What Medical, Urologic, and Radiation Oncologists Want from Molecular Imaging of Prostate Cancer

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As molecular imaging better delineates the state of prostate cancer, clinical management will evolve. The currently licensed imaging modalities are limited by lack of specificity or sensitivity for the extent of cancer and for predicting outcome in response to therapy. Clinicians want molecular imaging that—by being more reliable in tailoring treatment and monitoring response for each patient—will become a key facet of precision medicine, surgery, and radiation therapy. Identifying patients who are candidates for specific or novel treatments is important, but equally important is the finding that a given patient may not be a good candidate for single-modality therapy. This article presents prostate cancer scenarios in which managing clinicians would welcome molecular imaging innovations to help with decision making. The potential role of newer techniques that may help fill this wish list is discussed.

Key Words: prostate cancer; molecular imaging; clinical decision making

We summarize areas of clinical need in prostate cancer that could potentially be met with molecular imaging in the next 5 years (Table 1), and we assess recent and potential further progress in these areas.

THE SCREENING SCENARIO

One of the great limitations of prostate-specific antigen (PSA)–based screening is its relative lack of prediction of cancer aggression and cancer-specific mortality. Biopsy data bring more precision, but given the heterogeneity within an individual prostate gland, there are often questions related to sampling and sampling error—a large lesion is easier to biopsy but may contain indolent cancer, whereas a small lesion may carry high-grade or mutant-driven cancer that is more rapidly mortal. For this reason, multiparametric MRI is now commonly used to survey the prostate to assess heterogeneity and index and nonindex lesions. Molecular imaging has a lot of potential in this area, but there are relatively sparse data to support routine use at this point.

Transrectal ultrasound (TRUS) with needle biopsy of the prostate is the current standard of care for prostate cancer diagnosis (*6*). However, when performed in a blind fashion, this technique is subject to systematic and random errors, which may lead to poor sampling and poor cancer characterization. As an invasive method, TRUS with needle biopsy is associated with significant complications (*92*). There are strategies to improve TRUS-guided prostate biopsy performance, including increasing the number of cores (*6*). However, this may increase cost and morbidity and may overdetect clinically insignificant cancers that will not jeopardize the patient's life. As such, it seems more logical to visualize the prostate and then to biopsy suggestive intraprostatic areas with greater precision. As such, the concept of "if we can see, we can target" has been adopted. This approach has the benefit of potentially better characterizing and risk-stratifying prostate cancer, using noninvasive tests that can outperform the current TRUS biopsy strategy.

Over the past few years, MRI has evolved from a tool for staging prostate cancer after biopsy to a risk stratification test capable of predicting clinically significant prostate cancer (*7*). In fact, when combined with TRUS (i.e., MRI/TRUS coregistration), a greater number of clinically significant cancers and fewer clinically insignificant cancers can be detected from only a limited number of sampled cores (*8*). Furthermore, MRI/TRUS-guided biopsies are better able to predict pathology in subsequent radical prostatectomy specimens than TRUS alone (*8*). On this basis, multiparametric MRI/TRUS biopsy is now recommended by the American Urological Association for patients undergoing repeated prostate biopsy (*19*). However, multiparametric MRI may miss up to 20% of clinically significant cancers (*93*). As such, additional efforts have been made to improve or replace multiparametric MRI.

Several radiotracers associated with PET have been tested in an attempt to detect or characterize intraprostatic localized prostate cancer, either as a standalone test or combined with multiparametric MRI in a PET/MRI hybrid system (*1,2,15,16*). Studies correlating gross tumor volume on preoperative ^{11}C-choline PET/CT with tumor volume on radical prostatectomy specimens showed that ^{11}C-choline PET/CT as a standalone test has limited value and failed to correlate with intraprostatic cancer (*20,21*). Similarly, ^{11}C-acetate PET/CT and ^{18}F-FDG PET have questionable utility as independent tests to evaluate localized prostate cancer (*11,13*).

