PET/CT with Sodium ^{18}F-Fluoride for Management of Patients with Prostate Cancer

Prostate cancer is the most common type of cancer in men aside from skin cancer. It is estimated that 233,000 new cases of prostate cancer will occur in the United States in 2014 (*1*). Prostate cancer is the second leading cause of cancer death in men. Approximately 29,480 men in the United States will die of prostate cancer in 2014. The total estimated expenditure on prostate cancer in the United States was 9.862 billion dollars in 2006 (*2*). The optimal treatment of prostate cancer is a significant public health and economic concern.

Prostate cancer has a predilection to metastasize to bone. Bone scanning, with ^{99m}Tc-diphosphonate or sodium ^{18}F-fluoride, plays an important role in the management of patients according to National Comprehensive Cancer Center Guidelines for Prostate Cancer (*3*). Bone scanning is indicated for initial staging with any of the following criteria: Gleason score 8 or higher; T1 plus prostate-specific antigen (PSA) greater than 20; T2 plus PSA greater than 10; T3 or T4; or symptomatic. Bone scanning can be considered when PSA levels are still detectable after radical prostatectomy or when there is biochemical recurrence after radiation therapy.

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Sodium ^{18}F-fluoride was initially approved by the Food and Drug Administration in 1972 for clinical use as a bone imaging agent but was withdrawn from the market in 1975 after the introduction of ^{99m}Tc-diphosphonate. It was listed as a discontinued drug in 1984. In 2011, the Food and Drug Administration approved a New Drug Application from the National Cancer Institute for a new strength of sodium ^{18}F-fluoride. Sodium Fluoride ^{18}F Injection, USP, is a radioactive diagnostic agent for PET indicated for the imaging of bone to define areas of altered osteogenic activity.

PET has several advantages over single-photon planar imaging and SPECT, including higher resolution and the capability of scanning the entire body. Higher resolution and the ability to scan a larger area improves the sensitivity of PET for detecting cancer. Nearly all PET scanners in the United States are now PET/CT scanners. The addition of CT also improves sensitivity for detecting cancer by identifying metastases that are scintigraphically too small to detect and improves specificity by identifying nonmalignant causes of increased radioisotope uptake.

There have been a few studies comparing the accuracy of sodium ^{18}F-fluoride with ^{99m}Tc-diphosphonate for detection of skeletal metastatic disease. One of the earliest studies was reported in 2001 by Schirrmeister et al. The study compared ^{99m}Tc-diphosphonate (planar and SPECT) with sodium ^{18}F-fluoride PET in 53 men with lung cancer (*4*). Sodium ^{18}F-fluoride PET was more sensitive (100%) than planar ^{99m}Tc bone scanning (54%) and SPECT (92%) in 12 patients with bone metastases. Similar results were obtained by Even-Sapir in 2006, who studied 44 men with high-risk prostate cancer using ^{18}F-sodium fluoride PET/CT and ^{99m}Tc-diphosphonate with multi-field-of-view SPECT (*5*). In a patient-based analysis of 23 patients with bone metastases, the sensitivity and specificity of PET/CT versus SPECT were 100% versus 92% and 100% versus 82%, respectively. In the studies by Schirrmeister and Even-Sapir, the performance of ^{99m}Tc-diphosphonate planar imaging was poor.

A meta-analysis comparing sodium ^{18}F-fluoride with ^{99m}Tc-diphosphonate was published in 2010 by Tateishi et al. (*6*). In a patient-based analysis, the pooled sensitivity and specificity of sodium ^{18}F-fluoride in 10 studies were 96% and 98%, respectively, whereas the pooled sensitivity and specificity of ^{99m}Tc-diphosphonate planar, or planar plus SPECT, bone scanning in 8 studies were 57% and 98%, respectively.

The Centers for Medicare and Medicaid Services (CMS) on June 4, 2009, opened a reconsideration of section 220.6 of the National Coverage Determinations Manual to review evidence on the use of sodium ^{18}F-fluoride to identify bone metastasis. In a National Coverage Decision posted on February 26, 2010, CMS concluded that the evidence was not sufficient to determine that the results of sodium ^{18}F-fluoride PET imaging to identify bone metastases improved health outcomes of beneficiaries with cancer (*7*). CMS concluded, however, that the available evidence was sufficient to determine that sodium ^{18}F-fluoride PET imaging to identify bone metastasis to inform the initial antitumor treatment strategy or to guide subsequent antitumor treatment strategy after the completion of initial treatment was reasonable and necessary under Coverage with Evidence Development.

The National Oncologic PET Registry (NOPR) is a collaboration of the American College of Radiology Imaging Network, the American College of Radiology, and the Academy of Molecular Imaging to ensure access to Medicare reimbursement for certain types of PET scans.

NOPR, which previously had worked with CMS on a national registry for ^{18}F-FDG, created a new registry to evaluate sodium ^{18}F-fluoride for the detection of metastatic disease in the skeleton. The registry was opened on February 11, 2010. As of April 17, 2013, 20,238 patients were enrolled (*8*). The most common cancer types were prostate, breast, other cancer, and cancer of unknown

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primary. The first results are published in this issue of *The Journal of Nuclear Medicine* (*9*).

The authors report on a subset of the registry including only patients with prostate cancer, who accounted for 67% of all patients. The results are based on 3,531 scans in 3,396 patients. The study shows that sodium ^{18}F-fluoride PET/CT substantially affected intended management across 3 groups of patients: initial staging, suspected first skeletal metastasis, and suspected progression of known skeletal metastatic disease. PET/CT had a high overall impact, primarily related to replacing intended use of other advanced imaging in about half of the cases. More significantly, when intended management was classified either as treatment or as nontreatment, the intended management after sodium ^{18}F-fluoride was changed in 44%–52% of patients. After adjustment for those cases for which the pre-PET plan—including other advanced imaging—may have led to the same changes in intended management, the impact of sodium ^{18}F-fluoride on intended management was still 12%–16%.

