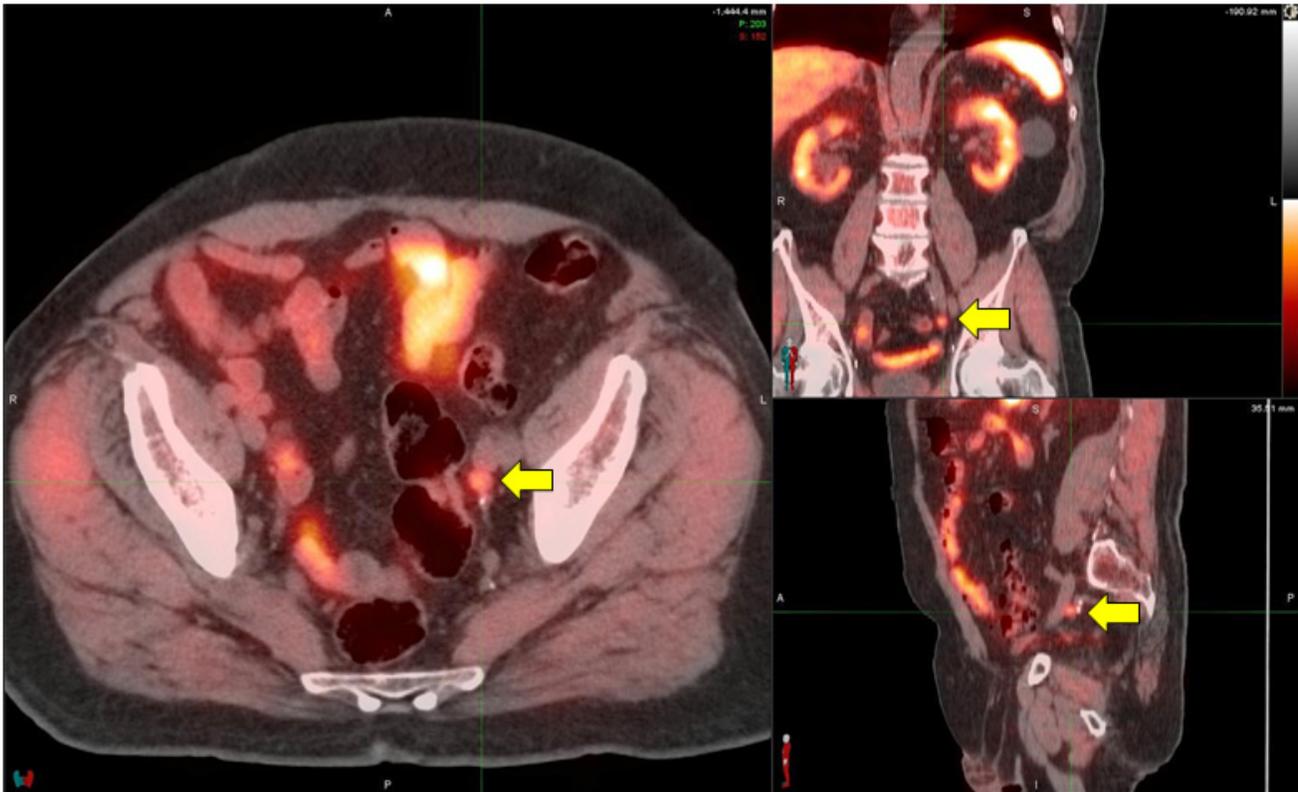
As part of an ongoing FDA-approved clinical investigation, the Arizona Molecular Imaging Center has thus far performed over 120 C11-Acetate PET/CT imaging studies, significantly more than have been previously published from a single institution in the U.S.

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Preliminary results from our studies have been very encouraging, and demonstrate a direct benefit to many patients that would not be achievable with any other standard imaging technique. See Case 1-3 below for examples of positive imaging studies.

In our experience thus far, the overall detection rate of C11 Acetate PET/CT imaging for recurrent or metastatic disease has been 85%. When we separate the positive findings into various PSA levels, the detection rate has been 73% for PSA values of 0.4 – 1.0 ng/mL, 89% for 1.0 – 2.0 ng/mL and 93% for > 2.0 ng/mL. Our results to date have shown a higher detection rate than data from previously published studies, likely in part due to our use of more modern, state-of-the-art PET/CT imaging technology which allows for better detectability and localization of smaller lesions, and due to establishing a standardized imaging protocol based on tracer kinetics which had been lacking in prior studies.

Most of our study patients are still in early follow-up. However, in several patients with initial follow-up after additional therapy, such as radiation therapy directed toward the recurrence or metastasis, or after surgical removal of the lesion identified on the C11-Acetate images, there has been a significant decrease in PSA, confirming the accuracy of the C11-Acetate imaging.

