

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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The Timing of Molecular Imaging in Prostate Cancer



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H&O What molecular imaging techniques are available for use in prostate cancer?

MM The US Food and Drug Administration (FDA) has approved 2 tracers for use in molecular imaging in the United States: ^{11}C -choline and ^{18}F -fluciclovine. The agents are injected before positron emission tomography (PET) acquisition, which is fused with computed tomography (CT) or magnetic resonance imaging (MRI) in men with a suspected recurrence of prostate cancer. Fluciclovine is also known as anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid (^{18}F -FACBC), or by its brand name Axumin (Blue Earth Diagnostics). Fluciclovine is commercially available, whereas choline is available in selected academic institutions.

From an investigational standpoint, several tracers are available in the United States, but among the most common are the tracers that target prostate-specific membrane antigen (PSMA). These are labeled with either gallium 68 or fluorine 18.

H&O When is molecular imaging used?

MM Physicians and patients can face a difficult decision when a patient's PSA level begins to rise following primary treatment. The key question is whether the disease is confined to the prostate or the prostate bed, in which case salvage treatments can be applied. Or is the disease outside the prostate, in which case salvage approaches to therapy will not be curative? Standard imaging with CT, MRI, or bone scans frequently is not able to detect such low-volume disease, but molecular imaging may well be able to provide guidance in these ambiguous cases. This

information can spare the patient from unnecessary salvage therapy when metastatic disease is present, or may prompt the clinician to administer potentially curative salvage therapy for locally recurrent disease.

H&O Are there any potential uses other than those that are on label?

MM One of the most promising applications of molecular imaging is used during the initial staging of prostate cancer, especially in those men who have high-risk localized disease. Molecular imaging may detect otherwise

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undetected metastatic disease in a patient with high-risk localized disease. These findings can influence the treatment plan, whether that is surgery or radiation. Such findings may alter the surgical template or radiation portal. Molecular imaging may even steer the clinician away from local therapy in favor of multimodality or systemic therapy if molecular imaging reveals distant disease. It is important to stress, however, that treatment alterations based on these new imaging methods are investigational, and their clinical benefits are at present unknown.

Photo: Memorial Sloan Kettering Cancer Center

In addition to their potential usefulness in staging, these imaging modalities may be used as prognostic indicators in patients with metastatic disease because they can detect disease burden more accurately than standard modalities. Also, these agents may be better than our standard imaging techniques at examining response to treatment. I would stress again, however, that molecular imaging has not been clinically validated for staging and assessing response to treatment, and it is still experimental for these uses.

H&O Why might molecular imaging be superior to standard imaging for assessing metastatic disease?

MM When prostate cancer metastasizes, it generally localizes to bone, for which no good standard imaging modality exists. Bone scans are able to detect bony disease only when it is extensive. Also, bone scans detect damage to bone rather than the cancer itself. As a result, standard imaging can detect spread to bone only relatively late and only indirectly. Molecular imaging assesses the disease directly, even if it is in bone. It can also detect disease in lymph nodes earlier than is possible with standard CT or MRI.

H&O What are the shortcomings of molecular imaging?

MM First, the target must be present for prostate cancer to be detected by molecular imaging. Prostate cancer can be biologically heterogeneous, and so the target may not be present in all patients, or in all lesions within a given patient. In addition, false positives can occur. For example, PSMA can be present in some noncancerous tissues, and is also expressed in the neovasculature of nonprostate cancers. Finally, there is a real risk for stage migration from nonmetastatic to metastatic disease with these agents, significantly altering our current prognostication methods for both patients with nonmetastatic and those with metastatic disease.

H&O How effective is molecular imaging in patients with biochemical relapse?

MM PSMA imaging, for example, can detect disease in patients with very low PSA levels, within the range at which many clinicians make decisions about administering salvage radiation therapy. For example, a study by Afshar-Oromieh and colleagues found that PSMA imaging detected disease after surgery in 50% of patients with a PSA of 0.5 ng/mL or less and in about 60% of

those with a PSA between 0.5 and 1.0 ng/mL. These are patients in whom disease would generally not be detectable by standard imaging.

