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A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (RADAR III).

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A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence [RADAR] III)

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ABSTRACT (265 words)

PURPOSE: The advanced prostate cancer therapeutic landscape has changed dramatically over the last several years, resulting in improved overall survival for patients with both castration-naive and castration-resistant disease. The evolution and development of novel next generation imaging (NGI) techniques will affect diagnostic and therapeutic decision-making. Clinicians must navigate when and which NGI techniques to use and how to adjust treatment strategies based upon their results, oftentimes in the absence of correlative therapeutic data. Therefore, guidance is needed based on best available information and current clinical experience.

MATERIALS AND METHODS: The RADAR III Group convened to offer guidance on the use of NGI to stage prostate cancer based on available data and clinical experience. The group also discussed the potential impact of NGIs on treatment options based on earlier detection of disease.

RESULTS: The group unanimously agreed that progression to metastatic disease is a seminal event for patient management. NGI techniques are able to detect previously undetectable

metastases, which could redefine the phases of prostate cancer progression. Hence, earlier treatment, either systemic or locally directed, may positively alter patient outcomes.

CONCLUSIONS: The RADAR III Group recommends NGI techniques for select patients suspected of disease progression based on laboratory (biomarker) values, comorbidities, and symptoms. Currently, ^{18}F-fluciclovine and ^{68}Gallium (Ga) PSMA PET/CT are the NGI agents with a favorable combination of availability, specificity, and sensitivity. There is ongoing research for additional NGI technologies, which may offer improved diagnostic accuracy and therapeutic options. As NGI techniques evolve and presumably result in improved global accessibility, a clinician's ability to detect micrometastases may be enhanced for both decision-making and patient outcomes.

Key Words: Next generation imaging, guidelines, treatment, metastatic prostate cancer.

MANUSCRIPT (~4235 words—will be less once the references are superscripted)

INTRODUCTION

Prostate cancer is the most frequently diagnosed noncutaneous cancer in men according to the 2018 estimates by the American Cancer Society. (ACS facts and figures 2018) In the United States (US), approximately 164,690 new cases will be diagnosed, and an estimated 29,430 men will die from prostate cancer. (ACS facts and figures 2018) Prostate cancer, especially for the high-risk patient, is a progressive disease (table 1). With ongoing advancements in imaging technology, the ability to identify previously undetectable metastases may result in a shift in the definition of disease states and improved outcomes.

Table 1. Phases of Prostate Cancer Disease States

Prostate Cancer Phase	References
Localized prostate cancer	Mena *EJNMMI* 2017
Biochemically recurrent (BCR)/persistent disease after local therapy	Mena *EJNMMI* 2017
Nonmetastatic castration-resistant prostate cancer (M0 CRPC) or nmCRPC	Tombal *Ann Oncol* 2012 Anantharaman *ERAT* 2017
Metastatic hormone-sensitive prostate cancer (M1 HSPC)	Hoimes *TAMO* 2010
Metastatic castration-resistant prostate cancer (MCRPC)	Hoimes *TAMO* 2010
Treatment-emergent neuroendocrine prostate cancer	Epstein *Am J Surg Pathol* 2014

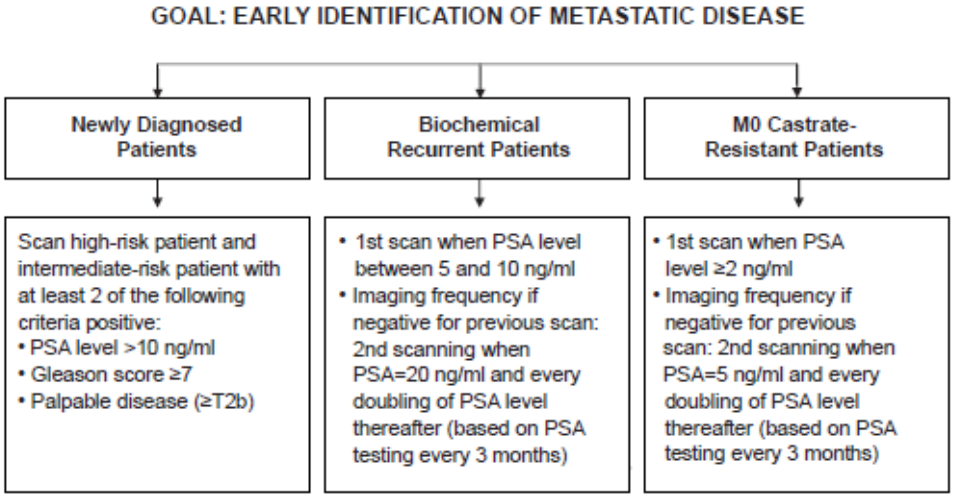
Treatment options and regimens for patients with advanced prostate cancer, both hormone naive and castration resistant, have increased in recent years and now include novel androgen axis inhibitors, immunotherapy, targeted alpha particle therapy, and chemotherapy. (Lindenberg JAMA Oncology 2017) Six treatments for metastatic CRPC (mCRPC) and nonmetastatic CRPC (nmCRPC), all with different mechanisms of action and overall survival (OS) benefit, have been approved since 2010 (i.e., sipuleucel-T, cabazitaxel, abiraterone acetate plus prednisone, enzalutamide, radium-223, apalutamide). (Crawford Urology 2015; Smith N Engl J Med 2018) Additional therapies are being studied, such as poly-(adenosine diphosphate-ribose) polymerase (PARP) and PI3K/AKT pathway inhibitors. Studies suggest that earlier detection of advanced disease in specific patient populations, coupled with these newer treatment options, will potentially increase the OS benefit for these patients, especially in correlation with improved predictive markers to help guide treatment selection. (Schellhammer Urology 2013; Ost JCO 2017)