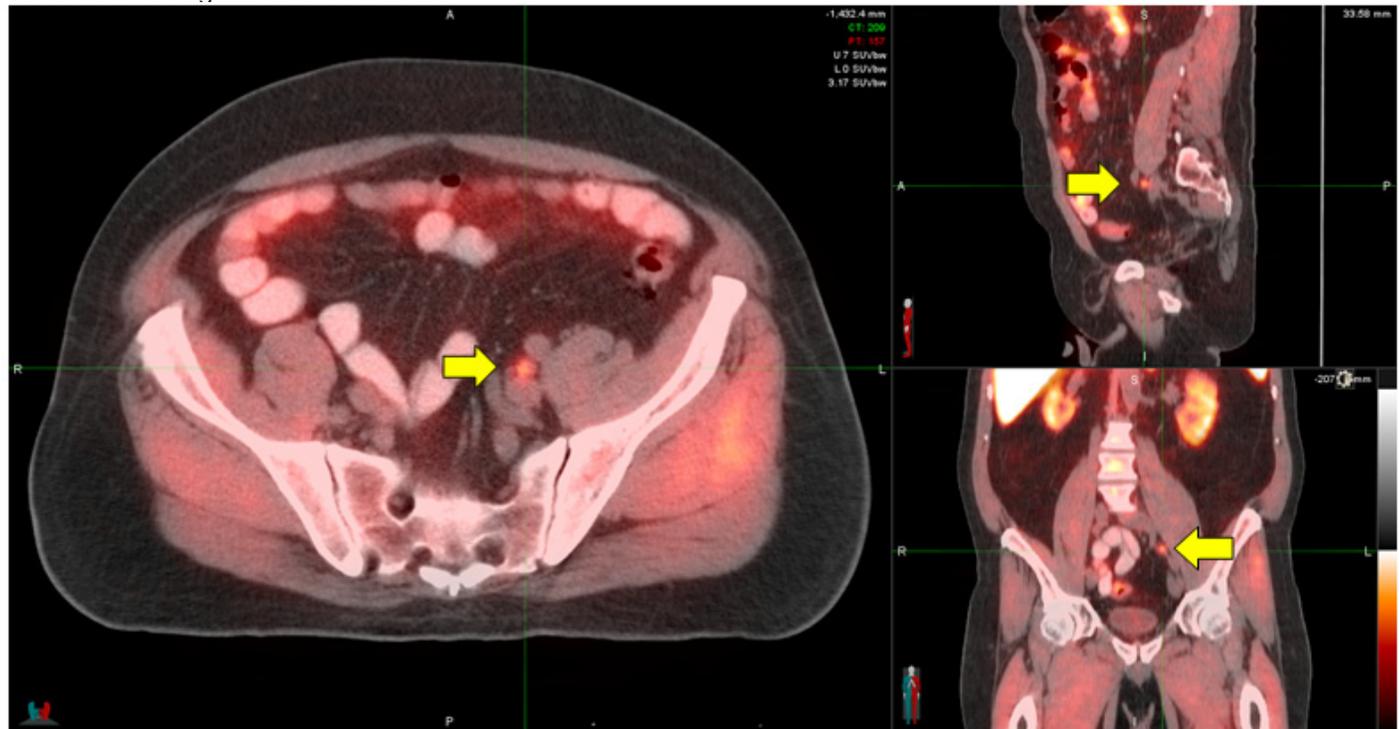


Case Example 1. Gentleman with prostatectomy 10 years previously. External beam radiation 1 year previously for a rising PSA. The PSA continued to increase up to 6.9 ng/mL. The 3 dimensional Carbon-11 Acetate PET/CT images show a small metabolic lymph node in the left pelvis (yellow arrows). This would not have been diagnosed on CT alone based on its small size. Other areas of 'red' seen on the images are of normal Carbon Acetate in the intestines, kidneys, liver and spleen. No other lesions were seen. The left pelvis node was treated with IMRT and the PSA then decreased to 0.9 ng/mL, confirming involvement of the identified node.

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Case Example 2. Gentleman with Gleason 7 prostate cancer and external beam radiation (EBRT) to the prostate 4 years previously. PSA nadir was 0.43ng/mL. Rising PSA to 3.9 ng/mL. The 3 dimensional Carbon-11 Acetate PET/CT images show a metabolic focus in the right side of the prostate gland (yellow arrows). No other lesions were seen. The prostate recurrence was confirmed by biopsy with subsequent Brachytherapy performed. The PSA decreased to 0.6 ng/mL after treatment.



Case Example 3. Gentleman with Gleason 6 prostate cancer. Brachytherapy and external beam radiotherapy 12 years previously. PSA nadir was 0.16 ng/mL. Rising PSA to 2.17 ng/mL. The 3 dimensional Carbon-11 Acetate PET/CT images show a single small metabolic lymph node in the left upper pelvis (yellow arrows). As in Case example #1, this would not have been diagnosed on CT alone based on its small size. Bilateral pelvic lymph node dissection was performed with 13 nodes removed. The node identified on the C11-Acetate imaging study was confirmed to be involve with prostate cancer (Gleason 4+4=8) and all other removed nodes were negative/benign, confirming the solitary finding on the imaging study. The PSA decreased to 0.19 ng/mL after the lymph node surgery.

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Due to recent changes in FDA regulations regarding new radiopharmaceuticals such as C11 agents, access to C11-Acetate now requires participation in an approved clinical study.

The Arizona Molecular Imaging Center has worked with the FDA to open an approved Phase II clinical investigation, and is pleased to offer Carbon-11-Acetate PET/CT imaging studies for localizing recurrent prostate cancer. Because this type of scan requires an on-site cyclotron, we are one of the few sites in the country capable of doing these studies, and currently the only FDA-approved private site for C11-Acetate.

Our center is equipped with state-of-the-art PET/CT imaging, which provides an extra advantage in the detection of small lesions. The C11-Acetate study requires only a single intravenous injection of the tracer and the imaging procedure can be completed in about 20 minutes.

For information about participating in this clinical trial, please visit the ClinicalTrials.gov website: <http://clinicaltrials.gov/ct2/show/record/NCT01304485> or call Dr. Fabio Almeida directly at 602.331.1771.

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