**Appropriate Use Criteria for Imaging Evaluation of Biochemical Recurrence of Prostate Cancer following Definitive Primary Treatment**

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**EXECUTIVE SUMMARY**

Imaging is often employed in the evaluation of men with biochemical recurrence (BCR) of prostate cancer after definitive primary treatment (prostatectomy, radiation therapy). The goal of imaging is to identify the source of elevated or rising serum prostate specific antigen (PSA) since subsequent management depends on disease location and extent. Salvage therapy (with surgery or radiation) may be considered for local or biochemical recurrence providing additional potential opportunity for cure. The salvage treatment strategy may be extended to regional adenopathy. Patients with limited distant metastases on imaging, referred to as oligometastatic disease, may be candidates for close observation, systemic hormonal therapy or metastases-directed therapies with or without local prostate bed therapy. Patients with metastatic disease are typically treated with systemic therapy.

The purpose of this document is to describe the appropriate use of imaging in the diagnostic evaluation of patients with biochemical recurrence after definitive primary treatment. The imaging modalities that were considered included computed tomography (CT), bone scintigraphy, and the US Food and Drug Administration (FDA) approved positron emission tomography (PET) radiotracers that track malignancy-induced lipogenesis, 11C-choline, and amino acid metabolism, 18F-fluciclovine. The prostate-specific membrane antigen (PSMA) targeted monoclonal antibody, 111In-capromab pendetide, is also included for historical perspective since it is neither available nor used clinically. On the other hand, the new class of PSMA-targeted PET radiotracers have generated considerable interest and will be discussed briefly although these agents are currently not approved for routine clinical use in the United States.

Representatives from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Nuclear Medicine (EANM), the American Society of Clinical Oncology (ASCO), the American College of Nuclear Medicine (ACNM), the American Society for Radiation Oncology (ASTRO), the American Urological Association (AUA), the American College of Physicians (ACP), and the World Molecular Imaging Society (WMIS) assembled under the auspices of an autonomous workgroup to develop the following appropriate use criteria (AUC). This process was performed in accordance with the Protecting Access to Medicare Act of 2014 (4). This legislation requires that all referring physicians consult AUC by using a clinical decision support mechanism before ordering advanced diagnostic imaging services. These services include diagnostic MRI, CT, and nuclear medicine procedures such as PET, among other services specified by the Secretary of Health and Human Services in consultation with physician specialty organizations and other stakeholders (Protecting Access to Medicare Act of 2014, Pub L No. 113-93, 128 Stat 1040 (2014)). The AUC herein is intended to aid referring medical practitioners in the appropriate use of imaging for diagnostic evaluation of patients with biochemical recurrence of prostate cancer after definitive primary treatment.

**INTRODUCTION**

Prostate cancer is the second most commonly diagnosed cancer worldwide (13.5% of cancer diagnoses in men, or 1,276,106 cases in 2018) and the fifth most common cause of cancer-related mortality among males (6.7%, or 358,989 deaths in 2018) (Bray 2018). In the United States, prostate cancer is the most commonly diagnosed cancer in men (projected 19% of all new cases of cancer, or 164,690 cases in 2018) and the second most common cause of cancer-related mortality (projected 29,430 deaths in 2018) (Siegel 2018). Despite local definitive therapy, up to 40% of patients will develop recurrent disease (Mullins 2012). The majority of these patients will have biochemical recurrence with no evidence of metastasis using widely used standard of care imaging techniques (contrast-enhanced abdomen and pelvis CT, whole body 99mTc-based bone scan, and typically pelvis multiparametric MRI) and only manifest with elevated serum prostate specific membrane antigen (PSA) levels.

The definition of biochemical recurrence (also referred to as PSA relapse) depends on the type of prior definitive therapy. In post-prostatectomy patients, the American Urological Association (AUA) defines biochemical recurrence when serum PSA is >=0.2 ng/mL, measured 6-13 weeks after surgery, and confirmed by a second determination with a PSA >0.2 ng/mL (Cookson 2007). In patients treated with radiation therapy, the American Society for Radiation Oncology (ASTRO) Phoenix Criteria defines biochemical recurrence as PSA rise of 2 ng/mL or more above the nadir regardless of androgen deprivation therapy (Roach 2006).

The significance of biochemically recurrent disease varies considerably according to individual risk factors. One clinically important prognostic variable is PSA doubling time. For instance, prostate cancer-specific survival is approximately 90% in patients with a PSA doubling time of ≥15 months (highest quartile), whereas it was about 20% for patients with a PSA doubling time of <3 months (lowest quartile) (Freedland 2005). In part because of this wide variability in disease aggressiveness, coupled with competing causes of mortality and the typically long time to metastatic disease (median metastasis-free survival is 10 years in patients with biochemical failure and no treatment), there is no defined standard of care for this patient population (Antonarakis 2012). Since the 1940s, the foundation of treatment for metastatic prostate cancer has been testosterone-lowering therapy. The development of metastasis in a patient signals that a change in treatment approach is warranted. It is likely that using more sensitive imaging techniques will identify patients earlier who are at higher risk of developing overt metastases identified by more commonly used techniques. In some scenarios, earlier intervention in the disease process may result in improved outcomes for patients, as has been seen with post-operative radiotherapy (Stephenson 2007).