The development of metastases is a seminal event during prostate cancer progression, as the development of CRPC heralds a potentially fatal disease. Although OS has improved from approximately 18 months to 3 years since approval of new therapeutic agents, CRPC is invariably fatal. There are risk factors that are prognostic of worse outcomes. In a retrospective study of 205 patients with mCRPC, advanced age, time since diagnosis, greater number of bone metastases, higher prostate-specific antigen (PSA) levels, and shorter PSA doubling time (PSADT) were all associated with shorter OS time. (Moreira CGC 2017)

REVIEW OF PRIOR RADAR GROUP RECOMMENDATIONS

The RADAR I Group initially convened to provide recommendations for the early identification of prostate cancer metastases. RADAR I recommended preferred traditional imaging modalities, and specifically when and how often the imaging should be performed (figure 1). (Crawford Urology 2014)

Figure 1. RADAR I Recommendations



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Subsequently, the RADAR II Group met to elaborate on the work of the original RADAR I Group and provided recommendations on the therapeutic sequencing, combining, or layering of approved treatments for patients with metastatic prostate cancer who developed CRPC. (Crawford Urology 2017)

METHODS

The RADAR III Group convened to evaluate the use of next generation imaging (NGI) modalities and reviewed the rationale for obtaining specific scans, the frequency of imaging, interpreting imaging results and their subsequent clinical utility, and finally, proposing a clinical decision-making treatment algorithm. RADAR III discussed both accessibility and utilization amongst medical oncologists, radiation oncologists, and urologic oncologists within various practice settings (eg, academic vs community; rural vs urban). Recommendations were made regarding prostate cancer nomenclature in order to accurately represent the changing landscape of imaging and subsequent treatment decision-making. RADAR III acknowledges the limitations of making recommendations when level one evidence-based data are not yet available. However, given the rapid development and increased availability of these newer imaging modalities, and as practitioners are faced with making clinical decisions, recommendations are needed. RADAR III, based on their expert opinion and clinical experience, herein provide guidance for the utilization of these NGIs.

Updates were made to the original RADAR I guidelines to include recommendations on emerging NGI technologies, based on specificity and sensitivity of published reports and real-world availability. RADAR III also acknowledged the importance of incorporating NGI into future clinical trial designs. Importantly, it was agreed that earlier initiation of treatment may lead to better outcomes with optimal patient selection. More definitive clinical trials are required to determine the optimal utilization of NGI technologies.

NEXT GENERATION IMAGING MODALITIES

Novel Positron Emission Tomography (PET) Radiotracers

PET is a functional imaging technique that is able to detect metabolic activity, blood flow, apoptosis, etc. (Evans PRO 2017)

The use of PET/CT in patients with prostate cancer has been advanced by the development of new radiotracers, including ^{18}F-fluciclovine, ^{11}C-choline, agents targeting prostate-specific membrane antigen (PSMA), 16beta-^{18}F-fluoro-5alpha-dihydrotestosterone (^{18}F-FDHT), and ^{11}C acetate. (Fischer EJNMMI 2016) (Lindenberg JAMA Oncology 2017)

These NGI PET/CT radiotracers allow for the detection of previously undetectable metastases by traditional imaging studies (CT and technetium-99m bone scans) due to improved sensitivity and specificity. Several of these NGI techniques have been approved by the Food and Drug Administration (FDA) for use in patients with prostate cancer. These include ^{18}F-fluciclovine (^{18}F-FACBC), ^{11}C choline, sodium fluoride (^{18}F-NaF), and fluorodeoxyglucose ^{18}F-(FDG). FDA approval generally signifies that the scans can be performed reproducibly and safely. Additionally, the FDA—as well as reimbursement agencies—generally require a demonstration of clinical utility via alterations in treatment decisions based on the use of the specific imaging modality. (Evans 2018; FDA Press Release) However, FDA approval for these scans does not necessarily mean that proven value in clinical practice has been established; specifically, it does not mandate that treatment decisions are altered in a fashion that leads to clinical benefit for a patient, either through efficacy, safety, or quality of life. In fact, there is currently very little clinical data demonstrating that the use of NGI improves outcomes. Moreover, FDA approval does not guarantee reimbursement by Medicare or third-party payers.

