Prostate cancer is often associated with metastases to bone and/or soft tissue. The progression to metastatic castrate-resistant prostate cancer is a seminal event in disease progression affecting treatment decisions. A multidisciplinary group was convened to review the currently available imaging guidelines for metastatic disease in prostate cancer and found no consensus on eligibility criteria, type of imaging modality, and the frequency of scanning for detecting metastatic disease. The aim of this review was to present the recommendations from the group to identify optimal strategies for early identification of metastases in patients with prostate cancer.


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important therapeutic implications when metastases are found radiographically. With initial prostate cancer staging, definitive local therapy with surgery or radiation might not be pursued in patients found to have metastatic disease. After local therapy, biochemically recurrent prostate cancer is often treated with intermittent androgen deprivation therapy (ADT), as survival outcomes were not different when compared with continuous ADT. Therefore, different approaches to ADT should be pursued in these distinct clinical states. Finally, there is no U.S. Food and Drug Administration–approved therapy for M0 CRPC, yet recent advances in mCRPC have led to regulatory approval of multiple agents carrying low toxicity, yet significant survival or supportive care benefits.

**REVIEW OF CURRENT GUIDELINES AND RELEVANT CLINICAL VALIDATION STUDIES**

A literature search was conducted using the following terms: prostate cancer, guidelines, metastasis, and imaging. Relevant US and European clinical practice guidelines were reviewed, and recommendations of scanning for metastatic disease in patients with prostate cancer were summarized on the basis of patient type, imaging criteria, imaging modality, and frequency. A review by the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group of relevant guidelines found no consensus on optimal indications or methods for imaging (eg, PSA level, PSA kinetics, Gleason score, or clinical T stage). There was also a lack of consensus on when to initiate imaging for metastases and frequency of testing in clinical practice (Table 1). Evidence-based recommendations focus mainly on primary prostate cancer staging and not on follow-up after biochemical recurrence or hormonally refractive disease. For example, the Prostate Cancer Working Group 2 recommendation, intended for patients with CRPC on clinical trials, focuses on patients with known pre-existing mCRPC and does not give guidelines for M0 CRPC. Most of the guidelines do not have specific recommendations for assessing soft tissue or lymph node metastases. Frequency of assessment is suggested for prostate cancer clinical trials only, which might not be suitable for routine clinical practice. For assessing bone metastasis, radionuclide bone scan alone is still considered to be the standard of care, although other modalities not commented on might provide more accurate early assessment. In addition, the most recent published American Urological Association guidelines for early detection of prostate cancer and the management of CRPC made no recommendations on appropriate timing of imaging in M0 patients to monitor disease progression. Because decision making for the approval of imaging testing and reimbursement by insurance companies is often based on those guidelines and varies among health plans, as a result, a significant number of patients with prostate cancer did not receive appropriate imaging scans for metastatic disease.

Findings from clinical validation studies demonstrate a lack of consensus on the standard of care for detection of metastatic disease in prostate cancer. A large UK retrospective study showed PSA level and Gleason score were both independent predictors of bone scan positivity and their predictive value was additive. The authors concluded that bone scans can be omitted in newly diagnosed patients with a PSA level <20 ng/mL and Gleason score ≤6, as these criteria have a negative predictive value for bone metastases of 100%. These results validate the guidelines issued by the European Association of Urology and American Urological Association. Another study showed reasonably low incidences of bone metastases in newly diagnosed asymptomatic patients with a PSA level <20 ng/mL and Gleason score ≤6; suggesting a bone scan is not necessary as a routine examination at the initial staging of prostate cancer. However, other studies found that approximately 25% of patients with bone metastasis had a PSA level ≤20 ng/mL and Gleason score ≤7, and bone scans might be necessary in patients with a PSA level between 10 and 20 ng/mL.

In contrast, in one study, approximately 25% of bone metastases after radical prostatectomy occurred at a PSA level <10 ng/mL in hormone-naive men in whom bone metastases developed at a mean of 6 years postoperatively. Because metastasis occurred at a low PSA level before symptoms, it was suggested that patients with biochemical progression need to be managed with regular bone scans to detect metastasis even if PSA is low. In another study, patients on ADT after biochemical recurrence following radical prostatectomy were found to have increased bone scan positivity at lower PSA values or longer PSADT compared with hormone-naive patients. However, other trials using a novel classification and regression tree with higher accuracy than multiple guidelines determined that baseline bone scans should be considered in newly diagnosed patients with a biopsy Gleason score >7 or with a PSA level >10 ng/mL and palpable disease (cT2/T3). The authors believe that the implementation of classification and regression tree in clinical practice can help avoid over- or under-scanning of metastases in patients with newly diagnosed prostate cancer.