Radiotherapy following prostatectomy is commonly used to eradicate microscopic residual disease in the prostate bed thereby reducing the risk of recurrence. Defining who needs post-operative radiotherapy (RT) is most often based on surgical pathology and post-operative PSA since conventional imaging rarely detects residual or recurrent disease in patients with low PSA (<1ng/mL). In the adjuvant setting, pathology (pT3a/b and or positive surgical margins) currently drives the addition of RT. In the salvage setting, when men have persistently detectable PSA (PSA persistence) or a delayed rise in PSA (>= 0.2ng/mL), conventional imaging does not have sufficient sensitivity to identify early recurrences. The ability to detect residual or recurrent disease within the pelvis can affect RT dose and target. In the absence of molecular imaging, the question of whether to include pelvic lymph nodes in the RT field in pathologic node negative patients is a question that has been studied by the RTOG (RTOG 0534) and is awaiting final results. With the ability to visualize prostate cancer cells, molecular imaging can help define RT treatment fields. Similarly, molecular imaging can identify patients who have early metastatic disease and could avoid RT to the prostate fossa. The use of molecular imaging to identify oligometastatic prostate cancer has allowed for additional treatment strategies in patient care (Jadvar 2018). Studies show a benefit (e.g. biochemical progression free survival, distant progression-free survival) to metastasis-directed stereotactic body radiotherapy (SBRT) in the setting of oligometastatic prostate cancer (Ost 2016, Muldermans 2016). Molecular imaging can enhance the post-operative treatment algorithm for prostate cancer patients by identifying targets for RT.

This document is the product of extensive literature search in combination with expert opinion. Its intent is to provide up-to-date information and recommendations for appropriate use criteria for approved (in the US) imaging technologies in the setting of biochemical recurrence of prostate cancer after definitive treatment. We will also discuss the outlook for upcoming imaging technologies which are anticipated to be approved in the US relatively soon.

**METHODOLOGY**

**Expert Workgroup Selection**

The experts of this AUC workgroup were convened by the SNMMI to represent a multidisciplinary panel of health care providers with substantive knowledge in the use of imaging evaluation of biochemical recurrence of prostate cancer following definitive primary treatment. In addition to SNMMI members, representatives from ASCO, ASTRO, EANM, ACP, ACNM, AUA, ENETS, WMIS, ACP and ACR were included in the workgroup. Fourteen physician members were ultimately selected to participate and contribute to the AUC. A complete list of workgroup participants and external reviewers can be found in Appendix A.

**AUC Development**

The process for AUC development was modeled after the RAND/ UCLA Appropriateness Method for AUC development (Fitch 2001). It included identifying a list of relevant clinical scenarios where nuclear medicine can be used for imaging evaluation of biochemical recurrence of prostate cancer following definitive primary treatment, a systematic review of evidence related to these clinical scenarios, and a systematic synthesis of available evidence followed by the development of AUC for each of the various clinical scenarios by using a modified Delphi process. Additionally, this process strove to adhere to the Institute of Medicine’s standards for developing trustworthy clinical guidance (IOM 2001). The final document was drafted based on group ratings and discussions.

**Scope and Development of Clinical Scenarios**

To begin this process, the workgroup discussed various potential clinical indications and applicable scenarios for the evaluation of biochemical recurrence of prostate cancer following definitive primary. For all indications, the relevant populations were patients with prostate cancer. The workgroup identified 2 clinical indications with 12 scenarios for this document. The indications are intended to be as representative of the relevant patient population as possible for development of AUC. The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each indication. Other factors affecting the AUC recommendations were potential harm— including long-term harm that may be difficult to capture—costs, availability, and patient preferences.

**Systematic Review**

The American Society of Clinical Oncology conducted a systematic review to develop a comprehensive clinical practice guideline for optimum imaging strategies for advanced prostate cancer and the same systematic review was used by the AUC workgroup. The workgroup selected the following key questions to guide the review:

(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 inclusion and exclusion criteria for papers for this review were based on the study parameters established by the workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. A protocol for each systematic review defines parameters for a targeted literature search. Additional parameters include relevant study designs, literature sources, types of reports, and pre-specified inclusion and exclusion criteria for literature identified. The protocol for this guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee’s Genitourinary Cancer Guideline Advisory Group.

PubMed and the Cochrane Collaboration Library electronic databases (± meeting abstracts) were searched for evidence reporting on outcomes of interest.

**Data Extraction**

Literature search results were reviewed and deemed appropriate for full text review by one ASCO staff reviewer in consultation with the Expert Panel Co-Chairs. Data were extracted by one staff reviewer and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary. Discrepancies were resolved through a consensus process.

**Study Quality Assessment**

Study quality was formally assessed for the studies identified. Design aspects related to the individual study quality were assessed by one reviewer and included factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc. The risk of bias is assessed as “low,” “intermediate,” or “high” for most of the identified evidence.

Database searches resulted in 6,378 potentially relevant abstracts. After dual review of abstracts and titles, 66 articles were selected for full-text dual review. Of these, 35 studies were determined to meet inclusion criteria and were included in this review, including 17 systematic reviews and 18 primary research papers.

**Rating and Scoring**

In developing these criteria, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: “The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics” (AQA 2009).

At the beginning of the process, workgroup members convened via webinars to develop the initial clinical indications. On evaluating the evidence summary of the systematic literature review, the workgroup further refined its draft clinical indications to ensure their accuracy and facilitate consistent interpretation when scoring each indication for appropriateness. Using the evidence summary, workgroup members were first asked individually to assess the appropriateness and provide score for each of the identified indication. Workgroup members then convened in a group setting for several successive webinars to discuss each indication and associated scores from the first round of individual scoring. After deliberate discussion, a consensus score was determined and then assigned to the associated appropriate use indication. For this scoring round, the expert panel was encouraged to include their clinical expertise in addition to the available evidence in determining the final scores. All members contributed to the final discussion, and no one was forced into consensus. After the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA Appropriateness Method.