Table 2. Next Generation Imaging (Lindenberg JAMA Oncol 2017, Bach-Gansmo J Urol 2017)

Radiotracer	Action/ Target	Sensitivity (%)	Specificity (%)	Pros	Cons	Indications
^{18}F-FACBC (fluciclovine)	Amino acid transport	89-100	67-70	More sensitive than choline and acetate, slow urinary excretion improving signal	Moderate specificity and moderate performance at low PSA cut-offs, needs validation in larger studies	Detection of local and distant recurrence
^{11}C-choline	Cell membrane synthesis	38-98	50-100	Minimal bladder excretion	Variable sensitivity and specificity for BCR especially at low PSA cut-offs; short half-life, only a few centers have cyclotron on-site	Detection of recurrent disease in lymph node and soft tissues
^{68}Ga-PSMA	Targets PSMA	63-86	95-100	Superior sensitivity and specificity even at low PSA cut-offs compared to alternative scans	Requirement of a ^{68}Ga generator, need more validation	High detection rate of local and distant sites of recurrence, also risk of metastatic disease in high-risk of patients undergoing a primary definitive therapy
^{18}F-DCFBC	Targets PSMA	92	88	Slightly longer half-life than ^{68}Ga	First generation of ^{18}F-labeled urea. Considerable blood pool activity, being investigated in clinical trials, need more validation	For better selection of primary definitive therapy, both hormone-sensitive and CRPC
^{18}F-DCFPyL	Binds PSMA	71	89	Higher tumor to background ratios owing to high affinity, more sensitive to detect occult lymph nodes before primary definition therapy	Still being investigated in phase 3 clinical study	Detection of occult lymph nodes before primary definitive treatment, early local and distant recurrence
^{11}C-acetate	Lipid synthesis	42-90	64-96	Ability to image both soft tissue and skeletal mets; minimal bladder excretion (Yu Clin Nucl Med 2011)	Short half-life, few centers have a cyclotron on-site	Identification of metastatic disease

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NGI TRACERS

^{18}F-fluciclovine PET/CT (^{18}F-FACBC, Axumin®)

^{18}F-fluciclovine is a synthetic L-leucine analog that exhibits high tumor-specific accumulation in both primary and metastatic prostate carcinomas through targeting amino acid transports, which are upregulated in prostate cancer. (Okudair JNM 2011, Schuster JNM 2007) It was recently approved by the FDA for patients with suspected recurrence based on elevated PSA following prior treatment. (Axumin PI 2016)

^{18}F-fluciclovine demonstrated superiority when compared with other NGIs, such as ^{18}F-choline and ^{11}C-choline. A meta-analysis of different PET tracers demonstrated that ^{18}F-fluciclovine had greater ability to detect locally recurrent disease versus ^{18}F-choline, although the difference was not statistically significant. (Yu AJNMMI 2014) In a prospective study of 89 patients comparing the accuracy of ^{18}F-FACBC and ^{11}C-choline PET/CT in patients undergoing prostatectomy who presented with biochemical relapse, ^{18}F-FACBC demonstrated detection superiority over ^{11}C-choline. Categorizing patients by PSA level, the percent of patients with true-positive findings were generally higher with ^{18}F-FACBC than with ^{11}C-choline (table 2). (Nanni Eur J Nucl Med Mol Imaging 2016)

Limitations of ^{18}F-fluciclovine include potential long-term risk of secondary cancers, unknown responsiveness to ADT, limited information regarding imaging in the CRPC setting, and overall limitations of potential variability in sensitivity and specificity as it relates to location of metastases (eg, PSA, PSADT). (Bach-Gansmo J Urol 2017)

^{11}C-choline PET/CT

^{11}C-choline has variable sensitivity and specificity for biochemical recurrence, especially at low PSA levels. (Nanni Eur J Nucl Med Mol Imaging 2016) ^{11}C-choline has limited availability due to its very short half-life of 20.4 minutes, which requires an on-site cyclotron that few centers in the US possess. (Czernin PET Clin 2009)

^{18}F-sodium fluoride (^{18}F NaF) PET/CT

^{18}F-NaF is a radioactive tracer that diffuses into the bone, leading to an exchange of fluoride ions with hydroxide ions of the hydroxyapatite crystals, eventually forming fluorapatite. (Kurdziel J Nucl Med 2012) ^{18}F-NaF PET/CT has higher specificity and sensitivity than traditional bone scans or planar single-photon emission CT imaging. (Harmon JCO 2017) Despite this, the Centers for Medicare and Medicaid Services (CMS) is no longer reimbursing ^{18}F-NaF for prostate cancer management.

PSMA Ligands

Novel imaging modalities using radiolabeled tracers with PSMA, such as ^{68}Gallium (Ga) PSMA PET/CT, have shown promising results with best utilization in biochemical recurrence. (Perera 2016; Udovicich 2017) Review of the literature generally favors PSMA-based agents versus choline and fluciclovine for detection of recurrence as a function of low PSA levels; however, comparison studies have not been performed (table 3). (Evans 2018) Based on the growing body of literature regarding its clinical utility, the availability of PSMA within the US is limited but beginning to increase. (Evans 2018)

Table 3. Summary of Data Evaluating Prostate Cancer PET Detection Rates as a Function of PSA (Evans 2018)