Fluciclovine might not detect disease at quite such low PSA levels; a study by Nanni and colleagues demonstrated disease detection in 45% of patients with PSA levels of 2 to less than 3 ng/mL and in 30% of patients with PSA levels of 1 to less than 2 ng/mL. Finally, fluciclovine may be more sensitive than choline at detecting early disease.

H&O What have studies found about the effect of molecular imaging on salvage radiation treatment?

MM Studies of fluciclovine have found that molecular imaging alters decision making, including the decision of whether to administer salvage radiation therapy at all, and if so, at what dose and target. The preliminary

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results of one prospective study by Teoh and colleagues demonstrated that the management plan was revised following the scan in 61.2% of patients. In 78.8% of cases, changes were made owing to a positive scan result. The big question from an oncologic standpoint is whether these altered decisions yield superior cancer outcomes, and we don't know that yet.

H&O Are any studies looking at the use of molecular imaging for monitoring response to treatment?

MM Studies are just beginning to examine the use of molecular imaging for monitoring treatment response. None of these agents are FDA-approved for this purpose. These clinical trials are ongoing. At least in theory, however, we could get a much more accurate reflection of treatment effects by using molecular imaging because these techniques directly assess the tumor as opposed to the surrounding bone.

H&O Is the use of molecular imaging to aid in the selection of systemic agents being studied?

MM Investigators are using PSMA-directed imaging to select patients for treatment with PSMA-directed therapies because patients who do not have detectable PSMA-avid disease on imaging probably will not benefit from PSMA-directed therapy. We refer to this as a *theragnostic* approach, meaning that the targeting agent has both a therapeutic and a diagnostic component. The ability to use the diagnostic component to select treatment, calculate a safe dose, and assess response to therapeutic doses of PSMA-directed radiation is a very exciting aspect of this approach.

H&O What is the optimal timing of molecular imaging?

MM The optimal timing depends on the context of use. In the case of a patient whose disease has relapsed biochemically after primary therapy, it is advantageous to detect disease early, and therefore to perform molecular imaging early, so that a decision about salvage radiation therapy or other salvage strategies can be made before the opportunity for cure has passed. In the case of localized disease, one would want to do molecular imaging before surgery or radiation therapy. In using molecular imaging to assess treatment response for patients with metastatic disease, we don't know the optimal timing, but it likely depends on the mechanism of action of the therapy.

H&O What are some of the most important studies that have been published regarding the use of molecular imaging in prostate cancer?

MM A very nice summary by Rahbar and colleagues of the German experience with ¹⁷⁷Lu-PSMA-directed therapy has been published in the *Journal of Nuclear Medicine*. Some of the important studies demonstrating the performance characteristics of fluciclovine, one by Schuster and colleagues and one by Odewole and colleagues, can be found in the *Journal of Urology* and the *European Journal of Nuclear Medicine and Molecular Imaging*, respectively. For choline, studies by Fanti and colleagues and by Evangelista and colleagues, published in the *European Journal of Nuclear Medicine and Molecular Imaging* and *Clinical Nuclear Medicine*, respectively, are useful.

H&O Is molecular imaging covered by insurance?

MM Although choline and fluciclovine are FDA-approved, many third-party payers do not reimburse for them. As a result, we run into economic and geographic disparities in terms of the opportunity to use these tools. Insurers based in the United States also may not cover PSMA-based imaging because it has not been approved by the FDA. Cost can be a significant barrier to accessing these technologies.

Disclosure

Dr Morris has been a paid and unpaid consultant to Progenics Pharmaceuticals, an unpaid consultant to Endocyte, and a paid consultant to Blue Earth Diagnostics. He has received institutional research funding for clinical trials from Progenics and Endocyte.

Suggested Readings

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