Most promising is hybrid PET/MRI, as this approach combines the strengths of both methods, overcoming the limitations of PET/CT and standalone multiparametric MRI (*1,2*). In fact, studies evaluating ^{11}C-choline PET/CT and apparent diffusion coefficient maps—an

TABLE 1
Clinical Scenarios with Areas of Need That Should Be Addressed with Molecular Imaging

Clinical scenario	Specific clinical questions	References
Screening		
Screening and stratification in patients with no diagnosis of cancer	Identify significant vs. nonsignificant cancer	(1–7)
	Determine predictive value of index and nonindex lesions within intact prostate	(8–21)
Therapy for localized prostate cancer		
Planning therapy for clinically localized cancer	Perform staging to determine whether metastatic disease is present	(22–26)
	Locate disease within pelvic lymph nodes that can be incorporated into radiotherapy field or planned lymph node dissection	(27–35)
Evaluating after definitive local therapy		
Adjuvant therapy	Identify early micrometastatic disease that would eliminate need for radiotherapy	(22,36–43)
PSA elevation after local therapy	Reliably delineate recurrence in patients in whom nadir or PSA rise is lacking after radiotherapy or radical prostatectomy	(43–60)
	Distinguish between M0 hormone-naïve prostate cancer and M0 castration-resistant prostate cancer	(61–63)
Salvage radiotherapy	Identify sites of recurrent disease that can or cannot be targeted by radiation (either in prostate bed or elsewhere)	(64–70)
Metastatic disease		
Oligometastatic prostate cancer	Identify sites of oligometastases to determine whether stereotactic body radiotherapy or resection is appropriate	(40,70–76)
Diffuse metastatic disease	Obtain reliable information on bone metastases for palliative radiotherapy targeting	(67,77–80)
Delineation of metastatic distribution	Determine low- and high-risk patients for selection of systemic therapy	(41,73,78,81,82)
Early imaging response	Predict response to therapy or duration of survival	(42,63,83–91)

important component of multiparametric MRI—have shown that these tests are likely complementary in detecting the index lesion on primary prostate cancer (3), and other work has suggested that the combination of ^{18}F-fluoroethylcholine PET and endorectal coil MRI best delineates the index cancer focus (94). However, in a 49-patient study assessing the value of ^{11}C-choline PET/CT over T2-weighted MRI in localizing intraprostatic cancer—using whole-mount histopathology sections after radical prostatectomy as the standard—the authors found differential sensitivity (33.5% vs. 77.4%), specificity (94.6% vs. 44.9%), and accuracy (70.2% vs. 61.1%) for T2-weighted MRI versus ^{11}C-choline PET/CT, respectively. When both tests were combined, there was an improvement in sensitivity but a decrease in specificity. The authors concluded that the value of combined ^{11}C-choline PET/CT and T2-weighted MRI is limited (15).

Studies evaluating prostate-specific membrane antigen (PSMA)–based PET/CT are encouraging (4,16). An interesting study assessed performance in localizing primary prostate cancer by PSMA-based PET/MRI versus multiparametric MRI alone and PET alone in 53 patients undergoing radical prostatectomy. The cancer detection rate was 66% for multiparametric MRI, 92% for PET, and 98% for PET/MRI. Furthermore, in an analysis of area under the receiver operator curve, PET/MRI was found to outperform multiparametric MRI and PET alone for localization of prostate cancer (16).

Although promising and exciting, these technologies should be cautiously analyzed because of the small sample sizes of some studies and the fact that the study populations have already been diagnosed with prostate cancer. The future challenge is for these techniques and technologies to be made broadly reproducible and applicable for biopsy guidance in the population of patients at risk of prostate cancer. Additionally, these technologies should be able to localize and risk-stratify clinically significant prostate cancer while the tumor is still small.

