Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline

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Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline

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abstract

PURPOSE Provide evidence- and expert-based recommendations for optimal use of imaging in advanced prostate cancer. Due to increases in research and utilization of novel imaging for advanced prostate cancer, this guideline is intended to outline techniques available and provide recommendations on appropriate use of imaging for specified patient subgroups.

METHODS An Expert Panel was convened with members from ASCO and the Society of Abdominal Radiology, American College of Radiology, Society of Nuclear Medicine and Molecular Imaging, American Urological Association, American Society for Radiation Oncology, and Society of Urologic Oncology to conduct a systematic review of the literature and develop an evidence-based guideline on the optimal use of imaging for advanced prostate cancer. Representative index cases of various prostate cancer disease states are presented, including suspected high-risk disease, newly diagnosed treatment-naïve metastatic disease, suspected recurrent disease after local treatment, and progressive disease while undergoing systemic treatment. A systematic review of the literature from 2013 to August 2018 identified fully published English-language systematic reviews with or without meta-analyses, reports of rigorously conducted phase III randomized controlled trials that compared ≥ 2 imaging modalities, and noncomparative studies that reported on the efficacy of a single imaging modality.

RESULTS A total of 35 studies met inclusion criteria and form the evidence base, including 17 systematic reviews with or without meta-analysis and 18 primary research articles.

RECOMMENDATIONS One or more of these imaging modalities should be used for patients with advanced prostate cancer: conventional imaging (defined as computed tomography [CT], bone scan, and/or prostate magnetic resonance imaging [MRI]) and/or next-generation imaging (NGI), positron emission tomography [PET], PET/CT, PET/MRI, or whole-body MRI) according to the clinical scenario.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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With panel representation from the American College of Radiology, American Urological Association, Society of Abdominal Radiology, Society of Nuclear Medicine and Molecular Imaging, and the Society of Urologic Oncology.

At the time of publication, this ASCO Guideline has been endorsed by the American College of Radiology.

INTRODUCTION

The purpose of this clinical practice guideline is to provide referring and imaging clinicians (including medical oncologists, radiation oncologists, urologists, radiologists, nuclear medicine physicians, and molecular imagers), other health care practitioners, patients, and caregivers with recommendations and future directions regarding optimum imaging for patients with advanced prostate cancer based on the best available evidence. The fluid and rapidly evolving nature of the topic is acknowledged, and although regulatory approvals of some of the techniques presented are currently limited, this guideline is intended to preemptively address the ongoing barrage of studies that will most certainly transform the landscape for the management of patients with advanced prostate cancer. The term *advanced prostate cancer* encompasses a wide swath of patients with different disease states and clinicopathologic factors, including men with localized prostate cancer at initial diagnosis with a high or very high risk of metastasis (as defined recently in an American Urological Association/American Society of Radiation Oncology/Society of Urologic Oncology guideline[1]); men who have been treated and subsequently present with clinical, biochemical, or radiographic evidence of disease progression; and men with known metastatic disease either at initial presentation or after one or more lines of treatment. This guideline examines the optimal use of imaging for men in each of these disease states.

THE BOTTOM LINE

Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline

Endorsed by the Society of Abdominal Radiology, American College of Radiology, Society of Nuclear Medicine and Molecular Imaging, American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology.

Guideline Question

What are the optimum imaging options that should be offered to patients with advanced prostate cancer?

Target Population

Men with advanced prostate cancer, including newly diagnosed clinical high-risk disease, suspected or confirmed metastatic disease, recurrent disease, or progressive disease while under treatment.

Target Audience

Medical oncologists, radiation oncologists, urologists, radiologists, nuclear medicine and molecular imaging physicians, other health care practitioners such as nurses and social workers, patients, and caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Definitions

- Conventional imaging: computed tomography (CT), bone scan, and/or prostate magnetic resonance imaging (MRI).
- Next-generation imaging (NGI): positron emission tomography (PET), PET/CT, PET/MRI, whole-body MRI.
- Advanced prostate cancer: disease states/clinical scenarios described.
- Biochemical recurrence: detectable prostate-specific antigen (PSA) with a subsequent rise after radical prostatectomy or a rise of 2 above nadir PSA achieved after radiotherapy (Phoenix criteria)[15]; high risk without evidence of disease locally or distantly on conventional imaging where the definition of undetectable PSA is dependent on the assay used and may change over time as more-sensitive assays become available; in general, a PSA value < 0.2 ng/mL has been considered undetectable,[1] while lower values (PSA ≤ 0.01 ng/mL) have been advocated when clinically available.[16]

Recommendations

Recommendation 1. Imaging is recommended for all patients with advanced prostate cancer. See the recommendation under clinical question 4 for specific details according to clinical scenario (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 2. One or more of the following imaging modalities should be used for patients with advanced prostate cancer: conventional imaging (defined as CT, bone scan, and/or prostate MRI) and/or NGI (PET, PET/CT, PET/MRI, whole-body MRI), according to clinical scenario (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Recommendation 3. It is recommended when choosing an imaging modality that disease states and clinical scenarios as outlined are taken into consideration, as the imaging modality may guide treatment or change clinical treatment decisions (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Newly Diagnosed Clinically High-Risk/Very High-Risk Localized Prostate Cancer

Recommendation 4.1. Conventional imaging negative. When conventional imaging (defined as CT, bone scan, and/or prostate MRI) is negative in patients with a high risk of metastatic disease, NGI (defined as PET, PET/CT, PET/MRI, whole-body MRI) may add clinical benefit, although prospective data are limited (Type: informal consensus, benefits/harm ratio uncertain; Evidence quality: weak; Strength of recommendation: moderate).

Recommendation 4.2. Conventional imaging suspicious/equivocal. When conventional imaging is suspicious or equivocal, NGI may be offered to patients for clarification of equivocal findings or detection of additional sites of disease, which could potentially alter management, although prospective data are limited (Type: informal consensus, benefits/harm ratio uncertain; Evidence quality: weak; Strength of recommendation: moderate).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Rising PSA After Prostatectomy and Negative Conventional Imaging (either initial PSA undetectable with subsequent rise or PSA never nadirs to undetectable)

Recommendation 4.3. Both disease states are indicative of potentially undetected, residual local, locoregional, or micrometastatic disease, and imaging options are not distinct or different between these scenarios. The goal of therapy and the potential use of salvage local therapies in these scenarios should guide the choice of imaging. For men who are not candidates or are unwilling to receive salvage local or regional therapy, additional NGI should not be offered (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 4.4. For men for whom salvage radiotherapy is contemplated, NGI should be offered (PSMA imaging [where available]; ^{11}C-choline or ^{18}F-fluciclovine PET/CT; or PET/MRI, whole-body MRI, and/or ^{18}F-NaF PET/CT) as they have superior disease detection performance characteristics and may alter patient management (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Rising PSA After Radiotherapy and Negative Conventional Imaging

Recommendation 4.5. For men in whom salvage local or regional therapy is not planned or is inappropriate, there is little evidence that NGI will alter treatment or prognosis. The role of NGI in this scenario is unclear and should not be offered, except in the context of an institutional review board–approved clinical trial (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.6. For men for whom salvage local or regional therapy (eg, salvage prostatectomy, salvage ablative therapy, or salvage lymphadenectomy) is contemplated, there is evidence supporting NGI for detection of local and/or distant sites of disease. Findings on NGI could guide management in this setting (eg, salvage local, systemic or targeted treatment of metastatic disease, combined local and metastatic therapy). PSMA imaging (where available), ^{11}C-choline or ^{18}F-fluciclovine PET/CT or PET/MRI, whole-body MRI, and/or ^{18}F-NaF PET/CT have superior disease detection performance characteristics compared with conventional imaging and alter patient management, although data are limited (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Metastatic Prostate Cancer at Initial Diagnosis or After Initial Treatment, Hormone Sensitive

Recommendation 4.7. In the initial evaluation of men presenting with hormone-sensitive disease with demonstrable metastatic disease on conventional imaging, there is a potential role for NGI to clarify the burden of disease and potentially shift the treatment intent from multimodality management of oligometastatic disease to systemic anticancer therapy alone or in combination with targeted therapy for palliative purposes, but prospective data are limited (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: intermediate; Strength of recommendation: moderate).

Nonmetastatic Castration-Resistant Prostate Cancer

Recommendation 4.8. For men with nonmetastatic castration-resistant prostate cancer (CRPC), NGI can be offered only if a change in the clinical care is contemplated. Assuming patients have received or are ineligible for local salvage treatment options, NGI may clarify the presence or absence of metastatic disease, but the data on detection capabilities of NGI in this setting and impact on management are limited (Type: consensus, benefits/harms ratio uncertain; Evidence quality: weak; Strength of recommendation: moderate).

Metastatic CRPC

Recommendation 4.9. PSA progression. As recommended by the Prostate Cancer Working Group 3 consensus statements, PSA progression alone for men on treatment of metastatic CRPC should not be the sole reason to change therapy. Conventional imaging can be used for initial evaluation of PSA progression and should be continued to facilitate changes/comparisons and serially to assess for development of radiographic progression (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.10. The use of NGI in this cohort is unclear, with a paucity of prospective data. When a change in clinical care is contemplated, in an individualized manner, and there is a high clinical suspicion of subclinical metastasis despite negative conventional imaging, the use of NGI could be contemplated, especially in the setting of a clinical trial (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: insufficient; Strength of recommendation: weak).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 4.11. Radiographic progression on conventional imaging. In men with metastatic CRPC with clear evidence of radiographic progression on conventional imaging while on systemic therapy, NGI should not be routinely offered. NGI may play a role if performed at baseline to facilitate comparison of imaging findings/extent of progression of disease (Type: consensus, benefits/harms ratio uncertain; Evidence quality: insufficient; Strength of recommendation: moderate).

Additional Resources

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Prostate cancer is the most common nondermatologic cancer in men. In 2019, it was estimated that there would be 174,650 new cases in the United States, and in spite of advances in diagnosis and treatment, an estimated 31,620 deaths would occur.[2] In addition to its prevalence, prostate cancer poses unique challenges, including a distinct clinical disease state characterized by an elevated serum prostate-specific antigen (PSA) consistent with recurrent disease without findings of metastases on historically conventional imaging studies and difficulty in monitoring patients with metastatic bone disease due to the poor test characteristics of conventional bone imaging. For these reasons, coupled with increasing evidence for local salvage therapy or metastasis-directed therapy or increasingly effective systemic therapies that have been shown to be beneficial ever earlier in the natural history of the disease, there is great interest in identifying better imaging strategies to inform the optimum management for patients with advanced prostate cancer.

The predilection for prostate cancer to metastasize to bone and lymph nodes requires both bone and soft tissue imaging techniques to assess for staging and to monitor for response to therapy and progression of disease. Conventional standard imaging modalities include ^{99m}Tc-labeled methylene diphosphonate (^{99m}Tc-MDP) bone scan and computerized tomography (CT) or magnetic resonance imaging (MRI). The relatively poor specificity of ^{99m}Tc-MDP relates to the fact that MDP adsorbs onto the crystalline hydroxyapatite mineral of bone and is not prostate cancer–specific, thus providing only an indirect measure of tumor activity based on osteoblastic activity in the tumor microenvironment. In addition, the interpretation of a bone scan is subjective, relying on manual assessments of lesion number, size, and intensity. Such subjective assessments are problematic in the setting of clinical trials and lead to difficulty in accurately interpreting treatment effects. Patients treated with effective therapy can have paradoxically worsening scans in the face of response to treatment.[3] Standard criteria have been developed to standardize bone scan interpretation and to distinguish response from progression.[4,5] These semiquantitative criteria have been shown to be feasible, have demonstrated in prospective studies to correlate with survival, and have been recognized as clinically relevant to warrant their use by regulatory authorities for drug approval.[6-8] In addition, quantitative tools for the assessment of bone scan data have been developed, including the automated bone scan index (BSI), which represents the total tumor burden as the fraction of the total skeleton weight.[9-11] These quantitative tools improve bone scan interpretation but are still subject to the relatively poor specificity of ^{99m}Tc-MDP in patients with metastatic bone disease, the inability to detect nodal and visceral metastatic disease, and the poor ability of ^{99m}Tc-MDP and CT or MRI to detect metastatic disease in patients with early biochemical recurrence.

In the same way that molecularly targeted therapies have transformed decision making of many diseases, advances in nuclear medicine and molecular imaging are poised to re-invent the way in which we diagnose, stage, and monitor response to therapy in patients with prostate cancer. These next-generation imaging (NGI) modalities promise improved diagnostic accuracy for staging prostate cancer, especially at lower tumor burdens. New radiopharmaceuticals coupled to prostate cancer–specific targets, such as prostate-specific membrane antigen (PSMA), are defined in this guideline as external domain PSMA-binding ligands labeled with the positron emission tomography (PET)–emitters ^{68}Ga and ^{18}F, exclusive of the PSMA antibody capromab pendetide that binds the internal domain of PSMA. These have demonstrated improvements in the sensitivity for the detection of metastatic disease and the monitoring of a treatment effect in patients with advanced

prostate cancer compared with conventional imaging. The recent US Food and Drug Administration (FDA) approvals of ^{11}C-choline and ^{18}F-fluciclovine for PET imaging in men with a suspected prostate cancer recurrence based on an elevated PSA following prior treatment represent watershed moments in the development of novel imaging tools for advanced prostate cancer.[12]

While patients and clinicians may find additional imaging, especially NGI, attractive for advanced prostate cancer in a variety of clinical states, there are several disadvantages associated with their use. These NGI modalities are costly and are not routinely covered by all third-party payers in the United States. Their routine use could significantly increase overall expenditure for prostate cancer care. While the NGI modalities have excellent sensitivity to detect low-burden disease, false-positive results may lead to incorrect patient management in some patients. Moreover, the presence of NGI-detected lesions may trigger additional procedures, imaging modalities, and invasive biopsies, which carry risks and additional cost in addition to mental burden and uncertainty for patients. Figure 1 provides the imaging algorithm for high/very high-risk disease at initial presentation (per National Comprehensive Cancer Network). Figure 2 provides the imaging algorithm for patients with rising PSA after local treatment.

Another important consideration is concern for the Will Rogers phenomenon, which may ensue when patients who are classified as nonmetastatic with conventional imaging become reclassified as metastatic after NGI. This may alter treatment decisions with unknown consequences on the overall disease course.[13] The Will Rogers phenomenon also makes comparison with historical standards and controls very difficult, with the risk of artifactual changes in stage-specific survival.[14]

This guideline addresses the goals of imaging in advanced prostate cancer, considering conventional imaging techniques and newer NGI modalities, as well as unmet needs, the potential impact of imaging according to different advanced prostate cancer clinical disease states, and the type of imaging that is most appropriate in each scenario. The guideline focuses on appropriate utility of imaging for advanced prostate cancer and not on treatment decisions; any discussion of treatment decisions are given in the context of the impact of imaging on clinical decision making. Evaluation of treatment options and treatment decisions are beyond the scope of this guideline.