The workgroup scored each indication as “appropriate,” “may be appropriate,” or “rarely appropriate” on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific clinical indication and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific indication. This implies that more research is needed to classify the indication definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific indication and generally is not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is partially arbitrary, and the numeric designations should be viewed as a continuum. In addition, if there was a difference in clinical opinion for an indication such that workgroup members could not agree on a common score, that indication was given a ‘may be appropriate’ rating to indicate a lack of agreement on appropriateness based on the available literature and the members’ collective clinical opinion, indicating the need for additional research.

**CATEGORY 1: PRIOR DEFINITIVE TREATMENT WITH RADICAL PROSTATECTOMY OR WITH RADIATION THERAPY, PSA RELAPSE**

**CATEGORY 2: PRIOR DEFINITIVE TREATMENT, SURGICAL OR NONSURGICAL, NEGATIVE OR EQUIVOCAL STANDARD OF CARE IMAGING**

**Clinical Scenarios and AUC Scores**

Clinical scenarios and final AUC scores for the use of imaging in the evaluation of biochemical recurrence of prostate cancer following definitive primary treatment with radical prostatectomy (RP) or with radiation therapy (RT) are presented in Table 1.

Clinical scenarios and final AUC scores for the use of imaging in the evaluation of biochemical recurrence of prostate cancer following definitive primary treatment with radical prostatectomy or with radiation therapy, and with negative or equivocal standard of care imaging are presented in Table 2.

***Category 1, Scenario 1: CT abdomen and pelvis with IV contrast (8 - Appropriate)***

The role of abdomen and pelvis CT in prostate cancer treatment follow-up is focused on the assessment of metastatic disease in the lymph nodes, bone, and visceral organs. In the evaluation of nodal disease, CT relies on nodal size to detect tumor. Using a short axis diameter of 1.0 cm as a cut-point, studies have reported sensitivities between 27% and 75% with specificities between 66% and 100% (Oyen 1994). However, the sensitivity of abdominopelvic CT for the detection of low-volume recurrent disease is limited, particularly when PSA levels are low. Studies have shown CT to be positive in only 11–14% of men with biochemical relapse after radical prostatectomy (Kane 2003). The mean PSA value associated with a positive computed tomography examination was 12.4 ng/ml and the mean PSA velocity was 30.6 ng/ml/year (Johnstone 1997). In patients with disease recurrence following treatment, the usual pattern of vertical nodal spread beginning in the pelvis can be absent in nearly 75% of patient (Spencer 1994) In these patients, most of whom had undergone previous pelvic lymph node dissection at the time of radical prostatectomy, only retroperitoneal adenopathy is commonly detected by CT. In addition, CT is useful to detect advanced-disease in bone and visceral metastases and in radiotherapy treatment planning to define the prostate bed, locoregional and distant metastatic target volumes. Bone lesions from prostate cancer are often seen as sclerotic lesions, consistent with osteoblastic metastases although there are numerous other causes for dense bone lesions. Bone scan is superior to CT in the diagnosis and follow-up of bone metastases as it provides functional information about a bone lesion. In summary, despite recognized limitations of abdominopelvic CT, it is readily available at relatively low cost and has traditionally been considered as standard of care imaging in this clinical setting, which prompted the panel to recommend an appropriateness score of 8 (Appropriate).

***Category 1, Scenario 2: CT chest with IV contrast (2 – Rarely Appropriate)***

Lung metastasis from prostate cancer is relatively uncommon. In autopsy series among 316 patients with metastatic prostate cancer only 17 (5%) had lung involvement, compared to 283 (90%) had bone involvement. Moreover, most lung metastases appear later in the disease and not early in the recurrence setting. Therefore, the panel recommended that CT of the chest receive an appropriateness score of 2 (Rarely Appropriate)

***Category 1, Scenario 3: Bone scintigraphy (99mTc-MDP whole-body scan, 18F-NaF PET/CT) (8 –Appropriate)***

In the clinical setting of primary staging, current NCCN guidelines state that any patient with PSA > 20 ng/mL, Gleason 8 or greater, or clinical stage T3 or greater and any of two of PSA >10 ng/mL, Gleason 7 or over, and clinical stage T2b/T2c or greater. A recent systematic review of 54 studies encompassing a total sample size of 20,421 patients with treatment-naïve cancer1, found yield rates of 4% with PSA <= 10 ng/mL, 7% with 10 < PSA <= 20 ng/mL, and 42% with PSA <20 ng/mL, 4% with Gleason 6 or less, 10% with Gleason 7, and 29% with Gleason 8 or greater (Suh 2018). In subgroup analyses, a Gleason score of 7 with a PSA <20 ng/mL had a 3% yield, whereas a Gleason score of 8 with a PSA <=10 ng/mL had a yield of 20%, suggesting bone scan would be useful with a PSA > 20 ng/mL or a Gleason of 8 or over.

However, it is probable that the case for patients with biochemical recurrence of prostate cancer will be different. One study of 1197 post-RP patients found that positive studies always had a PSA of at least 7 ng/mL (Gomez 2004), and in another study of 100 post-RP patients suggested an optimal trigger PSA cutoff of 30-40 ng/mL (Cher 1998). One report of 142 post-RP patients with PSA up to 1 ng/mL found only 2% bone scan yield (Vargas 2016). Therefore, at least these investigations suggest that the PSA trigger cutoff for a positive bone scan in post-RP patients may be in the range 7-30 ng/mL and not lower.

