^{11}C-acetate PET imaging in prostate cancer

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The patient population with a rising PSA following definitive local therapy represents the second largest group of prostate cancer patients [1]. These patients are characterized by a rising marker following definitive local therapy with either surgery or radiation, and by definition have no evidence of disease on standard imaging studies [2]. By some estimates, approximately 50,000 men in the USA enter this clinical state each year [3]. Although some reports suggest that the median amount of time that a patient will spend in this clinical state before developing metastatic disease is 8 years [4], in actuality these patients represent a wide spectrum of clinical risk. Some have rapidly progressive micrometastatic disease and are at high risk for developing metastases; others experience locally persistent disease or an otherwise indolent clinical course.

Distinguishing between these patients plays a critical role in selecting appropriate treatment. A patient with aggressive micrometastatic disease is a candidate for systemic treatments. On the other hand, patients who have no systemic disease and an exclusively local residual tumor may be cured with local salvage strategies [5, 6].

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This rising-PSA population is regarded by many clinical investigators as the most challenging in terms of testing and developing new therapies for prostate cancer care. These patients experience a highly variable clinical course, and often have no radiographic findings, no symptoms, and no tissue-based assessments by which treatment effects can be evaluated. To address these limitations, consensus guidelines have been published to define a framework for conducting trials, but even these guidelines recommend that investigators be cautious about testing drugs early in such patients, given the methodological challenges [7].

Paradoxically, though, radiologists are attracted to trials involving this clinical state because it is literally defined by the inadequacies of present imaging modalities for prostate cancer. Bone and CT scans are insensitive in detecting osseous metastases. For locally recurrent disease, magnetic resonance imaging (MRI), with a specific acquisition protocol that focuses on the pelvis, can detect abnormalities in the prostate bed, but again, distinguishing postoperative changes from active tumor is challenging, and many of these sites are in areas that are not routinely biopsied based on standard algorithms.

Positron emission tomography (PET) has been posited by some as a solution to these limitations. Rather than examining the derivative effects on bone, it can demonstrate the biology of the tumor itself; it also offers the potential to image sites in bone and soft tissue simultaneously and to survey the entire body rapidly. It could possibly distinguish fibrosis from active cancer in the prostate bed in a postsurgical patient, a disease-free residual prostate from one containing active cancer in a postradiation therapy (post-RT) patient, and early bone metastases from nonmalignant injuries and inflammatory osseous lesions.

A study by Dr. Albrecht and colleagues examined the use of PET with ^{11}C-acetate, a tracer of fatty acid synthesis. Although the mechanism of tracer uptake in cancers is not wholly clear, it has been posited that metabolic activity in the tumor occurs in a low-oxygen microenvironment, in

Table 1. Studies of detection of residual prostate cancer by ^{11}C-acetate PET

Authors	Patient characteristics	No. of patients	Prostate bed/prostate positive[a]	Putative nodal mets[a] (any site)	Putative bone mets[a]
Oyama et al. [12]	Rising PSA	46 (30 post prostatectomy, 16 post radiation)	RRP: 2/30 (7%); RT: 10/16 (62%) (3 bx confirmed)	RRP: 12/30 (40%); RT: 8/16 (50%)	RRP: 1/30 (3%); RT: 2/16 (13%)
Kotzerke et al. [13]	Rising PSA	31 post-RRP patients	15/31 (48%) (18 of whom were positive by bx or TRUS)	6/31 (19%)	5/31 (16%)
Kotzerke et al. [14]	Mixed (metastatic, suspected metastatic, and localized)	23	Not reported	8/8 with known mets had uptake at all bone and nodal sites (100%)	
Fricke et al. [15]	Follow-up after primary therapy	25; 14 on hormones	14/25 (56%)	12/25 (48%)	4/25 (16%)
Sandblom et al. [16]	Rising PSA	20, post RRP	10/20 (50%) in the fossa; only 4/10 bx positive	6/20 (30%) regional	7/20 (35%)
Albrecht	Rising PSA	32 (17 post RT; 15 post RRP)	RT: 82%; RRP: 33%	RT: 29%; RRP: 7%	RT: 1 pt and only selected mets; RRP: 0

mets metastases, *RRP* radical retropubic prostatectomy, *RT* radiation therapy, *bx* biopsy, *pts* patients

[a]Identified by PET

association with an increased lipid pool that accompanies rapid cell growth [8, 9]. Uptake may also relate to the androgenic basis of prostate cancer growth [10, 11].