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions:

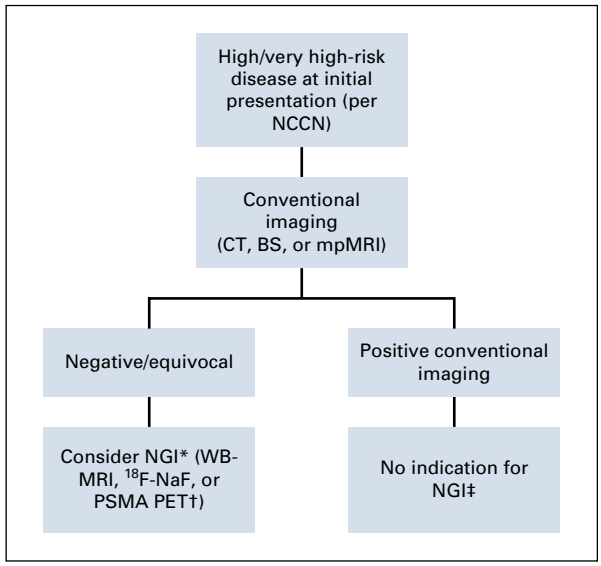

FIG 1. Imaging algorithm for high/very high-risk disease at initial presentation (per National Comprehensive Cancer Network [NCCN]). (*) Suspicious findings on NGI would influence treatment decisions in patients with advanced prostate cancer and negative conventional imaging, opening the scope for multimodality treatment of primary and oligometastatic disease or systemic therapy for more extensive metastatic states, although prospective data are limited. (†) There is enthusiasm for the potential added value of PSMA PET/CT and PET/MRI for the assessment of the local and metastatic extent of prostate cancer in this context, although PSMA imaging is not currently FDA approved and should thus be only performed as part of a clinical trial or other controlled research setting. (‡) NGI could offer clinical benefit in this scenario by redefining the true extent of disease and shifting treatment decisions accordingly, although prospective data in this context are limited. BS, bone scintigraphy; CT, computed tomography; mpMRI, multiparametric magnetic resonance imaging; NGI, next-generation imaging; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; WB, whole body.

1. What is the goal of imaging in advanced prostate cancer?
2. What imaging techniques are available for imaging advanced prostate cancer?
3. What are the unmet needs and potential impact of imaging according to different advanced prostate cancer disease states?
4. When and what type of imaging is appropriate in each scenario?

The recommendations are framed according to these clinical scenarios:

A. Newly diagnosed clinically high-risk/very high-risk prostate cancer
   i. Conventional imaging negative
   ii. Conventional imaging suspicious/equivocal
B. Rising PSA after prostatectomy and negative conventional imaging
   i. Initial PSA undetectable with subsequent rise
   ii. PSA never nadirs to undetectable

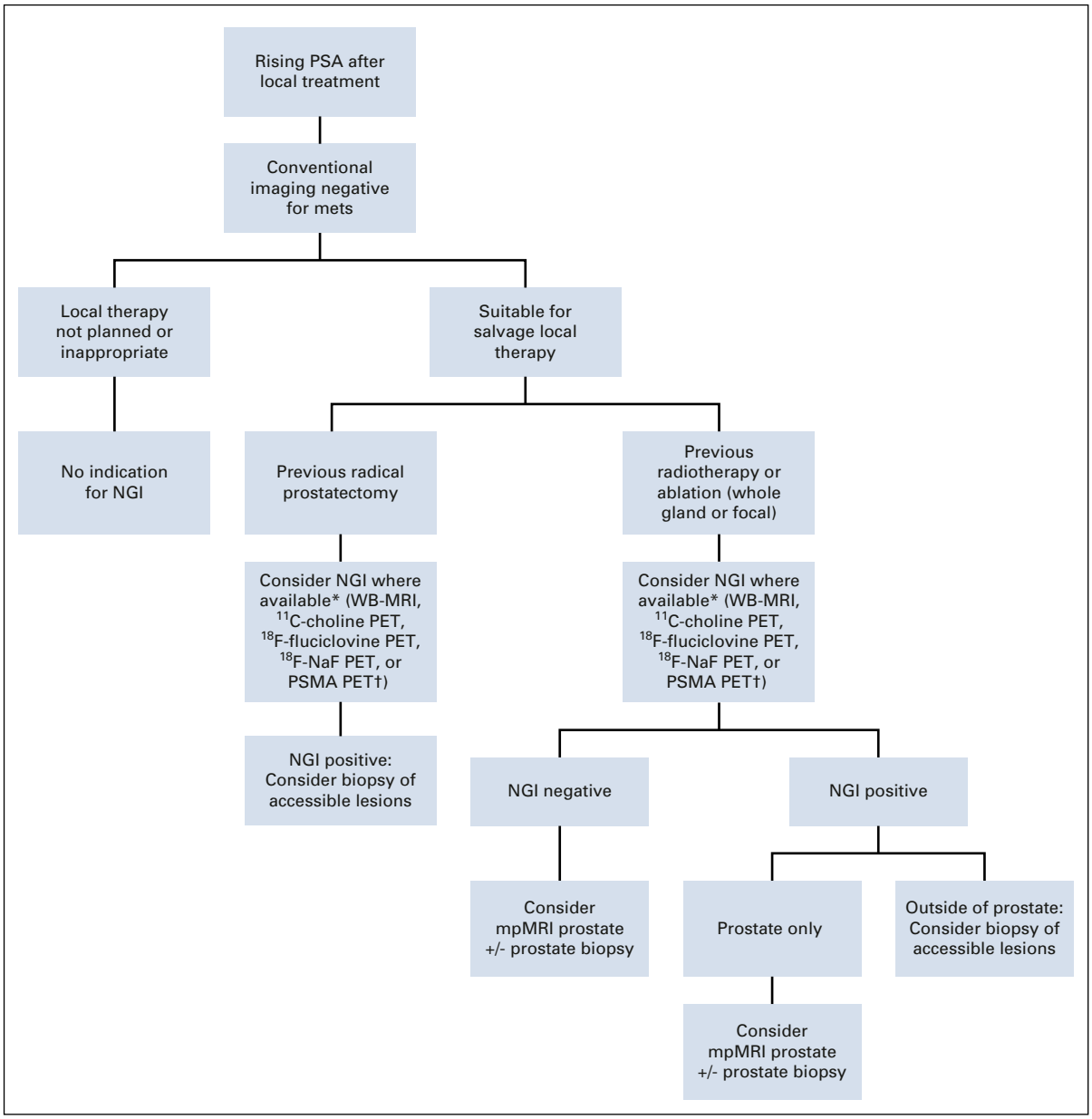

FIG 2. Imaging algorithm for patients with rising prostate-specific antigen (PSA) after local treatment. (*) For men for whom salvage local therapy (e.g. salvage radiation, salvage prostatectomy) is an option, there is evidence supporting the use of NGI to assess local or distant sites of disease, which may guide therapy away from salvage local therapy if indicative of distant metastatic disease. (†) There is enthusiasm for the potential added value of PSMA PET/CT and PET/MRI for the assessment of the local and metastatic extent of prostate cancer in this context, although PSMA imaging is not currently FDA approved and should thus be only performed as part of a clinical trial or other controlled research setting. Mets, metastatic disease; mpMRI, multiparametric magnetic resonance imaging; NGI, next-generation imaging; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; WB, whole body.

C. Rising PSA after radiotherapy and negative conventional imaging
D. Metastatic prostate cancer at initial diagnosis or after treatment, hormone sensitive
E. Nonmetastatic castration-resistant prostate cancer (CRPC)
F. Metastatic CRPC
   i. PSA progression
   ii. Radiographic progression on conventional imaging

METHODS

Guideline Development Process

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel comprising members from all the partner organizations (herein, the Expert Panel), which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only).

The Expert Panel met in person several times as well as via teleconference and/or webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee (CPGC) prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review (2013 through September 2017 and then updated in August 2018) of systematic reviews with or without meta-analysis, phase III randomized clinical trials (RCTs), comparative nonrandomized studies, and clinical experience. Articles reporting on other study designs were considered if they included outcomes, interventions, or comparisons unavailable elsewhere. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: men with advanced prostate cancer
- Fully published or recent meeting presentations of English-language systematic reviews with or without meta-analyses, reports of rigorously conducted phase III RCTs that compared two or more imaging modalities, and noncomparative studies that report on the efficacy of a single imaging modality
- Reported on a minimum number of patients (> 50)

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; or (3) published in a non-English language. The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[17] In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice (see Data Supplement 5: Implementability Survey Results). Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

Detailed information about the methods used to develop this guideline is available in the Methodology Manual at www.asco.org/guideline-methodology. Other information may be found in the Data Supplement, including the clinical questions (Data Supplement 1), the search strategy (Data Supplement 2), the QUORUM diagram (Data Supplement 3), the study quality assessment (Data Supplement 4A), and the study risk of bias assessment (Data Supplement 4B).

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an “as is” basis and makes no warranty, expressed or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation

for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Evidence Overview

A total of 35 articles comprising 17 systematic reviews[18-34] with or without meta-analysis and 18 primary research articles[35-52] met eligibility criteria and form the evidentiary basis for the guideline recommendations. Table 1 provides a brief description of each. Other articles were brought in for discussion purposes as warranted.

Systematic Reviews

The 17 systematic reviews[18-34] underwent evaluation of their pooled results from studies published between 1998 and 2017. Eight reviews[19,23,24,26,28,30,32,33] compared various PET radiopharmaceuticals labeled with ^{18}F or ^{11}C; three reviews[18,20,22] reported on ^{68}Ga-PSMA binding ligand PET alone using various radiopharmaceuticals; two reviews[21,34] compared PET/CT using various radiopharmaceuticals with MRI; two reviews[25,31] reported on ^{68}Ga-PSMA binding ligand PET and MRI alone using various radiopharmaceuticals; and two[27,29] reported on a pooled analysis that included ^{11}C PET/CT, MRI, bone single-photon emission computed tomography (SPECT), and bone scintigraphy with various radiopharmaceuticals. Eleven of these reviews[18,19,21,22,24,25,27-29,32,34] reported on recurrence, staging, or restaging, five[20,23,26,30,33] reported on diagnostic utility, and one[31] reported on the results of pooling outcomes related to determining extraprostatic extension and seminal vesicle involvement. Table 1 provides more detail.

Primary Research Articles

The 18 primary research articles[35-52] obtained reported on studies published between 2014[52] and 2018[35] that accrued patients between 2007 and 2017 (six articles[38,41,44,47,48,51] did not report on the years the study was open to accrual). Seven of these articles[37,38,44,48-50,52] used a prospective design, and 11 articles[35,36,39-43,45-47,51] were retrospective studies. Five of these articles[35,36,38,40,43] reported on studies investigating PSMA binding ligand imaged with PET (*v* other PSMA binding ligands imaged with PET, histology, or other end points), eight articles[37,39,41,42,45,46,49,51] reported on PSMA binding ligand with PET imaging modalities compared with PET/CT or PET/MRI alone, and five articles[44,47,48,50,52] reported on ^{18}F or ^{11}C PET/CT. As no pooling was performed, studies that were also included in any of the previously summarized systematic reviews were retained and are reported on. Table 1 provides more detail.

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed. Findings were that the evidence obtained was a representative body of literature that recommendations could be based on. For the systematic reviews, the risk of bias was lower than that of the primary articles, mostly due to the study designs used in assessments of diagnostic utility (predominantly retrospective designs with within-group comparisons). See Data Supplement 4A (Study Quality Assessment, systematic reviews with or without meta-analysis) and Data Supplement 4B (Study Risk of Bias Assessment, primary studies) for the complete results of the quality assessment.

Study Results

Systematic reviews. Seventeen systematic reviews[18-34] were obtained, and the main findings (Table 2) include the following:

- In a systematic review comprising 56 studies and 7,329 patients published between 2005 and 2015, Liu et al[23] found ^{18}F-fluorocholine (FCH) PET/CT superior to ^{11}C-choline, ^{11}C-acetate, and ^{18}F-fludeoxyglucose (FDG) for both sensitivity and specificity in the initial detection of prostate cancer.
- Treglia et al,[28] in a systematic review comprising 14 studies and 1,869 patients published between 2008 and 2013, found ^{18}F-choline or ^{11}C-choline PET/CT detection rates were affected by PSA doubling times and rising PSA velocity, and these two factors should be taken into account when deciding which patients are appropriate for restaging with choline PET/CT.
- In a systematic review of 47 studies involving 3,167 patients published between 1998 and 2013, von Eyben et al[26] found either ^{11}C-choline PET/CT or ^{18}F-choline PET/CT informative for recurrence detection in patients with PSA levels between 1 and 50 ng/mL. Performing either test also resulted in a change to the treatment plan in 41% of patients (381 of 938), while 25% (101 of 404) experienced a complete PSA response.
- Mohsen et al,[30] in a systematic review of 25 studies (number of patients not reported), reported pooled sensitivity of 75.1% (95% CI, 69.8% to 79.8%) and pooled specificity of 75.8% (95% CI, 72.4% to 78.9%) in the detection of initial prostate cancer and a pooled sensitivity of 64% (95% CI, 59% to 69%) and pooled