Study	PET Radiotracer	% of Patients With BCR	% of Patients With Positive PET/CT		
			PSA <1.0	PSA 1.0-2.0	PSA >2.0
Choline					
Mitchell	^{11}C-choline	100% (176/176)	44% (15/34)	67% (21/31)	86% (96/111)
Giovacchini	^{11}C-choline	100% (358/358)	19% (27/141)	46% (39/85)	72% (95/132)
Richter	^{11}C-choline	100% (73/73)	7% (1/15)	46% (6/13)	80% (36/45)
Krause	^{11}C-choline	100% (63/63)	36% (8/22)	43% (3/7)	71% (24/34)
Castellucci	^{11}C-choline	100% (190/190)	19% (10/51)	25% (10/39)	54% (54/100)
Nanni	^{11}C-choline	100% (89/89)	14% (4/28)	29% (8/28)	55% (18/33)
Schwenck	^{11}C-choline	100% (101/101)	44% (8/18)	81% (21/26)	89% (51/57)
Cimitan	^{18}F-choline	100% (1000/1000)	31% (66/211)	43% (66/153)	81% (513/636)
Schillaci	^{18}F-choline	100% (49/49)	20% (2/10)	56% (5/9)	83% (25/30)
Morigi	^{18}F-methchol	100% (38/38)	13% (2/16)	36% (5/14)	63% (5/8)
PSMA					
Schwenck	^{68}Ga-PSMA	100% (101/101)	61% (11/18)	76% (20/26)	93% (53/57)
Morigi	^{68}Ga-PSMA	100% (38/38)	50% (8/16)	71% (10/14)	88% (7/8)
Afshar-Oromieh	^{68}Ga-PSMA	100% (319/319)	53% (27/51)	72% (28/39)	92% (204/221)
Eiber	^{68}Ga-PSMA	100% (248/248)	67% (35/52)	93% (67/72)	97% (120/124)
Bluemel	^{68}Ga-PSMA	100% (32/32)	29% (4/14)	46% (5/11)	71% (5/7)
Verburg	^{68}Ga-PSMA	100% (155/155)	44% (12/27)	79% (15/19)	89% (97/109)
Fluciclovine					
Nanni	^{18}F-FACBC	100% (89/89)	21% (6/28)	46% (13/28)	55% (18/33)
Odewole	^{18}F-FACBC	100% (53/53)	38% (3/8)	78% (7/9)	86% (31/36)
Bach-Gansmo	^{18}F-FACBC	100% (596/596)	41% (53/128)	58% (N?)	75%-85% (N?)
Schuster	^{18}F-FACBC	100% (93/93)		72% (N?)	

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^{68}Gallium (Ga)-PSMA PET/CT

Rapidly developed and implemented in different centers and clinics in Europe, Australia, South America, and the US, gallium citrate (^{68}Ga)-PSMA-HBED-CC is one of the more utilized ligands in this class of small molecule inhibitors worldwide and has high sensitivity (63%-86%) and specificity (95%-100%) even at low PSA levels based on different single- and multi-institutional trials. (Öbek EJNMMI 2017; Maurer J Urol 2016; Kranzbühler EJNMMI 2017)

In a systematic review and meta-analysis of reported predictors of positive ^{68}Ga-PSMA PET and corresponding sensitivity and specificity profiles, 16 articles involving 1309 patients were analyzed. The overall percentage of positive ^{68}Ga-PSMA PET among patients was 40% (95% confidence interval [CI] 19%-64%) for primary staging and 76% (95% CI 66%-85%) for BCR. Positive ^{68}Ga-PSMA PET scans for BCR patients increased with pre-PET PSA. For the PSA categories 0–0.2, 0.2–1, 1–2, and >2 ng/ml, 42%, 58%, 76%, and 95% scans, respectively, were positive. Shorter PSADT increased ^{68}Ga-PSMA PET positivity. The summary sensitivity and specificity were both 86% on per-patient analysis, and the summary sensitivity and specificity were 80% and 97%, respectively, on pre-lesion analysis. (Perera 2016)

A prospective survey of referring physicians showed that PSMA-11 PET/CT results in actually implemented management changes in more than 50% of prostate cancer patients with BCR (54/101; 53%). (Calais 2017)

In a study of ^{68}Ga-PSMA in 70 patients with biochemical recurrence after radical prostatectomy with extended lymph node dissection, the sites of recurrent disease included the prostatic fossa (27%), pelvic lymph nodes (14.3%), both the fossa and pelvic lymph nodes (4.3%), and outside the pelvis (8.6%). (van Leeuwen BJUI 2016a) These results show that ^{68}Ga-PSMA is able to detect local, regional, and distant metastatic disease even in patients with low PSA levels. The investigational nature of ^{68}Ga-PSMA, as well as the requirement for a gallium 68 generator limits its current availability in the US.

N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-^{18}F-fluorobenzyl-L-cysteine (^{18}F-DCFBC) PET/CT

^{18}F-DCFBC is a small molecule PSMA inhibitor useful for detecting high-grade (Gleason 8 and 9) and larger sized (≥1.1 ml) primary tumors reliably. (Rowe JNM 2015) It displays little uptake in benign prostatic hyperplasia and, therefore, may be useful in differentiating malignant from nonmalignant prostate tissues.

^{18}F-DCFPyL PSMA PET/CT

^{18}F-DCFPyL is a second-generation ^{18}F-labeled PSMA agent. In a small comparative study with ^{68}Ga-PSMA in 14 patients with BCR disease, the ^{18}F-DCFPyL scan was slightly more sensitive with higher tumor-to-background ratios than ^{68}Ga-PSMA. (Dietlein Mol Imag Bio 2015) In that study, ^{18}F-DCFPyL detected all the suspicious lesions detected by ^{68}Ga-PSMA plus additional suspicious lesions in 3/14 patients, indicating a high sensitivity for ^{18}F-DCFPyL.