As shown in Table 1, several studies have studied the effectiveness of ^{11}C-acetate PET in patients with prostate cancer. All of these studies examined patients who had completed definitive local therapy, and most focused on the rising-PSA population. These studies sought to determine the ability of ^{11}C-acetate PET to detect local, nodal, and osseous disease, but all of them share common design pitfalls.

The rising-PSA population is defined by an absence of detectable distant disease [2]. To verify this state, systematic evaluation of the extent of disease must be done to rule out nodal or bony metastases, but that evaluation was not performed in the studies cited in Table 1. Instead, the studies involved heterogeneous groups: some patients had bony and nodal disease, others simply had locally recurrent disease, and still others were without any detectable disease. In addition, these studies shared the common features of low numbers and multiple subsets of patients defined by a heterogeneous array of histologic and radiographic assessments intended to "prove" or "disprove" the PET findings as "true." As a result, the data are exceedingly difficult to interpret.

For example, the study by Oyama and colleagues [12] scanned 46 patients with a rising PSA following either surgery or radiation. A total of 12 local sites of disease were felt to be suspicious by PET; only 3 were confirmed by biopsy. Less than half of these patients underwent standard scans as well; of these, three were positive for bone or lymph node disease. PET scans were positive in these three patients, but they were also positive in ten additional patients who did not undergo standard scans. Whether these lesions on PET represented true or false positives cannot be determined.

Similarly, in a study by Sandblom [16], 20 patients with a rising PSA who underwent a radical retropubic prostatectomy (RRP) were scanned with ^{11}C-acetate PET. While patients with local lesions underwent biopsy, only "selected cases" underwent standard scanning for systemic disease. Seven men had uptake exclusively in the prostate bed, and the remaining 13 men had uptake in a variety of other areas. The authors do not report a correlation with standard studies, or whether patients were followed prospectively to establish whether the "false positive" scans that the authors report were simply early detection of disease.

Kotzerke and colleagues [14] examined patients with mixed disease status; eight had been treated with hormones and/or chemotherapy, while the remainder were untreated. For standard metastasis evaluations, four patients had a bone and CT scan, and two had a biopsy and CT; for determination of local recurrence, four had a biopsy. Fourteen patients had no standard evaluations. Three patients with "positive" PET scans revealing distant disease had no standard imaging to establish whether any were false positives, and the number of false negatives will never be known because 16 patients underwent no standard imaging.

Finally, in the Fricke et al. study [15], 25 patients were scanned using FDG and ^{11}C-acetate, but once again, patients underwent a variety of correlating imaging and histologic studies. Adding to the heterogeneity, 14 of these patients were already undergoing treatment with hormones, thereby fundamentally altering the biologic and metabolic profile of the disease.

To the investigators' credit, all patients in the Albrecht trial underwent CT scans for correlation with the PET studies. Nonetheless, these patients at baseline represented an array of clinical states other than that of rising PSA.

Some had pathologic adenopathy (≥1 cm) by CT and positive bone scintigraphy. In addition, there was a bewildering array of subgroups—patients who had undergone various standard evaluations with which to evaluate the positive PET scans. Thirty-two patients who biochemically relapsed following definitive local therapy were examined. Seventeen patients underwent primary therapy with radiation, and 15 patients were postoperative. Of the 17 post-RT patients, 12 also had endorectal MRI, eight underwent bone scintigraphy, and six had prostatic biopsies. Of the 15 post-RRP patients, all underwent endorectal MRI, and seven underwent bone scintigraphy.

Once these subgroups are broken down, the numbers are too small to draw anything but the most preliminary of conclusions. Fourteen of the 17 post-RT patients had uptake in the residual gland, six of whom were biopsied and were positive. Five of the 17 post-RT patients had focal uptake in lymph nodes, one had a metastasis documented in the corpus cavernosum, and four of eight patients with positive bone scans were positive by PET. For the post-RRP patients, 9/15 were positive or equivocal in the prostate bed (although 13 had positive or suspicious endorectal MRI), and a node was detected in one patient. To "prove" detection of local disease in the post-RRP setting, patients underwent salvage RT. Eight had a ≥50% decline in PSA, but no post-RT PET scans were performed to determine the impact on the PET scans (only five of which were either positive or equivocal before treatment).

