

PET Imaging of Prostate Cancer with ^{11}C -Acetate

Prostate cancer is second only to lung cancer as the leading cause of cancer deaths in American men. In 1997, approximately 209,900 new cases of prostate cancer were diagnosed, and more than 41,800 deaths were attributed to this malignancy (1). Primary or recurrent prostate cancer can be curatively treated when it is confined to the gland. The therapy of choice is radical prostatectomy. Therefore, curative treatment for localized tumors may be the best hope for lowering the mortality rate of prostate cancer (2). If the tumor has spread beyond the gland, chemotherapy, immunotherapy, or hormonal therapy are at present used. However, metastatic prostate cancer cannot be cured with these modalities. According to this viewpoint, it is clear that the primary focus of prostate cancer management should be the detection and aggressive treatment of tumors while they are still confined to the prostate.

A great step forward was the discovery of prostate-specific antigen (PSA), which has made possible the detection of tumors before they become palpable on rectal examination. In general, diagnosis of primary or recurrent prostate tumors is based on clinical examination, PSA level, and radiologic imaging modalities such as ultrasound, CT, and MRI. When PSA testing is used alone, it can detect up to 80% of prostate cancers. However, the PSA test lacks specificity, since only one third of men with an abnormal serum PSA level actually have cancer (3). The task of nuclear medicine is to en-

hance the sensitivity and specificity of the diagnostic procedures.

^{18}F -FDG PET has been shown to be helpful for the diagnosis of primary, recurrent, and metastatic lesions in a variety of tumors. However, problems exist in the diagnosis of tumors with low metabolism, such as prostate tumors, low-grade sarcomas, low-grade lymphomas, and well-differentiated hepatocellular carcinomas. ^{18}F -FDG PET for the diagnosis of primary prostate cancer is not highly effective, at least for wide clinical use. Effert et al. found a low ^{18}F -FDG uptake in 81% of primary, untreated prostate tumors and no correlation with increasing tumor grade or stage (4). The authors noted a significant overlap of ^{18}F -FDG uptake values in prostate tumors and benign prostate hyperplasia and concluded that ^{18}F -FDG PET could not differentiate prostate cancer from benign prostate hyperplasia. Hofer et al. showed that ^{18}F -FDG cannot differentiate between benign prostate hyperplasia, prostate carcinoma, postoperative scarring, or local recurrence after radical prostatectomy (5). The authors observed a low ^{18}F -FDG uptake in histologically confirmed prostate carcinomas. Interestingly, Oyama et al. found a low sensitivity of 64% for the detection of primary, histologically confirmed prostate tumors, but they noticed a relationship with the stage: ^{18}F -FDG uptake was higher in patients with metastatic prostate tumors (6). Concerning the detection of metastatic sites with ^{18}F -FDG, Shreve et al. reported a low sensitivity of 65% but a positive predictive value of 98% for untreated bone metastases (7). The authors emphasized the problems in the detection of pelvic lymph node metastases and concluded that ^{18}F -FDG PET can help identify osseous or soft-tissue metastases but is less sensitive than bone scintigraphy. In contrast, Morris

et al. examined patients with progressive metastatic prostate cancer and found that ^{18}F -FDG PET can distinguish active osseous disease from scintigraphically quiescent lesions (8).

Because of the limited sensitivity of ^{18}F -FDG, other tracers were evaluated in a limited number of patients. Nunez et al. reported about double-tracer studies with ^{11}C -methionine and ^{18}F -FDG in 12 patients with newly progressive metastatic cancer and increasing PSA levels (9). The authors found a sensitivity of 48% for ^{18}F -FDG and of 72.1% for ^{11}C -methionine. Twenty-six percent of the lesions had no detectable ^{18}F -FDG or ^{11}C -methionine uptake. The findings reflected the biologic features of the prostate tumors and suggested that a time-dependent metabolic cascade may occur, consisting of an enhanced initial uptake of ^{11}C -methionine followed by an increase in ^{18}F -FDG-uptake during progression of disease.

More recently, a new radiopharmaceutical, ^{11}C -acetate, a tracer used originally for heart studies, has been evaluated in patients with prostate cancer. Shreve et al. examined for the first time 18 patients with renal diseases using ^{11}C -acetate (10) and found a difference in clearance of the radiopharmaceutical for neoplastic and nonneoplastic renal tissue.