The rate of change of serum PSA level may also be relevant. A study of 132 post-RP patients suggested that PSA velocity was more important, with 0.5 ng/mL/mo serving as an optimal cutoff (Kane 2003). A study of 292 mostly post-RP patients suggested trigger PSA value of 5 ng/mL and a PSA doubling time of 10 mo (Choueiri 2008), whereas another study of 128 post-RP patients suggested cutoffs of 10 ng/ml and 6 mo, respectively (Okotie 2007). Another investigation of 438 post-RP patients also incorporated the presence or absence of androgen deprivation therapy (ADT). While with pre-ADT patients, a threshold PSA doubling time of 9 mo was a fairly effective cutoff (yield of 1-5% for >9 mo vs. 11-44% for <9 mo), for post-ADT patients, there was a yield of at least 10% even with long PSA doubling times and low PSA levels (below 10 ng/ml)(Moreira 2014). A study of 239 patients used trigger PSA and PSA slope and velocity to create a nomogram (Dotan 2005). The results concurred with the NCCN guidelines recommending a bone scan with PSA of 20 ng/ml, or 10 ng/ml with a Gleason 7 or greater or stage T2 or greater, adding a PSA doubling time of 9 mo or less as another indication.

For sodium fluoride (18F-NaF) PET, dedicated studies focusing specifically on recurrence are few, and these studies do not separate RP from RT patients. Theoretically, the higher photon flux and coincidence detection with PET and concurrent CT should increase sensitivity and specificity, respectively, over planar whole-body scintigraphy, and multiple studies, albeit mostly for initial staging (Wondergem 2018) or mixed indications of initial staging and biochemical recurrence (Apolo 2016, Schirrmeister 1999, Even-Sapir 2006). Interestingly, one study showed a decline in specificity from 82% to 54% (Poulsen 2014), while another study showed a small drop from 88% to 82% vis-à-vis SPECT-CT, but with an overall improvement in both sensitivity and specificity over planar bone scan (Jambor 2016). Moreover, a large retrospective study of the National Oncologic PET Registry found a change in management over bone scintigraphy in 12-16% of cases (Hillner 2014). A recent study of 62 patients with mixed indications suggests a PSA cutoff of 6 ng/mL for previously treated patients, lower than previously suggested for bone scan (Sarikaya 2018).

A few studies have compared 18F-NaF to other PET tracers. These generally do not separate RP from RT (Beheshti 2008). Results of studies comparing 18F-NaF to fluorocholine are mixed. Some show increased sensitivity (for bone lesions) at the expense of specificity (Poulsen 2014, Beheshti 2008). One study focusing on initial staging found similar performance for bone lesions (Kjolhede 2012), while another, with a mix of initial and recurrent indications showed some loss in specificity with 18F-NaF (Langsteger 2011). In comparing FDG and 18F-Naf, the latter is more sensitive for detecting bone metastases at biochemical recurrence even at PSA levels as low as 2-4 ng/mL, albeit at the expense of specificity (Jadvar 2012, Iagaru 2012, Damle 2013). For PSMA tracers, mostly in a mixed primary and recurrent population, studies show a similar pattern, with 18F-NaF detecting more bone lesions at the expense of decreased specificity (Uprimmy 2018, Zacho 2018, Harmon 2018); one study showed no significant difference (Dryberg 2018). A consistent result is that, compared to other PET tracers, 18F-NaF is more sensitive for bone lesions at the expense of specificity. It outperforms conventional 99mTc-based bone scan which may be relevant in clinical management decisions (Jadvar 2018). In summary, bone scintigraphy is considered standard of care imaging and received an appropriateness score of 8 (Appropriate).

***Category 1, Scenario 4: Pelvis MRI without and with IV contrast (8–Appropriate)***

MRI of the pelvis can be effective in identifying sites of recurrent prostate cancer and its use is rapidly increasing [1](Oberlin 2017). Most studies demonstrate that MRI of the pelvis is reliable for the detection of local recurrence either at the site of the prostate bed in post prostatectomy patients or within the prostate in post radiation therapy patients [2-6](Barchetti 2016, Counago 2017, Hayman 2018, Kitajima 2014, Sobol 2017). The combination of diffusion weighted, T2 weighted and DCE MRI are particularly effective for detecting local recurrence [5, 7](Kitajima 2014, Giannarini 2012). For pelvic nodal metastatic detection, pelvic MRI has similar limitations to CT, namely low sensitivity due to the dependence on size criteria. Many positive lymph nodes are too small to meet the 0.8-1cm size threshold for positivity on MRI. Although there was initial enthusiasm for diffusion weighted imaging (DWI) for detecting normal sized lymph nodes at initial staging, there is no literature evidence that this method is valid in patients with biochemical recurrence [8](Theony 2014) and the method has proven difficult outside of research settings. When lesions are present in the pelvic bones, MRI is highly sensitive, equaling PET scans in this regard with the caveat that findings may not be specific for bone metastases. [5](Kitajima 2014). MRI can be predictive of response to salvage radiation therapy based on the extent of the recurrent disease[9](Sharma 2018). Thus, pelvic MRI provides useful information especially for local recurrence and bone metastases in the setting of biochemical recurrence that led to an appropriateness score of 8 (Appropriate).