TABLE 1. Evidence Overview

First Author	No. of Included Studies	No. of Included Patients	Purpose	Comparisons
Systematic reviews and meta-analysis				
Fitzpatrick[18]	24 clinical trials and retrospective analyses (2011-2017) that compared ^{68}Ga-PSMA-PET/CT to other tracers or imaging modalities	2,408 patients (min:max, 144:532) previously treated with RT and/or RP with BCR or were suspected of having progressive disease as indicated via other imaging modalities	To detect recurrence	^{68}Ga-PSMA *v* Choline-based tracers
von Eyben[20]	15 studies: 7 staging, 9 restaging (1 both), 4 prostate segment localization, and 4 pelvic LNI	1,256 patients; staging (n = 203), restaging (n =983), prostate segment localization (n = 116), and pelvic LNI (n = 224)	To compare detection rate, diagnostic test accuracy, and adverse effects	^{68}Ga-PSMA for staging and restaging (subanalyses for postsurgical and pelvic LNI)
von Eyben[19]	18 cohort studies (2006-2015) on BCR in prostate cancer	2,219 patients suspected of BCR	To detect metastases	^{11}C-choline *v* ^{18}F-FCH PET/CT
Ren[21]	6 mostly prospective studies	251 patients	To detect recurrence	^{18}F-FACBC PET/CT
Perera[22]	16 studies, 5 of which have surgical nodal data	1,309 patients, 239 of whom have surgical nodal data	Restaging	^{68}Ga-PSMA for restaging; sensitivity and specificity data available for LNI only
Liu[23]	56 studies (2005-2015) that focused on investigating the diagnostic performance of four PET/CT radiotracers in prostate cancer	3,743 cases and 3,586 healthy controls for initial detection of prostate cancer	To compare diagnostic accuracy	^{18}F-FDG *v* ^{11}C-choline *v* ^{18}F-FCH *v* ^{11}C-acetate
Fanti[24]	29 diagnostic accuracy cross-sectional studies with prospective or retrospective recruitment; 18 with detection rates	2,686 patients previously treated with RT or RP suspected of BCR; any relapse (n = 2,126), local relapse (n = 993), LN and distant metastases (n =752), bone metastases (n = 775)	Restaging and recurrence detection	^{11}C-choline PET and/or PET/CT Reference standard for locoregional recurrence, TRUS-guided biopsy; for distant metastases see[a]
de Rooij[25]	75 studies with RP for assessing local staging, 45 for ECE, 34 for SVI, and 38 for overall T3 stage detection	5,681 patients for ECE, 5,677 patients for SVI, and 4,001 patients for overall stage T3 detection	To detect recurrence	MRI including mpMRI
von Eyben[26]	47 studies (1998-2013)	3,167 patients with suspected prostate cancer (^{11}C-choline [n = 1,798]; ^{18}F-choline [n = 550])	To compare diagnostic accuracy	^{11}C-choline PET *v* ^{18}F-choline PET or *v* BS Clinical judgment based on conventional imaging and follow-up
Shen[27]	18 retrospective and prospective (9 choline PET/CT, 3 bone SPECT, 6 MRI, and 12 BS)	1,102 patients with suspected bone metastases	To detect bone metastases	^{11}C-choline PET, MRI, bone SPECT, bone scintigraphy (^{99m}Tc-MDPBS)
Treglia[28]	14 articles (2008-2013) on radiolabeled choline in restaging prostate cancer	1,869 patients with suspected BCR	Restaging and recurrence detection	^{18}F-choline or ^{11}C-choline PET/CT

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TABLE 1. Evidence Overview (continued)

First Author	No. of Included Studies	No. of Included Patients	Purpose	Comparisons
Umbehr[29]	44 (case-control and cohort [prospective and retrospective]); 29 in M-A	2,293 patients	Staging and restaging	^{11}C-choline PET *v*
				^{18}F-choline PET *v*
				PET/CT
				Index tests included PET without CT
				Reference tests included biopsy, histology from surgery, CT and/or MRI and/or BS, and/or clinical follow-up, and/or PSA
Mohsen[30]	24	NR, but included patients with suspected initial and recurrent prostate cancer	To determine the diagnostic utility of recurrence detection	^{11}C-acetate PET
Silva[31]	7 studies (2008-2013) that investigated MRI in detection of EPE and SVI in prostate cancer	603 patients for the detection of EPE and SVI in prostate cancer	To detect EPE and SVI in prostate cancer	1.5-T MRI with endorectal coil
Evangelista[32]	19 M-As and 36 SRs (included if reporting certain outcomes, certain reference standards, and sufficient sample size)	1,555 (M-A) with suspected recurrent prostate cancer	To detect local or distant metastases	^{18}F-choline PET or
				^{11}C-choline PET or
				PET/CT
				Reference standard pathology or other common imaging modalities
Evangelista[33]	10 were pooled from a total of 18 studies (included if reporting certain outcomes, certain reference standards, and sufficient sample size)	441 (M-A) in the detection of LNI	To determine diagnostic utility	^{18}F-choline PET/CT or
				^{11}C-choline PET or
				PET/CT
				Reference standard pathology or other common imaging modalities
Alfarone[34]	16 retrospective and primarily single-center studies	PET/CT studies range: 20-358; MRI range: 46-84 to detect local recurrence	To detect local recurrence	^{18}F-choline PET/CT or ^{11}C-choline PET/CT and mpMRI (with DCE or alone)
Primary studies				
Schmidkonz[35]	Retrospective (2013-2017)	93 patients with prostate cancer	Staging prior to primary treatment	PSMA ligand ^{99m}Tc-MIP-1404
Schmidkonz[36]	Retrospective (2013-2017)	225 patients with BCR	To detect recurrence	PSMA ligand ^{99m}Tc-MIP-1404
Habl[37]	Prospective (2013-2016)	100 patients with BCR following RP with or without prior RT	To detect recurrence	PSMA ligand ^{68}Ga PET/CT or
				PET/MRI
Goffin[38]	Prospective phase II trial	105 (104 evaluable) patients with intermediate- or high-risk disease prior to RP or eLND	To determine extent of disease prior to initial treatment	PSMA ligand ^{99m}Tc-MIP-1404 *v*
				Histology
Freitag[39]	Retrospective (2013-2016)	119 patients with BCR following RP	To detect local recurrence	PSMA ligand ^{68}Ga-11 PET/CT *v*
				^{68}Ga-11-PET/mpMRI
Einspieler[40]	Retrospective (2012-2016)	118 patients with BCR following RT (EBRT, n = 77; brachytherapy, n = 41)	To detect recurrence	PSMA ligand ^{68}Ga-11 PET/CT

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TABLE 1. Evidence Overview (continued)

First Author	No. of Included Studies	No. of Included Patients	Purpose	Comparisons
Dietlein[41]	Retrospective analysis of a prospective series	191 patients with BCR following RP or RT	To detect recurrence	PSMA ligand ^{68}Ga-11 PET (n = 129) *v*
				^{18}F PET (n = 62)
Berliner[42]	Retrospective (2015-2016)	83 patients with BCR following prostatectomy	To detect recurrence	PSMA ligand ^{68}Ga-11 I&T PET/CT *v*
				^{68}Ga-11 HBED-CC PET/CT
Albisinni[43]	Retrospective (2015-2015)	131 patients with BCR following treatment with curative intent; RP (n = 11); surgery, RT, or both (n = 120)	To measure the change in treatment plan	PSMA ligand ^{68}Ga-11 PET/CT
Akin-Akintayo[44]	Prospective	87 patients with BCR following RP	To measure the change in RT treatment plan	^{18}F PET/CT (n = 44, 42 evaluable) *v*
				PET/CT (n = 43)
Rahbar[45]	Retrospective (2014-2015)	82 (74 evaluable) patients with mCRPC	To determine response and tolerability	PSMA ligand ^{177}Lu-617 followed by ^{68}Ga PET/CT
Pfister[46]	Retrospective (2014-2015)	66 patients: ^{18}F (n = 38); ^{68}Ga, (n = 28) to detect recurrence	To detect recurrence	PSMA ligand ^{68}Ga-HBED-CC PET/CT *v*
				^{18}F PET/CT *v*
				Histology
Odewole[47]	Retrospective	53 BS-negative patients to detect recurrence	To detect recurrence	^{18}F PET/CT *v*
				CT
Nanni[48]	Prospective	100 (89 evaluable) patients to detect recurrence	To detect recurrence	^{18}F PET/CT *v*
				^{11}C PET/CT
Larbi[49]	Prospective (2012-2013)	119 patients with prostate cancer with BCR	To detect local recurrence	PSMA ligand ^{68}Ga PET/CT *v*
				PET/MRI
Barchetti[50]	Prospective (2011-2014)	152 patients with BCR following RP or EBRT	To detect LNI and distant metastases	^{18}F PET/CT *v*
				WB-MRI
Ceci[51]	Retrospective	70 patients with BCR following RP or RT	To restage recurrent disease	PSMA ligand ^{68}Ga PET/CT
Schuster[52]	Prospective (2007-2012)	93 (91 evaluable) patients	To detect recurrence	^{18}F PET/CT *v*
				^{111}In PET/CT

Abbreviations: ^{68}Ga, Gallium-68; BCR, biochemical recurrence; BS, bone scintigraphy; CT, computed tomography; DCE, dynamic contrast enhanced; DWI, diffusion-weighted imaging; EBRT, external beam radiotherapy; ECE, extracapsular extension; eLND, extended lymph node dissection; EPE, extraprostatic extension; FACBC, fluciclovine; FCH, fluorocholine; FDG, fludeoxyglucose; HBED-CC, N,N′-Bis(2-hydroxy-5-[ethylene-β-carboxy]benzyl)ethylenediamine N,N′-diacetic acid; I&T, imaging and therapy; LN, lymph node; LNI, lymph node involvement; M-A, meta-analysis; max, maximum; mCRPC, metastatic castration-resistant prostate cancer; min, minimum; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; NR, not reported; PET, positron emission tomography; PMSA, prostate-specific membrane antigen; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy; SPECT, single-photon emission computed tomography; SR, systematic review; SVI, seminal vesicle involvement; TRUS, transrectal ultrasound; WB-MRI, whole-body magnetic resonance imaging.

[a]Histopathological findings on lymphadenectomy or biopsy; composite standard; clinical follow-up ≥ 12 months for C-choline PET-negative studies.

TABLE 2. Results: Systematic Reviews

First Author	No. of Included Studies	No. of Included Patients	Comparisons	Results
Systematic reviews with or without meta-analysis				
Initial detection, staging, and restaging				
Liu[23]	56 studies that focused on investigating the diagnostic performance of 4 choline PET/CT radiotracers (^{18}F-FDG, ^{11}C-choline, ^{18}F-FCH, and ^{11}C-acetate) in prostate cancer (2005-2015)	3,743 cases and 3,586 healthy controls for initial detection of prostate cancer	^{18}F-FDG *v* ^{11}C-choline *v* ^{18}F-FCH *v* ^{11}C-acetate	Specificity, 0.84% (95% CI, 0.77 to 0.89)
				Sensitivity, 0.80% (95% CI, 0.74 to 0.85)
				AUC of SROC, 0.89% (95% CI, 0.86 to 0.91)
				^{18}F-FDG PET/CT > other 3 (^{18}F-FCH PET/CT had the highest AUC, 0.94 % (95% CI, 0.92 to 0.96), and ^{18}F-FDG had the lowest AUC, 0.73% (95% CI, 0.69 to 0.77)
Treglia[28]	14 articles on radiolabeled choline in restaging prostate cancer (2008-2013)	1,869 patients with suspected BCR	^{18}F-choline or ^{11}C-choline PET/CT	Pooled detection rate, 58% (95% CI, 55 to 60)
				Pooled detection rate: PSA dt ≤ 6 months, 65% (95% CI, 58 to 71)
				Pooled detection rate: PSA vel > 1 ng/mL/year, 71% (95% CI, 66 to 76)
				Pooled detection rate: PSA vel > 2 ng/mL/year, 77% (95% CI, 71 to 82)
				PSA dt ≤ 6 months and PSA vel > 1 or > 2 ng/mL/year are predictive factors in detecting positive results of radiolabeled choline PET/CT
von Eyben[26]	47 studies (1998-2013)	3,167 (1,798 ^{11}C-choline; 550 ^{18}F-choline) with suspected prostate cancer	^{11}C-choline PET/CT *v* ^{18}F-choline PET/CT or *v* BS (clinical judgment based on conventional imaging and follow-up)	Detection rate PET/CT using the F-choline tracer compared with scanning using C-choline as the tracer (334 of 550 [60%] *v*828 of 1,798 [46%]; $P < .0005$, Fisher's exact test)
				Sensitivity, 0.59 (95% CI, 0.51 to 0.66)
				Specificity, 0.92 (95% CI, 0.89 to 0.94)
				PPV, 0.70
				NPV, 0.85
				LR+, 6.86 (95% CI, 4.23 to 11.12)
				LR–, 0.45 (95% CI, 0.28 to 0.73)
				DOR, 19.17 (95% CI, 8.39 to 43.79)

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TABLE 2. Results: Systematic Reviews (continued)

First Author	No. of Included Studies	No. of Included Patients	Comparisons	Results
Mohsen[30]	24 studies examining ^{11}C-acetate PET imaging in prostate cancer	NR, but included patients with suspected initial and recurrent prostate cancer	^{11}C-acetate PET	Primary prostate cancer: pooled sensitivity, 93% (95% CI, 90% to 96%)
				LN staging: pooled sensitivity, 73% (95% CI, 54% to 88%)
				Recurrence detection (localization): sensitivity, 64% (95% CI, 59% to 69%); specificity, 93% (95% CI, 83% to 98%)
				LN staging: pooled specificity, 79% (95% CI, 72% to 86%)
				Accuracy for evaluation of primary tumor: pooled lesion basis sensitivity, 75.1 (95% CI, 69.8 to 79.8); specificity, 75.8 (95% CI, 72.4 to 78.9); LR+, 2.044 (95% CI, 1.303 to 3.204); LR–, 0.311 (95% CI, 0.156 to 0.619); DOR, 6.712 (95% CI, 4.826 to 9.335)
				Patients with PSA relapse: LR+, 1.774 (95% CI, 0.642 to 4.906); LR–, 0.449 (95% CI, 0.216 to 0.934); DOR, 3.876 (95% CI, 0.607 to 24.755)
Umbehr[29]	44 (case-control and cohort [prospective and retrospective]); 29 in M-A	2,293 patients in the staging and restaging of prostate cancer	^{11}C-choline PET *v* ^{18}F-choline PET *v* PET/CT (index tests included PET without CT; reference tests: biopsy; histology from surgery; CT and/or MRI and/or BS, and/or clinical follow-up, and/or PSA)	M-A outcome category staging patients with proven untreated prostate cancer:
				Per patient (10 studies; n = 637): pooled sensitivity, 84% (95% CI, 68% to 93%); specificity, 79% (95% CI, 53% to 93%); DOR, 20.4 (95% CI, 9.9 to 42.0), LR+, 4.02 (95% CI, 1.73 to 9.31), LR–, 0.20 (95% CI, 0.11 to 0.37)
				Per lesion (11 studies; n = 5,227): pooled sensitivity, 66% (95% CI, 56% to 75%); specificity, 92% (95% CI, 78% to 97%); DOR, 22.7 (95% CI, 8.9 to 58.0), LR+, 8.29 (95% CI, 3.05 to 22.54); LR–, 0.36 (95% CI, 0.29 to 0.46)
				Restaging patients with biochemical failure after local treatment with curative intent, per patient (12 studies; n = 1,055): pooled sensitivity, 85% (95% CI, 79% to 89%); specificity, 88% (95% CI, 73% to 95%); DOR, 41.4 (95% CI, 19.7 to 86.8); LR+, 7.06 (95% CI, 3.06 to 16.27); LR–, 0.17 (95% CI, 0.13 to 0.22)
von Eyben[20]	15 studies; 7 staging, 9 restaging (1 both), 4 prostate segment localization, 4 pelvic LNI comparing ^{11}C-choline and ^{18}F-FCH and PET/CT	1,256 patients; 203 staging, 983 restaging, 116 prostate segment localization, 224 pelvic LNI	^{68}Ga-HBED-CC for staging and restaging (subanalyses for postsurgical and pelvic LNI)	Detection rate: 74% staging, 50% restaging, PSA 0.2-0.49 ng/mL; 53% restaging, PSA 0.5-0.99 ng/mL
				Prostate segment localization sensitivity, 70%; specificity, 84%
				Pelvic LNI sensitivity, 61%; specificity, 97%
				The detection rates of ^{11}C-choline (30 ± 5%) and ^{18}F-FCH (39 ± 5%) were not statistically different (P = .26)

