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Challenges in Clinical Prostate Cancer: Role of Imaging

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Abstract

Objective—This article reviews a recent 2-day workshop on prostate cancer and imaging technology that was conducted by the Cancer Imaging Program of the National Cancer Institute. The workshop dealt with research trends and avenues for improving imaging and applications across the clinical spectrum of the disease.

Conclusion—After a summary of prostate cancer incidence and mortality, four main clinical challenges in prostate cancer treatment and management—diagnostic accuracy; risk stratification, initial staging, active surveillance, and focal therapy; prostate-specific antigen relapse after radiation therapy or radical prostatectomy; and assessing response to therapy in advanced disease—were discussed by the 55-member panel. The overarching issue in prostate cancer is distinguishing lethal from nonlethal disease. New technologies and fresh uses for established procedures make imaging effective in both assessing and treating prostate cancer.

Keywords

diffusion-weighted MRI; dynamic contrast-enhanced MRI; FDG PET imaging; functional imaging; high-intensity focused ultrasound imaging; MRI; prostate cancer imaging; SPECT

Prostate carcinoma, the second most common cause of cancer death among American men, is not invariably lethal. A heterogeneous disease, it ranges from asymptomatic to rapidly progressive systemic malignancy. The prevalence of prostate cancer is so high that it could be considered a normal age-related phenomenon. The American Cancer Society estimated that 186,320 new cases of prostate cancer would be diagnosed in 2008, and approximately 28,660 men would die of the disease in the United States [1].

Recently, death rates from prostate cancer have declined, and the 5-year survival rate has seen a large increase (now 99% when combined for all stages), thought to be due primarily to screening, early detection, and changes in lifestyle [2]. This trend also reflects some improvement in successful treatment of prostate cancer. Nonetheless, more needs to be done to understand and manage this disease.

With this background, the National Cancer Institute (NCI), Cancer Imaging Program (CIP), conducted a 2-day workshop on prostate cancer and imaging technology covering research trends and avenues for improving imaging applications across the clinical spectrum of the disease. A multidisciplinary group of 55 experts (Appendix 1) and their audience were gathered

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to discuss such issues as how anatomic, functional, and molecular imaging techniques might add to more accurate characterization of disease at initial biopsy; how better staging or evaluation of early response to therapy would allow better patient management, improving effectiveness of therapies or avoidance of unnecessary treatments; and how and which imaging tools can best be used to inform prostate cancer clinical trial designs and accelerate the evaluation of potential novel breakthrough therapies.

The workshop was organized around four clinical management problems for prostate cancer from early to late disease in which imaging might be able to contribute to treatment strategies: first, diagnostic accuracy—reducing false-positive and false-negative biopsies and improving biopsy representation of underlying disease; second: risk stratification, initial staging, active surveillance, and focal therapy—localized disease management, distinguishing high- from low-risk disease, accurately determining staging, and using imaging to monitor disease progression and evaluate efficacy of focal therapy; third, D_0 disease (prostate-specific antigen [PSA] relapse after radiation therapy or radical prostatectomy)—recurrent disease management using imaging to distinguish local from distant recurrence and assessing the value of imaging to direct radiotherapy in local recurrence; and fourth, assessing response to therapy in advanced disease—using imaging in prostate cancer drug development and management of advanced disease.

In plenary sessions, workshop participants reviewed the overall state of the science in prostate cancer and use of imaging in its diagnosis and treatment and then considered the four clinical problems and possible imaging solutions in more detail. Finally, breakout groups were formed to discuss strategies to address the four challenges and to develop specific research recommendations, particularly clinical trials. This article summarizes discussions on the role of imaging across the spectrum of prostate cancer disease states and distinguishing lethal from nonlethal prostate cancer. This is followed by a summary of the discussion of the four clinical management problems and the associated clinical issues and role of imaging.

The Role of Imaging in Different Prostate Cancer Disease States

A major goal for prostate cancer imaging is more accurate disease characterization through the synthesis of anatomic, functional, and molecular imaging information. Other important goals include evaluating response to therapy to allow earlier cessation of ineffective therapies, shorter duration of phase 2 trials to evaluate new drugs, and accelerated approval in phase 3 trials. To date, no consensus exists regarding the use of imaging techniques for evaluating primary prostate cancers, although it is recognized that the selection of an imaging technique should be based on questions that need to be answered to address a patient's needs. Each technique has advantages, disadvantages, and specific indications (Table 1).

Current standard imaging techniques, such as ultrasound, MRI, CT, and nuclear medicine, cannot detect early disease, and they provide limited information for disease staging [3–8]. However, several promising emerging techniques are under investigation, either alone or in conjunction with standard imaging techniques.

Transrectal ultrasound (TRUS), a standard imaging tool in prostate cancer, is primarily used for biopsy guidance and brachytherapy seed placement but is unreliable in differentiating normal prostate gland from cancer tissue, resulting in biopsies not specifically targeted to areas most likely to be malignant. Several new technologies used in conjunction with standard TRUS include contrast-enhanced color Doppler imaging, intermittent harmonic imaging, and contrast-enhanced flash-replenishment imaging [9]. One particularly promising strategy, contrast-enhanced ultrasound, takes advantage of the difference in the microvasculature between areas of prostate cancer and benign prostate tissue. Ultrasound spectroscopy uses

radiofrequency echo signals that are expressed as spectral parameters to characterize tissue microarchitecture to discriminate malignant from benign prostate tissue [10].

Conventional MRI of the prostate relies on morphologic changes within the prostate to define the presence and extent of cancer [11]. Currently, the prostate is imaged by MRI using an endorectal coil in combination with four external coils (pelvic phased-array). Endorectal coil MRI provides higher spatial and contrast resolution on prostate zonal anatomy than TRUS or CT [12,13]. T2-weighted MRI has shown high sensitivity in prostate cancer localization (97%), although performance varies with the patient population studied [14]. It is also not sensitive in detecting cancer in regions other than the peripheral zone of the prostate [12]. Functional MRI imaging techniques, such as MR spectroscopy (MRS), diffusion-weighted MRI (DWI), and dynamic contrast-enhanced MRI (DCE-MRI), have been investigated for potential to complement T2-weighted MRI in improving prostate cancer localization.

The functional imaging techniques, PET and SPECT, detect pathologic processes using specific molecular probes labeled with radionuclides. To date, most oncologic clinical studies have used ^{18}F-FDG for PET. However, the results of FDG PET in detecting prostate cancer have been mixed [15–18]. To improve the usefulness of PET and SPECT in prostate cancer detection, molecular probes with higher sensitivity and specificity are being developed and validated. PET tracers such as ^{11}C-acetate, ^{11}C-choline, and ^{18}F-choline have been investigated as alternatives to FDG [19].

Significant issues relating to the role of imaging in risk stratification, initial staging, active surveillance, and focal therapy for prostate cancer are identifying low-risk disease that does not need aggressive therapy, linking tissue specimens to imaging markers, determining the patients who would benefit most from nodal imaging and staging, identifying how the predictive value of an accurate technique affects therapeutic options, and determining the best way to follow patients after therapy.

CT and MRI are the main imaging technologies currently used for staging nodal disease. PET and FDG PET/CT, which have been successful in imaging evaluation of a large number of tumor types, have also been evaluated for prostate cancer staging but not widely used because prostate cancer has variable accumulation of FDG and high interference from excretion in the bladder [16]. Lymphotropic nanoparticle–enhanced MRI is a promising technique for malignant nodal evaluation. This technique is highly accurate for nodal staging in patients with various primary cancers [20]. It evaluates nodal macrophage function and does not rely on nodal size to detect metastatic disease [21,22].