^{18}F-FDHT PET/CT

The androgen receptor is overexpressed in the majority of patients with CRPC. ^{18}F-FDHT, which is chemically similar to dihydrotestosterone, is a ligand for the androgen receptor. (Bednarova TAU 2017) In a clinical trial of patients with advanced aggressive prostate cancer, ^{18}F-FDHT showed lower sensitivity for prostate cancer detection compared to ^{18}F-FDG (86% versus 97%, respectively). For in vivo estimation of the androgen receptor expression in patients on ADT, however, ^{18}F-FDHT may be the better PET tracer for the assessment of treatment response. (Larson J Nucl Med 2004) Overall, there are very limited clinical data to date on ^{18}F-FDHT. (Bednarova TAU 2017) This radiotracer has demonstrated utility in assessing androgen receptor blockade with second-line antiandrogens. (Lindenberg Curr Urol Rep 2016; Talbot Q J Nucl Med Mol Imaging 2015)

^{11}C-acetate PET/CT

In a pooled meta-analysis of 23 studies investigating ^{11}C-acetate PET, this radiotracer had a suboptimal sensitivity of 75.1% at detecting primary tumors, although it did have a high specificity of 93% in identifying the location of relapse. (Mohsen BJUI 2013) Taking into account the complexity of imaging with this tracer and the short half-life of ^{11}C (20.4 minutes) requiring on-site synthesis, the availability of ^{11}C-acetate PET for imaging in prostate cancer is very limited. (Mohsen BJUI 2013) The isotope's short half-life requires an on-site cyclotron, and there are only a few centers in the US that have this access.

Medicare Coverage

Only a few NGI PET/CT scans are currently covered by Medicare (table 4). As of early 2018, the CMS has withdrawn the National Oncology PET Registry (NOPR) program for ^{18}NaF PET/CT. The NOPR program was a collaboration of the American College of Radiology Imaging Network (ACRIN), the American College of Radiology (ACR), and the Academy of Molecular Imaging (AMI), to ensure access to Medicare reimbursement for certain types of PET.

Table 4. Medicare Coverage for Several NGI Techniques

Scan Type	Medicare Coverage
^{18}F-fluciclovine PET/CT	Yes
^{11}C-choline PET/CT	Yes (Limited[a])
^{18}F-NaF PET/CT	No
^{18}F-FDG PET/CT	Yes (STS)
^{68}Ga-PSMA PET/CT	No

[a]On-site cyclotron with site-specific/ANDA.
ANDA, abbreviated new drug application; NDA, new drug application; STS, subsequent treatment strategy.

Whole-body MRI has been used successfully in Europe and has shown good sensitivity and specificity in bone metastases. In the US, there are no established current procedural terminology (CPT) codes for reimbursement for whole body MRI. (Wibmer 2015)

DISCUSSION

POTENTIAL CLINICAL IMPACT OF NGI

Disease evaluation following unsuccessful initial interventional therapy is critical as salvage therapies may be curative but may also be associated with morbidity and not beneficial if distant disease exists. Local recurrence of prostate cancer can be detected by multiparametric MRI with components such as anatomical T2 weighting and functional imaging (e.g., diffusion weighted

imaging, dynamic contrast-enhanced imaging). (Lindenberg JAMA Oncol 2017) However, both local recurrences and distant metastases can be better confirmed with NGI. (Evans 2018)

NGI techniques are able to identify previously undetectable prostate cancer metastases, allowing for consideration of earlier treatment that has the potential to affect long-term outcomes. There has been a body of evidence that suggests that earlier therapeutic intervention leads to better outcomes for patients with advanced prostate cancer in both the hormone-sensitive and castration-resistant settings. This has been demonstrated for chemotherapy (CHAARTED), immunotherapy (IMPACT/quartiles data), and novel androgen receptor-targeted agents (LATITUDE/STAMPEDE). (NCCN PC 2018; Sweeney NEJM 2015; Schellhamer Urology 2013; Fizazi NEJM 2017; James NEJM 2017; Ost JCO 2017) However, the use of NGI has the potential to enhance outcomes as it can allow for earlier therapy in a patient with a very low PSA, when theoretical cure or significant tumor reduction may lead to benefits. In 2018, this notion is still hypothesis-generating, and thus requires prospective trials in order to evaluate the efficacy and risks of such earlier interventions. However, a recently published phase 2 study in patients with oligo-recurrent prostate cancer does suggest benefit of early intervention. (Ost JCO 2017)

The availability of NGI has the potential to redefine the traditionally accepted stages in prostate cancer progression. Many patients diagnosed as M0 hormone sensitive (m0 HS) and M0 castration-resistant prostate cancer (m0 CRPC) based on traditional scans, would now be potentially upgraded as M1 HS and M1 CRPC using the improved NGI techniques. (Lei 2016; Botrel 2016; Gundem 2015) PROSPER and SPARTAN trials now support the use of enzalutamide and apalutamide in men with M0 CRPC (also identified as nmCRPC). These studies have utilized traditional imaging studies to determine the M0 disease state, nmCRPC, and

to ascertain progression. It is the opinion of RADAR III that NGI should be evaluated and could find utility for both M0 disease states.