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TABLE 2. Results: Systematic Reviews (continued)

First Author	No. of Included Studies	No. of Included Patients	Comparisons	Results
Recurrence				
Fitzpatrick[18]	24 clinical trials and retrospective analyses that compared ^{68}Ga-PSMA PET/CT to other tracers or imaging modalities (2011-2017)	2,408 (min:max, 144:532) patients previously treated with RT and/or RP with BCR or were suspected of having progressive disease as indicated via other imaging modalities	^{68}Ga HBED-CC PSMA *v* choline-based tracers	Specificity, > 99%
				Sensitivity, 33% to 94% (where prostate LNI was detected with ^{68}GA-PSMA, subsequent nodes detected resulted in a > 90% sensitivity)
				Detection rates: PSA < 0.5 ng/mL, 50%; PSA > 2 ng/mL, 95%
				SUVmax, ^{68}GA-PSMA > choline-based tracers
von Eyben[19]	18 cohort studies on BCR in prostate cancer (2006-2015)	2,219 patients suspected of BCR	^{11}C-choline *v* ^{18}F-FCH PET/CT	Detection rates:
				^{11}C-choline, 30% ± 5%
				^{18}F-FCH, 39 ± 5%
				P = .26
Fanti[24]	29 diagnostic accuracy cross-sectional studies with prospective or retrospective recruitment; 18 with detection rates	2,686 patients previously treated with RT or RP, suspected of BCR, 2,126 any relapse, 993 (local relapse), 752 (LN and distant metastases), 775 (bone metastases)	^{11}C-choline PET and/or PET/CT (reference standard: for locoregional recurrence, TRUS-guided biopsy, for distant metastases[a])	Overall detection rate any relapse (n = 18), 62% (95% CI, 53 to 71); sensitivity (n = 12), 89% (95% CI, 83 to 93); specificity, 89% (95% CI, 73 to 96)
				Local relapse detection rate (n = 10), 27% (95% CI, 16 to 38); sensitivity (n = 6), 61% (95% CI, 40 to 80); specificity, 97% (95% CI, 87 to 99); detection rate (n = 7), 36% (95% CI, 22 to 50)
				Bone metastases (n = 8), detection rate, 25% (95% CI, 16 to 34)
Evangelista[32]	19 M-As and 36 SRs (included if reporting certain outcomes, certain reference standards, and sufficient sample size)	1,555 (M-A) with suspected recurrent prostate cancer	^{18}F-choline PET or ^{11}C-choline PET or PET/CT (reference standard pathology or other common imaging modalities)	Pooled diagnostic accuracies for ^{11}C/^{18}F-choline PET and PET/CT in all sites of disease:
				^{11}C-choline: sensitivity, 81.8% (95% CI, 77.9% to 85.2%); specificity, 91.4% (95% CI, 88.3% to 93.9%); LR+, 7.19 (95% CI, 2.59 to 19.99); LR–, 0.20 (95% CI, 0.13 to 0.29); DOR, 53.77 (95% CI, 29.02 to 99.62)
				^{18}F-choline: sensitivity, 91.8% (95% CI, 88.0% to 94.7%); specificity, 95.6% (95% CI, 91.2% to 98.2%); LR+, 11.75 (95% CI, 1.86 to 74.39); LR–, 0.11 (95% CI, 0.03 to 0.46); DOR, 132.55 (95% CI, 7.59 to 2,315.5)
				All: sensitivity, 85.6% (95% CI, 82.9% to 88.1%); specificity, 92.6% (95% CI, 90.1% to 94.6%); LR+, 8.53 (95% CI, 3.62 to 20.09); LR–, 0.17 (95% CI, 0.11 to 0.28); DOR, 62.123 (95% CI, 24.78 to 155.72)
				Pooled diagnostic accuracies for LN metastases: sensitivity, 100% (95% CI, 90.5% to 100%); specificity, 81.8% (95% CI, 48.2% to 97.7%); LR+, 3.72 (95% CI, 0.98 to 14.17); LR–, 0.03 (95% CI, 0.05 to 0.23); DOR, 138.5 (95% CI, 11.27 to 1,703.8)
				Prostatic fossa relapse: sensitivity, 75.4% (95% CI, 66.9% to 82.6%); specificity, 82.0% (95% CI, 68.6% to 91.4%); LR+, 2.35 (95% CI, 1.03 to 5.39); LR–, 0.44 (95% CI, 0.26 to 0.74); DOR, 5.86 (95% CI, 1.81 to 18.94)

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TABLE 2. Results: Systematic Reviews (continued)

First Author	No. of Included Studies	No. of Included Patients	Comparisons	Results
Alfarone[34]	16 retrospective and primarily single-center studies	1,447 patients (including 23 controls) to detect local recurrence	^{18}F-choline PET/CT or ^{11}C-choline PET/CT and mpMRI (with DCE or alone)	Results not pooled, but PET/CT has not demonstrated efficacy in the detection of local recurrence in patients with low levels of PSA
				mpMRI was superior to PET/CT in detecting local recurrence in patients with low PSA and with small diameter lesions
Ren[21]	6 mostly prospective studies	251 patients with suspected recurrence	^{18}F-FACBC PET/CT	Sensitivity, 88%; specificity, 67%
Detection of bone metastases, EPE, LNI				
Shen[27]	18 retrospective and prospective (9 choline PET/CT, 3 bone SPECT, 6 MRI, 12 BS) (1990-2012)	1,102 with suspected bone metastases	^{11}C-choline PET, MRI, bone SPECT, bone scintigraphy (^{99m}Tc-MDPBS)	Per-lesion basis,[b] pooled sensitivities: PET/CT, 0.83 (95% CI, 0.81 to 0.85)
				Bone SPECT, 0.90 (95% CI, 0.86 to 0.93); BS, 0.59 (95% CI, 0.55 to 0.63)
				Pooled specificities: PET/CT, 0.95 (95% CI, 0.94 to 0.97); bone SPECT, 0.85 (95% CI, 0.80 to 0.90); BS, 0.75 (95% CI, 0.71 to 0.79); DOR, 99.78 (95% CI, 78.16 to 6.21); AUC, 0.9494 (95% CI, 0.938 to 0.7736)
				Per-patient PET/CT: sensitivity, 0.87 (95% CI, 0.79 to 0.93); specificity, 0.97 (95% CI, 0.93 to 0.99); DOR 150.70 (95% CI, 49.67 to 457.23), AUC, 0.9541
				Per-patient MRI: sensitivity, 0.95 (95% CI, 0.90 to 0.98); specificity, 0.96 (95% CI, 0.92 to 0.98); DOR, 343.16 (95% CI, 111.04 to 1,060.57); AUC, 0.9870
				Per-patient BS: sensitivity, 0.79 (95% CI, 0.73 to 0.83); specificity, 0.82 (95% CI, 0.78 to 0.85), DOR, 20.32 (95% CI, 5.53 to 74.60), AUC, 0.8876
Silva[31]	7 studies that investigated MRI in detection of EPE and SVI in prostate cancer (2008-2013)	603 patients for the detection of EPE and SVI in prostate cancer	1.5-T MRI with endorectal coil	MRI for detection: specificity, 0.58; sensitivity, 0.6
				MRI for detection of EPE: specificity, 0.82; sensitivity, 0.49
				Detection of SVI: specificity, 0.96; sensitivity, 0.5
Evangelista[33]	10 were pooled from a total of 18 studies (included if reporting certain outcomes, certain reference standards, and sufficient sample size)	441 (M-A) in the detection of LNI	^{11}C-choline PET/CT or ^{18}F-choline PET/CT or PET/CT (reference standard pathology or other common imaging modalities)	PET alone: sensitivity, 0.74 (95% CI, 0.55 to 0.88); specificity, 0.91 (95% CI, 0.83 to 0.96); LR+, 6.22 (95% CI, 0.97 to 39.96); LR–, 0.37 (95% CI, 0.18 to 0.76); DOR, 17.72 (95% CI, 1.83 to 171.90)
				PET/CT: sensitivity, 0.43 (95% CI, 0.33 to 0.53); specificity, 0.95 (95% CI, 0.91 to 0.97); LR+, 6.81 (95% CI, 3.08 to 15.04); LR–, 0.66 (95% CI, 0.45 to 0.95); DOR, 13.07 (95% CI, 4.08 to 41.86)

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TABLE 2. Results: Systematic Reviews (continued)

First Author	No. of Included Studies	No. of Included Patients	Comparisons	Results
de Rooij[25]	75 studies with RP for assessing local staging, 45 for ECE, 34 for SVI, and 38 for overall T3 stage detection	5,681 patients for ECE, 5,677 patients for SVI, 4,001 patients for overall stage T3 detection	MRI (DWI, DCE), including mpMRI	ECE: sensitivity, 57%; specificity, 91%
				SVI: sensitivity, 58%; specificity, 96%
				T3 stage detection: sensitivity, 61%; specificity, 88%
Perera[22]	16 studies, 5 of which have surgical nodal data	1,309 patients, 239 of whom have surgical nodal data	^{68}Ga-HBED-CC PSMA for restaging; sensitivity and specificity data available for LNI only	LNI (per lesion): sensitivity, 80%; specificity, 97%
				LNI (per patient): sensitivity, 86%; specificity, 86%

Abbreviations: ^{99m}Tc-MDPBS, ^{99m}Tc-methylene diphosphonate bone scintigraphy; AUC, area under the curve; BS, bone scintigraphy; CT, computed tomography; DCE, dynamic contrast-enhanced; DOR, diagnostic odds ratio; dt, doubling time; DWI, diffusion-weighted imaging; ECE, extracapsular invasion; EPE, extraprostatic extension; FACBC, fluciclovine; FCH, fluorocholine; FDG, fludeoxyglucose; HBED-CC, N,N′-Bis(2-hydroxy-5-[ethylene-β-carboxy]benzyl)ethylenediamine N,N′-diacetic acid; LN, lymph node; LNI, lymph node involvement; LR–, negative likelihood ratio; LR+, positive likelihood ratio; M-A, meta-analysis; max, maximum; min, minimum; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; SPECT, single-photon emission computed tomography; SR, systematic review; SROC, summary receiver operating characteristic; SUVmax, maximum standardized uptake value; SVI, seminal vesicle invasion; vel, velocity.

[a]Histopathological findings on lymphadenectomy or biopsy; composite standard; clinical follow-up ≥ 12 months for C-choline PET-negative studies.

[b]Per patient.

TABLE 3. Results: Primary Studies

First Author	No. Evaluated	Comparisons	Sensitivity	Specificity	Accuracy	PPV	NPV	Detection Rate	Other Outcomes
PSMA studies									
Schmidkonz[35]	93 (2013-2017)	PSMA ligand ^{99m}Tc-MIP-1404 WB planar and SPECT/CT compared with histology	82%	76%	NR	NR	NR	97% (95% CI, 0.91 to 0.99)	Interobserver agreement was > 96% for prostate cancer
Schmidkonz[36]	225 (2013-2017)	PSMA ligand ^{99m}Tc-MIP-1404 WB planar and SPECT/CT compared with histology	NR	NR	NR	NR	NR	77% (95% CI, 0.72 to 0.83)	NR
								PSA ≥ 2 ng/mL: 90% (95% CI, 0.85 to 0.95)	
								PSA < 2 ng/mL: 54% (95% CI, 0.42 to 0.65)	
								ADT+ *v* ADT−: 86% *v* 71% ($P < .001$)	
Goffin[38]	105 (104)	PSMA ligand ^{99m}Tc-MIP-1404 WB planar and SPECT/CT compared with MRI confirmed with histology	NR	NR	NR	NR	NR	SPECT/CT: 94%	NR
								MRI: 86%	
Einspieler[40]	118 (2012-2016)	PSMA ligand ^{68}Ga-HBED-CC PET/CT	NR	NR	NR	NR	NR	PSA 2 to < 5 ng/mL: 81.8%	NR
								PSA 5 to < 10 ng/mL: 95.3%	
								PSA ≥ 10 ng/mL: 96.8% ($P = .038$)	
								ADT+ *v* ADT−: 97.7%, 86.3% ($P = .038$)	
Albisinni[43]	131 (2015-2015)	PSMA ligand ^{68}Ga-HBED-CC PET/CT	NR	NR	NR	NR	NR	NR	76% (99 of 131) had a change to their treatment plan due to ^{68}Ga results
PSMA compared with PET/CT, PET/MRI, or PET alone									
Habl[37]	100 (2013-2016)	PSMA ligand ^{68}Ga-HBED-CC PET/CT compared with PET/MRI	NR	NR	NR	NR	NR	NR	43% of patients had a stage change due to ^{68}Ga PET/CT
									59% of patients had a change to the RT plan based on ^{68}Ga PET/CT

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TABLE 3. Results: Primary Studies (continued)

First Author	No. Evaluated	Comparisons	Sensitivity	Specificity	Accuracy	PPV	NPV	Detection Rate	Other Outcomes
Freitag[39]	119 (2013-2016)	PSMA ligand ^{68}Ga PET/CT compared with ^{68}Ga PET/MRI and mpMRI	NR	NR	NR	NR	NR	^{68}Ga PET/CT: 7.6% ^{68}Ga PET/MRI: 7.6% mpMRI: 15.1% $P = .004$	NR
Berliner[42]	83 (2015-2016)	PSMA ligand ^{68}Ga I&T PET/CT compared with ^{68}Ga-HBED-CC PET/CT	NR	NR	NR	NR	NR	$P > .05$ for all PSA levels	NR
Rahbar[45]	82 (2014-2015)	PSMA ligand ^{177}Lu 617 therapy followed by ^{68}Ga PSMA PET to confirm PSMA expression	NR	NR	NR	NR	NR	NR	64% experienced a PSA decline (31% experienced a > 50% decline in PSA)
Pfister[46]	66 (38) (2014-2015)	PSMA ligand ^{68}Ga-HBED-CC PET/CT compared with ^{18}F-fluoroethycholine PET/CT and histology	86.9% *v* 71.2%	93.1% *v* 86.9%	91.9% *v* 82.5% ($P < .05$)	75.7% *v* 67.3%	96.6% *v* 88.8% ($P < .05$)	NR	NR
Larbi[49]	96 (2012-2013)	WB-MRI/DWI	NR	NR	NR	NR	NR	NR	28% of patients with mHNPC were oligometastatic 50% of patients with mCRPC were oligometastatic
Ceci[51]	70	PSMA ligand ^{68}Ga-HBED-CC PET/CT	NR	NR	NR	NR	NR	74.2% PET+: higher PSA and faster PSA dt PET−: lower PSA and longer PSA dt	NR
^{18}F PET/CT or ^{11}C PET/CT									
Akin-Akintayo[44]	87	^{18}F-FACBC PET/CT pre– and post–radiation treatment decision	NR	NR	NR	NR	NR	81%	40.5% of patients experienced a change in their treatment plan after ^{18}F PET/CT ($P < .001$)