Local recurrence can be detected with digital rectal examination (DRE), TRUS-guided sextant biopsy, and various MRI (conventional T1- and T2-weighted MRI, DCE-MRI, and MRS) and nuclear medicine (FDG PET and ^{11}C and ^{18}F choline and acetate PET/CT) methods. At present, only TRUS is universally available, and it is used primarily to guide biopsies. Conventional MRI and FDG PET are frequently available, whereas other imaging methods are still experimental (DCE-MRI, TRUS with microbubble contrast agent, MRS, and ^{11}C and ^{18}F choline and acetate PET/CT) [23].

The recent standard for bone scanning in metastatic disease has been ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP); however, ^{18}F sodium fluoride (^{18}F-NaF) PET is getting increasing interest because it is more sensitive and specific. In addition to its utility for detection, this technique might be more useful, along with FDG PET, for measuring changes due to therapy.

Imaging is a powerful tool because most imaging techniques are non- or minimally invasive; nondestructive; minimally perturb the system; and can provide dynamic real-time data,

repeated measurements, and integrative results (systems data). However, standardizing imaging measurements across techniques is critically needed to assess the meaning of these measurements in relation to a specific clinical outcome.

Progress in prostate cancer imaging is beginning to translate into better treatment selection and more accurate imaging-guided therapies, including surgery and radiation therapy. In addition, the need to detect local and distant recurrences early is leading to more accurate assessments of patients with increasing PSA levels after therapy. It is hoped that these advances in imaging, including molecular imaging, will contribute to long-term improvements in quality of life and decreases in prostate cancer morbidity and accelerate the decline in mortality from prostate cancer that we are now just beginning to realize [21].

Distinguishing Lethal from Nonlethal Disease: The Overarching Problem in Clinical Management of Prostate Cancer

Earlier detection of prostate cancer in the PSA era has brought new challenges to clinical assessment and treatment selection—challenges compounded by variability in the natural history of the disease. Today, cancers are detected at smaller, lower stages and lower grades than they were 20 years ago, but a wide range of aggressiveness remains [21,24]. It is assumed that evidence-based application of the findings from diagnostic parameters such as histopathologic grading; tumors, nodes, and metastases (TNM) staging; and new molecular biomarkers will help practitioners avoid the dilemma of overdiagnosis and overtreatment versus underestimating cancers with lethal biologic potential. However, the best currently available assessment tools provide less than precise predictions. It is believed that the addition of functional as well as anatomic imaging information to various clinical nomograms will add to their accuracy for forecasting outcomes and directing interventions (Table 2).

Many men who develop prostate cancer never have symptoms or undergo therapy and eventually die of other causes. The natural history of prostate cancer is remarkably heterogeneous and still not completely understood. Autopsy and early observational studies have shown that approximately one in three men ≥ 50 years old has histologic evidence of prostate cancer; a significant portion of these tumors are small and possibly clinically insignificant, although others are extremely aggressive and lethal [25]. The challenge is to distinguish between the two. Currently, prostate cancer cases are classified into risk groups (low, intermediate, or high) based on serum PSA level, biopsy Gleason score, and clinical stage. These risk groups are used as a guide to making treatment decisions. However, the three risk groups are broad categories with a range of pathologic characteristics and clinical behaviors. For example, low-risk prostate cancer (defined by the National Comprehensive Cancer Network as a tumor that either cannot be felt on DRE or, if palpable, occupies one half of one lobe or less, with a Gleason score of 2–6 and PSA below 10 ng/mL) could turn out to be either significant or insignificant [24].

PSA

The widespread use of PSA screening has led to earlier detection and a dramatic down-staging of prostate cancer at diagnosis but also has resulted in overdiagnosis and overtreatment of indolent disease.

PSA is the most commonly used biochemical marker for prostate cancer and at present the only widely accepted screening tool for prostate cancer (besides DRE). It is a protease manufactured by the secretory epithelial cells and drains into the ductal system, where it catalyzes liquefaction of the seminal coagulum after ejaculation. Serum levels are normally < 4 ng/mL but vary according to age and race. Many urologists now use a PSA cutoff of 2.5 ng/

mL for biopsy, increasing detection of prostate cancer cases but also leading to a significant number of additional, possibly unnecessary, biopsies [26]. Currently, overdetection rates are estimated to be between 27% and 56% [25]. PSA is prostate specific but not prostate cancer specific. Any process that disrupts the normal architecture of the prostate allows diffusion of PSA into the stroma and microvasculature (e.g., elevated serum PSA levels are seen with prostatitis, infarcts, hyperplasia, and transiently after biopsy). Although serum PSA level correlates positively with clinical stage, tumor volume, histologic grade, and the presence of capsular perforation and seminal vesicle invasion, it is of limited value in predicting stage for individual patients [27].

Despite its limitations, PSA remains the only generally accepted biomarker for prostate cancer. To improve on traditional serum PSA, other tests based on PSA (PSA derivatives) have been and are being developed—for example, PSA density, velocity, and age-specific reference range—and PSA isoforms—for example, distinct molecular forms of free PSA, proPSA, and BPSA (benign PSA) [26,28].

PSA density, the ratio of serum PSA to prostate volume measured by TRUS, has shown discriminatory power between benign prostatic hyperplasia (BPH) and prostate cancer in many studies, although other studies have been negative. PSA velocity, the change in PSA level over a specified time interval, has been much advocated as a means of identifying men with prostate cancer. PSA velocity is strongly associated with the diagnosis of prostate cancer and with the risk of recurrence or cancer-specific death after treatment. Age-specific reference ranges have been proposed as a means of increasing the sensitivity of detection in younger men and the specificity in older men; however, these ranges have been criticized, mainly for missing clinically significant cancers in older men, and have not become uniformly accepted.

PSA isoforms, or related PSA proteins, have been evaluated for the ability to predict prostate cancer. The majority of PSA in the blood occurs in stable covalent complexes with protease inhibitors. Noncomplexed forms, known as free PSA, have established clinical utility by increasing the specificity of PSA testing, especially after a negative prostate needle biopsy, although the magnitude of the effect has varied across studies. ProPSA is the precursor protein for PSA. Several studies have suggested that proPSA might aid in discriminating prostate cancer from benign disease. Elevated levels of the proPSA protein have been associated with prostate cancer; combined with PSA and free PSA, these measurements increased the specificity of prostate cancer detection. BPSA, a cleaved form of PSA, has been associated with prostate volume and therefore might also help to discriminate prostate cancer from BPH. All of these PSA forms are worthy of further research to determine whether they can improve the accuracy of clinically relevant prostate cancer detection, particularly if combined into a panel of markers [29].

Gleason Score

At present, prostate cancer is diagnosed based on examination of histopathologic or histologic specimens from the gland, obtained by several systematic transrectal core biopsies. Biopsies are graded for prostate adenocarcinoma using the Gleason score, currently the best prognostic indicator and the most commonly used grading system for prostate cancer. Pathologists observe the microscopic appearance and histopathologic patterns of tumor growth and assign a grade (ranging from 1 to 5, with 5 being the most aggressive) to the most common tumor and a second grade to the next most common tumor. The two grades are added together to obtain a Gleason score (ranging from 2 to 10, with 10 having the worst prognosis). Lower scores are associated with small, well-differentiated, closely packed glands; as the grade increases, cells spread out, lose glandular architecture, and are poorly differentiated. Cancers with Gleason scores of 6 or lower are considered well differentiated and associated with a good prognosis. Those with a Gleason score of 8–10 have the worst prognosis and the highest risk for recurrence. Tumors

with a Gleason score of 7 have a variable prognosis and intermediate risk of recurrence [2]. However, there are a few drawbacks to this method: Interobserver variation can occur, grading on biopsies may not correlate with the prostatectomy specimen because of sampling problems, and cases of morphologically identical prostate cancer can behave differently [30].