NGI RECOMMENDATIONS BY THE RADAR III GROUP

The transition to advanced prostate cancer is of crucial clinical importance and NGI techniques allow for the early identification of previously undetectable prostate cancer metastases. No single NGI imaging scan can detect all metastases required for clinical decision-making. Of all the NGI tests considered, the ^{18}F-fluciclovine PET scan has the best combination of availability, specificity, and sensitivity in the US. PSMA PET/CT scans show great diagnostic potential, but likely won't be available for widespread use in the US for several years, although it is being regularly used in some other nations (eg, Australia, New Zealand, Germany, and Brazil). It also may be ideal to couple with the development of novel therapeutic radiopharmaceuticals targeted to PSMA. In general, RADAR III recommends the use of available NGI techniques, but the use of these scans varies based on each stage of advanced disease, as outlined in figure 2.

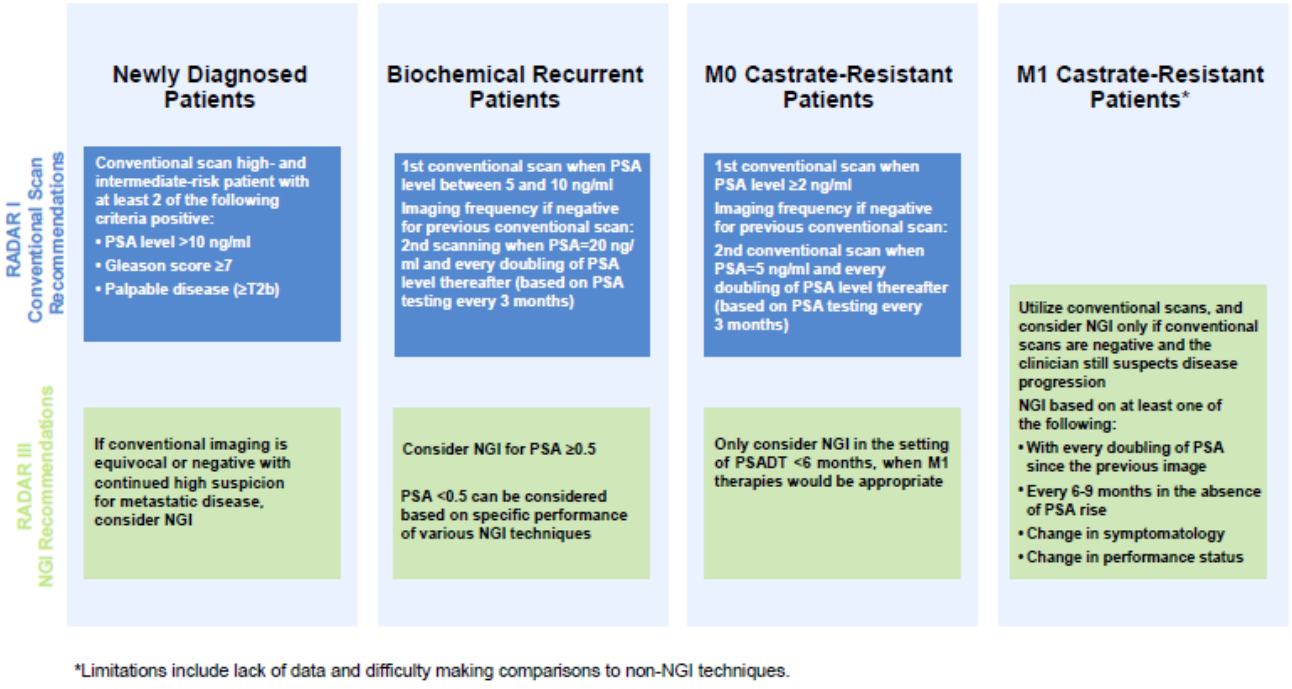
The RADAR III group recommends FDA-approved systemic therapy (sipuleucel-T, cabazitaxel, abiraterone acetate plus prednisone, enzalutamide, radium-223) for patients with confirmed M1 CRPC who are clinically deemed fit enough to undergo such treatment. (Crawford Urology 2015) These treatments, which have been proven to extend OS in men with mCRPC, require confirmation of metastatic disease on scan before being initiated.

In early 2018, the FDA approved apalutamide, a next-generation androgen receptor inhibitor, for patients with M0 CRPC. A phase 3 SPARTAN trial of 1207 men with nonmetastatic CRPC and PSADT of 10 months or less demonstrated that median metastasis-free survival was 40.5 months

with apalutamide compared with 16.2 months with placebo ($p<0.001$). Time to symptomatic progression was also significantly longer with apalutamide than with placebo. (Smith N Engl J Med 2018)

There are also promising new treatments under development for patients with M0 CRPC, including earlier use of enzalutamide based on the positive PROSPER trial, for which an expanded approval is currently being sought. Another agent, darolutamide, has potential to help delay the progression to metastatic disease. It will be important to consider the inclusion of NGI techniques in clinical trials involving these agents in the M0 setting.

Figure 2. RADAR III Recommendations on NGI (Crawford 2014)



Top portion of figure adapted from Crawford 2014.

Newly Diagnosed Patients

In newly diagnosed patients with suspected localized prostate cancer, RADAR I recommended the use of traditional CT/bone scans for men who had at least 2 of the 3 following criteria:

- PSA level >10 ng/ml
- Gleason score ≥7
- Palpable disease (≥T2b)

RADAR III recommends utilization of traditional scans with consideration for NGI only if the traditional scans are equivocal or negative and the clinician still suspects disease progression

based on various factors, including—but not limited to—the following criteria: (NCCN V1.2018)

- Gleason score
- PSA levels
- PSA velocity in untreated patients
- Patients meeting NCCN very high risk or locally advanced/N1 disease should be considered for NGI at initial diagnosis

As an example, consider a healthy 63-year-old male with PSA of 60 ng/ml, Gleason score of 7 in 10/12 cores, and negative technetium-99m bone scan and pelvic CT scan. We would recommend an NGI evaluation.