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TABLE 3. Results: Primary Studies (continued)

First Author	No. Evaluated	Comparisons	Sensitivity	Specificity	Accuracy	PPV	NPV	Detection Rate	Other Outcomes
Odewole[47]	Prostatic bed (51/53)	^{18}F-FACBC PET/CT *v* CT	88.6% (95% CI, 72.3% to 96.3%) *v*	56.3% (95% CI, 30.6% to 79.2%) *v*	78.4% (95% CI, 64.7% to 88.7%) *v*	81.6% (95% CI, 65.1% to 91.7%) *v*	69.2% (95% CI, 38.7% to 89.6%) *v*	58.5%	NR
			11.4% (95% CI, 3.7% to 27.7%)	87.5% (95% CI, 60.4% to 97.8%)	35.3% (95% CI, 22.4% to 49.9%)	66.7% (95% CI, 24.1% to 94.0%)	31.1% (95% CI, 18.6% to 46.8%)	7.5%	
			$P < .05$	$P < .05$	$P < .05$	$P < .05$	$P < .05$		
	Extraprostatic (41/53)		46.2% (95% CI, 27.1% to 66.4%)	100% (95% CI, 74.7% to 100%)	65.9% (95% CI, 49.4% to 79.9%)	100% (95% CI, 69.8% to 100%)	51.7% (95% CI, 32.9% to 70.1%)	22.6%	
			11.5% (95% CI, 3.0% to 31.3%)	100% (95% CI, 74.7% to 100%)	43.9% (95% CI, 28.5% to 60.3%)	100% (95% CI, 31% to 100%)	39.5% (95% CI, 24.5% to 56.5%)	5.7%	
			$P < .001$	$P = .32$	$P = .05$	$P = .3$	$P < .001$		
Dietlein[41]	191	^{18}F-DCFPyL PET/CT (n = 62); ^{68}GA-HBED-CC PET/CT (n = 129)	88% *v* 66%	NR	NR	NR	NR	NR	NR
			PSA 3.5 μg/L						
			$P < .05$						
Nanni[48]	100	^{18}F-FACBC PET/CT	37%	67%	38%	97%	4%	NR	NR
		^{11}C-choline PET/CT	32%	40%	32%	90%	3%		
Barchetti[50]	152 (2011-2014)	^{18}F-choline PET/CT	99%	98%	98%	98%	96%	NR	NR
		WB-MRI	98%	99%	98%	97%	98%		
Schuster[52]	115 (2007-2012)	^{18}F-FACBC PET/CT	Prostatic bed: 90.2%	Prostatic bed: 40%	Prostatic bed: 73.6%	Prostatic bed: 75.3%	Prostatic bed: 66.7%	NR	NR
			EPE: 55%	EPE: 96.7%	EPE: 72.9%	EPE: 95.7%	EPE: 61.7%		
		^{111}In-capromab pendetide SPECT/CT	Prostatic bed: 67.2%	Prostatic bed: 56.7%	Prostatic bed: 63.7%	Prostatic bed: 75.9%	Prostatic bed: 45.9%		
			EPE: 10%	EPE: 86.7%	EPE: 42.9%	EPE: 50%	EPE: 41.9%		

Abbreviations: ^{177}Lu 617, lutetium; ^{99m}Tc MIP-1404, ^{99m}Tc-trofolastat; ADT–, androgen deprivation therapy not administered; ADT+, androgen deprivation therapy administered; CT, computed tomography; DCFPyL, *N*-[*N*-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine; dt, doubling time; DWI, diffusion-weighted imaging; EPE, extraprostatic extension; FACBC, fluciclovine; HBED-CC, N,N′-Bis(2-hydroxy-5-[ethylene-β-carboxy]benzyl)ethylenediamine N,N′-diacetic acid; I&T, imaging and therapy; mCRPC, metastatic castration-resistant prostate cancer; mHNPC, metastatic hormone-naïve prostate cancer; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; NR, not reported; PET, positron emission tomography; PET+, PET positive; PET−, PET negative; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RT, radiotherapy; SPECT, single-photon emission computed tomography; WB, whole body.

specificity of 93% (95% CI, 83% to 98%) for the detection of recurrent disease with ^{11}C-acetate PET. It also found recurrence detection was higher for patients following surgery and/or radiotherapy and for patients with PSA at > 1 ng/mL at relapse.

- Umbehr et al,[29] in a systematic review of 44 studies including 2,293 patients in which 29 studies were pooled, found both ^{11}C-choline PET and ^{18}F-choline PET to be useful in restaging patients with biochemical recurrence to determine the best treatment plan.
- In a systematic review of 15 studies involving 1,256 patients, von Eyben et al[20] found ^{68}Ga-PSMA PET/CT to have utility in the detection of disease recurrence for patients with rising PSA after radical prostatectomy with PSA levels < 1.0 ng/mL.
- Fitzpatrick et al,[18] in a systematic review of 24 studies involving 2,408 patients, found ^{68}Ga-PSMA PET/CT associated with good sensitivity (33% to 93%) and high specificity (> 99%). The likelihood of detection was found to increase with rising PSA levels and at low PSA levels, was greater than that of current choline tracers. Early detection of recurrence does allow for changes to any follow-up treatment plan. The authors note that detection may be affected by tracer trapping, androgen deprivation therapy (ADT), and levels of PSMA expression.
- In a systematic review of 18 cohort studies involving 2,219 patients, von Eyben et al[19] found no difference in detection rates between ^{11}C-choline PET/CT and ^{18}F-FCH PET/CT in patients with suspected recurrence (P = .26).
- Fanti et al,[24] in a systematic review of 29 diagnostic studies involving 2,686 patients, found ^{11}C-choline PET/CT to have high accuracy and good sensitivity (89%) and specificity (89%) to detect local and/or distant recurrence in previously treated patients with prostate cancer.
- In a systematic of review of 19 studies involving 1,555 patients, Evangelista et al[32] found both ^{18}F-choline PET or ^{11}C-choline PET or PET/CT to have high pooled sensitivity (81.8%; 95% CI, 77.9% to 85.2%) and specificity (91.4%; 95% CI, 88.3% to 93.9%) to detect local and/or distant recurrence in previously treated patients with prostate cancer.
- In a systematic review of 16 studies involving 1,447 patients (including 23 controls), Alfarone et al[34] found multiparametric MRI (mpMRI) superior to ^{18}F-choline or 11C-choline PET/CT in detecting local recurrence in patients with low PSA and with small-diameter lesions.
- Ren et al,[21] in a systematic review of 6 studies involving 251 patients, found ^{18}F-fluciclovine PET/CT to have high sensitivity (88%) and acceptable specificity (67%) to detect prostate cancer recurrence.
- Shen et al,[27] in a systematic review of 18 studies involving 1,102 patients, found MRI superior to ^{11}C-choline PET/CT, SPECT, and bone scintigraphy in the detection of bone metastases on a per-patient basis but found PET/CT to be superior to bone SPECT and bone scintigraphy on a per-lesion basis, with a higher diagnostic odds ratio and maximum sensitivity and specificity scores (Q*).
- In a systematic review of 7 studies involving 603 patients, Silva et al[31] found 1.5-T MRI to have low sensitivity (49%) and specificity (58%) when used for the diagnosis and staging of prostate cancer but that specificity increased when used to determine seminal vesicle invasion (96%) and extraprostatic extension (82%), while sensitivity remained low for both (45% and 49%, respectively).
- In a systematic review of 18 studies (10 of which were pooled) involving 441 patients, Evangelista et al[33] found ^{11}C-choline PET/CT or ^{18}F-choline PET/CT to have low pooled sensitivity (0.43; 95% CI, 0.33 to 0.53) but high specificity (0.95; 95% CI, 0.91 to 0.97) in the detection of lymph node metastases prior to surgery in patients with prostate cancer.
- In a systematic review of 75 studies involving 5,681 patients, de Rooij et al[25] found MRI (diffusion-weighted [DW] imaging, dynamic contrast enhanced [DCE]) to have high specificity but low sensitivity for staging local prostate cancer. Use of an endorectal coil demonstrated no increase in detection rates for extracapsular extension but did demonstrate higher sensitivity for detecting seminal vesicle involvement.
- In a systematic review of 16 studies involving 1,309 patients, Perera et al[22] found ^{68}Ga-PSMA PET to have superior sensitivity and specificity compared with choline-based PET imaging options and that rising PSA values and positive ^{68}Ga-PSMA PET results are correlated.

Primary research articles. Eighteen primary research articles[35-52] were obtained. Full details are provided in Table 3:

- Three studies[35,36,38] investigated the role of the PSMA binding ligand ^{99m}Tc-MIP-1404 imaged with whole-body planar and SPECT/CT compared with histology, and one of these[38] compared the results of both against MRI findings. The detection rates with ^{99m}Tc-MIP-1404 whole-body planar and SPECT/CT were found to vary with PSA level in one study,[36] with higher PSA being associated with higher detection rates. In this same study, ADT was also associated with higher detection rates (ADT positive, 86%; ADT negative, 71%; P < .001). The study that compared ^{99m}Tc-MIP-1404 SPECT/CT with MRI found higher detection rates for SPECT/CT (SPECT/CT, 94%; MRI, 86%).[38]
- Seven[37,39,40,42,43,46,51] studies reported on PSMA binding ligand ^{68}Ga PET/CT. Two[40,43] reported on PSMA binding ligand ^{68}Ga imaged with PET, and five[37,39,42,46,51] reported on PSMA binding ligand ^{68}Ga imaged with PET in comparison with PET/CT,

PET/MRI, or mpMRI. Einspieler et al,[40] in a study of the PSMA binding ligand ^{68}Ga imaged with PET/CT, found that the detection rate increased with both PSA and with ADT (PSA 2 to < 5 ng/mL, 81.8% *v* PSA 5 to < 10 ng/mL, 95.3% *v* PSA ≥ 10 ng/mL, 96.8%; $P = .038$) and ADT (ADT positive, 97.7% *v*; ADT negative, 86.3%; $P = .038$). Two studies[37,43] reported that changes to the treatment plan were made based on the results, with the study by Albisinni et al[43] reporting changing 76% (99 of 131) of the planned treatments and the study by Habl et al[37] reporting changing the staging of 43% of patients and 59% of patients having a change made to the radiation treatment plan due to ^{68}Ga-PSMA PET/CT outcomes. For detection of prostate cancer, the study reported by Freitag et al[39] found equivalent rates between ^{68}Ga-PSMA-11 PET/CT and ^{68}Ga-PSMA-11 PET/MRI (PET/CT, 7.6%; PET/MRI, 7.6%) but found both to be inferior to mpMRI (15.1%; $P = .004$). The two ^{68}Ga-HBED-CC studies reported by Berliner et al[42] and Ceci et al[51] both found that detection rates increased with PSA. For Berliner et al, this difference was significant at all PSA levels ($P < .05$), and for Ceci et al, while reporting an overall detection rate of 74.2%, having a positive PET scan was associated with higher PSA rates and faster PSA doubling times, and negative PET scans were associated with the reverse. Of these 7 studies, only Pfister et al[46] reported on measures of diagnostic utility with ^{68}Ga-HBED-CC being associated with higher sensitivity (86.9% *v* 71.2%), specificity (93.1% *v* 86.9%), accuracy (91.9% *v* 82.5%), positive predictive value (PPV; 75.7% *v* 67.3%), and negative predictive value (NPV; 96.6% *v* 88.8%) compared with ^{18}F-fluoroethylcholine PET/CT, but only accuracy and NPV were statistically different at $P < .05$.

- One study, reported by Rahbar et al,[45] examined radionuclide therapy with the PSMA binding ligand ^{177}Lu 617 followed by ^{68}Ga-PSMA PET to confirm PSMA expression and found that 64% of patients (53 of 82) experienced a PSA decline (31% experienced a > 50% decline in PSA).
- One study, reported by Larbi et al,[49] examined whole-body MRI/DW imaging in the detection of oligometastatic disease (defined in that study as ≤ 3 synchronous lesions) for treatment planning and found 28% of all patients with metastatic and hormone-naive prostate cancer were oligometastatic and that 50% of patients with metastatic CRPC were oligometastatic.
- Six[41,44,47,48,50,52] reported on ^{18}F with various radiotracers against other modalities. The study by Akin-Akintayo et al,[44] in a comparison of ^{18}F-fluciclovine PET/CT pre– and post–radiation treatment decision, reported a detection rate of 81%, while 40.5% of patients experienced a change in their treatment plan after PET/CT ($P < .001$). The study by Odewole et al,[47] in a comparison between ^{18}F-fluciclovine PET/CT and CT alone, reported a detection rate of 77.4% with PET/CT versus 18.9% with CT alone ($P < .05$). Five studies reported on measures of diagnostic utility. The study by Odewole et al,[47] in a comparison between ^{18}F-fluciclovine PET/CT and CT alone, found significantly higher sensitivity, accuracy, PPV, and NPV (all $P < .05$) associated with ^{18}F-fluciclovine PET/CT in the prostate/bed, while CT alone reported significantly higher specificity in the prostate/bed. For extraprostatic disease, ^{18}F-fluciclovine PET/CT in comparison with CT alone had significantly higher sensitivity and NPV ($P < .05$), borderline higher accuracy ($P = .05$), and similar high specificity and PPV of 100%, respectively. The study by Dietlein et al,[41] in a comparison between 2 PSMA binding ligands (^{18}F-DCFPyL PET/CT and ^{68}GA-HBED-CC PET/CT), reported sensitivity of 88% with ^{18}F-DCFPyL PET/CT *v* 66% with ^{68}Ga-HBED-CC PET/CT for PSA values < 3.5 μg/L ($P < .05$). The study by Nanni et al,[48] in a comparison between ^{18}F-fluciclovine PET/CT and ^{11}C-choline PET/CT, reported superior sensitivity, specificity, accuracy, PPV, and NPV associated with fluciclovine PET/CT over choline PET/CT (*P* values not reported). In a comparison between ^{18}F-choline PET/CT and whole-body MRI, Barchetti et al[50] found equivalent sensitivity, specificity, accuracy, PPV, and NPV. Schuster et al,[52] in a comparison between ^{18}F-fluciclovine PET/CT and ^{111}In-capromab pendetide SPECT/CT for measures of diagnostic utility in scans of the prostatic bed and extraprostatic extension, found ^{18}F-fluciclovine PET/CT superior to ^{111}In-capromab pendetide SPECT/CT for sensitivity and accuracy, and without significant differences for specificity, PPV, and NPV for scans of the prostatic bed; and found ^{18}F-fluciclovine PET/CT superior to ^{111}In-capromab pendetide SPECT/CT for sensitvity, accuracy, PPV, and NPV, and equivalent high specificity for scans of extraprostatic extension.