Oyama et al. presented the results of a double-tracer study on 22 patients with primary, histologically confirmed adenocarcinoma of the prostate (11). The authors used ^{11}C -acetate in 22 patients, as well as ^{18}F -FDG in 18 of 22 patients, and found a positive accumulation of ^{11}C -acetate in all primary tumors (standardized uptake values [SUVs] ranging from 3.27 to 9.87), in comparison with 15 of 18 positive ^{18}F -FDG findings (SUVs from 1.97 to 6.34). Furthermore, ^{11}C -acetate was superior for the detection of lymph

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node metastases and demonstrated an enhanced intrapelvic uptake in 5 patients, whereas ^{18}F -FDG showed positive findings in only 2 of 5 patients. Of 7 patients found to have bone metastases on bone scintigraphy, 6 showed positive ^{11}C -acetate findings and 4 showed positive ^{18}F -FDG findings at the sites of the scintigraphically demonstrated bone metastases. Therefore, bone scintigraphy was superior to PET. The authors noted a correlation between clinical stage and ^{18}F -FDG uptake but no correlation between clinical stage and ^{11}C -acetate uptake. Although the results were encouraging, the study was limited by having no histologic reference for the metastatic sites, only for the primary tumors. Furthermore, the authors did not include patients with benign prostate disease, such as hyperplasia, for comparison.

Kato et al. recently presented results with ^{11}C -acetate not only in prostate tumors but also in normal prostate glands and benign prostate hyperplasia (12). Interestingly, the authors emphasized that normal accumulation occurred in the normal prostate gland of patients aged <50 y (mean SUV, 3.4; SD, 0.7). Furthermore, they found a large overlap for prostate hyperplasia, with a mean SUV of 2.1 (SD, 0.6), and prostate tumors, with a mean SUV of 1.9 (SD, 0.6). The authors noted that, in their study, tracer accumulated in the bladder but did not cause problems for the differentiation. The absolute SUVs were lower in comparison with those found by Oyama et al. (11), perhaps because of the different acquisition protocols used in the studies. Kato et al. performed dynamic studies up to 20 min after tracer application, with 25 frames (10 frames of 30 s and 15 frames of 60 s), and used the SUV at 16–20 min after injection for evaluation. Oyama et al. did a static measurement covering 10–20 min after injection. A possible explanation for the data of Oyama et al. is the higher uptake of ^{11}C -acetate in the early phase, which influenced the results of just 1 static measurement over 10 min. The results demonstrated that there is a need for dynamic studies with longer

acquisition times to examine the pharmacodynamics of ^{11}C -acetate in normal as well as in pathologic prostate tissue. The results reported until now are not consistent because of the different acquisition protocols (dynamic vs. static) used and because of the use or lack of attenuation correction of the images and the lack of the standard use of iterative reconstruction, which is superior to filtered backprojection, in particular for the evaluation of lesions beneath the bladder. The data of Kato et al. show, however, that in comparison with normal or hyperplastic tissue, prostate cancer has a higher early-to-late activity ratio of the SUVs for ^{11}C -acetate.

Kotzerke et al. examined the use of ^{11}C -acetate for the detection of local recurrence of prostate cancer in 31 patients (13). The reference was transrectal ultrasound with biopsy for the tumors. The authors found uptake of ^{11}C -acetate in 15 of 18 tumors, no uptake in 13 patients without recurrent disease, and 3 false-negative results in tumors with a volume varying between 0.1 and 1.5 cm³. The study was performed using a whole-body protocol without transmission correction, starting 5 min after tracer injection. The results were promising, but whether they will be confirmed by other groups is an open question. A limitation of the study was that the authors did not use a control group, such as a group with scar tissue or benign hyperplastic tissue, for comparison.

The diagnosis of recurrent prostate cancer is the topic of the study presented by Oyama et al. in this issue of *The Journal of Nuclear Medicine* (14). The authors examined 46 patients using both ^{18}F -FDG PET and ^{11}C -acetate PET. The study included 2 groups with an enhanced serum PSA level. According to the literature, approximately 30% of these patients have local recurrence, whereas the remainder are anticipated to have distant metastases alone or combined with local disease. Thirty patients had a radical prostatectomy (group A), whereas 16 patients received radiation therapy as a primary treatment (group B). ^{11}C -Acetate PET