***Category 1, Scenario 5: 18F-FDG PET/CT (skull base to mid-thigh) (2 – Rarely Appropriate) Indication 2, Category 1, Scenario 1: 18F-FDG PET/CT (skull base to mid-thigh) (2 – Rarely Appropriate)***

FDG PET/CT has revolutionized the field of cancer imaging and has become one of the pillars of management of multiple cancers including lymphoma, lung and esophageal malignancies. This huge success is not reflected in prostate cancer, where many studies have documented disappointing detection capabilities or better alternative imaging tests. This is despite some results in the literature suggesting a potential utility, likely a result of variability in standards of reference used or changing paradigms in the management of BCR. For example, Ozturk et al (Öztürk 2016) evaluated FDG PET/CT in 28 patients with BCR after RP or RT using standard definitions and found that imaging was negative in 16 (57.1%) patients and positive in 12 (42.9%), however no summary PSA statistics for the study group were included, and no mention of biopsy confirmation or other measures to assess true positivity of the PET findings was provided. Schöder et al (Schöder 2005) reported sensitivities of 71-80% and specificities of (73-77%) for FDG PET in the recurrence setting where the median PSA was 2.4 ng/ml. These results probably over-estimate the clinical utility of FDG PET/CT, given that many of the patients included had positive findings on other standard of care imaging and the PSA thresholds are considerably above those which would trigger salvage RT in the contemporary setting (typically around 0.5 ng/mL). In a subset of patients with early (PSA < 1 ng/mL) BCR after RP, a more recent study reported FDG PET positivity in only 1 out of 5 patients, and upon directed biopsy only inflammatory tissue was identified at the site of FDG uptake in the thoracic spine (i.e. false positive) (Vargas 2016). Jadvar et al found FDG PET/CT detection rates of only 8.1% in a prospective study of 37 patients with BCR and negative standard of care imaging (Jadvar 2012). The same group published a comparative performance study of PET tracers in prostate cancer BCR found that FDG PET/CT exhibited the lowest detection rates compared to 11C-acetate, 11C- or 18F-choline, anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid (FACBC or 18F-fluciclovine), and radiolabeled ligand targeted to prostate-specific membrane antigen (PSMA) (Yu 2014). However, FDG PET/CT may play a role later in the course of prostate cancer, particularly in the context of metastatic disease (Jadvar 2013, Fox 2018, Jadvar 2019). In summary, FDG PET/CT is rarely appropriate for the evaluation of BCR of prostate cancer following prostatectomy or radiation therapy, even in the context of negative or equivocal standard of care imaging leading to an appropriateness score of 2 (Rarely Appropriate).

***Category 1, Scenario 6: 11C-choline PET/CT (skull base to mid-thigh) (6 – May be Appropriate)***

***Category 2, Scenario 2: 11C-choline PET/CT (skull base to mid-thigh) (9 – Appropriate)***

11C-Choline PET/CT has long been used in BCR and is currently incorporated into NCCN and EAU guidelines. 11C-choline was approved in the Unites States on September 12, 2012, for PET imaging in recurrent prostate cancer (FDA1). The fluorinated choline radiotracer (18F-fluorocholine) has also been investigated relatively extensively and is used clinically in many countries, however, the radiotracer is not FDA approved. Although the literature on 11C-choline PET/CT is relatively robust, most reports are retrospective and rarely compare 11C-choline PET/CT to conventional imaging (abdominopelvic CT, bone scan, and pelvis MRI). This is particularly true for patients with prior definitive treatment with radiation therapy that entails only 2 retrospective studies (Rybalov 2013, Ceci 2014). A first meta-analysis provided a pooled sensitivity of 85.6% (95% CI: 82.9%-88.1%) and pooled specificity of 92.6% (95% CI: 90.1%-94.6%) for all sites of disease (Evangelista 2013). A more recent meta-analysis (Fanti 2016), considering only 11C-Choline reported a pooled sensitivity of 89 % (95 % CI 83 - 93 %) and a pooled specificity was 89 % (95 % CI 73 - 96 %). For local relapse, the pooled sensitivity was 61% (95%CI: 40%-80%) and the pooled specificity was 97% (95%CI: 87%-99%); for nodal disease, the pooled detection rate was 36% (95% CI: 22%-50%) while for bone metastases, the pooled detection rate was 25% (95%CI: 16%-34%). As with all PET imaging methods, choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics (Treglia 2014). In patients with BCR after radical prostatectomy, choline PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL but rises to 67%-100% when the PSA level is > 5 ng/mL. Therefore, a PSA cut-off level of between 1 and 2 ng/mL has been suggested for choline PET/CT imaging. It may also be advantageous to consider PSA kinetics rather than PSA levels (Castellucci 2014). In balancing the strengths (relatively abundant literature despite its stated limitations, FDA approval, incorporation into patient management guidelines) and weaknesses (need for on-site cyclotron and hence less accessibility, relatively high cost), the panel regarded 11C-choline PET/CT “may be appropriate” (appropriateness score of 6) as the first imaging approach in BCR patients in comparison to the widely available and less costly conventional imaging. However, in patients with negative or equivocal conventional imaging, the appropriateness score was raised to 9 (Appropriate).