Although there is currently a lack of level one evidence to support the use of NGI, there are emerging clinical data to support this approach. A recently published prospective phase 2 PMSA-targeted PET/CT study was able to detect prostate cancer metastases in patients thought to have clinically localized disease based on traditional imaging, and thereby proceeded with interventional therapy. (Gorin J Urol 2018)

Biochemical Recurrent Patients

In BCR patients who have been definitively treated, RADAR III suggests that NGI may be considered for patients with PSA ≥0.5 ng/ml after treatment. Patients with PSA <0.5 ng/ml can be considered based on specific performance of various NGI techniques. NGI should only be performed if the patient is willing to undergo metastasis-directed therapy (MDT) in the event of a positive scan, or they are seeking a rationale to initiate systemic therapy. If a scan is not performed, PSA should be monitored closely and NGI be reconsidered if the PSA rises.

M0 Castration-Resistant Patients

For patients with M0 CRPC, RADAR I recommended that a CT/bone scan should be performed when PSA ≥2 ng/ml. If negative, subsequent scans should be performed when PSA = 5 ng/ml and every doubling of PSA levels thereafter (based on PSA testing every 3 months).

RADAR III reviewed NGI for M0 CRPC. NGI could identify metastases earlier, which would allow for patients to receive treatment with the 5 agents that have regulatory approval in the M1 CRPC setting. Although earlier intervention using this approach has not been validated through prospective clinical trials, there is evidence to support the concept that intervening earlier with systemic therapies for M1 CRPC (sipuleucel-T) and for M0 CRPC (apalutamide), when disease burden is lower, may have a positive impact for some patients.

RADAR III suggests follow-up imaging every 6-12 months or more frequently based on PSADT <6 months, and/or symptoms in patients undergoing therapy for M0 CRPC. If traditional imaging fails to detect metastatic disease, NGI can be performed only if approved therapies in the M1 space are being considered. RADAR III cautions against ceasing therapy for PSA rise alone.

Given the recent approval of apalutamide for M0, the value of NGI in this setting has yet to be determined. As such, NGI should only be considered when a patient progresses and M1 treatments are being considered.

Patients With M1 Prostate Cancer Undergoing Treatment

RADAR III expanded the original RADAR I recommendations to include additional guidance on imaging techniques for M1 patients. The expanded recommendations include imaging using traditional scans and moving on to NGI only if the traditional scans are negative and the clinician still suspects disease progression based on at least one of the following:

- With every doubling of PSA since the previous image was taken
- Every 6-9 months in the absence of PSA rise
- Change in symptomatology
- Change in performance status

The goal of scanning in the M1 setting is to confirm disease progression to inform clinical decision-making. If disease progression is confirmed on scan, RADAR III recommends the consideration of the use of therapeutic layering. Therapeutic layering is different from combination therapy, in which 2 or more therapies are initiated simultaneously. Therapeutic layering, as defined by the RADAR II Group, represents a clinical point where one or more agent(s) are added onto an existing therapy. In CRPC, all treatment interventions are technically layering of therapy since agents are added to the foundation of ADT. To see specific recommendations on therapeutic layering for M1 CRPC patients, please refer to the RADAR II manuscript. (Crawford 2017)

The use of NGI regarding treatment response has yet to be definitively established. Limitations include comparison of NGI and non-NGI techniques, as well as the significance of semiquantitative analysis of NGI.

CONSIDERATIONS FOR CHANGE IN NOMENCLATURE

Prostate cancer's heterogeneous nature requires better terminology that more clearly defines its response to specific therapies. As the disease has continued to evolve biologically over the years in a much different way, our recommendation is to re-name CRPC as endocrine-resistant prostate cancer (ERPC).

Clinicians created an iatrogenic disease state by treating men with ADT who have a rising PSA after a local treatment. Once men exhibit progression after ADT, they have developed endocrine resistance and if no metastasis are detected, they have been categorized as M0 or nmCRPC. The original intent of the term CRPC described metastatic disease while failing ADT. Consequently, the M0 CRPC was added to categorize these men. Two major advances have occurred that suggest a need to redefine this entire disease state. The first is NGI, which offers an opportunity to more accurately assess disease progression, and secondly, 2 trials have demonstrated a significant benefit to newer third generation antiandrogen in the nonmetastatic endocrine-resistant state. RADAR III believes these events dictate the need for reassessment and development of renewed nomenclature and guidelines.

Our recommendations are to now name these states as ERPC instead of CRPC. The rationale for this terminology was suggested several years ago. (Crawford & Petrylak JCO 2010). The RADAR III guidelines for this ERPC space include:

1. Men experiencing PSA or other signs of progression after adequate ADT for any stage of prostate cancer be labeled as ERPC
2. Men who experience progression after adequate ADT for biochemical progression and negative conventional imaging be labeled nmERPC (nonmetastatic conventional

imaging), nmERPC* (nonmetastatic *NGI performed and since nmERPC* nonmetastatic by NGI)

3. A similar system for positive imaging mERPC, mERPC* (metastatic by NGI) for metastatic disease; we believe these guidelines will better stratify men for future evaluations

In M1 disease, results of conventional scans may be different than NGI based on the dynamic and changing biology of the prostate cancer. Further head-to-head studies are warranted to investigate the different implications for appropriate therapeutic approaches.