THE LOCALIZED PROSTATE CANCER THERAPY SCENARIO

Is the patient a candidate for definitive surgery, radiation therapy, or a novel local approach? There is no definite benefit to treating the primary cancer in the presence of metastatic prostate cancer. Although this premise will be tested in upcoming trials, currently we try not to visit the morbidity of prostatectomy or prostatic radiation on patients with distant disease unless there are emergent or symptomatic issues that require intervention. On that basis, assessment for metastatic cancer in patients with clinically localized prostate cancer is typically undertaken with CT or MRI of the abdomen and pelvis with a ^{99m}Tc-based bone scan. Additional imaging may have a role when confirmation is needed or results are equivocal.

Newer molecular imaging techniques with choline, amino acids, peptides, PSMA, and sodium fluoride may detect a greater number of distant lesions than conventional staging (22,40–43). Problems arise, however, in assessing the relationship of these lesions to survival and other outcome measures, the false-positive and false-negative rates for these scans, and whether the results can be used to model therapeutic strategies that help patients.

One important area in which molecular imaging may be crucial is when there is lymph node involvement at diagnosis or soon after definitive local therapy. In such cases, it is technically feasible to surgically resect lymph nodes or to treat them with conventional or stereotactically guided radiation (70,95). Patients may experience improvement in surrogates such as serum PSA and have longer disease-free intervals, but prospective data are lacking. Prospective trials are needed in this area, but most importantly, we also need to use molecular imaging modalities in parallel if we are to optimize our progress.

The indications for postoperative radiotherapy after radical prostatectomy are positive surgical margins, extracapsular extension, seminal vesicle invasion, lack of a PSA nadir after radical prostatectomy, or a rising PSA level after radical prostatectomy (36–38). Radiotherapy in this setting is used to eradicate microscopic residual disease in the prostate bed, thereby reducing the risk of biochemical recurrence.

Postoperative radiotherapy to the prostate fossa is not currently used in patients with metastatic disease. Because of this difference in clinical treatment for patients with metastatic disease, identification of early metastatic disease is essential for the postoperative patient. If early metastatic disease could be accurately identified, those patients could avoid postoperative radiotherapy and the treatment could be focused on systemic therapy. Thus, molecular imaging can define the appropriate treatment algorithm.

In the adjuvant setting, detection of residual or recurrent prostate cancer is challenging because the patient's PSA level is typically less than 0.2 ng/mL, reflecting a low burden of disease. Reported outcomes for ^{11}C-choline PET show low detection rates for PSA levels of less than 1 ng/mL, although a shorter PSA doubling time predicts a positive PET study when the PSA level is less than 2.0 ng/mL (46,49,50,53). Giovacchini proposed a PSA threshold of 1.4 ng/mL for ^{11}C-choline PET/CT positivity (49,50), whereas Castellucci proposed a cutoff of 1.05 ng/mL with a PSA doubling time cutoff of 5.95 mo (53). ^{68}Ga-PSMA PET/CT may have better detection rates at lower PSA levels. In some studies, when the PSA level was below 0.5 ng/mL, ^{68}Ga-PSMA detected 50% of lesions, versus 12.5% for ^{18}F-fluoromethylcholine; these percentages compare with around 19% for ^{11}C-choline PET/CT when the PSA level was less than 1 (49,50,59). Moreover, in most studies that do report imaging abnormalities with very low PSA levels, the findings are not linked to pathologic proof of disease because the studies lack biopsy or resected material for correlation.

Finding a reliable and sensitive molecular imaging modality to detect micrometastatic disease in the setting of a very low PSA level could potentially eliminate unnecessary treatment to the pelvis in patients who would not benefit from it. Early detection of tumor recurrence would also be beneficial since the effectiveness of salvage therapy is greater in the setting of lower PSA values.

Radiotherapy is the standard salvage treatment in men with persistently detectable PSA or a delayed rise in PSA without evidence of metastasis after prostatectomy. Additional information that can affect postoperative radiotherapy is the identification of residual or recurrent disease within the pelvis. If the patient requires salvage radiotherapy, identification of disease within the pelvis allows for more targeted therapy and appropriate radiation dosing. In retrospective studies examining the effects of molecular imaging on treatment decision making, ^{11}C-choline PET/CT changed radiation treatment planning to include lymph node stations in 13% of patients (66). One group found that the therapeutic strategy was altered in about a third of patients after the results of ^{11}C-choline PET/CT were known (67), and another group found that the PSMA PET findings caused a change in radiotherapy management in 46% of cases (69). As technology and treatment techniques improve, it is hoped that these imaging modalities will not only better define treatment decisions but also allow for modification of radiotherapy field sizes.