Staging

TNM classification is the reference standard for staging prostate cancer—the primary goal being to define anatomic extent of the tumor and to distinguish patients with organ-confined, locally invasive, or metastatic disease. Subcategories within T1–T4 disease are based on a combination of findings obtained at both initial clinical evaluation (palpability) and after assessment of resected glandular tissue (percent of single lobe involvement, multiple lobe involvement, extension beyond the prostate, and so on). Histopathologic data from nodal dissection or data from imaging provide additional information used to determine the stage.

Nomograms

Mathematic models, such as nomograms, may offer more precise predictions of a prognosis or therapeutic response than staging alone. Models combining DRE, serum PSA level, and Gleason score (such as the D'Amico, Partin, or Kattan nomograms [2]) have been shown to improve accuracy in predicting the risk of treatment failure compared with a single parameter alone.

Furthermore, incorporating MRI or MRI–MRS findings into nomograms has been shown to improve the prediction of insignificant cancer [21,31]. However, these models provide general probabilities, not the specific risk for an individual patient.

As noted, patients can be stratified into subgroups depending on outcome after surgery with the parameters just described, which are widely used to guide clinical decision making. However, because of PSA-based cancer detection, patients increasingly present within a narrow range of these parameters, which then begin to lose their discriminatory power. In fact, among all patients undergoing prostatectomy for organ-confined disease, more than one third will relapse, showing that the tumor was not confined to the prostate [32,33]. On the other hand, we know that only 12–15% of the prostate cancers diagnosed are lethal [34].

Molecular Tools

New biomarkers that provide prognostic estimates of prostate cancer severity and predict treatment response will be among the tools needed to address this challenge. To this end, efforts have been made to improve knowledge of the genetics behind prostate cancer and identify new predictive biomarkers in both serum- and tissue-based assays. Some of these biomarkers will provide targets for imaging probes. Common genetic alterations in prostate cancer patients have been identified, including *CpG* hypermethylation of *GSPT1* and *TMPRSS2–ERG* gene fusion. Serum and urine detection of RNA biomarkers (e.g., *PCA3*) and prostate cancer tissue proteins using antibodies (e.g., *EPCA*) are being evaluated as detection and prognostic tools [24,26].

Thus, the ability to predict the biologic aggressiveness of prostate cancer remains limited, and given the disease prevalence, ease of diagnosis, aging of the population, and treatment morbidity, the ability to distinguish aggressive from indolent forms of cancer is critical. The need and opportunities for imaging to meet this challenge are summarized in Tables 1 and 3.

Strategies and Clinical Imaging Research Needed to Address Clinical Management Problems in Prostate Cancer

Following is a summary of the considerations and research recommendations for addressing the four problems in prostate cancer management evaluated at the workshop. For each issue, the current state of the science is briefly reviewed, potentially useful imaging techniques are noted, and research recommendations are presented.

Problem 1: Diagnostic Accuracy (Reducing False-Positive and False-Negative Biopsies)

Clinical issues—As noted above, prostate cancer is diagnosed by pathologic examination of needle biopsy specimens, commonly prompted by abnormal findings in DRE and by elevated serum PSA. Although PSA level has been correlated with prostate cancer risk and aggressiveness, a large portion of PSA-triggered biopsies are found to contain no disease, whereas high-grade prostate cancer has also been detected in patients with PSA levels below 0.5 ng/mL [35]. In addition, because of the inherent heterogeneity of prostate cancer (approximately 85% of prostate cancer being multifocal in origin [36]), current systematic biopsy methods (6–12 spatially distributed prostate core biopsies under TRUS guidance) may not provide accurate information on location, size, extent, and grade of the disease. Even systematic sampling done with TRUS guidance often results in underdiagnosis of prostate cancer extent. In fact, the histologic grade is almost always underestimated by needle biopsy [37]. Thus, using current diagnostic schemes, both overdiagnosis of clinically insignificant cancer and underdiagnosis of potentially lethal cancer exist in the population at risk of prostate cancer.

To address the limitations of current PSA screening and biopsy techniques in prostate cancer detection, a comprehensive approach is urgently needed. For example, new serum–tissue biomarkers with greater sensitivity and specificity need to be developed and validated. In addition, novel imaging techniques need to be explored for their potential in detecting early disease, guiding tissue biopsy, and planning treatment. More accurate characterization of the local tumor by serum–tissue markers, biopsy techniques, imaging, and nomograms is critical in improving risk assessment, which may translate into differential management of low- and high-risk cancers in the clinical setting. As a noninvasive means, imaging has an integral role in the management of prostate cancer. As a first step, images depicting sites of cancer burden should be investigated and integrated in the diagnostic scheme before biopsy, so the information can be applied to guide tissue sampling.

Role of ultrasound—TRUS is primarily used to direct the biopsy needle to desired anatomic locations to estimate the volume of the prostate and assist in sampling prostate tissue in a spatially systematic way, but it is unreliable in differentiating normal prostate gland from cancer tissue. As a result, biopsies are not specifically targeted to areas most likely to be malignant.

To increase biopsy sensitivity and reduce the number of core biopsies required for detecting clinically significant prostate cancer, several new technologies in conjunction with standard TRUS have been investigated, including contrast-enhanced color Doppler imaging, intermittent harmonic imaging, and contrast-enhanced flash replenishment imaging [9]. One particularly promising strategy, contrast-enhanced ultrasound, takes advantage of the difference in microvasculature between areas of prostate cancer and benign prostate tissue. Cancer presents increased microvessel density; these microvessels, although below the resolution of conventional ultrasound, can be visualized using microbubble contrast agents. After IV administration, microbubbles (1–10 μm in size) can diffuse into microvessels to selectively enhance areas with increased vascularity. Targeted biopsy guided by contrast-

enhanced ultrasound detected significantly more cancer and was twice as likely to sample cancerous tissue in the prostate as conventional systematic biopsy. The majority of cancers detected were high-grade (Gleason score > 6). Nevertheless, the ability of this technique to discriminate benign from malignant tissue is low [38], and its application in guiding ultrasound biopsy needs further validation in larger studies. Another factor that may impede its application in the oncology setting is that microbubble contrast agents approved by the Food and Drug Administration (FDA) for echocardiography have a boxed warning requiring close monitoring of high-risk patients receiving the agents to avoid potentially serious cardiopulmonary reactions that may occur (www.fda.gov/cder/drug/Info-Sheets/HCP/microbubbleHCP.htm).

Ultrasound spectroscopy uses radiofrequency echo signals expressed as spectral parameters to characterize tissue microarchitecture in order to discriminate malignant from benign prostate tissue. During a spectrum analysis, a region of interest is drawn surrounding the suspected area, and the spectrum of radiofrequency signals is compared with that from a normal reference area [10]. The utility of ultrasound spectroscopy in detecting prostate cancer has been shown in a clinical trial involving 300 patients conducted by the Memorial Sloan-Kettering Cancer Center; a trial involving 64 patients at the Washington, DC, VA Medical Center; and a group in Germany independently [39]. However, more studies are needed to validate its potential application.

Role of MRI—As previously discussed, conventional prostate MRI uses an endorectal coil in combination with phased-array surface coils depicting the presence and extent of cancer [11]; it provides higher spatial and contrast resolution than TRUS or CT but has low specificity [14]. Endorectal-coil T2-weighted MRI shows decreased signal intensity for prostate cancer relative to normal peripheral zone tissue but is less sensitive at detecting cancer in other prostatic zones. Also, low signal intensity is not specific for prostate cancer because benign conditions such as prostatitis, hemorrhage, and therapeutic effects also have a similar appearance at MRI [12,13].