***Category 1, Scenario 7: 18F-fluciclovine PET/CT (skull base to mid-thigh) (6 – May be Appropriate)***

***Category 2, Scenario 3: 18F-fluciclovine PET/CT (skull base to mid-thigh) (9 – Appropriate)***

18F-fluciclovine (Axumin ®) was FDA approved on May 26, 2016, for PET imaging in men with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment (FDA2). In comparison to 11C-choline it was prospectively shown in 89 patients that 18F-fluciclovine is superior for detection of recurrence especially for PSA values <2 ng/ml (21% vs. 14% for PSA <1 ng/mL, and 29% vs. 29% for PSA 1 to <2 ng/ml) (Nanni 2016). The overall sensitivity, specificity and positive predictive value were 37%, 67% and 97% for 18F-fluciclovine and 32%, 40% and 90% for 11C-choline, respectively. In a large multi-site study with 596 patients, an overall detection rate of 68% was reported. 18F-fluciclovine uptake suspicious for disease recurrence was found in the prostate bed and pelvic lymph node regions in 39% and 33% of scans, respectively. Metastatic involvement outside the pelvis was detected in 27% of scans. The corresponding PPV was 62% for all detected lesions, with 92% for extraprostatic and 72% for prostate/bed involvement (Back-Gansmo 2017). Another recent study focusing on patients with PSA <=1 ng/mL reported an overall positive lesion detection rate of 46.4% with local and nodal recurrences detected more often than distant metastases, and with Gleason score greater than 7 associated with positive scan results (England 2019). 18F-fluciclovine PET/CT impacts clinical management of patients with biochemical recurrence of prostate cancer. The prospective multicenter LOCATE trial reported change in management in 59% of patients. Within this cohort, there were changes from salvage or noncurative systematic therapy to watchful waiting in 25%, from noncurative systematic therapy to salvage therapy in 24%, and from salvage therapy to noncurative systemic therapy in 9% of patients (Andriole 2019). Another investigation reported change in salvage radiotherapy management of 41% of post-prostatectomy patients (Akin-Akintayo 2017). Although not as sensitive as PSMA targeted PET agents, 18F-fluciclovine nevertheless is approved in the US in the setting of recurrent disease. Similar to 11C-choline, the panel regarded 18F-fluciclovine PET/CT “may be appropriate” (appropriateness score of 6) as the first imaging approach in BCR patients in comparison to the widely available and lower cost conventional imaging. However, in the setting of negative or equivocal conventional imaging, the panel recommended a score of 9 (Appropriate) for 18F-fluciclovine.

***Category 1, Scenario 8: 111In-capromab pendetide (1 – Rarely Appropriate)***

***Category 2, Scenario 4: 111In-capromab pendetide (1 – Rarely Appropriate)***

111In-capromab pendetide is a radioimmunoconjugate consisting of the murine IgG1 kappa monoclonal antibody capromab (7E11-C5.3), conjugated to the linker-chelator glycyl-tyrosyl-(N,-diethylenetriaminepentaacetic acid)-lysine hydrochloride (GYK-DTPA-HCl) and labeled with radioisotope 111In, with ligand-binding and gamma-emitting activities. It binds to a cytoplasmic epitope of human prostate specific membrane antigen (PSMA). PSMA is a cell surface glycoprotein abundantly expressed by prostate epithelium and is typically overexpressed by prostate cancer cells (NCI 2019). Radioimmunoscintigraphy imaging with 111In-capromab pendetide scan for imaging prostate was approved by the U.S. Food and Drug Administration (FDA) on October 28, 1996, indicated as a diagnostic imaging agent in newly-diagnosed patients with biopsy-proven prostate cancer (Pharmacodia.com website. 2017).

The utility of imaging with 111In-capromab pendetide scan for imaging prostate cancer has been a subject of continual debate since its approval until recently. Its disappointing low levels of both sensitivity and specificity significantly limited its use and acceptance. This seems to be an inherent property of the labelled antibody which has not shown to yield progressively better accuracy with image interpreter experience, likely due to the dependence upon cytoplasmic binding which achieves better results with nonviable tumor than it does with viable tumor tissue. Another major limitation of this agent is that the antibody remains in the blood and leads to high background signals and consequently reduced target to background ratios and detection rates.

In a study of 30 men with biochemical relapse after prostatectomy and who received salvage radiation therapy, 111In-capromab pendetide scan results were compared with post-salvage radiation therapy PSA response (Thomas 2003). In these patients, pre-salvage radiotherapy 111In-capromab pendetidescan findings outside the prostate fossa were not predictive of biochemical control after radiotherapy. Pucar and colleagues (Pucar 2008) concluded that 111In-capromab pendetide to have “no added benefit over other imaging modalities (available at that time) in evaluating post-radical prostatectomy recurrence, due to its low sensitivity for detecting local recurrences and bone metastases.” Another study evaluated 111In-capromab pendetide against 18F-fluciclovine (Schuster 2011) (Schuster 2014). It found that PET/CT with 18F-fluciclovine demonstrated superior sensitivity, specificity and accuracy to111In-capromab for detection of disease both in the prostatic bed and in extra-prostatic sites.

It should also be emphasized that despite its FDA approval and diffuse widespread use in the US for more than 22 years, many health insurance providers still will not provide standard insurance coverage for imaging with 111In-capromab pendetide for Prostate Cancer, which continues to be categorized as “investigational.” with the notation that current medical literature “is insufficient to support conclusions concerning efficacy, optimal use and impact on the diagnosis, treatment or clinical management of prostate cancer using radioimmunoscintigraphy imaging with Indium-111 capromab pendetide.” (bcbst.com website. 2019) (bluecrossnc.com 2019). Thus, 111Indium-111 capromab pendetide (marketed exclusively as ProstaScint®) is no longer recommended in the setting of biochemical recurrence. As of July 9, 2018, the FDA also reports on their website that Aytu BioScience, the manufacturer of ProstaScint®, reported voluntary discontinuation of the product (FDA.gov website. 2019). As such, the panel assigned an appropriateness score of 1 (Rarely Appropriate) to 111In-capromab pendetide.