THE METASTATIC DISEASE SCENARIO

Delineation of sites of metastatic prostate cancer is important for a variety of reasons.

Oligometastatic disease presents a unique clinical scenario in which patients have a limited number of metastases. There have been many preliminary studies that have evaluated aggressive therapy for oligometastatic disease (74–76). The goal of aggressive therapy combined with effective systemic therapy in this scenario is to prevent further progression of disease and possibly improve survival. Stereotactic body radiotherapy uses higher doses of radiation per treatment to ablate tumor cells and offers a greater potential for cell kill than standard fractionated treatment. A key component to using stereotactic body radiotherapy for oligometastatic disease is the proper identification of metastatic sites of disease and identification of whether the picture is an oligometastatic one. Imaging is critical not only in identifying the number of metastatic foci but also in determining whether the radiotherapy can safely be delivered to the metastases.

Defining boney metastatic sites has traditionally involved correlation of clinical symptoms and ^{99m}Tc-based bone scanning. Radiation has been given to prevent imminent spinal cord compression, and in this instance the extent of the boundary and number of discrete lesions to be treated may vary with the sensitivity and specificity of the imaging technique. More recently, radiation has been used as a part of combination therapies for oligometastatic disease. Patients who have multiple bone metastases may be selected for different therapies. For example, a patient with diffuse bone metastases and some symptoms may be offered radionuclide therapy with [223]Ra either instead of external-beam radiation or after it (96).

The distribution of metastases in advanced prostate cancer is prognostic. Patients with visceral involvement, especially liver metastases, have a poorer survival than patients with bone metastases, whereas patients with only lymph node involvement have the best outcome when given standard therapies (97). Among patients with bone metastases, the distribution and most likely number of metastases in the axial and appendicular skeleton is prognostic (98).

Recent data from the CHAARTED trial suggest that patients with high-risk disease defined by either a high-risk distribution or a high-risk number of bone metastases or visceral metastases benefit from the addition of docetaxel chemotherapy to standard androgen deprivation therapy at the first evidence of metastases (99). The advent of more sensitive scans in this context raises interesting questions: Will patients with more sensitive scans have earlier detection of metastases, when the metastatic burden is lower, and be considered at low risk and not likely to benefit from addition of chemotherapy? Or will patients diagnosed with a lower burden of bone metastases on ^{99m}Tc-based

bone scans now have more metastatic disease defined by sodium fluoride PET and be considered at high risk and candidates for the addition of docetaxel to androgen deprivation therapy?

Patients who have a PSA elevation on androgen deprivation therapy but no metastases on imaging with conventional bone scintigraphy and CT (so-called M_0 castration-resistant prostate cancer) may be found to have evidence of metastases if imaged with a more sensitive and specific technique (22,43,46,53,80). These patients may then be candidates for therapy with an earlier androgen receptor pathway blockade, using agents such as enzalutamide or abiraterone acetate, or for immunotherapy with sipuleucel-T. Several lines of evidence suggest that prolonged progression-free and overall survival may be a benefit of earlier therapy in this setting, albeit with an extra cost when the hormonal agents are required (100,101).

Clinicians would very much like to know whether patients with metastatic disease are benefiting from therapy within 1 mo of starting it. The knowledge that a patient is unlikely to benefit from further use of a given therapy would decrease unnecessary costs and toxicity from a nonefficacious treatment. For nonimaging modalities, many surrogates of survival have been tested with limited success, leading to the formation of an international group to examine and define intermediate endpoints in advanced prostate cancer to make trials more efficient (102).