Functional MRI techniques, such as MRS, DWI, and DCE-MRI, have been investigated for their potential to complement morphologic T2-weighted MRI in improving prostate cancer localization. MRS is an FDA-cleared technology for noninvasively measuring metabolic activity on the basis of relative concentrations of metabolites in tissues. In the prostate, cancer tissue shows a decreased concentration of citrate but an elevated concentration of choline relative to normal prostate tissue. Studies showed that adding metabolic information obtained from MRS to morphologic information obtained by MRI improved cancer localization and predicted prostate cancer aggressiveness [11,40]. But results have been mixed. A recently completed multiinstitutional study concluded that there was no incremental benefit for MRI–MRS compared with MRI alone in tumor [41]. Furthermore, the technology is complex and requires physics support to ensure the quality of data acquisition.

Cancer cells in general have elevated glycolytic activity. By measuring the relative conversion of pyruvate into lactate or alanine, the glycolysis rate of the cells can be quantified. After injection of hyperpolarized ^{13}C-labeled pyruvate, its metabolic products lactate and alanine can be quantitatively measured in a short time frame using a dynamic nuclear polarization technique [42,43]. In a transgenic murine prostate cancer model, prostate cancer showed significantly higher lactate content relative to normal tissues on MRI–MRS after injection of ^{13}C-pyruvate. The utility of this technical advance in prostate cancer detection has not been investigated in human trials. A phase 1 dose-escalation clinical trial of hyperpolarized ^{13}C-labeled pyruvate in prostate cancer patients is planned for 2009 [44].

DWI is based on the diffusion properties of water within tissue. Regions of prostate cancer show increased cell density and reduced apparent diffusion coefficient (ADC) relative to

normal prostate [45]. DWI has improved prostate cancer detection accuracy when combined with either MRI or MRS [46,47]. The biologic significance of diffusion, however, is unclear. Although the technology has shown high resolution, further validation in larger trials is required.

DCE-MRI measures tumor vascularity. After injecting a gadolinium chelate contrast agent, areas of hypervasculature such as prostate cancer show rapid enhancement and early washout of signal intensity. However, some prostate cancers are not detectable by this method because of low vascularity. Combining DCE-MRI with T2-weighted MRI improved prostate cancer detection and staging accuracy [48,49]. For DCE-MRI results to be comparable among studies from different institutions, a standardized technique and analytic tools need to be further developed.

The most appealing aspect of these MRI techniques is an ability to conduct a single comprehensive multiparametric MRI examination that integrates all data acquisitions relevant to cancer diagnosis, staging, and characterization. In this way, the overall diagnostic performance of MRI is expected to improve.

Roles of PET and SPECT—*As* noted earlier, the results of FDG PET in detecting prostate cancer have been mixed. In one report, FDG PET only detected one of 24 locally confined prostate cancers in untreated patients [15]. FDG PET was incapable of differentiating prostate cancer from benign hyperplasia [16] or detecting pelvic lymph node metastases [50]; other studies reported good accuracy in detecting primary or locally recurrent prostate cancer [17, 18]. As noted, the utility of PET and SPECT to detect locally confined prostate cancer will be improved by molecular probes with higher sensitivity and specificity. Early results are promising, with increasing interest in ^{18}F-choline for lesion detection [23].

Other investigational imaging methods—Raman spectroscopy is an optical imaging technique to measure the properties of molecules in the tissue. The technology has only been tested on tissue specimens in vitro; thus, its clinical utility is unclear. Another investigational imaging technique is smart-needle optical scattering spectroscopy to probe tissue of interest in real time to identify the presence of cancer. If validated, this technology potentially could reduce the number of biopsies required for prostate cancer diagnosis. It could be used in combination with other imaging techniques for biopsy guidance. A drawback of the technology is that it is invasive.

Problem 2: Risk Stratification, Initial Staging, Active Surveillance, and Focal Therapy

Clinical issues—Imaging as a predictive tool for patient outcomes can be successfully evaluated by comparing models that incorporate the outcome of imaging with models that do not to determine incremental predictive value. The TNM staging system describes the extent of the primary tumor, the spread of tumor to nearby lymph nodes and glands, and the presence or absence of distal metastasis. In the United States, emphasis is placed on the T and N stages for initial prostate cancer staging because relatively few patients present with metastatic disease. However, detecting extracapsular extension and locating the intraprostatic extent of disease are important issues in disease management.

The incidence of extracapsular extension, particularly early microscopic extracapsular extension, is unknown. Statistically, patients with pathologic extracapsular penetration tend to have relatively worse 10-year disease-free survival than patients with organ-confined disease; the significance of extracapsular extension requires investigation to determine what findings could be seen from the imaging perspective.

Although recent studies found that lymph node metastasis incidence dropped to less than 10%, these numbers do not reflect true incidence [51] because patients who receive neoadjuvant hormonal therapy or radiation, those with high-risk prostate cancer, and those who have positive nodes with extended nodal dissection are excluded from these numbers. So, although the percentage of patients with positive lymph nodes has declined, a significant number of patients have lymph node–positive cancer (about 39% in high-risk patients). Knowing the lymph node status helps to inform decisions on therapy, predict recurrence, and assess prognosis. Imaging has not been reliable in identifying lymph node disease; until recently, lymph node size was the only widely used method of ascertaining nodal disease. However, size criteria are limited in accuracy because of significant overlap between the size of normal and malignant nodes.

The major challenge to improving staging technology is the need for improved pathologic markers. These markers serve as reference standards to find imaging techniques that predict patient outcomes and help guide therapy. Other important issues remain, including knowing what patient cohorts benefit most from nodal imaging and staging and learning how the predictive value of an accurate technique affects therapeutic options.

Traditionally, active surveillance (formerly called “watchful waiting”) in prostate cancer was a consideration for older men and men with significant health problems. It was applied ad hoc with limited success. The patient would be diagnosed with stage A1 prostate cancer after transurethral resection of the prostate and there would be nonstandardized follow-up. Contemporary active surveillance includes low-risk patients with low tumor volumes, low PSA levels, and low Gleason scores. Follow-up is standardized, patients are well informed, and periodic repeat prostate biopsies are performed. Although active surveillance may not be advised for all men, in general, it is underused.

Although prostate cancer is mainly a multifocal disease, about 15–30% of patients have unifocal or unilateral disease. Localized, unifocal cancer of clinical significance is usually considered the prerequisite for successful focal therapy. However, unilateral (multifocal but all on one side) disease may make performing focal therapy easier. With multifocal cancer, a dominating index lesion probably drives progression; thus, the cancer may be considered biologically unifocal disease. Focal tumor ablation is feasible with low morbidity. The problem is localizing suitable tumors and monitoring tissue ablation. In addition to identifying patients who are candidates for focal therapy, imaging may play a role in identifying the target lesion. An important issue is relating the target delivery device to the imaging technique to deliver treatment to the target. Another critical issue with focal therapy is residual PSA, which makes posttherapy follow-up more challenging. The biologic potential of not treating missed secondary tumors and the role of adjuvant therapy are additional issues.

There is interest in combining active surveillance with other interventions (“active surveillance plus”), such as aggressive dietary and lifestyle modification, perhaps 5α-reductase inhibitor drugs, complementary alternative medicines, oral antiandrogens, and novel future agents. Active surveillance remains debated because of the lack of adequate modern randomized controlled trials and lack of robust imaging. There are clearly social and economic factors that impact the use of active surveillance. A major concern with current protocols of active surveillance remains the limited ability to closely and noninvasively monitor tumor progression within the prostate gland. Imaging is well poised to address this concern, and imaging integration may improve general acceptance of active surveillance in the management of low-risk disease.