The above studies represent approximately 154 patients scanned with this technology, yet we are still left asking: Can ^{11}C-acetate detect prostate cancer?

Methodology matters

Imaging trials should be held to the same standard as therapeutic trials in terms of controlling for clinical state, intervention, and outcome measures. This methodology needs to be applied to four scenarios, each of which would be studied independently: local disease, lymph nodes, viscera, and bone.

Locally residual disease

The best way to establish how well ^{11}C-acetate detects locally advanced disease is by doing preprostatectomy PET scans and then comparing the PET findings with pathology in an adequately powered cohort. To our knowledge, such a study using this tracer has never been done. Instead, studies have focused on the rising-PSA population, in which patients have irradiated, hormonally treated or absent prostates.

The studies that come the closest to defining detection of disease by ^{11}C-acetate are the Kotzerke and Albrecht trials, both of which examined the rising-PSA population, not the local disease population. In the former study, 15/31 patients with a rising PSA following RRP had a positive PET; 13/15 had positive biopsies of the prostate bed.

Sixteen patients were negative by PET, and of those, 13 had negative biopsies as well as TRUS studies. In the Albrecht study, PET findings from 9/15 post-RRP patients were suspicious for local disease, and eight of those patients had significant reductions in PSA following salvage RT. These studies suggest that ^{11}C-acetate may detect local disease, but the trials cannot substitute for a definitive study of patients with localized disease.

We would argue that the critical question for the rising-PSA population is not what residual disease is detected in the prostate bed, but rather what is the status of distant disease. Even if an imaging study could detect local disease with 100% sensitivity and specificity, clinical decision-making is still stymied by the lack of tools for detecting distant disease. Without such tools, large numbers of patients undergo local salvage therapies that are noncurative because of occult metastases. In the world of clinical decision-making, the number of patients who undergo salvage RT will not be increased by a more sensitive PET scan for local disease, because the PSA is a sensitive indicator for relapse. However, large numbers of patients would be spared local salvage therapies if there were an accurate way to detect metastases.

Lymph nodes, viscera, and bone

None of the studies in Table 1 systematically addressed the issue of whether ^{11}C-acetate PET detects disease in lymph nodes, viscera, and bone. To determine whether this modality can detect metastatic prostate cancer, patients with known metastatic disease should be imaged in an adequately powered prospective trial. All patients should undergo the same imaging modalities so that all lesions in all patients can be compared across modalities and across time. This scanning set should comprise the investigational scan, a bone scan and CT. The sets should be repeated at 3-month intervals, so that lesions seen on standard scans but not on PET can be verified as either active cancer (false negative) or arthritic or posttraumatic changes (true negative). Similarly, positive PET findings not seen on standard scans can be defined as either true lesions that emerge as cancer on subsequent standard subsequent studies (true positive) or as false positives.

In conclusion, the development process for a drug and the process for an imaging modality are no different. By consensus, clinical trials in prostate cancer focus on patients who occupy a well-defined point in the natural history of the disease, having either localized disease, a rising PSA only, newly diagnosed metastases, or metastases that have progressed despite castrating hormonal therapy [1, 17]. None of the studies of ^{11}C-acetate PET have followed this pattern. Therapeutic clinical trials also demand that patients be followed using predefined, serial, identical radiological evaluation. This is even more appropriate when an imaging modality is being investigated, so that lesion comparisons across modalities and time are possible.

Therapeutic clinical trials demand that a study be adequately powered to allow for interpretable data when

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the study ends. Studies for ^{11}C-acetate PET have not done this to date, despite the fact that at least 154 patients have now been scanned in various studies. And finally, therapeutic trials demand that an intervention be assessed only in an appropriate population. To try to determine how well an imaging modality detects local disease in a population with treated primaries, and metastatic disease in a population that by definition does not have distant disease on standard scans, is to approach the problem backwards. The first step is to establish the sensitivity and specificity of ^{11}C-acetate PET for each disease site in the appropriate population, after which the modality can be tested in the rising-PSA group. It is time for the designs of therapeutic and imaging studies to converge.

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