Several blood-based tests have value when they indicate changes over the first 3–4 wk of therapy in prostate cancer, including serum PSA, lactate dehydrogenase, alkaline phosphate, and other bone markers and circulating tumor cells (103). Although the Food and Drug Administration does not accept the possibility that changes in PSA level indicate an altered prognosis necessitating a change in therapy, and the Prostate Cancer Working Group defines progression as clinical symptoms or unequivocal radiologic progression, many clinicians use serum PSA level as their major determinant of whether to change therapy in advanced prostate cancer. When changes in PSA level have been investigated as an intermediate endpoint, they have failed to definitively meet surrogacy criteria even though a small number of patients who show a major PSA increase after 4 wk of hormonal therapy are destined for rapid progression and a likely early death unless switched to a different effective therapy (104,105). Prospective studies are now under way to look at switching patients with a suboptimal early biomarker response to another therapy or continuing with the original treatment to determine any disease control or survival advantage. If successful, these studies will provide high-level evidence for such an approach. Other studies look at this question slightly differently based on sequencing of agents. For example, the PRIMCAB study enrolls patients with early progression on a novel androgen receptor pathway inhibitor and randomizes them to either another androgen receptor pathway blocker or chemotherapy (https://clinicaltrials.gov/show/NCT02379390). In the ARMOR3 trial, patients who progress on initial androgen deprivation therapy are screened for the presence of a resistance marker on circulating tumor cells called AR-V7—a truncation of the androgen receptor ligand binding domain at the site where both endogenous androgens and first- and second-generation androgen receptor blockers bind (106,107). The study entails randomizing patients with this resistance marker to either a conventional blocker of the androgen receptor binding domain (enzalutamide) or a drug that acts by binding at a different site in the N terminus of the androgen receptor (galeterone) (108,109). The TAXYNERGY study looks at changing the type of chemotherapy on the basis of early-response markers, including circulating tumor cell number and cellular androgen receptor distribution (110). These studies will initially

determine whether this approach is feasible and then seek to change practice. They are demanding and resource-intense but, hopefully, can be pivotal to optimal therapeutic use.

In terms of imaging studies, standard CT and ^{99m}Tc-based bone scanning do not predict outcome until at least 12 wk after the start of therapy, with the presence of new bone metastases on either modality, or both, being associated with a poorer survival, as is most likely due to RECIST progression in soft-tissue lesions (lymph nodes or viscera) (84). Because few novel molecular imaging techniques have been tested in parallel with these conventional techniques, there is a deficit of high-level evidence on which to base practice. In addition, because of the logistics of tissue acquisition in advanced prostate cancer, there are few studies that have characterized lesions histologically or provide molecular analysis. We are left with using observations from phase II studies to try to guide practice.

What do we know from molecular imaging in these situations? First, in patients with a rising PSA level and negative findings on conventional CT and ^{99m}Tc bone scanning, a positive ^{11}C-choline PET/CT scan is associated with worse overall survival (87). Second, adaptation of conventional imaging modalities such as ^{99m}Tc bone scanning and MRI may allow assessment of response and progression in bone, but broader application to centers with less technologic expertise will represent a challenge (111–113). Third, ^{18}F-FDG PET in metastatic castration-resistant prostate cancer is useful for following individual lesions on treatment and for determining whether there are relatively more metabolically active foci in the patient (42,91,112,114). However, whereas ^{18}F-FDG PET parameters at baseline correlate with survival, changes may be of limited value in predicting outcome. For example, changes in SUV for the sum of all lesions early in treatment do not appear to be associated with outcome, although further analyses of several cohorts are in longer-term follow-up (42). And finally, specific scanning targets such as the androgen receptor, PSMA, bombesin receptors, and other molecules may provide information that could indicate potential for early response prediction and therapeutic change (55,73,79–81,91,115). These targets will need to be tested in a series of prospective studies (116–118).

CONCLUSION

There is so much that molecular imaging can add to the modern treatment of prostate cancer. Molecular imaging is critical, and will become even more so, in the management of all stages of prostate cancer treatment.

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