Outcomes of local therapy, whether delivered up front or delayed after active surveillance, stand to improve with integration of imaging guidance. Standard-care therapeutic options

include radical prostatectomy, high-dose external beam radiotherapy, and brachytherapy, used alone or in combination. As a first step, recommending the most appropriate therapeutic technique depends on accurate staging and prognostication of disease. Ultimately, the objective of local therapy is to control disease with minimal collateral damage, thereby optimizing both cancer and toxicity outcomes. Because of the historical inability to accurately visualize the local extent of disease, all local therapeutic interventions were simply targeted to the prostate gland as a surrogate for cancer. This paradigm has invariably led to both over- and undertreatment of low-burden and locally extensive disease, respectively. In this manner, visualizing the location and extent of disease burden stands to more appropriately guide the execution of both surgery and radiation delivery. Visualizing disease that extends beyond the prostate gland could reduce the incidence of incomplete cancer resections and modify radiation delivery to include extraprostatic disease. Similarly, prostatic subsites of tumor burden can be focally selected for radiation dose intensification to improve cancer control and reduce unnecessary dose exposure to adjacent organs at risk of injury and subsequent toxicity. It is important to recognize that the radiation dose required to control microscopic disease is much lower than that required to control gross (dense) disease, and modulation of dose intensity on the basis of spatial distribution of disease burden has yet to be fully explored.

Focal ablative approaches do not deliver therapy to regions bearing microscopic disease within and around the prostate gland, which may impact cancer control. To address this concern, adjuvant therapies to focal ablation may be considered. In fact, immediate radiotherapy to presumed residual microscopic disease after prostatectomy has recently been shown to improve overall survival in patients with localized prostate cancer. Imaging techniques that could monitor progression of microscopic disease may obviate adjuvant local therapies altogether, restricting their use to the salvage of microscopic progression.

Role of imaging—The incremental predictive accuracy of imaging is of great interest in prostate cancer. However, before this can be determined, imaging technology must be more mature, stable, and standardized. MRI has been useful in identifying prostate cancer on the basis of reduced T2 signal intensity, increased choline, and decreased citrate and spermine [52]. Intraprostatic molecular imaging may identify areas of high tumor burden using techniques such as SPECT, MRS, and PET with choline. Improved tumor localization and lymph node staging can be achieved by combining molecular imaging with registration to anatomic CT and MR image sets [21]. In addition, validating intraprostatic biologic target volumes using in vivo fiducial markers has been shown to be feasible [53]. The correlated histopathology and marker placement system uniquely correlates pathology data for molecular image validation and discrete dose intensification, targeting tumor while sparing normal radiosensitive tissues (urethra, rectum, and neurovascular bundle). The correlated histopathology and marker placement system protocol showed clinical feasibility as a validation method for molecular imaging techniques such as SPECT-CT.

Techniques to directly integrate images in the offline and online guidance of local therapies are currently being developed and tested for technical performance. These include techniques for image display, registration, navigation, and online adaptation to movements and deformations that occur throughout the therapeutic intervention [54,55].

DCE-MRI is a powerful tool for visualizing the vascularity of solid tumors. DCE-MRI of the prostate gland has also provided useful information for prostate cancer detection and staging [56]. DWI uses diffusion constants to map the intraprostatic extent of cancer. The data are integrated into models to predict cancer localization [57].

CT and MRI are the main imaging technologies currently used for staging nodal disease. PET and FDG PET have also been evaluated for prostate cancer staging, but because prostate cancer

has variable accumulation of FDG, FDG PET is not widely used. However, FDG PET is gaining use for restaging [58]. Lymphotropic nanoparticle-enhanced imaging, a promising technique for malignant nodal evaluation, is highly accurate for nodal staging in patients with various primary cancers [59]. It evaluates nodal macrophage function and does not rely on nodal size to detect metastatic disease.

The software module MRProstateCare (Image Guided Prostate Therapy Core) was created for use with Slicer (open-source software), a computerized surgical navigation platform to help plan, control, and direct prostate biopsies [54,55]. MrBot (URobotics), a robot, was created to provide imaging-guided access to the prostate gland [60]. The robot is customized for transperineal needle insertion and designed to be compatible with MRI. It can accommodate various needle drivers for different percutaneous interventions, such as biopsy, thermal ablation, or brachytherapy.

TRUS-guided radiofrequency ablation involves ultrasound monitoring of the thermoablative technique. Several problems are associated with radiofrequency ablation in the prostate. The distributed energy is prone to variation because of heat sink by vasculature and is diffused over a wide area, making the temperature of adjacent organs difficult to control; and heating is slow, often resulting in insufficient apex ablation. There is also poor geometric correlation between the target lesion and energy input. Additionally, the procedure is difficult to monitor intraoperatively. These issues reduce the viability of radiofrequency ablation as an appropriate technique for definitive prostate cancer treatment; however, in later stages of the disease when targeting and monitoring are less critical, radiofrequency ablation may be useful as a palliative procedure.

High-intensity focused ultrasound (HIFU) delivers heat energy in focused ultrasound pulses. One advantage of HIFU is that it facilitates focal prostate ablation therapy without requiring direct tissue invasion and resultant direct damage to surrounding structures [61]. Another advantage of HIFU is that tissue heating is very rapid, causing immediate coagulation and necrosis. Full prostate ablation with HIFU is relatively straightforward to implement but associated with significant morbidity. Focal HIFU was attempted early on, and has been found to be feasible with low morbidity. Imaging-guided HIFU ablation allows the process to be monitored using ultrasound to detect lesions. MR-guided HIFU systems allow use of real-time MR thermometry to effectively optimize heat deposition. However, there are challenges with measuring efficacy because of persisting PSA elevation after treatment; also complicating treatment is variability in lesion size and location.

Problem 3: D_0 Disease: Role of Imaging in Disease Management

Clinical issues—After definitive local radical prostatectomy or radiation therapy, a rise in serum PSA, also known as biochemical recurrence, is usually the first indication of cancer recurrence. Biochemical recurrence occurs in 20–40% of patients within 10 years of definitive prostate cancer therapy [62–64]. It often precedes clinically detectable recurrence by years [62]. However, disease progression within the group of patients with rising PSA is heterogeneous; only 30% eventually progress to clinical disease [65,66].

Biochemical recurrence after radical prostatectomy—After radical prostatectomy, serum PSA should fall to undetectable levels (< 0.1 ng/mL) within 3–4 weeks, as measured by standard immunoassays. However, the definition of biochemical recurrence in the literature varies from a cutoff value of 0.2–0.5 ng/mL for a single measurement or two consecutive values exceeding 0.2 or 0.4 ng/mL [66–68]. A PSA level of 0.4 ng/mL or greater is associated most strongly with PSA progression or disease progression, and is considered most meaningful to define biochemical recurrence [68,69], which can occur years after radical prostatectomy. For example, about 20% of PSA recurrences happened 5 or more years after radical prostatectomy,

suggesting the necessity of prolonged PSA follow-up. Current clinical practice monitors patients for PSA levels every 3 months in year 1, every 6 months for years 2–5, and annually thereafter [70]. The time from biochemical recurrence to metastases depends on preoperative pathologic stage, Gleason score, and postoperative PSA doubling time [65,66]. A shorter PSA doubling time (< 10 months) is the most powerful predictor for disease progression [65,66]. In rare cases, patients may develop distant metastatic disease after radical prostatectomy without an elevated PSA level [71].