**TABLE 1**

Indication 1: Clinical scenarios for imaging evaluation of biochemical recurrence of prostate cancer following prior definitive treatment with radical prostatectomy or with radiation therapy

|  |  |  |  |
| --- | --- | --- | --- |
| Scenario no. | Description | Appropriateness | Score |
|  | CT abdomen and pelvis with IV Contrast | Appropriate | 8 |
|  | CT chest with IV contrast | Rarely Appropriate | 2 |
|  | Bone scintigraphy (99mTc-, 18F-NaF) | Appropriate | 8 |
|  | Pelvis MRI without and with IV contrast | Appropriate | 8 |
|  | 18F-FDG PET/CT (skull base to mid-thigh) | Rarely Appropriate | 2 |
|  | 11C-choline PET/CT (skull base to mid-thigh) | May be Appropriate | 6 |
|  | 18F-fluciclovine PET/CT (skull base to mid-thigh) | May be Appropriate | 6 |
|  | 111In-capromab pendetide | Rarely Appropriate | 1 |

**TABLE 2**

Indication 2: Clinical scenarios for Prior Definitive Treatment, Surgical or Nonsurgical, Negative or Equivocal Standard of Care Imaging

|  |  |  |  |
| --- | --- | --- | --- |
| Scenario no. | Description | Appropriateness | Score |
|  | 18F-FDG PET/CT (skull base to mid-thigh) | Rarely Appropriate | 2 |
| 2. | 11C-choline PET/CT (skull base to mid-thigh) | Appropriate | 9 |
| 3. | 18F-fluciclovine PET/CT (skull base to mid-thigh) | Appropriate | 9 |
| 4. | 111In-capromab pendetide | Rarely Appropriate | 1 |

**QUALIFYING STATEMENTS**

**Special Commentary**

In addition to the currently approved radiotracers for imaging of prostate cancer (18F-fluciclovine and 11C-choline), a new class of radiotracers have been developed targeting the prostate specific membrane antigen (PSMA) (Afshar-Oromieh 2016, Eiber 2015). The most commonly used compound is 68Ga-PSMA-11, which is limited in production and distribution as it is labeled with gallium-68 (t1/2=68 min) and is not yet approved in the US (Hope 2018, Perera 2016).  68Ga-PSMA-11 has been shown to have a higher detection sensitivity compared to 18F-fluorocholine (Morigi 2015, Afshar-Oromieh 2014), and has also recently been compared to 18F-fluciclovine and shown to be superior in lesion detection (Calais 2019 -in review). Recently, a 635-patient single-arm clinical trial of 68Ga-PSMA-11 demonstrated substantial interreader reproducibility and high detection sensitivity and accuracy compared to a composite endpoint in patients with biochemical recurrence (Fendler 2019). 68Ga-PSMA-11 PET localized recurrent prostate cancer in 75% of patients; detection rates significantly increased with PSA level: 38% for <0.5 ng/mL, 57% for 0.5 to <1.0 ng/mL, 84% for 1.0 to <2.0 ng/mL, 86% for 2.0 to <5.0 ng/mL, and 97% for ≥5.0 ng/mL. In patients undergoing definitive radiation therapy, PSMA PET resulted in changes in RT plans in 53% of patients (Wu 2019, Calais-1 2018). In the salvage setting, Calais et al showed in 270 patients with PSA <1 ng/mL that 68Ga-PSMA-11 PET/CT implied a major impact on radiotherapy planning 19% of patients justifying a randomized imaging trial of salvage radiotherapy (Calais-2 2018, Calais-BMC 2019).

Although much of the data with PSMA-targeted PET radiotracers have focused on 68Ga-labeled agents, there are a number of advantages to the use of 18F as a radionuclide including nearly unlimited cyclotron-based production, feasible central distribution due to a 110-minute physical half-life (versus 68 minutes for 68Ga), higher positron yield, and lower positron energy (leading to shorter positron annihilation distances and higher spatial resolution) (Sanchez-Crespo 2013, Gorin 2016).These intrinsic advantages may lead to the widespread adoption of 18F-labeled ligands as the worldwide demand for PSMA-targeted radiotracers continues to increase.18F-labeled, PSMA-targeted radiotracers have shown high sensitivity for the detection of putative sites of prostate cancer in men with biochemical recurrence after attempted curative therapy. More recently, Giesel, et al. used a different 18F-labeled radiotracer known as 18F-PSMA-1007 in a retrospective analysis of 251 prostate cancer patients with biochemical recurrence (Giesel 2018).This tracer exhibits more hepatic and less renal excretion potentially simplifying evaluation of the pelvis. In total, 204/251 (81.3%) patients had findings on 18F-PSMA-1007 PET deemed to be evidence of a site or sites of recurrent disease.The patient detection efficiency at the PSA range of 0.2 – 0.5 ng/mL was 40/65 (61.5%).Currently it is unclear whether there is a benefit of one PSMA targeted agent over another, but due to the physical advantages for 18F-labeled compounds they will likely play a dominant role once approved and available.

