Molecular Imaging and Targeted Radionuclide Therapy of Prostate Cancer

Wolfgang A. Weber and Michael J. Morris

Memorial Sloan Kettering Cancer Center, New York, New York

During the last five years, there has been enormous progress in molecular imaging and radionuclide therapy of prostate cancer. Two molecular imaging agents (^{11}C-choline and 1-amino-3-^{18}F-fluorocyclobutyl-1-carboxylic acid [^{18}F-FACBC]) (*1,2*) and one radionuclide therapy (^{223}Ra-dichloride) (*3*) have been approved by the Food and Drug Administration for clinical use in prostate cancer patients. PET/CT imaging with sodium fluoride (*4*) continues to be evaluated as part of the National Oncology PET Registry, and a final decision on reimbursement is expected in 2017. During the same time, exciting clinical results have been obtained with ^{68}Ga- and ^{18}F-labeled small-molecule inhibitors of prostate-specific membrane antigen (PSMA) (*5,6*). Several groups have consistently reported exceptionally high accuracy for detection of recurrent prostate cancer in large numbers of patients. On the basis of these data, the ability of PSMA PET to localize the site of recurrence in patients with a rising level of prostate-specific antigen (PSA) appears to be markedly superior to all other clinically available imaging tests.

Small-molecule PSMA inhibitors have also shown significant promise for treatment of metastatic prostate cancer. ^{131}I- and ^{177}Lu-labeled PSMA inhibitors have been used in heavily pretreated patients with metastatic prostate cancer (*7–9*). A significant fraction of patients demonstrated a marked reduction of PSA, and some patients even achieved a complete response. At the recent annual meeting of the Society of Nuclear Medicine and Molecular Imaging, so many abstracts on PSMA-based imaging and therapy were presented that there were separate sessions for PSMA and non-PSMA imaging. Because of the high incidence and prevalence of prostate cancer, imaging and therapy of prostate cancer could soon become an important part of clinical nuclear medicine. Therefore, it is timely that this supplement of *The Journal of Nuclear Medicine* focuses on prostate cancer.

In addition to ^{11}C-choline, ^{18}F-FACBC, and various PSMA inhibitors, several other molecular imaging agents have shown promise for detection and biologic characterization of prostate cancer. These include (among others) PSMA antibodies and antibody fragments (*10*), ^{11}C-acetate (*11*), ^{18}F-fluorocholine (*12*), the androgen receptor ligand ^{18}F-FDHT (16β-^{18}F-fluoro-5α-dihydrotestosterone) (*13*), and ^{68}Ga-labeled peptides targeting the gastrin-releasing peptide receptor (*14*). Specifically, ^{18}F-labeled choline analogs have been used extensively in Europe for localization and staging of recurrent prostate cancer and have had an impact on patient management in relatively large series of patients (*12*). This raises the question of how all these different imaging agents can be systematically studied and their diagnostic performance compared. An even more important question is how the clinical utility of the new imaging techniques can be established.

Sensitivity and specificity are commonly used to describe the performance of imaging tests but are problematic for whole-body imaging, for which there is generally no reference standard to prove or exclude the presence of metastatic disease. This is a specific problem for molecular imaging of recurrent prostate cancer. All patients with a rising PSA level after surgery or radiotherapy have, by definition, recurrent prostate cancer. Imaging is therefore not used to detect or exclude recurrence, but to localize recurrence. Therefore, analysis of sensitivity and specificity is not meaningful on a patient basis and needs to be performed on a region or lesion basis. However, there are no independent reference standards for the presence or absence of a lesion in a specific body region. Frequently, a combination of "other imaging tests," clinical history, follow-up, and biopsies of selected lesions is therefore used as the reference standard. However, it important to note that the reported sensitivity and specificity of new imaging tests depend heavily on the performance characteristics of the "other imaging tests," the duration of follow-up, and other factors. Therefore, it can become difficult to compare the results of two studies evaluating the same new imaging test. Considering these issues, it may be preferable not to use the terms *sensitivity* and *specificity* but to describe diagnostic performance by the positivity rate and the positive predictive value—that is, the frequency of correct tumor localization.

A further problem with sensitivity and specificity analyses of whole-body imaging studies is that the results will heavily depend on the number of body regions used for analysis. Generally, the sensitivity of an imaging test will decrease as more regions are analyzed, because there are more regions that are potentially false-negative. Conversely, specificity will increase as more regions are analyzed because the number of false-positive findings is divided by a larger denominator. For the future evaluation of new molecular imaging tests in recurrent prostate cancer, it will therefore be helpful if investigators agree on a reference standard for the presence or absence of disease and a standard definition of the body regions being analyzed. A standardized template of regions would also be highly beneficial for describing the performance of imaging tests in detecting lymph node metastases. Any reference

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For correspondence or reprints contact: Wolfgang A. Weber, Memorial Sloan Kettering Cancer Center, 1275 York Ave., Box 77, New York, NY 10065.