Biochemical recurrence after radiation therapy—After radiation, PSA levels decrease slowly and may never reach undetectable levels. The time to reach nadir after radiation therapy may be months or even years, depending on factors such as radiation dose, prostate size, and pretreatment PSA level [72]. Defining biochemical recurrence after radiation therapy is more complex. The American Society for Therapeutic Radiology and Oncology (ASTRO) recommended in 1997 that the definition of biochemical recurrence be three consecutive PSA increases after PSA nadir has been reached, with the date of failure backdated to the mid point between the nadir and the first of these three increases. The definition has been criticized for biases caused by backdating. In 2006, a revised definition known as the Phoenix definition ([Radiation Therapy Oncology Group] RTOG-ASTRO) was devised, which defines biochemical recurrence as an absolute increase of 2 ng/mL or greater above the nadir with no backdating. This definition has higher sensitivity and specificity in predicting clinical failure after external radiation therapy and brachytherapy compared with the original ASTRO definition [73]. However, as with radical prostatectomy, clinical failure after radiation therapy can be better predicted by PSA doubling time than by absolute PSA levels [74].

Role of imaging—When a rise in PSA is observed in patients after radical prostatectomy or radiation therapy, the next step is to determine whether cancer recurs locally or in distant organs. Accurately delineating the location and the extent of cancer is critical in selecting appropriate treatment, that is, local salvage therapy or systemic therapy. The primary role of imaging in this setting is to help distinguish local recurrence from distant metastatic disease.

PET and SPECT—As noted, prostate cancer grows slowly and is rarely FDG avid. Consequently, FDG is not an optimal PET tracer in assessing recurrence, although FDG PET detected local or systemic disease in 31% of 91 patients with PSA relapse referred for this test [75]. However, recent studies suggested a high sensitivity with ^{11}C-acetate and ^{11}C-choline PET in detecting local recurrence and regional lymph node involvement after radical prostatectomy and radiation therapy [5,6,8,76]. The very short half-life of ^{11}C (20 minutes) may make it less practical than ^{18}F as a PET label because of logistic issues. Recently, a novel PET tracer, anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (anti-^{18}F-FACBC), a synthetic L-leucine analog, was evaluated in six patients with recurrent prostate cancer. Anti-^{18}F-FACBC showed very low renal excretion; it showed intensive uptake in lymph node metastases and recurrent prostate bed cancer and was found superior to ProstaScint (^{111}In-capromab pendetide, Cytogen) SPECT in detecting lymph nodes [77].

ProstaScint SPECT uses a murine monoclonal antibody that reacts against prostate-specific membrane antigen (PSMA), which is overexpressed in prostate cancer compared with normal tissues. ProstaScint SPECT has been used to detect lymph node metastases and recurrent prostate cancer after radical prostatectomy or radiation therapy. However, its sensitivity and specificity in detecting recurrent disease are suboptimal [78]. Other novel SPECT tracers currently in preclinical and early clinical development include small-molecule PSMA inhibitors [79–81]. These molecules selectively accumulated in PSMA-positive human prostate cancer xenografts. Also, a PMSA inhibitor, MIP-1095 (Molecular Insight Pharmaceuticals), accumulated in metastatic prostate cancer in a human study [82]; its utility requires further validation in larger clinical studies.

Bone is the most common site for prostate cancer metastasis. Radionuclide bone scanning is a sensitive method to assess skeleton metastases. Currently, ^{99m}Tc-MDP planar bone scintigraphy is the standard bone imaging technique. However, accurate detection of bone metastases may be improved by SPECT with rotating 3D acquisition [83]. Studies also suggested that ^{18}F-NaF PET is superior to ^{99m}Tc-MDP planar scintigraphy or SPECT in detecting skeleton metastases from prostate cancer [84]; ^{18}F-NaF PET detected more lesions and showed higher contrast between malignant and normal bone. Unlike ^{99m}Tc-MDP scanning, which has a low detection rate for lesions in the spine and pelvis, the detection efficiency of ^{18}F-NaF PET is independent of anatomic lesion localization [85]. The very high resolution and target-to-background contrast of ^{18}F-NaF PET can potentially reduce its specificity; however, correlating PET with CT findings substantially helps to differentiate malignant from benign lesions [84].

MRI and CT—Although MRI is widely used in assessing local recurrence after prostatectomy and/or radiation therapy, interpretation can be confounded due to tissue changes such as glandular atrophy and fibrosis induced by radiation, the presence of radiotherapy seeds, and scarring and the presence of surgical clips. Because of reports that MRI and CT detection of nodal recurrence is limited by low sensitivity (~ 36%) and poor spatial resolution (~ 8 mm) for MRI, some centers consider MRI and CT to be of benefit only to high-risk patients with PSA levels > 20 ng/mL. Consequently, improved functional or contrast-enhanced imaging methods such as MRS, DWI, and DCE-MRI are being explored [86,87]. In a recent study, MRI with a superparamagnetic nanoparticle (monocrystalline iron oxide, Combidex, Advanced Magnetics) showed higher accuracy than conventional MRI in detecting pelvic lymph node metastases. Lymph node metastases as small as 2 mm in diameter were detected using this technique [88].

Problem 4: Assessing the Response to Therapy and the Role of Imaging in Prostate Cancer Drug Development and Management of Advanced Disease

Clinical issues—Despite an array of imaging techniques, assessing prostate cancer with imaging remains challenging in many important clinical situations, including detecting recurrent disease in men with biochemical failure after definitive therapy. Advances in imaging technology, such as the development of hybrid imaging systems (e.g., PET/CT and SPECT-CT), which depict both structural and metabolic information, have contributed to more accurate imaging assessment by reducing false-positive and false-negative findings. Initial interest was also generated by the use of tracers such as radiolabeled monoclonal antibodies to PSMA; however, results are mixed. The patient populations studied were varied, the imaging protocols required multiday imaging sessions, and image interpretation was challenging due to nonspecific tracer accumulation and delayed clearance.

Various clinical and pathologic parameters, including surgical Gleason score, pain, time to PSA relapse after primary treatment, and PSA doubling time, have been used to predict the probability of distant metastasis development in prostate cancer patients with rising serum PSA. PSA doubling time appears to be the most important predictor of distant metastasis development and prostate cancer–specific mortality [89–91].

As previously indicated, prostate cancer is the most commonly diagnosed lethal malignancy and the second leading cause of cancer mortality in American men. Although high response rates are achieved using androgen blockade as first-line therapy, most men progress toward hormone-refractory prostate cancer. Systemic chemotherapies have been shown to improve clinical outcome in hormone-refractory prostate cancer patients; however, such thrapies are not curative. Advanced prostate cancer has a particular propensity to metastasize to lymph nodes and bones, where it produces predominantly osteoblastic lesions and local bone

formation. The tropism for bone is thought to be due in part to specific interactions between prostate cancer cells and cells present in the bone environment, particularly bone marrow endothelial cells and osteoblasts [92]. Such interactions involve numerous signaling pathways that could serve as targets for new therapeutic agents. For example, agents that block the activity of growth factors implicated in advanced prostate cancer development (e.g., ET-1 or vascular endothelial growth factor) are being tested for their effect on bone metastases. Other strategies involve the development of PHSCN, a synthetic peptide analog that acts to decrease fibronectin-mediated basement membrane invasion and inhibition of matrix metalloproteinases.

Bone metastasis significantly affects quality of life through symptoms such as bone pain, pathologic fractures, anemia, and nerve impingement; incidence varies from 5% to 27% [92]. With the advent of PSA testing and earlier detection, few patients (< 5%) present with metastases at the time of diagnosis. However, despite early detection and intervention, disease in many men will still progress to bone metastasis. In addition to its negative effects on quality of life, the development of bone metastases also significantly affects survival—median survival time for men with metastatic hormone-resistant disease is less than 12 months [92].

Thus, detection of bone metastases is clinically important because the onset of bone metastasis often warrants initiation of chemotherapy and/or bone-targeted therapy. Response Evaluation Criteria in Solid Tumors (RECIST), the published rules that define when cancer patients respond, remain stable, or progress during treatments, considers bone metastasis a nontarget lesion. Therefore, RECIST is not useful in measuring antitumor effects. Technology that could reliably and accurately measure antitumor effects would provide a significant advance in prostate cancer because it would facilitate timely evaluation of new agents in clinical trials.