RECOMMENDATIONS

CLINICAL QUESTION 1

What is the goal of imaging in advanced prostate cancer?

Recommendation 1

Imaging is recommended for all patients with advanced prostate cancer. See the recommendation under clinical question 4 for specific details according to clinical scenario (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Literature review, analysis, and clinical interpretation. All the evidence obtained in this clinical practice guideline (17 systematic reviews with or without meta-analysis and 18 primary articles) supported the use of imaging in advanced prostate cancer. The goal of imaging in advanced prostate cancer is to facilitate the accurate and timely detection and localization of sites of prostate cancer spread and extent,

thus contributing to the decision-making process for treatment planning, follow-up, and response assessment.

CLINICAL QUESTION 2

What imaging techniques are available for imaging advanced prostate cancer?

Recommendation 2

One or more of the following imaging modalities should be used for patients with advanced prostate cancer: conventional imaging (defined as CT, bone scan, and/or prostate MRI) and/or NGI (PET, PET/CT, PET/MRI, whole-body MRI), according to clinical scenario (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Literature review, analysis, and clinical interpretation. **Plain film/CT.** Plain film radiography relies on the differential penetration of ionizing radiation (x-rays) through body tissues of variable density to produce a 2-dimensional representation of part of the anatomy. Its use in prostate cancer is limited, including assessment of questionable bone scan findings as a crude measure of bony metastasis, as well as for rapid assessment of complications (eg, bone fractures, pneumonia). Although large bone metastases can be visible on plain radiography, the modality plays a limited role in achieving the presented goals of imaging in advanced prostate cancer.

CT also relies on x-rays but takes advantage of computational postprocessing tools to generate high-resolution 3-dimensional images with exquisite anatomic detail. CT is extensively used in staging and response assessments of many cancers. Its main advantages are wide availability and rapid imaging acquisition (a whole-body scan can be performed in only a few seconds). The main limitations in advanced prostate cancer are (1) relatively poor performance for detection of bone metastases, as a substantial amount of cortical destruction is necessary before bone lesions are visible on CT, and thus early metastases are not detected, and (2) limited assessment of lymph node metastases primarily due to heavy reliance on morphologic features (eg, size, shape, borders). CT is unable to identify micrometastases in normal-sized nodes and unable to accurately distinguish enlarged hyperplastic (benign) from malignant nodes. CT is useful for the assessment of questionable bone scan findings by demonstrating benign conditions (trauma, degenerative changes) that result in false-positive appearances on bone scan.

MRI. MRI produces multiplanar images without the need for potentially harmful ionizing radiation. The strong magnetic field in the bore of an MRI scanner causes protons (which are naturally abundant in the human body) to align in its direction. A radiofrequency (RF) pulse is then applied to "spin" the body's protons out of equilibrium. Advanced computational tools are then used to generate images based on the data collected, including the amount of energy released and the time it takes protons to "realign" with the magnetic field once the RF pulse is turned off. Multiple imaging acquisition parameters can be modified to provide different "weighting" of the images (eg, T1, T2 weighting), each providing different degrees of visualization representing different physical and biologic properties of tissues. Compared with CT, MRI is particularly useful in the assessment of the bone marrow, as bone marrow edema resulting from early seeding of metastatic cancer foci, not visible on CT, can be depicted on MRI. MR also superbly delineates the prostatic zonal anatomy not clearly visualized on other modalities and has thus firmly established itself as the imaging tool of choice for the assessment of primary prostatic tumors, using a multiparametric acquisition approach combining "anatomic" (T1- and T2-weighted) and "functional" (DW and DCE) sequences. Limitations of MRI include longer examination times compared with CT (pelvic MRI typically 20-30 minutes; whole-body MRI approximately twice as long); interpretation expertise not as widely available; and shortcomings with regard to lymph node metastases, which also rely heavily on the same morphological features assessed with CT. Due to increasing evidence of gadolinium deposition in normal tissues (eg, brain) and lack of knowledge of the long-term health implications of this finding, it is widely advocated that intravenous gadolinium for MRI is only used when potential benefits outweigh risks.

Improvements in diagnostic performance for detection of lymph node metastasis can be obtained by using nomograms that consider the pretest probability based on the risk status of the primary tumor and local staging information.[51] Taken together, the general test performance of morphologic imaging remains limited when histologic correlations using template lymphadenectomy is used as the standard of reference; a recent meta-analysis showed a CT scan sensitivity of 42% (95% CI, 20% to 56%) and specificity of 82% (95% CI, 80% to 83%), while MRI had a sensitivity of 39% (95% CI, 19% to 56%) and specificity of 82% (95% CI, 79% to 83%).[52] Thus, morphologic CT and MRI misrepresent nodal status and can misdirect the therapeutic approach. There have been concerted efforts to improve metastatic nodal detection test performance, and one promising technique is ferumoxtran-10–enhanced MRI, which has been shown to be able to detect microscopic nodal disease.[53] Unfortunately, lack of general commercial availability and regulatory approval makes this method of assessment unobtainable for most.

Bone scintigraphy. Bone scans date back to the 1960s. Over the course of time, the technique found favor for being relatively inexpensive and capable of whole-body assessment. It involves administration of a diphosphonate, which mimics phosphate in bone mineral and adsorbs to areas of active bone formation, particularly around metastases where osteoblastic activity is prominent. In some cases, it can detect lesions not seen by CT.[54-56] However, there are

numerous disadvantages. As the bone scan images not the tumor itself but the body's response to it, new bone formation in response to tumor responding to therapy can appear as a new lesion (flare response).[57,58] As a result, Prostate Cancer Working Group 3 guidelines require new bone lesions to be seen on two consecutive scans, and new lesions to be seen on the second scan, before progression can be called.[4] Although this approach leads to a reliable diagnosis of bone metastases, there is an inherent delay in establishing this due to the need for confirmatory scans. It can also be difficult to quantify disease and therefore track progression. A quantitative measure of involved bone, the BSI, has been developed, and correlates with overall survival; however, its validity as a biomarker is still under study.[59] A normal bone scan produces two-dimensional images; the three-dimensional imaging option, SPECT, is very slow, only allowing imaging of perhaps one or two anatomic segments of the body, such as the chest and abdomen or abdomen and pelvis, over the course of 30 minutes (compare this with a PET scanner, which can scan the whole body in about 15 to 20 minutes or less). Finally, of course, a bone scan only examines the bones and will ignore lymphatic or visceral metastases detected by CT, MRI, or PET.

There is a large generic body of evidence for the use of bone scan in prostate cancer. A recent meta-analysis looked specifically at the yield of bone scintigraphy in the initial staging of treatment-naïve prostate cancer, and found a (relatively low) yield of 3.5% with PSA $\leq$ 10, 6.9% with 10 $<$ PSA $\leq$ 20, and 41.8% with PSA $>$ 20 over 54 studies.[60] Detection rate is similarly 4.1% with Gleason score $\leq$ 6, 10% with Gleason score 7, and 28.7% with Gleason score $\geq$ 8. This suggests that the existing practice of using bone scan specifically for initial staging of higher-risk patients (and not using it for lower-risk patients) is sound.

PET and PET/CT. PET/CT with a variety of radiopharmaceuticals has received much attention in oncology over the past several years in alleviating many of the limitations of standard imaging methods. The radiopharmaceutical used in PET consists of a pharmaceutical agent or "tracer" (with biologic properties [eg, receptor binding] determining its site of accumulation in the body) labeled with a positron emitting radioisotope (eg, ^{18}F [absorption half-life [$t_{1/2}$], 110 minutes], ^{11}C [$t_{1/2}$, 20 minutes], ^{68}Ga [$t_{1/2}$, 68 minutes]), which will allow its detection with a PET camera. FDG labeled with the isotope ^{18}F is the most common PET radiopharmaceutical used in oncology. FDG accumulation in tumors is related to elevated glucose metabolism in malignant tissue. In prostate cancer, the diagnostic performance of FDG PET/CT is highly dependent on the phase of the disease. Cumulative current evidence suggests that FDG PET may be useful in the imaging evaluation of extent and treatment response in metastatic castration-resistant disease[61] but not in localized prostate cancer or in early noncastrate metastatic states. Lipogenesis radiopharmaceuticals, including ^{11}C-acetate and ^{18}F- or ^{11}C-labeled choline, have also been investigated relatively extensively. Most studies, primarily from Europe and Japan, with choline-based radiotracers have focused on the biochemical recurrence of disease. ^{11}C-choline was approved in the United States in 2012 for imaging evaluation of men with biochemical recurrence of prostate cancer after definitive primary therapy. More recently in 2016, the amino acid analog PET radiotracer ^{18}F-fluciclovine was also approved in the United States for imaging evaluation of men with biochemical recurrence of prostate cancer. There are several other unapproved PET radiotracers that are actively being investigated in the imaging evaluation of prostate cancer. Of these radiotracers, those targeting the PSMA receptor have received much attention with exciting results. PSMA is a transmembrane protein expressed in the secretory cells of the prostate epithelium as well as non-prostate normal and malignant tissues. In prostate cancer, the PSMA cleavage of vitamin B9 (folic acid) stimulates oncogenic signaling through glutamate receptors with downstream activation of the PI3K-Akt-mTOR signaling pathway.[62] Recent strides in synthesis of small-molecule inhibitors of PSMA targeting the extracellular epitope of PSMA have demonstrated major potential utility in targeted radionuclide imaging and treatment (theranostics) of metastatic prostate cancer. Most studies have reported on ^{68}Ga-PSMA-11 (also known as HBED-CC). Other PSMA binding ligands include ^{68}Ga-PSMA imaging and therapy; ^{68}Ga-PSMA-617; and more recently, ^{18}F-DCFPyL and ^{18}F-PSMA-1007.[63,64] Studies have generally shown superior diagnostic performance of these radiotracers over other relevant radiotracers in the clinical settings of intermediate- to high-risk primary cancer, biochemical recurrence after definitive therapy, and delineation of extent of metastatic disease and patient eligibility for PSMA-targeted radioligand therapy.[22] 89-Zr–labeled PSMA-targeting antibodies and minibodies have also been reported, but practicalities surrounding their use (eg, serial days uptake required between administration and imaging) have resulted in their development being largely restricted to tertiary academic centers. It must be noted that false-negatives and false-positives can occur with PSMA PET imaging.[65] There is also literature on proposed procedure guidelines and interpretation and reporting standards.[66-70] A number of studies have reported on the major impact of PSMA PET imaging on management of patients with prostate cancer, although the potential influence on outcome will need additional investigations.[71-73] It is hoped that of the several PSMA-based imaging agents that have been evaluated, the most optimal agent will emerge that will become approved, available, and accessible.

In general, radiocholine may be useful in this clinical setting when PSA $>$ 2 ng/mL (or PSA $<$ 1 ng/mL if primary Gleason score was 7or more), PSA doubling time is less than 6 months, or PSA velocity is greater than 2 ng/mL/year.

Higher serum PSA level during biochemical recurrence is generally associated with higher detectability on choline PET, with a pooled sensitivity and specificity of 80.9% and 84.1%, respectively.[74] The diagnostic performance of ^{18}F-fluciclovine in the detection of potential lesions is also positively associated with PSA level. In the clinically relevant low PSA range of < 1 ng/mL in men with biochemical recurrence of prostate cancer after radical prostatectomy and off hormonal therapy, the detectability of ^{18}F-fluciclovine PET has been reported to be 21% in comparison with 14% with ^{11}C-choline.[48] However, in general, these two approved radiotracers appear to be similar in terms of lesion detectability and positive correlation with serum PSA level in the clinical setting of biochemically recurrent prostate cancer.[75]

PET/MRI. PET/CT has dominated the molecular imaging landscape for almost two decades as it combines the sensitivity and specificity of PET and the anatomic depiction of CT. PET/MRI devices have been available since 2010 and have been tried in a broad range of clinical settings. However, in general, they have not provided a distinct advantage over PET/CT beyond the simultaneous acquisition of diagnostic PET and MRI when both tests are clinically indicated. PET/MRI can be helpful in specific cases. In theory, PET/MRI devices have several advantages over PET/CT, including that MRI provides not only anatomy but also functional imaging information that could increase the specificity of PET findings, and in several regions, such as the pelvis and bones, MRI provides additional information that could help to characterize a lesion with PET uptake.

In the initial diagnosis and biopsy of primary prostate cancer, numerous studies have documented an advantage to tumor localization using a combination of PET and MRI either at separate settings or obtained simultaneously in PET/MRI scanners.[76] The most documented advantage is found for PSMA PET imaging in which numerous studies document improvement in detection when combining PET and MRI,[76-81] although similar findings have been noted with fluciclovine.[82-84] Not all studies are positive, and PET/MRI with ^{11}C-choline[76,85] and one study of PSMA[86] showed no advantage to PET/MRI. Occasionally, MRI is negative, but PET, particularly with PSMA-targeted agents, is positive,[78,81] aiding in diagnosis. On the other hand, PSMA-negative primary tumor occurs in up to 5%-10%.[87] MRI also provides better evaluation of local staging in high-risk patients, such as extraprostatic extension or seminal vesicle invasion, than can PET/CT due to superior spatial and contrast resolution.

In biochemical recurrence, the ability to document sites of localized recurrence (*v* nodal or bony disease) is perceived as a potential advantage for PET/MRI across many agents.[63,76,77,80] Particular benefits of MRI versus CT include absence of clip artifacts from prior node dissections and absence of streaking artifacts from dense contrast media within the bladder that can interfere with CT scans. In metastatic disease, there is a perceived advantage of whole-body MRI in detecting bone marrow changes[76,81] based on the sensitivity of DW-MRI for subtle bone disease and the high contrast of T1-weighted sequences for bone marrow replacement. However, few studies of prostate cancer with PET/MRI have been performed, and so there is an absence of strong data in this setting. For metastatic disease, whole-body imaging sequences can add considerable time to the scan. Thus, such whole-body imaging is limited to one sequence (eg, DW or T2-weighted turbo spin echo) and/or postcontrast-enhanced MRI, which are the most time efficient methods of evaluating the bones in conjunction with PET. However, this causes a significant increase in scanning time. Thus, while the increased sensitivity of MRI for bone lesions could be helpful in patients with suspected metastatic disease, especially with a negative CT, clinical trial evidence is not yet available to support this.