E-mail: weberw@mskcc.org

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standard or template of regions will necessarily be imperfect, but overall it will be much more informative to evaluate all the new imaging agents against one standard with known limitations than to perform studies with several potentially better, but different, standards of reference.

Additionally, sensitivity and specificity can be estimated from biopsies of a limited number of lesions by Bayesian analysis (*10*). This method has not been commonly used so far but merits further investigation in metastatic prostate cancer because many patients present with multiple lesions and it becomes impossible to validate imaging findings for each of these lesions. By performing biopsies of discrepant lesions, one can also use Bayesian analysis as a potentially powerful approach for comparing two imaging tests (*10*).

The high sensitivity and specificity of these new molecular imaging agents raises numerous questions that must be studied in clinical trials to establish how the agents may be used to affect clinical outcomes favorably. Molecular imaging can upstage patients at each clinical stage of prostate cancer. Some patients who once were thought, using standard imaging modalities, to have high-risk localized disease will be found to have early locoregional or systemic disease; those with a rising PSA level after definitive therapy may now be found to have early pelvic or extrapelvic recurrence; and those with limited metastatic disease by traditional imaging techniques may be found to have extensive disease. From a clinical trial perspective, such recategorization of patients will introduce lead-time bias in interpreting survival data. In addition, trials will be subjected to the Will Rogers phenomenon, in which the worst patients in one group may be recategorized as the best patients in another, improving the outcomes in both. This phenomenon can occur, for example, when patients with the highest-risk localized disease are recast as having low-volume metastatic disease on the basis of molecular imaging (*15*).

From a therapeutic standpoint, this upstaging may cause clinicians to alter surgical templates and radiation portals in an attempt to address systemic disease with more extensive local therapies, or they may initiate systemic therapies ever earlier in the disease course. Such fundamental changes in the type, timing, and scope of therapies based on the results of more sensitive imaging must be systematically tested and proven to be beneficial before being adopted as practice. If these trials are not performed, novel imaging could trigger a new era of overtreatment based on improvised treatment patterns predicated on the misapprehension that seeing disease confers the knowledge of how or when to treat it.

As a field, we faced a similar challenge when the PSA was introduced into clinical practice in the 1980s. Then, as now, we had a means to detect disease far earlier than could standard imaging techniques, whether it be in the context of a making a new diagnosis or detecting relapsed disease (*16*). Although this ability yielded many beneficial treatment paradigms to be sure, it also introduced significant overtreatment of large groups of men (*17–19*). With molecular imaging, we have an obligation to our patients to perform trials demonstrating how to utilize these agents to guide therapy that will improve how patients feel, function, or survive. These trials will need to be conducted to characterize primary prostate cancer, perform staging before radiotherapy or surgery, localize the site of recurrence in patients with a rising PSA level after primary therapy, monitor tumor response to therapy, and select patients for targeted radionuclide therapy.

However, the potential of these modalities goes beyond identification of the presence or absence of disease. The biologic characterization of prostate cancer is also a potential future application that may be used to personalize treatment plans. Differentiation of indolent from aggressive primary prostate cancer would be of enormous clinical benefit because many patients with primary prostate cancer currently undergo surgery or radiotherapy for a disease that might not have affected their health if it had remained untreated (*20,21*). Furthermore, many patients with recurrent prostate cancer die with, but not from, prostate cancer. In a review of 397 patients with biochemical recurrence not treated by salvage radiotherapy, 10-year prostate cancer–specific survival was approximately 60% but ranged from 5% to 82% depending on various clinical factors (*22*). This demonstrates that an imaging test that identifies patients who do not need salvage radiotherapy would be highly beneficial. However, it also shows that validation of such an imaging test will be challenging because of the good prognosis of many patients.

Monitoring tumor response to therapy is another important application of molecular imaging that has not been studied extensively in prostate cancer so far. Since bone metastases are not measurable by standard response criteria (RECIST), and bone is frequently the only or the dominant site of metastatic disease in prostate cancer, there is currently no accepted imaging-based criterion to assess tumor response. Only tumor progression as defined by Prostate Cancer Clinical Trials Working Group criteria is an accepted endpoint for clinical trials. Molecular imaging techniques to assess regression, instead of just lack of progression, could be of significant benefit both in research and in clinical practice (*23*).

In the future, the most intriguing application of molecular imaging may be the selection of patients for targeted radionuclide therapy. PSMA-based radionuclide therapy of prostate cancer is clearly in its early stages, but several groups have shown impressive responses in patients with only limited other therapeutic options (*7–9*). Systematic controlled studies establishing the effectiveness of PSMA-targeted radiotherapy in well-defined patient populations are therefore eagerly awaited. Perhaps most importantly, it is necessary to study how PSMA-targeted radionuclide therapy can be combined with established therapies of prostate cancer and at which stage of the disease PSMA-targeted radionuclide therapy is most effective.

In conclusion, nuclear medicine is now in the fortunate situation of offering several promising new approaches for imaging and treatment of prostate cancer with radiopharmaceuticals. This provides many opportunities for clinical research and is generally expected to result in new theranostic applications of nuclear medicine in a very common oncologic disease.

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