In summary, there is disparity and a lack of agreement in the current clinical practice guidelines and available literature on patient selection, imaging modality, and timing of scanning for metastatic disease, which represents a key transition that influences the treatment decision-making process. In fact, high frequency of asymptomatic metastasis found in patients thought to have M0 CRPC in a screening failure trial (ENTHUSE M0) highlights the urgent need to improve imaging strategies for metastatic disease.
<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Patient Type</th>
<th>Imaging for Bone Mets</th>
<th>Imaging for Soft Tissue Mets</th>
<th>Imaging Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWG2(^7)</td>
<td>2007</td>
<td>Trial eligibility for metastatic CRPC or baseline diagnosis</td>
<td>Progression = appearance of 2 or more new lesions</td>
<td>Bone scan; CT/MRI to confirm ambiguous lesions</td>
<td>Only report changes in lymph nodes ≥2 cm in diameter at baseline</td>
</tr>
<tr>
<td>ACR(^{17})</td>
<td>2010</td>
<td>Diagnosis and staging</td>
<td>PSA ≥20 ng/mL or poorly differentiated primary tumors Back pain and partially collapsed vertebra on radiography</td>
<td>Bone scan</td>
<td>CT</td>
</tr>
<tr>
<td>ESMO(^{18})</td>
<td>2010</td>
<td>Diagnosis and staging</td>
<td>PSA ≥15 ng/mL, Gleason ≥7, or ≥T3</td>
<td>Bone scan; pelvis CT/MRI</td>
<td>Every 12 wk in clinical trials</td>
</tr>
<tr>
<td>AUA(^{19,20})</td>
<td>2007 Update 2011 Annual meeting</td>
<td>Diagnosis and staging</td>
<td>PSA &gt;20 ng/mL or Gleason &gt;7</td>
<td>Bone scan; CT</td>
<td></td>
</tr>
<tr>
<td>AUA(^{19,20})</td>
<td>2007 Update 2011 Annual meeting</td>
<td>Diagnosis and staging</td>
<td>PSA &gt;20 ng/mL, T2c, or Gleason ≥8</td>
<td>Bone scan; CT</td>
<td></td>
</tr>
<tr>
<td>EAU(^{21})</td>
<td>2012</td>
<td>Diagnosis and staging</td>
<td>PSA &gt;20 ng/mL</td>
<td>Bone scan; PET/CT or MRI for equivocal cases</td>
<td></td>
</tr>
<tr>
<td>EAU(^{21})</td>
<td>2012</td>
<td>Follow-up after treatment with curative intent</td>
<td>PSA &gt;20 ng/mL or patient has bone pain Symptomatic with unstable PSA</td>
<td>Bone scan; pelvic CT/MRI</td>
<td>Symptoms suggested the possibility of soft tissue mets</td>
</tr>
<tr>
<td>EAU(^{21})</td>
<td>2012</td>
<td>Follow-up after hormonal treatment</td>
<td>PSA &gt;20 ng/mL or PSA velocity &gt;20 ng/mL/y</td>
<td>Bone scan</td>
<td>X-ray; ultrasound; CT/MRI</td>
</tr>
<tr>
<td>EAU(^{21})</td>
<td>2012</td>
<td>Diagnosis for PSA relapse after RP</td>
<td>PSA &gt;20 ng/mL or PSA velocity &gt;20 ng/mL/y</td>
<td>Bone scan; CT</td>
<td></td>
</tr>
<tr>
<td>NCCN(^{22})</td>
<td>2013</td>
<td>Initial clinical assessment and staging</td>
<td>T1 with PSA &gt;20 ng/mL; T2 with PSA &gt;10; Gleason ≥8; T3, T4 or symptomatic</td>
<td>Bone scan</td>
<td>T3 or T4; T1 or T2 and nomogram indicated probability of lymph node involvement &gt;20%</td>
</tr>
<tr>
<td>NCCN(^{22})</td>
<td>2013</td>
<td>Postradical prostatectomy recurrence</td>
<td>Symptomatic or PSA increasing rapidly</td>
<td>Bone scan</td>
<td>Pelvic CT/MRI</td>
</tr>
<tr>
<td>NCCN(^{22})</td>
<td>2013</td>
<td>Systemic therapy for metastatic CRPC</td>
<td>Should be monitored closely</td>
<td>Bone scan; CT</td>
<td></td>
</tr>
</tbody>
</table>

ACR, American College of Radiology; AUA, American Urological Association; CRPC, castration-resistant prostate cancer; CT, computed tomography; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NA, not addressed; NCCN, National Comprehensive Cancer Network; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PET, positron emission tomography; PSA, prostate-specific antigen; RP, radical prostatectomy; SPECT, single photon emission computed tomography.
NEW IMAGING STRATEGIES

Although conventional bone scintigraphy using technetium 99 (99mTc) is sensitive for osteogenic activity and can assess the entire skeleton quickly, it has several major limitations. Bone scintigraphy images the secondary effect of the tumor on the skeleton (osteoblastic reaction) rather than tumor proliferation itself. False positives occur from trauma and various other noncancerous sources. Microscopic infiltrations are not detected, and osteolytic lesions are poorly detected, limiting sensitivity and specificity. A “flare” phenomenon can confound response assessment, in which uptake initially increases after chemotherapy or hormone therapy as bone turnover increases as part of the healing process.