The advantages of PET/MRI must be weighed against multiple disadvantages. The cost of such hybrid devices is approximately 2-3 times that of a conventional PET/CT. Cost recovery is more difficult as the scans take longer to obtain, reducing throughput compared with PET/CT. Additional unresolved issues include the accuracy of standardized uptake value measurements on PET/MRI compared with PET/CT. Moreover, it is unclear whether it is vital that MRI and PET be obtained simultaneously in a PET/MRI hybrid scanner or can be obtained separately as a PET/CT and a dedicated MRI. It is possible that a PET/CT and a stand-alone MRI could be performed and achieve the same advantages without the cost of an expensive hybrid scanner.[85,88]

Capromab pendetide. Capromab pendetide is an ^{111}In-labeled antibody directed against the intracellular epitope of PSMA. It is imaged using SPECT/gamma cameras and is currently approved for initial staging of high-risk patients and in localization of recurrence after biochemical failure. Due to the difficulties of antibody imaging (imaging is slow, occurring 3-5 days after injection, and burdened by physiologic and generic antibody uptake in the bone marrow, liver, and spleen) and the poor sensitivity due to the intracellular localization of the epitope (making it unable to visualize living cancer cells, particularly in bone), the study is rarely performed at present. Among the few studies comparing capromab pendetide directly to other imaging modalities (no meta-analyses exist), one of 93 patients found it inferior to the new agent fluciclovine at 10% sensitivity and 87% specificity for extraprostatic disease versus 55% sensitivity and 97% specificity[48] for recurrence. A similar study with 50 patients showed 10% sensitivity and 100% specificity versus fluciclovine with 100% sensitivity and specificity for extraprostatic disease.[89] An old study comparing capromab pendetide to FDG PET and CT showed lower detection rates, although sample size was very small (n = 21 patients).[90]

CLINICAL QUESTION 3

What are the unmet needs and potential impact of imaging according to different prostate cancer disease states?

Recommendation 3

It is recommended when choosing an imaging modality that disease states and clinical scenarios as outlined are taken into consideration, as the imaging modality may guide treatment or change clinical treatment decisions (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Literature review, analysis, and clinical interpretation. Prostate cancer frequently recurs despite negative conventional imaging, presumably partly due to unrecognized residual disease after treatment or distant metastatic disease. For this reason, there is an unmet need for accurate diagnosis of metastatic disease for accurate staging, appropriate counseling, and adequate treatment planning for all stages of the disease. Improved and more accurate diagnosis of disease outside of the prostate or subclinical metastatic disease offers the potential to modulate or change treatment. More accurate staging at initial diagnosis could influence the local therapy offered (surgery, radiotherapy, ablation, surveillance, and so on). For initial surgery, imaging can impact planning of nerve-sparing procedures and help to determine the extent of lymphadenectomy. For radiotherapy, the duration of concurrent and adjuvant ADT could be impacted as well as the extent of radiation field (whole pelvic to include nodal drainage or just prostate). At the time of biochemical recurrence after local therapy, the aggressiveness and targeting of salvage local therapy could also be impacted. For patients with advanced disease, the timing of changes in systemic therapies and the accurate ability to monitor response to therapy could be impacted by more accurate imaging.

CLINICAL QUESTION 4

When and what type of imaging is appropriate in each scenario?

Newly Diagnosed Clinically High-Risk/Very High-Risk Localized Prostate Cancer

Recommendation 4.1. Conventional imaging negative

When conventional imaging (defined as CT, bone scan, and/or prostate MRI) is negative in patients with a high risk of metastatic disease, NGI (defined as PET, PET/CT, PET/MRI, whole-body MRI) may add clinical benefit, although prospective data are limited (Type: informal consensus, benefits/harm ratio uncertain; Evidence quality: weak; Strength of recommendation: moderate).

Recommendation 4.2. Conventional imaging suspicious/equivocal

When conventional imaging is suspicious or equivocal, NGI may be offered to patients for clarification of equivocal findings or detection of additional sites of disease, which could potentially alter management, although prospective data are limited (Type: informal consensus, benefits/harm ratio uncertain; Evidence quality: weak; Strength of recommendation: moderate).

Literature review, analysis, and clinical interpretation. Patients presenting with high-risk, including locally advanced, prostate cancer have a high probability of harboring metastatic disease. The prevalence of metastases is reported to be between 30% and 50% of patients, depending on the sensitivity of the method used for disease detection.[91] Metastases are most commonly located within regional pelvic lymph nodes and in bone, with metastases located at other distant sites being rare at this stage of the disease.

There is wide geographic variation in the availability of NGI technologies (whole-body MRI and PET/CT), but when available, they should be considered in the context of a clinical trial so that generalizable data can be recorded. For the detection of metastatic bone disease, the combination of bone scans and CT perform suboptimally compared with whole-body MRI and various PET/CT radiopharmaceuticals.[92] Systematic analyses, prospective clinical studies, and meta-analyses have shown comparative test performance of whole-body MRI to NaF and choline PET/CT for the skeletal assessments in advanced prostate cancer.[27,84] Shen et al[27] conducted a meta-analysis of 27 studies in advanced prostate cancer showing MRI was superior to choline PET/CT and bone scan for metastasis detection on a per-patient basis. On a per-patient basis, the pooled sensitivities for bone disease by using choline PET/CT, whole-body MRI, and bone scan were 91% (95% CI, 83% to 96%), 97% (95% CI, 91% to 99%), and 79% (95% CI, 73% to 83%), respectively. The pooled specificities for bone metastases detection using choline PET/CT, whole-body MRI, and bone scan were 99% (95% CI, 93% to 100%), 95% (95% CI, 90% to 97%), and 82% (95% CI, 78% to 85%), respectively. On a per-lesion analysis, choline PET/CT had a higher diagnostic odds ratio that exceeded both bone scan and bone SPECT for detecting bone metastases. A recent meta-analysis also underscored the usefulness of DW-MRI in detecting bone metastases. Liu et al[93] evaluated 32 studies with 1,507 patients and showed a pooled sensitivity, specificity, and area under the curve for DW-MRI of 95% (95% CI, 90% to 97%), 92% (95% CI, 88% to 95%), and 0.98, respectively, on a per-patient basis, and 91% (95% CI, 87% to 94%), 94% (95% CI, 90% to 96%), and 0.97, respectively, on a per-lesion basis. This was recently confirmed by a prospective clinical trial where whole-body MRI was compared with NaF PET/CT.[84]

Suspicious findings on NGI would influence treatment decisions in patients with advanced prostate cancer and negative conventional imaging, opening the scope for multimodality treatment of primary and oligometastatic disease or systemic therapy for more extensive metastatic states. When evaluating the results of the meta-analyses, and indeed in all studies reporting test performance of imaging studies with any modality, it should be noted that there are intrinsic verification biases that are particularly

prevalent at lesion-level analyses because it is simply not possible to obtain histopathology for every bone lesion detected for ethical/practical clinical reasons. As a result, most studies use combinations of imaging methods and/or follow-up as the standards of reference.[84,94] Furthermore, as with all external imaging methods, microscopic metastasis are unlikely to be detected so that true-negative rates are difficult to ascertain.

When conventional imaging is suspicious or equivocal for nodal or visceral lesions in castration-sensitive patients at the highest risk of metastatic disease, there is no clear consensus or level 1 evidence to support ^{18}F-FDG PET/CT and should not be routinely offered. Whole-body MRI and NaF PET/CT may offer clinical benefit in this scenario by redefining the true extent of disease and shifting treatment decisions accordingly, although prospective data are limited.[95] There is limited experience with other PET and radionuclide agents, such as ^{18}F-fluciclovine and ^{11}C- and ^{18}F-choline, and they are not FDA approved in this setting. There is enthusiasm for the potential added value of PSMA PET/CT and PET/MRI for the assessment of the local and metastatic extent of prostate cancer in this context,[80,96,97] although PSMA imaging is currently not FDA approved and should thus be only performed as part of clinical trials or other controlled research settings.

Rising PSA After Prostatectomy and Negative Conventional Imaging (either initial PSA undetectable with subsequent rise or PSA never nadirs to undetectable)

Recommendation 4.3

Both disease states are indicative of potentially undetected, residual local, locoregional, or micrometastatic disease, and imaging options are not distinct or different between these scenarios. The goal of therapy and the potential use of salvage local therapies in these scenarios should guide the choice of imaging. For men who are not candidates or are unwilling to receive salvage local or regional therapy, additional NGI should not be offered (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 4.4

For men for whom salvage radiotherapy is contemplated, NGI should be offered (PSMA imaging [where available]; ^{11}C-choline or ^{18}F-fluciclovine PET/CT; or PET/MRI, whole-body MRI, and/or ^{18}F-NaF PET/CT) as they have superior disease detection performance characteristics and may alter patient management (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Rising PSA After Radiotherapy and Negative Conventional Imaging

Recommendation 4.5

For men in whom salvage local or regional therapy is not planned or is inappropriate, there is little evidence that NGI will alter treatment or prognosis. The role of NGI in this scenario is unclear and should not be offered, except in the context of an institutional review board–approved clinical trial (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.6

For men for whom salvage local or regional therapy (eg, salvage prostatectomy, salvage ablative therapy, or salvage lymphadenectomy) is contemplated, there is evidence supporting NGI for detection of local and/or distant sites of disease. Findings on NGI could guide management in this setting (eg, salvage local, systemic or targeted treatment of metastatic disease, combined local and metastatic therapy). PSMA imaging (where available), ^{11}C-choline or ^{18}F-fluciclovine PET/CT or PET/MRI, whole-body MRI, and/or ^{18}F-NaF PET/CT have superior disease detection performance characteristics compared with conventional imaging and alter patient management, although data are limited (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Metastatic Prostate Cancer at Initial Diagnosis or After Initial Treatment, Hormone Sensitive

Recommendation 4.7

In the initial evaluation of men presenting with hormone-sensitive disease with demonstrable metastatic disease on conventional imaging, there is a potential role for NGI to clarify the burden of disease and potentially shift the treatment intent from multimodality management of oligometastatic disease to systemic anticancer therapy alone or in combination with targeted therapy for palliative purposes, but prospective data are limited (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.8. Nonmetastatic CRPC

For men with nonmetastatic CRPC, NGI can be offered only if a change in the clinical care is contemplated. Assuming patients have received or are ineligible for local salvage treatment options, NGI may clarify the presence or absence of metastatic disease, but the data on detection capabilities of NGI in this setting and impact on management are limited (Type: consensus, benefits/harms ratio uncertain; Evidence quality: weak; Strength of recommendation: moderate).

Recommendation 4.9. Metastatic CRPC (PSA progression)

As recommended by the Prostate Cancer Working Group 3 consensus statements,[98] PSA progression alone for men on treatment of metastatic CRPC should not be the sole reason to change therapy. Conventional imaging can be used for initial evaluation of PSA progression and should be continued to facilitate changes/comparisons and serially to assess for development of radiographic progression. (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.10

The use of NGI in this cohort is unclear, with a paucity of prospective data. When a change in clinical care is contemplated, in an individualized manner, and there is a high clinical suspicion of subclinical metastasis despite negative conventional imaging, the use of NGI could be contemplated, especially in the setting of a clinical trial (Type: informal consensus, benefits/harms ratio uncertain; Evidence quality: insufficient; Strength of recommendation: weak).

Recommendation 4.11. Radiographic progression on conventional imaging

In men with metastatic CRPC with clear evidence of radiographic progression on conventional imaging while on systemic therapy, NGI should not be routinely offered. NGI may play a role if performed at baseline to facilitate comparison of imaging findings/extent of progression of disease (Type: consensus, benefits/harms ratio uncertain; Evidence quality: insufficient; Strength of recommendation: moderate).

DISCUSSION

There has been tremendous excitement in the prostate cancer community for advanced, molecular-based, NGI. This is driven in large part by the biology of the disease as well as by the clinical need to accurately stage patients and assess the burden and extent of disease. Prostate cancer categorization utilizes the clinical disease states model, which is determined by tumor characteristics, radiographic extent of disease, and prior therapies administered, making accurate imaging paramount. The anatomy of the prostate in the pelvis, with the very delicate surrounding structures that control crucial bodily functions (urinary, rectal, and sexual function), makes accurate assessment of extent of local disease crucial. For men whose disease is no longer localized and widespread, aggressive local therapy that will adversely impact urinary, sexual, and bowel domains could carry unacceptably high adverse effects with detriment to quality of life. Conversely, aggressive local therapy that could offer potential cure may be inappropriately withheld when conventional clinical parameters, such as PSA or Gleason score, deem a man high risk, for which NGI could indicate organ-confined disease without evidence of distant disease. The availability and clinical utility of PSA, an exquisitely sensitive serum-based tumor marker for prostate cancer, can add to the complexity of accurately determining the disease state, again highlighting the importance of accurate imaging. Following the disease states model, we have drafted our recommendations utilizing common clinical scenarios in the natural history of prostate cancer treatment, for which appropriate use of imaging can be categorized.

The primary driver for obtaining imaging should be when clinicians and patients are at a treatment nexus; therefore, imaging studies that will not impact or inform treatment decisions should be minimized. The urge or instinct to order multiple imaging modalities is common for solid tumor oncology, particularly to accurately assess burden of disease and risk to the patient. The overuse of imaging, especially NGI, does carry risks of increased cost, inappropriate ionizing radiation delivery to patients, and the risk of false-positive findings, which generate fear and anxiety for patients and clinicians as well as generate other unnecessary interventions.

As previously stated, the decision for NGI for patients experiencing biochemical recurrence is predicated on the potential treatment plan. If no additional salvage therapy, such as salvage radical prostatectomy, salvage radiotherapy, salvage ablative therapy (eg, cryotherapy, high-intensity focused ultrasound therapy), or salvage lymphadenectomy, is planned because of patient concerns or preference due to potential adverse effects or medical comorbidities that preclude aggressive therapy, then the utilization and benefit of NGI is questionable.

In the arena of PET-directed imaging, there are multiple compounds in use that have been proposed, including small-molecule agents targeting PSMA as well as amino acid and fatty acid agents. There is a paucity of comparative data among these agents, and accurate comparisons between them are limited. This is an area in the future where prospective comparative studies would clarify the appropriate role and utility of these agents.