revealed 27 of 46 positive findings, in comparison with the 8 of 48 ^{18}F -FDG scans that showed positive findings. A limitation of the presented study was the lack of histologic data for reference. The interpretation of positive ^{11}C -acetate PET findings was therefore difficult. Only 3 prostate lesions (1 in group A and 2 in group B) were confirmed by histology. There was no reference for any other evaluated lesions. The authors compared the PET data with CT or bone scintigraphy data, when available. But neither CT nor bone scintigraphy was performed on all patients included in the study. Furthermore, the authors did not use a semiquantitative evaluation of tracer uptake, such as SUV, although they performed static measurements with transmission correction. Instead, they preferred visual analysis using a 3-group classification, namely high probability, intermediate probability, and negative for tumor. In particular, the term *intermediate probability* sounds problematic. However, despite the limitations of the presented study, it is likely that ^{11}C -acetate PET is more sensitive than ^{18}F -FDG PET for the diagnosis of prostate cancer. If one focuses only on the high-probability scans, the results of this study show 30% (14/46) ^{11}C -acetate scans with positive findings, in comparison with 9% (4/46) ^{18}F -FDG scans with positive findings. Although the likelihood of positive ^{11}C -acetate findings may be high for tumor tissue, we believe that it is not the appropriate approach for validation of a new tracer. In contrast to Kotzerke et al. (13), who used biopsy for reference, Oyama et al. did not provide a reliable reference by histology. A validation of the tracer on this basis is not possible.

As noted previously, the task of nuclear medicine is to enhance both sensitivity and specificity. On the basis of the current literature data, ^{18}F -FDG has a low sensitivity but is specific for progredient malignant disease. In contrast, ^{11}C -acetate has a superior sensitivity but a low specificity because of accumulation in hyperplastic tissue. Therefore, examination of the pharma-

codynamics of ^{11}C -acetate as a tracer for oncologic studies is mandatory for explaining positive findings. Because of the lack of quantitative dynamic data, there is controversy about the urinary excretion of ^{11}C -acetate. This process seems to be time dependent. Although in the early phase, up to 15 min after injection, no urinary excretion occurs, Kato et al. noted tracer accumulation in the bladder using a dynamic acquisition for 20 min after injection (12). In our opinion, quantitative, dynamic studies for 30 min after injection are needed to assess the pharmacodynamics of ^{11}C -acetate in tumors generally. Such studies are a prerequisite to obtain quantitative data about tracer accumulation in normal prostate tissue, as well as in benign prostate disease and in normal tissue such as kidneys and bladder.

The exact uptake mechanism of ^{11}C -acetate is not known, but studies suggest that it is incorporated into the lipid pool in cancer tissue with low oxidative metabolism and high lipid synthesis. An in vivo study of rats found that ^{14}C -acetate was incorporated into free and esterified cholesterol in the ventral prostate. Yoshimoto et al. examined ^{14}C -acetate accumulation in 4 different tumor cell lines and a fibroblast cell line and found a higher acetate accumulation in all tumor cell lines than in the fibroblast cell line (15). Tumor cells incorporated ^{14}C activity into the lipid-soluble fraction, mostly of phosphatidylcholine and neutral lipids, more prominently than fibroblasts did. The data suggest that the acetate accumulation was caused by enhanced lipid synthesis. Acetate is not only a metabolic substrate of β -oxidation but also a precursor of amino acids, fatty acids, and sterol. Liu reported on the use of ^{11}C -acetate in 513 patients with different malignancies (16). He found that ^{11}C -acetate was taken up by meningiomas, gliomas, nasopharyngeal carcinomas, lymphomas, non-small cell cancers, colon cancers, renal cell cancers, and ovarian cancers. He also re-

ported an increased uptake in salivary glands, pancreas, and bowel. These data imply that ^{11}C -acetate may be helpful in detecting other tumor entities besides prostate cancer. Furthermore, the uptake of ^{11}C -acetate was not specific for prostate cancer.

Moreover, other tracers, such as positron-labeled choline analogues, have been introduced and used for imaging prostate cancer. ^{11}C -Choline has been used in a limited number of patients with prostate cancer, and the results have been encouraging (17). Choline is a component of phosphatidylcholine, an essential element of phospholipids in the cell membranes. Malignant tumors show a high proliferation and increased metabolism of cell membrane components, leading to increased uptake of choline. DeGrado et al. and Hara et al. introduced ^{18}F -choline analogues and reported their characteristics (18,19). The preliminary results in patients were promising, in particular for the detection of prostate cancer. From the current viewpoint, it is difficult to decide which tracer is more useful for wide clinical application in the diagnosis of prostate cancer. ^{18}F tracers are generally more convenient for PET centers without an on-site cyclotron. On the other hand, ^{11}C -labeled radiopharmaceuticals provide a unique chance to perform dynamic, multitracers studies. Multitracers studies, using, for example, ^{11}C -acetate and ^{18}F -choline, may help us gain more information about the biochemical pathways of each tracer. Using this approach, we may succeed in enhancing both sensitivity and specificity for the diagnosis of prostate cancer.

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