Other imaging modalities, such as plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT), might be needed to clarify equivocal lesions. PET/CT scans using tracers, such as 18F-Sodium Fluoride (NaF) or 18F-choline, showed sensitivity and specificity values superior to bone scintigraphy and have been frequently incorporated into guidelines in recent years. PET/CT is a promising substitute for conventional bone scans. NaF is a small molecule that has a higher affinity for bone and is rapidly cleared, allowing for early imaging, and it is commercially available and included on the United States Pharmacopeial Convention chemicals list. PET/CT has many advantages over a 2-dimensional planar imaging examination such as 99mTc-methylene diphosphonate bone scintigraphy. PET/CT offers improved image quality and enables quantitation that can measure tumor metabolism. Acquisition and fusion of PET with CT also allow for localization and morphologic evaluation of abnormalities, which leads to increased specificity. A study conducted by Even-Sapir et al demonstrated that NaF PET/CT is a highly accurate modality (100% for sensitivity, specificity, positive predictive value, and negative predictive value) for the detection of bone metastases in patients with prostate cancer. It can detect many metastatic lesions overlooked by bone scan. A prospective study in patients with biochemical relapse of prostate cancer showed that NaF PET/CT is useful in the detection of occult osseous metastases and that its positivity tends to associate with increasing PSA level and might occur in lower PSA ranges than conventionally recognized.

Pelvic lymph node dissection is currently the gold standard for evaluating the presence of nodal involvement in men undergoing a radical prostatectomy deemed at risk of nodal disease. There are limited imaging methods for detecting nodal involvement in patients with prostate cancer. Reliable and optimal detection rates have not been achieved by CT or MRI or even with PET/CT using 18F-fluoromethylcholine or 18F-fluorodeoxyglucose. However, PET/CT scan with new tracer 11C-choline has been demonstrated to be highly specific and more sensitive than PET alone or MRI as a noninvasive means of staging pelvic lymph nodes in prostate cancer.

Taken together, modern imaging modalities have improved accuracy but have major limitations, including variations in accuracy, high cost, and lack of availability. Prospective, rigorously controlled, clinical imaging trials are needed to establish the optimal role of new imaging strategies in prostate cancer, so appropriate patient management decisions can be made early in this disease stage.

RECOMMENDATIONS FROM THE WORKSHOP

The disparity in current practice guidelines and findings from clinical studies warrant the development of recommendations that promote early detection of metastases in patients with prostate cancer and help guide disease management. Scanning for metastatic disease is particularly important when considering starting or changing therapy. The RADAR Group focused on answering the following questions: Who should undergo an imaging...
scan? What is the preferred imaging modality? At what time point and frequency should imaging be done? They also recognized that there are distinct patient groups to consider when determining which diagnostic test should be used in the evaluation of metastatic disease in prostate cancer.4,5 The RADAR Group considered PSADT to be the best and the most consistent predictor and useful in different patient groups. Limited data showed that acceleration or slow down of PSADT correlated with outcomes (eg, time to metastasis).6 However, it was recognized that long-term PSADT (>3 years) is difficult to interpret because some patients develop metastases during this time course.

RECOMMENDATION: ELIGIBILITY CRITERIA AND FREQUENCY OF SCANNING
On the basis of review of the data and clinical practice experience by the RADAR Group, recommendations were made for imaging criteria/frequency for different patient groups with prostate cancer (Fig. 1). It is worth noting that the group recommended against scanning newly diagnosed low-risk patients and most intermediate-risk patients to prevent overimaging in practice. In addition, scanning before change of therapy to establish a new baseline is also warranted. Because clinical data on the subject are sparse in the published data, these recommendations are generalized suggestions based mainly on a consensus of clinical experience that need verification from appropriate clinical trials.

RECOMMENDATION: IMAGING MODALITIES
Considering the cost-effectiveness when implementing new techniques/strategies for bone and soft tissue imaging, the RADAR Group recommended 99mTc bone scintigraphy and abdomen/pelvis/chest CT as the imaging modalities for initial testing. Additional tests recommended were plain radiography, MRI, and NaF PET to be conducted at the physician’s discretion when necessary. As more data arise with newer imaging modalities, it might become apparent that the higher cost of novel imaging might be offset with more refined and appropriate therapeutic selection for patients. It was also recommended that imaging guidelines should allow for physicians’ clinical judgment when patients with low/borderline PSA levels, PSA kinetics, or Gleason score are suspected of having metastatic disease. This is a crucial stage for evaluating treatment decisions.

CONCLUSION
Initiating proper clinical strategies for the detection of metastases in advanced prostate cancer is important for optimal patient management. However, there is inconsistency in the published data and current available clinical practice guidelines in terms of eligibility criteria, type of imaging modality, and the frequency of scanning for metastatic disease. Recommendations to promote early identification of metastatic disease were developed during the workshop with the objective of improving clinical patient management and facilitating appropriate treatment practices. The recommendations will need to be validated and updated in a timely fashion on the basis of new information and novel technologies. To definitively conclude that refinements in imaging could improve survival for patients with prostate cancer, prospective, rigorously controlled, clinical imaging trials will be needed.

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