Similarly, there have been multiple isotopes in use with varying half-lives and source generators. These include primarily ^{11}C, ^{18}F, and ^{68}Ga, with several smaller studies investigating other isotopes. Comparative studies to assess the accuracy of imaging different isotopes are also lacking, and the clinical implementation of specific isotopes have been driven mostly by half-life, ease of distribution, and method of isotope generation. This is another area of opportunity for analysis in the future.

In reviewing the published literature, there is a paucity of well-designed prospective studies in NGI for prostate cancer, and this Guideline Panel endeavored to create a reasonable, evidence-based, malleable framework to guide the optimal use of imaging in patients with advanced prostate cancer. As technology evolves and current and future prospective evaluations of NGI become available, we expect that these guidelines may require updates or changes in the future.

The Advanced Prostate Cancer Consensus Conference 2017 guideline[99] recommended that imaging be performed at baseline, PSA nadir, and progression at least in patients with the usual presentation of metastatic hormone-sensitive prostate cancer. Imaging should also be performed in between these dates if there are additional clinical needs. Additionally, regular imaging monitoring of disease is recommended if there is a likelihood of aggressive variant prostate cancer (including small-cell and neuroendocrine)

when the following clinical/pathologic/imaging features are present[100]:

- Exclusively visceral metastases
- Radiographically predominant lytic bone metastases by plain x-ray or CT scan
- Bulky (≥ 5 cm) lymphadenopathy *or* bulky (≥ 5 cm) high-grade (Gleason ≥ 8) tumor mass in prostate/pelvis
- Low PSA (≤ 10 ng/mL) at initial presentation (prior to ADT or at symptomatic progression in the castrate setting) *plus* high-volume (≥ 20) bone metastases
- Presence of neuroendocrine markers on histology or in serum; marked hypercalcemia
- Raised carcinoembryonic antigen
- Short interval (≤ 6 months) to androgen-independent progression following the initiation of hormonal therapy with or without the presence of neuroendocrine markers

SPECIAL COMMENTARY

The recommendations provided are based on systematic literature review and do not specifically address the lack of universal availability of NGI modalities worldwide. Approval and payment for many NGI modalities have been hampered in the United States and other countries, both regionally and nationally, with significant angst for both patients and clinicians. This aspect is fluid and evolving, and availability should be considered when clinicians and patients pursue specific NGI modalities. As more evidence is presented that support the clinical utility of these imaging modalities, the availability of these tests may widen in the future.

PATIENT AND CLINICIAN COMMUNICATION

In panel discussions, there was robust discussion about patient counseling and concerns for false-positive and false-negative imaging results for conventional imaging as well as for NGI. It should be acknowledged that improved sensitivity for detection of low-volume metastatic disease may not be clinically relevant if there is a high false-positive rate, with attendant secondary testing, biopsy, and so forth. Additionally, there was also agreement that patients should be counseled on the life-long risk of ionizing radiation that NGI testing, particularly involving CT (eg, PET/CT), carry with the risk of subsequent malignancies. While perhaps not relevant for patients with advanced prostate cancer who have exhausted multiple lines of therapy, this does pertain to men in earlier disease states. Awareness of these issues with careful and deliberate communication is recommended between clinicians and patients.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[101]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[102-105] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

For patients with prostate cancer under 65 years of age, the 10 most common comorbidities are (in descending order) hypertension, hyperlipidemia, diabetes, ischemic heart disease, anemia, arthritis, chronic kidney disease, depression, chronic obstructive pulmonary disease (COPD), and heart failure. For patients with prostate cancer over 65 years of age, the 10 most common comorbidities are (in

descending order) hypertension, hyperlipidemia, ischemic heart disease, anemia, diabetes, arthritis, chronic kidney disease, cataract, heart failure, and COPD.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

Men with advanced prostate cancer commonly may have medical comorbidities and chronic kidney disease, which preclude the use of iodinated contrast or gadolinium. This may limit the applicability and administration of conventional and NGI in specific patient populations. An individualized approach is recommended to account for these conditions.

COST IMPLICATIONS

There has been a dramatic expansion in health care expenditures over the past 2 decades, and imaging technologies represent one of the fastest growing areas of health care spending. In particular, advanced imaging technologies, such as MRI, CT, and PET, may drive as much as 50% of these increased costs.[106] Policy levers may be able to control some of these spiraling costs[107]; however, increasingly, individuals diagnosed with cancer are required to pay a larger proportion of their treatment costs.[108-110] These higher out-of-pocket payments may represent a barrier to the initiation of and adherence to recommended cancer treatments.[111-113] Therefore, a tailored discussion of potential diagnostic and treatment costs is an important component of shared treatment decision making.[114] When feasible, clinicians should counsel patients regarding the use of less expensive alternatives for diagnosis and treatment when there is clinical equipoise or rapidly evolving therapy options, such as the case with imaging for advanced prostate cancer.[114]

Importantly, there is considerable heterogeneity in health care costs for diagnostic imaging. Variation in expenditure may be related to region, payer, hospital system, negotiated contracts, insurance status, or severity of illness, and this variability precludes a systematic and generalizable evaluation.[115] With regard to advanced imaging modalities in particular, there is substantial variation in organizational costs related to isotope procurement from external sources (^{18}F-choline), possible cyclotron expenses (^{11}C-choline), generator expenses, and radiopharmacy (^{68}Ga-PSMA) as well as the direct costs of disposable equipment and indirect costs of physicians, technologists, and radiopharmacists.[116] When discussing financial issues surrounding care delivery, patients should be made aware of any economic counseling services available to address this very complex landscape.[114]

Given the recent and rapid expansion of imaging modalities for advanced prostate cancer, there are no exhaustive comparative effectiveness analyses that encompass each of the techniques described in this guideline. There are data that suggest that advanced imaging modalities can be cost effective for patients with cancer, in general, particularly when used for monitoring therapy, staging, or diagnosis, rather than screening.[117] A formal cost-effectiveness evaluation of advanced imaging for patients with prostate cancer will have to balance the important patient-level factors specifically associated with a prostate cancer diagnosis, such as the relative longevity associated with a high-risk prostate cancer diagnosis, the loss of physical productivity, and the substantial costs associated with skeletal-related events.[118-120]

As this field continues to rapidly expand and we endeavor to clarify the most sensitive and cost-effective imaging modality for advanced prostate cancer, it will be important to consider the potential impact of the inevitable regionalization and the subsequent access challenges that these emerging, advanced technologies will likely create. This will be a particularly important consideration for populations at already increased risk of health care disparities.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from February 22, 2019, through March 8, 2019. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation, with 13 submissions received. A total of 100% of the 13 respondents either agreed or agreed with slight modifications to the recommendations, and 0% of the respondents disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to CPGC review and approval.

The draft was submitted to 2 external reviewers with content expertise. It was rated as high quality, and it was agreed that it would be useful in practice. Comments received assisted in presenting the strength of the evidence that supported each of the recommendations and helped to contextualize this guideline in relation to other ASCO guidelines within this disease site. Review comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the CPGC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline

recommendations among frontline practitioners and survivors of cancer and caregivers as well as to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO web site and most often published in *JCO* and a summary in *Journal of Oncology Practice*.

LIMITATIONS OF THE RESEARCH AND FUTURE RESEARCH

This guideline is based on the best available evidence regarding the use of imaging in advanced prostate cancer. However, it is recognized that there are gaps in knowledge related to insufficiency or absence of data in various scenarios related to this condition. Specifically, there are limited data on head-to-head comparisons of diagnostic performance of different imaging modalities or different radiopharmaceutical agents in the same patient population. Also, while there is evidence of feasibility of use and change in management as a result of imaging findings, none of the imaging modalities show prospective evidence conferring patient benefit in terms of outcomes (ie, how patients feel, function, or survive). These should be areas for focused future research. Finally, some of the agents that have been shown to have higher detection capabilities in prostate cancer (eg, PSMA) do not have regulatory approval for use in the United States.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Practice[121] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[101] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Hypofractionated Radiation Therapy for Localized Prostate Cancer[122] (http://ascopubs.org/doi/10.1200/JCO.18.01097)
- Clinically Localized Prostate Cancer[123] (http://ascopubs.org/doi/10.1200/JCO.18.00606)
- Optimizing Anticancer Therapy in Metastatic Noncastrate Prostate Cancer[124] (http://ascopubs.org/doi/10.1200/JCO.2018.78.0619)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/genitourinary-cancer-guidelines.

EQUAL CONTRIBUTION

E.J.T. and H.A.V. were Expert Panel co-chairs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.02757.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Optimum Imaging Strategies for Advanced Prostate Cancer: ASCO Guideline

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Travel, Accommodations, Expenses: Siemens Healthineers, Bayer AG, Vital, Curagita, Bracco Diagnostics

Matthias Eiber
Consulting or Advisory Role: Blue Earth Diagnostics, ABX Advanced biochemical compounds
Research Funding: Siemens, Blue Earth Diagnostics, ABX Advanced biochemical compounds
Patents, Royalties, Other Intellectual Property: Patent application for radiohybrid prostate-specific membrane antigen
Travel, Accommodations, Expenses: Bayer Schering Pharma

Michael J. Morris
Consulting or Advisory Role: Astellas Pharma, Bayer AG, Endocyte, Advanced Accelerator Applications, Blue Earth Diagnostics, Tokai Pharmaceuticals, Tolmar Pharmaceuticals, ORIC Pharmaceuticals, Johnson & Johnson
Research Funding: Bayer AG (Inst), Sanofi (Inst), Endocyte (Inst), Progenics (Inst), Corcept Therapeutics (Inst), Roche (Inst), Genentech (Inst), Janssen Pharmaceuticals (Inst),
Travel, Accommodations, Expenses: Bayer AG, Endocyte, Fujifilm

Peter L. Choyke
Patents, Royalties, Other Intellectual Property: Patent holder for MRI-ultrasound fusion technology licensed to Invivo, which markets it as UroNav; as a government employee, however, does not personally financial benefit from this patent
Other Relationship: Aspyrian Therapeutics, Philips Healthcare, GE Healthcare

Anwar Padhani
Honoraria: Janssen Oncology, Astellas Scientific and Medical Affairs Siemens Healthineers
Travel, Accommodations, Expenses: Siemens Healthineers

Jorge Oldan
Honoraria: Wolters Kluwer

Stefano Fanti
Honoraria: Bayer AG, Blue Earth Diagnostics, Sanofi, Astellas Pharma, Janssen Pharmaceuticals
Research Funding: Blue Earth Diagnostics
Travel, Accommodations, Expenses: Bayer AG, Blue Earth Diagnostics, Sanofi, Astellas Pharma

Suneil Jain
Consulting or Advisory Role: Janssen-Cilag, Movember, Bayer AG, Astellas Pharma, Boston Scientific
Speakers' Bureau: Janssen-Cilag, Augmenix
Travel, Accommodations, Expenses: Janssen-Cilag, Astellas Pharma, Bayer AG

Peter A. Pinto
Patents, Royalties, Other Intellectual Property: National Institutes of Health (NIH) and Philips have a cooperative research and development agreement. NIH has intellectual property in the field, including, among other patents and patent applications, "System, methods, and instrumentation for image guided prostate treatment," US patent number 8948845, with inventors/authors Brad Wood and Peter A. Pinto. NIH and Philips (Invivo) have a licensing agreement. NIH and authors receive royalties for a licensing agreement with Philips/Invivo. NIH does not endorse or recommend any commercial products, processes, or services. The views and personal opinions of authors expressed herein do not necessarily state or reflect those of the US government, nor reflect any official recommendation or opinion of the NIH or National Cancer Institute.

Kirk A. Keegan
Travel, Accommodations, Expenses: Intuitive Surgical, Taris BioMedical

Christopher R. Porter
Speakers' Bureau: Genomic Health

Jonathan A. Coleman
Travel, Accommodations, Expenses: Digital Angiography Reading Center (I)
Other Relationship: Steba Biotech

Ashesh B. Jani
Consulting or Advisory Role: Blue Earth Diagnostics

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Optimum Imaging Strategies for Advanced Prostate Cancer Expert Panel Membership

Name (and designation)	Affiliation/Institution	Role/Area of Expertise
Edouard J. Trabulsi, MD (co-chair)	Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA	Urology
H. Alberto Vargas, MD (co-chair)	Memorial Sloan Kettering Cancer Center, New York, NY	Radiology
Glenn S. Bauman, MD	London Health Sciences Centre, London, Ontario, Canada	Radiation oncology
Jonathan A. Coleman, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Urology
Peter L. Choyke, MD	National Cancer Institute, Bethesda, MD	Radiology
Matthias Eiber, MD	Technische Universität München, Munich, Germany	Radiology, nuclear medicine
Stefano Fanti, MD	University of Bologna, Bologna, Italy	Nuclear medicine
Adam Froemming, MD	Mayo Clinic, Rochester, MN	Radiology
Thomas Hope, MD	University of California, San Francisco, San Francisco CA	Abdominal imaging and nuclear medicine
Kirk A. Keegan, MD	Vanderbilt Urologic Surgery, Nashville, TN	Urology
Hossein Jadvar, MD, PhD	University of Southern California, Los Angeles, CA	Radiology, nuclear medicine
Suneil Jain, NMD	Queen's University Belfast, Belfast, Northern Ireland	Clinical oncology
Ashesh B. Jani, MD	Winship Cancer Institute, Atlanta, GA	Radiology
Jeffrey M. Kamradt, MD	Hartford Hospital, Hartford, CT	PGIN
Daniel J. Margolis, MD	Weill Cornell Medical College, New York City, NY	Radiology
Matthew I. Milowsky, MD	UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC	Medical oncology
Michael J. Morris, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Jorge Oldan, MD	UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC	Nuclear medicine
Aytekin Oto, MD	The University of Chicago, Chicago, IL	Radiology
Anwar Padhani, MD	Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, United Kingdom	Radiology
Andrew B. Rosenkrantz, MD	NYU Langone Health, New York, NY	Radiology
Heinz-Peter Schlemmer, MD	German Cancer Research Center (DKFZ), Heidelberg, Germany	Radiology
Peter A. Pinto, MD	National Cancer Institute, Bethesda, MD	Urology
Martin Pomper, MD	Johns Hopkins Medicine, Owings Mills, MD	Radiology
Christopher R. Porter, MD	Virginia Mason Medical Center, Seattle, WA	Urology
Andrei Purysko, MD	Cleveland Clinic, Cleveland, OH	Radiology
Westley Sholes, MPA		Patient representative
Baris Turkbey, MD	National Cancer Institute, Bethesda, MD	Radiology
Sadhna Verma, MD	University of Cincinnati Medical Center, Cincinnati, OH	Radiology
R. Bryan Rumble, MSc	American Society of Clinical Oncology	Staff/health research methodologist

Abbreviation: PGIN, Practice Guideline Information Network.