In summary, PSMA PET is anticipated to have a significant role in the imaging evaluation of patients with BCR given its higher sensitivity and accuracy, although currently we are awaiting approval of these agents in the US. Aside from regulatory approval, there will be a need for ongoing and future prospective investigations to inform how PSMA-based theranostics provide added clinical value and impact treatment strategy, patient outcome and relative economic outlay (Vapiwala 2019).

**IMPLEMENTATION OF THE AUC GUIDANCE**

The society has been developing the AUC for high value nuclear medicine procedures since early 2015. This initiative was primarily undertaken to assist referring physicians and ordering professionals fulfill the requirements of the 2014 Protecting Access to Medicare Act (PAMA) (PAMA 2014). Section 218(b) of PAMA established a new program under the statute for fee-for-service Medicare to promote the use of AUC for Advanced Diagnostic Imaging Services (ADIS), including CT, MRI as well as all nuclear medicine procedures, including PET. PAMA requires referring physicians to consult AUC developed by a CMS-approved Qualified Provider Led Entity or ‘Q-PLE” to ensure cost-effective and appropriate utilization of ADIS. After going through a rigorous and extensive application that required SNMMI to document their guideline development process, including conflicts of interest adjudication and composition of expert panels, the society was approved as a qualified PLE in June 2016.

The PAMA legislation requiring the development of AUC also stipulated the mechanism of their delivery through a ‘qualified clinical decision support mechanism’ (Q-CDSM) prior to ordering any advanced imaging. Therefore, successful implementation and complete adoption of this program relies on integration of AUC developed by PLEs into these Q-CDSMs. The Society has partnered with leading CDSM providers to facilitate the adoption and utilization of SNMMI AUC.

Final implementation of the AUC program has been delayed until January 2020, in part so that Centers for Medicare and Medicaid Services (CMS) can issue more substantive guidance for the priority clinical areas and exceptions for ordering professionals for whom consultation with AUC would pose significant hardship. Delaying implementation also provides more preparation time for the referring physicians and healthcare institutions to comply with the legislative requirements.

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The workgroup acknowledges staff support from the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (Roger Chou, MD, FACP, Director).

**APPENDIX A: WORKGROUP MEMBERS AND EXTERNAL REVIEWERS**

**Workgroup**

The members of the workgroup are Hossein Jadvar, MD, PhD, MPH, MBA (Chair), University of Southern California Keck School of Medicine, Los Angeles, CA (SNMMI); Leslie Ballas, MD, University of Southern California Keck School of Medicine, Los Angeles, CA (ASTRO); Peter Choyke, MD, National Institutes of Health, Bethesda, MD (ASCO); Stefano Fanti, MD, University of Bologna, Bologna, Italy (EANM); James Gulley, MD, PhD, National Institutes of Health, Bethesda, MD (ACP); Ken Hermann, MD, Department of Nuclear Medicine, Universitätsklinikum Essen, Essen, Germany and Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Los Angeles, CA (EANM); Thomas Hope, MD, University of California San Francisco, San Francisco, CA (SNMMI); Alan Klitzke, MD, Roswell Park Cancer Institute, Buffalo, NY (ACNM); Jorge Olden, MD, University of North Carolina, Chapel Hill Hospitals, Chapel Hill, NC (ASCO, SNMMI); Martin Pomper, MD, PhD, Johns Hopkins University Medical School, Baltimore, MD (WMIS); Steven Rowe, MD, PhD, Johns Hopkins University Medical School, Baltimore, MD (SNMMI); Rathan Subramaniam, MD, PhD, MPH, University of Texas Southwestern Medical Center, Dallas, TX (ACNM, ACR); Samir Taneja, MD, NYU Langone Medical Center, New York, NY (AUA); Herbert Alberto Vargas, MD, Memorial Sloan Kettering Cancer Center, New York, NY (ASCO~~)~~.

**External Reviewers**

The external (peer) reviewers were…...

**SNMMI**

The staff support from SNMMI is Sukhjeet Ahuja, MD, MPH, Sr. Director, Health Policy & Quality Department; Teresa Ellmer, MIS, CNMT, senior program manager, Health Policy & Quality Department; Julie Kauffman, program manager, Health Policy & Quality Department.

**APPENDIX B: DISCLOSURES AND CONFLICTS OF INTEREST (COI)**

SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures of the workgroup members can be found in Table 4. A COI was defined as a relationship with industry—including consulting, speaking, research, and nonresearch activities—that exceeds $5,000 in funding over the previous or upcoming 12-mo period. In addition, if an external reviewer was either the principle investigator of a study or another key member of the study personnel, that person’s participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of this AUC. All external reviewers were asked about any potential COI.

**TABLE 4**

Relationships with Industry and Other Entities

|  |  |
| --- | --- |
| Workgroup member | Reported relationships |
| Ballas, Leslie |  |
| Choyke, Peter |  |
| Fanti, Stefano |  |
| Gulley, James |  |
| Hermann, Ken |  |
| Hope, Thomas |  |
| Jadvar, Hossein |  |
| Klitzke, Alan |  |
| Olden, Jorge |  |
| Pomper, Martin |  |
| Rowe, Steven |  |
| Subramaniam, Rathan |  |
| Taneja, Samir |  |
| Vargas, Hebert Alberto |  |

**APPENDIX C: PUBLIC COMMENTARY**

The workgroup solicited information from all communities through the SNMMI website and through direct solicitation of SNMMI members. The comments and input helped to shape the development of these AUC on imaging evaluation of biochemical recurrence of prostate cancer following definitive primary treatment.

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