The impact of sodium ^{18}F-fluoride on intended management if ^{99m}Tc-diphosphonate bone scanning is performed first is unknown. Prior ^{99m}Tc bone scanning results were available only for a few patients in the NOPR study (315/3,396 [9.3%]). Understanding the value of sodium ^{18}F-fluoride as a first imaging study is important because access to PET/CT is more limited than access to ^{99m}Tc-diphosphonate bone scanning, and the cost is higher.

In patients with very high PSA levels, it is likely that ^{99m}Tc-diphosphonate and sodium ^{18}F-fluoride will show widespread metastatic disease. Even if sodium ^{18}F-fluoride were to show more metastatic lesions, it is likely that the treatment plan would be the same. In patients with a low likelihood of metastatic disease in whom bone scanning is still considered appropriate, most patients would not have skeletal metastases on either study. In this type of patient, an examination with higher specificity, such as sodium ^{18}F-fluoride PET/CT, might avoid additional imaging, but this point is unproven. The potential greatest value of sodium ^{18}F-fluoride as a first imaging study is to identify patients with early skeletal metastatic disease who have a few small metastatic lesions that ^{99m}Tc-diphosphonate bone scanning might not detect. Such a cohort of patients is difficult to identify, although Gleason score, tumor stage, and PSA level may serve as a guide.

^{11}C-choline is another radiopharmaceutical that has been extensively studied for the detection metastatic prostate cancer. In 2012, the United States Food and Drug Administration approved the manufacture and use of ^{11}C-choline in patients with suspected prostate cancer recurrence and noninformative bone scintigraphy, CT, or MR imaging (*10*).

Fuccio et al. retrospectively evaluated ^{11}C-choline PET/CT in 123 patients with prostate cancer with biochemical relapse and a negative ^{99m}Tc bone scan result (*11*). ^{11}C-choline identified 30 bone lesions in 18 of 123 (14.6%) patients and identified additional metastases in lymph nodes (27 patients) and lung (2 patients).

Poulsen et al. prospectively evaluated 50 patients with prostate cancer and positive ^{99m}Tc-diphosphonate bone scan results to compare the diagnostic accuracy of ^{99m}Tc-diphosphonate bone scanning, ^{18}F-choline PET/CT, and sodium ^{18}F-fluoride PET/CT for the detection of spinal metastases (*12*). MR imaging was used as the reference standard. There were 526 bone lesions, including 363 malignant and 163 nonmalignant lesions. Sensitivity and specificity were, respectively, 51% and 82% for ^{99m}Tc-diphosphonate bone scanning, 85% and 91% for ^{11}C-choline, and 93% and 54% for sodium ^{18}F-fluoride. The authors concluded that ^{18}F-choline and ^{18}F-fluoride were both superior to ^{99m}Tc-diphosphonate bone scanning.

A recent meta-analysis of ^{11}C-choline and ^{18}F-choline for management of patients with prostate cancer was published by von Eyben et al. in 2014. The meta-analysis included 3,167 patients and 47 articles published between 1998 and September 2013 (*13*). Head-to-head studies that included 280 patients showed that choline PET/CT results were positive in more patients than ^{99m}Tc-diphosphonate bone scans, 127 (45%) versus 46 (16%), respectively. Pooled sensitivity and specificity for pelvic lymph node metastases in 609 patients was 62% and 92%, respectively. The authors concluded that ^{11}C-choline or ^{18}F-choline was useful as the first imaging examination in patients with biochemical recurrence of prostate cancer.

A major disadvantage of ^{11}C-choline is the 20-min half-life of ^{11}C, which limits use of this radiopharmaceutical to medical centers with a cyclotron. Nevertheless, choline PET/CT is included in National Comprehensive Center Guidelines for Prostate Cancer with the caveat that further study is needed to determine the best use of choline PET/CT imaging in patients with prostate cancer.

Several additional radiotracers are currently being investigated for PET imaging of prostate cancer including ^{11}C-acetate; 16α-^{18}F-fluoro-5α-dihydrotestosterone; anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid; and radiotracers based on prostate-specific membrane antigen, prostate stem cell antigen, and gastrin-releasing peptide receptor. Molecular imaging of prostate cancer has been recently reviewed in *The Journal of Nuclear Medicine* by Jadvar (*14*).

Physicians who manage patients with prostate cancer have several choices for evaluating the skeleton for metastatic disease, including CT, MR, and scintigraphy performed with ^{99m}Tc-diphosphonate, sodium ^{18}F-fluoride, or ^{11}C-choline. PET/CT with sodium ^{18}F-fluoride or ^{11}C-choline will detect more skeletal lesions than ^{99m}Tc-diphosphonate bone scanning. There is increasing evidence that sodium ^{18}F-fluoride and ^{11}C-choline change management of patients, either as a secondary test after ^{99m}Tc-diphosphonate bone scanning or as a first imaging study, as shown in the NOPR study with sodium ^{18}F-fluoride.

The demonstration of cost-effectiveness of sodium ^{18}F-fluoride and ^{11}C-choline will likely depend on the identification of patient subgroups that would benefit from the higher sensitivity and specificity of PET/CT with either of these agents as compared with ^{99m}Tc-diphosphonate bone scanning. Identification of these subgroups is the challenge facing physicians who manage patients with prostate cancer.

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