Role of imaging—The utility of molecular imaging for clinical medicine includes early detection of changes occurring in tissue, enabling changes in individual patient management in real time and facilitating drug development. A promising new imaging technique, ^{18}F-fluorodihydrotestosterone (FDHT) PET, may help to define the exact role of androgen receptor imaging in prostate cancer, including predicting and assessing response to hormonal ablation therapy. In patients with advanced metastatic prostate cancer, abnormal localization of FDHT was seen in most metastatic lesions but only in a few primary tumors, and FDHT uptake in metastatic lesions decreased after hormonal ablation therapy with flutamide [93].

Animal and preliminary clinical studies have shown that FDG PET may be useful in evaluating advanced disease in patients with high Gleason scores and serum PSA levels, to detect active osseous and soft-tissue metastases, and to assess response after androgen ablation and treatment with novel chemotherapies [94–96].

Three-dimensional volumetric CT is an effective method for localizing prostatic structures for radiation therapy treatment planning in prostate cancer patients because it eliminates the need for an invasive procedure and the related side effects [97]. Three-dimensional volumetric CT may also play a role in measuring response to therapy.

Early data suggest that the response of prostate cancer bone metastases to treatment can be quantitatively assessed using DWI, with functional diffusion mapping [98] having greater utility for lytic than for sclerotic disease. The functional diffusion mapping biomarker is based on MRI diffusion maps used to quantify spatially distinct therapy-induced changes in the diffusion of water within tumor tissue. Initial studies verified the capability of functional diffusion mapping as a biomarker for detecting bone cancer treatment efficacy, thus warranting further clinical evaluation [99].

Whole-body planar bone scanning using ^{99m}Tc-MDP is the established clinical standard for imaging bone metastasis. For SPECT of the bone, metastable ^{99m}Tc is tagged onto a phosphonate compound such as MDP to generate ^{99m}Tc-MDP, which selectively concentrates in the bone. For scintigraphy, the labeled compound is administered IV and SPECT is subsequently performed after a suitable time period. Imaging with ^{99m}Tc-MDP is the initial method of choice for detecting skeletal metastases in cancer patients. Compared with other imaging techniques such as planar scintigraphy, SPECT provides detailed information about the anatomy and physiologic state of the bone and has been used to monitor bone metastasis in prostate cancers.

Early metastases may be missed with ^{99m}Tc-MDP uptake because this technique relies on the osteoblastic reaction rather than the actual tumor being detected [100]; ^{18}F-NaF PET has been shown to have a high sensitivity for detecting bone metastases due to increased ^{18}F-NaF uptake in malignant bone lesions. Taking advantage of favorable characteristics of ^{18}F-NaF and better performance of PET, ^{18}F-NaF PET has been reported to be more sensitive for detecting bone metastases than ^{99m}Tc-MDP bone scanning. In light of the increased sensitivity of ^{18}F-NaF PET and the advent of novel therapies to treat bone metastases, it is possible that planar bone scanning should be replaced with PET, including FDG PET, in which there is promising data, as well as ^{18}F-NaF PET.

Summary

The overall goal of this workshop was to bring together multidisciplinary scientists to consider new or improved imaging strategies that could help address four major challenges in prostate cancer treatment and management—diagnostic accuracy; risk stratification, particularly for application of active surveillance and focal therapy; D_0 disease; and assessing response to treatment—as well as methods for evaluating these strategies in clinical settings. A discussion of these four clinical challenges was preceded by a summary of prostate cancer incidence and mortality; the current role of imaging across the spectrum of early through metastatic prostate cancer; and the overarching issue in prostate cancer, which is distinguishing lethal from nonlethal disease. The discussions then focused on the specific clinical issues and the role of imaging in addressing the four defined clinical management problems. These discussions and accompanying recommendations are summarized in the text and Tables 1–4.

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TABLE 1

Current and Future Imaging Techniques for Detecting, Staging, and Managing Prostate Cancer

Disease Stage	Available Clinical and Laboratory Assessment Methods	Currently Used Imaging Techniques	Pros and Cons, Utility	Future Opportunities for Imaging Technology Development
Diagnosis and detection	PSA, DRE	TRUS for biopsy guidance	Most cancers cannot be seen by current TRUS techniques	TRUS with microbubble contrast agents, color Doppler imaging MRI examination before biopsy Development of imaging-guidance techniques for biopsy Smart-needle optical imaging
Localized, organ-confined cancer	PSA, Gleason score, T stage, tumor burden as represented by biopsy core cancer involvement	TRUS (with or without MRI) for conventional BT guidance	Poor spatial representation of disease	Advanced ultrasound for tumor localization and therapy guidance, multiparametric MRI depicting cancer boundaries
Extracapsular extension		CT (with or without MRI) for conventional RT treatment planning	Patient-specific representation of prostate gland location and geometry	USPIO MRI LN contrast agent
After radical prostatectomy RT local recurrence (D_0) Regional (lymph nodes, pelvis) Advanced metastatic disease	PSA, histopathology	MRI ProstaScint[a] using SPECT	Limited diagnostic accuracy (poor sensitivity and specificity)	^{11}C Choline/acetate, (^{13}C hyperpolarized) anti-^{18}F FACBC, androgen receptor probe, radiolabeled PSMA antibodies, FLT, possibly ^{18}F-NaF
		Bone scan		^{18}F-NaF
Metastatic disease	PSA>20, bone pain	^{99m}Tc-MDP bone scan	Sensitive, but poor spatial resolution	
			Visceral disease, limited specificity	Radiolabeled PSMA antibodies, FLT
		CT staging	Not dependent on bone remodeling by lesion (i.e., shows more lesions)	^{11}C choline/acetate (^{13}C hyperpolarized); anti-^{18}F-FACBC, androgen receptor probe

Note—PSA = prostate-specific antigen, DRE = digital rectal examination, TRUS = transrectal ultrasound, RP = radical prostatectomy, RT = radiation therapy, BT = brachytherapy, D_0 = PSA relapse after RT or RP, USPIO = ultrasmall superparamagnetic iron oxide, LN = lymphotropic nanoparticle, anti-^{18}F-FACBC = anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, PSMA = prostate-specific membrane antigen, FLT = ^{18}F-3′-fluoro-3′-deoxy-L-thymidine, ^{18}F-NaF = ^{18}F sodium fluoride, MDP = methylene diphosphonate.

[a] Indium-111-capromab pendetide manufactured by Cytogen.

TABLE 2

Prostate Cancer Risk Definitions, Incidence, Screening Parameters, Treatments, and Imaging Use

Risk Category[a]	Incidence	Definition	Screening Parameters	Disease Management/Treatments	Treatment Trends[a]	Imaging Techniques Used to Monitor and Stage[b]
Normal	NA	Age≥55y, normal PSA and DRE	Regular PSA and/or DRE screening	None	None	None
Elevated	NA	PSA>4 ng/mL, negative biopsy or HGPIN	Active surveillance to differentiate BPH	Periodic repeat biopsy, dietary and lifestyle modification	NA	TRUS, MRI
Low	34	PSA ≤ 10 ng/mL, Gleason score < 6, and stage T1–T2a	Confirmed cancer, tumor confined to prostate, no extracapsular penetration	Possibly neoadjuvant hormonal therapy or focal treatment	Watchful waiting (8.9), brachytherapy (18.4) external-beam RT (6.8), prostatectomy (52), ADT (14.2)	CT (10.4), MRI (0.9), bone scanning (18.6)
Intermediate	36	PSA 10.1–20 ng/mL, Gleason score 7, and stage T2b	Confirmed cancer, tumor confined to prostate, no extracapsular penetration	Radiation therapy (brachytherapy, external-beam irradiation), RP	Watchful waiting (4.5), brachytherapy (11.8), external-beam RT (19.1), prostatectomy (45), ADT (19.7)	CT (15.3), MRI (1.4), bone scanning (50.9)
High	30	PSA > 20 ng/mL, Gleason score 8–10, and stage T3–T4	TMN, extracapsular extension, local lymph nodes, seminal vesicles, pelvic structures	Same as for intermediate risk plus pelvic dissection, increased radiation field, ADT	Watchful waiting (4.8), brachytherapy (2.4), external-beam RT (23), prostatectomy (22.7), ADT (48.2)	CT (25), MRI (2.5), bone scanning (69)
Relapse or recurrence after definitive therapy	30–50% of previously treated patients	Any PSA after nadir (RP vs RT definitions distinct)	PSA doubling time	ADT, salvage RT, RP; if moving toward advanced disease, treatment and techniques are indicated below	No definitive data of overall trends for ADT; possibly adjuvant, cytotoxics, etc.	Multiple techniques used: TRUS, CT, MRI, MRS, DWI, DCE-MRI, bone scanning, ProstaScint[d], FDG PET; ^{18}F-NaF, FLT, FDHT, etc.; no definitive data on trends for extent of use; radiolabeled choline, acetate
Advanced disease, bone metastases[c]	NA	Visceral, axial, or appendicular skeletal lesions	Pain, markedly elevated PSA, bone scanning-detected lesions	ADT, bisphosphonates, chemotherapy, RT, bone-targeted radioisotopes	FDA-approved therapies (e.g., docetaxel) vs investigational drugs	Multiple techniques used: TRUS, CT, MRI, MRS, DWI, DCE-MRI, bone scanning, ProstaScint[d], FDG PET; ^{18}F-NaF, FLT, FDHT, etc.; no definitive data on trends for extent of use; radiolabeled choline, acetate

Note—Numbers in parentheses are percentages. PSA = prostate-specific antigen, DRE = digital rectal examination, HGPIN = high-grade prostatic intraepithelial neoplasia, BPH = benign prostatic hyperplasia, TRUS = transrectal ultrasound, RP = radical prostatectomy, RT = radiation therapy, ADT = androgen deprivation therapy, MRS = MR spectroscopy, DWI = diffusion-weighted MRI, DCE-MRI = dynamic contrast-enhanced MRI, FDG PET = ^{18}fluoro-2-deoxyglucose PET, ^{18}F-NaF = ^{18}F sodium fluoride, FLT = ^{18}F-3′-fluoro-3′-deoxy-L-thymidine, FDHT = ^{18}F-fluorodihydrotestosterone, N A = not available.

[a] Based on 1999–2001 data; adapted from [101].

[b] Data are based on information available through 1997. Since that time, there has been increased use of MRI. Adapted from [102].

[c] Median actuarial time to metastases = 8 years from biochemical recurrence and median time to death after metastases detected = 5 years [66].

[d] ProstaScint: ^{111}In-capromab pendetide manufactured by Cytogen.

TABLE 3
Recommendations for Future Work Directed at Challenges in Prostate Cancer Treatment and Patient Management

Challenge	Recommendation	Imaging Methods to Develop or Improve
Diagnostic accuracy	Supplement PSA screening to increase accuracy of diagnosis, develop more sensitive serum and/or tissue biomarkers, consider cancer imaging before biopsy, move from 2D to 3D imaging and/or histopathologic validation, develop new imaging techniques that depict disease and guide tissue biopsy	Contrast-enhanced ultrasound, ultrasound spectroscopy, MRS, DWI, DCE-MRI, molecular probes with SPECT/PET, Raman spectroscopy, smart needle
Risk stratification, initial staging, active surveillance, focal therapy	Imaging-based monitoring during active surveillance (with or without other interventions such as dietary and lifestyle modifications, 5α-reductase inhibitors, complementary alternative medicines, oral antiandrogens, or chemoprevention), imaging guidance of focal therapies	MRI, MRS, SPECT or CT, CHAMPS, DCE-MRI, DWI, LNMRI, MRProstateCare[a] and Slicer[b], MrBot[c], HIFU
D_0 disease	Accurately determine location and extent (local or distant) of cancer recurrence, assist in treatment planning	PET and SPECT with ^{11}C tracers and/or rotating 3D acquisition, anti-^{18}F-FACBC, ^{99m}Tc-MDP, ^{18}F-NaF PET, MRI, MRI with Combidex[d]
Assessing response to therapy and/or role of imaging in drug development and advanced disease management	Develop technology to reliably and accurately measure antitumor effects via change in metastatic bone images, conduct clinical trials to evaluate new treatment and new agents and qualify new biomarkers	FDHT PET, FDG PET, 3D volumetric CT, fDM, ^{99m}Tc-MDP/SPECT, ^{18}F-NaF PET, DCE-MRI, DWI, HIFU, and MR-guided HIFU

Note—PSA = prostate-specific antigen, MRS = MR spectroscopy, DWI = diffusion-weighted MRI, DCE-MRI = dynamic contrast-enhanced MRI, CHAMPS = correlated histopathology and marker placement system, LNMRI = lymphotrophic nanoparticle–enhanced MRI, HIFU = high-intensity focused ultrasound, D_0 = PSA relapse after radiation therapy or radical prostatectomy, anti-^{18}F-FACBC = anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid, MDP = methylene diphosphonate, ^{18}F-NaF = ^{18}F sodium fluoride, FDHT = ^{18}F-fluorodihydrotestosterone, fDM = functional diffusion mapping.

[a] MRProstateCare: software module manufactured by Image Guided Prostate Therapy Core.

[b] Slicer surgical navigator platform is open-source software.

[c] MrBot robot for imaging-guided access to the prostate manufactured by URobotics.

[d] Combidex: monocrystalline iron oxide manufactured by Advanced Magnetics.

TABLE 4

Example Clinical Trial Design Opportunities for Qualifying Novel Imaging Techniques and Probes in Prostate Cancer

Imaging Probe or Technology	Clinical Setting	End Point/Comparator	Value Proposition
^{18}F-NaF	Bone metastatic disease	Correlation with treatment response and/or survival, ^{99m}Tc-MDP scan	Simpler preparation, more sensitive
MRI (T2-weighted, DCE-MRI, DWI, MRS)	All localized or locally recurrent disease	Repeat biopsy and/or PSA outcomes, disease control outcomes, pathological outcomes	Identification of indolent vs aggressive lesions, active surveillance more acceptable to patients
	Localized disease—androgen deprivation therapy before RP or RT	K^{trans} response to therapy, histopathology, conventional MRI, TRUS	Prediction of antiangiogenic therapy performance in other stages and other cancer types
DWI, FDG PET, FDHT, FLT, or other tracers	Bone and lymph node metastatic disease	Correlation with treatment response and/or survival; ^{99m}Tc-MDP scanning	Assess relative performance of probes to cytotoxic vs androgen targeting agents, evaluate standards for lesion enumeration, SUV quantitation, etc.

Note—^{18}F-NAF = ^{18}F sodium fluoride, MDP = methylene diphosphonate, MRS = MR spectroscopy, DWI = diffusion-weighted MRI, DCE-MRI = dynamic contrast-enhanced MRI, RP = radical prostatectomy, RT = radiation therapy, PSA = prostate-specific antigen, K^{trans} = volume transfer constant, TRUS = transrectal ultrasound, FDG PET = ^{18}fluoro-2-deoxyglucose PET, FLT = ^{18}F-3′-fluoro-3′-deoxy-L-thymidine, FDHT = ^{18}F-fluorodihydrotestosterone, SUV = standardized uptake value.