CONCLUSIONS

While traditional CT, MRI, and bone scans still have a role in initially diagnosing prostate cancer, NGI modalities are more sensitive in visualizing advanced prostate cancer. These new scans are recommended for select patients where aggressive intervention earlier may be indicated. Currently, the ^{18}F-fluciclovine PET scan is the NGI technique with the best combination of availability, specificity, and sensitivity in the US. PSMA PET/CT scans show great diagnostic potential, but likely won't be available for widespread use in the US for several years.

Our strongest recommendation for use of NGI is in patients with BCR prostate cancer. This is where the data are strongest, and the likelihood of site-directed therapy is greatest for patients interested in such strategies. This group recognizes the lack of current efficacy and safety data however, the purpose of a consensus manuscript is to provide guidance in an area where clinical decision-making is less than certain. Hence, we believe the greatest potential impact to alter

therapy and improve patient outcomes with NGI are in a setting where reintroduction of local therapy +/- systemic therapy has the greatest potential.

Abbreviations and Acronyms

^{18}F-FACBC = ^{18}F-fluciclovine

^{18}F FDG = ^{18}F-fluorodeoxyglucose

^{18}F-FDHT = ^{18}F-fluoro-5alpha-dihydrotestosterone

^{18}F NaF = sodium fluoride

ACR = American College of Radiology

ACRIN = American College of Radiology Imaging Network

AMI = Academy of Molecular Imaging

ANDA = abbreviated new drug application

BCR = biochemically recurrent

CHAARTED = ChemoHormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer

CI = confidence interval

CMS = Centers for Medicare and Medicaid Services

CPT = current procedural terminology

CT = computed tomography

ERPC = endocrine-resistant prostate cancer

FDA = Food and Drug Administration

Ga = ^{68}Gallium

IMPACT = IMmunotherapy for Prostate AdenoCarcinoma Treatment

LATITUDE = A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)

mCRPC = metastatic castration-resistant prostate cancer

mHSPC = metastatic hormone-sensitive prostate cancer

MDT = metastasis-directed therapy

MRI = magnetic resonance imaging

NDA = new drug application

NGI = next generation imaging

nmCRPC = nonmetastatic castration-resistant prostate cancer

NOPR = National Oncology PET Registry

OS = overall survival

PARP = poly-(adenosine diphosphate-ribose) polymerase

PET = positron emission tomography

PFS = progression-free survival

PROSPER = A Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled, Efficacy And Safety Study Of Enzalutamide In Patients With Nonmetastatic Castration-resistant Prostate Cancer

PSA = prostate-specific antigen

PSADT = prostate-specific antigen doubling time

PSMA = prostate-specific membrane antigen

RADAR = Radiographic Assessments for Detection of Advanced Recurrence

SPARTAN = Selective Prostate Androgen Receptor Targeting with ARN-509

STAMPEDE = Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy

STS = subsequent treatment strategy

US = United States

REFERENCES (50 count)

American Cancer Society. *Cancer Facts & Figures 2018*. Atlanta, GA: American Cancer Society; 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed March 20, 2018.

Anantharaman A and Small EJ: Tackling non-metastatic castration-resistant prostate cancer: special considerations in treatment. Expert Rev Anticancer Ther 2017; **17:** 625.

Axumin (fluciclovine F 18) prescribing information. Oxford, UK: Blue Earth Diagnostics Ltd; 2016.

Bach-Gansmo T, Nanni C, Nieh PT et al: Multisite experience of the safety, detection rate and diagnostic performance of fluciclovine (18F) positron emission tomography/computerized tomography imaging in the staging of biochemically recurrent prostate cancer. J Urol 2017; **197:** 676.

Bednarova S, Lindenberg ML, Vinsensia M et al: Positron emission tomography (PET) in primary prostate cancer staging and risk assessment. Transl Androl Urol 2017; **6:** 413.

Botrel TE, Clark O, Lima Pompeo AC et al: Efficacy and safety of combined androgen deprivation therapy (ADT) and docetaxel compared with ADT alone for metastatic hormone-naive prostate cancer: A systematic review and meta analysis. PLoS One 2016; **11:** e0157660.

Calais J, Fendler WP, Eiber M et al: Impact of 68Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. J Nucl Med 2018; **59:** 434.

Crawford ED, Stone NN, Yu EY et al: Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology 2014; **83:** 664.

Crawford ED, Higano CS, Shore ND et al: Treating patients with metastatic castration resistant prostate cancer: a comprehensive review of available therapies. J Urol 2015; **194:** 1537.

Crawford ED, Petrylak D. Castration-resistant prostate cancer: descriptive yet pejorative? J Clin Oncol 2010; **28:** e408.

Crawford ED, Petrylak DP, Shore N et al: The role of therapeutic layering in optimizing treatment for patients with castration-resistant prostate cancer (prostate cancer radiographic assessments for detection of advanced recurrence II). Urology 2017; **104:** 150.

Czernin J, Benz MR and Allen-Auerbach MS: PET imaging of prostate cancer using ^{11}C-acetate. PET Clin 2009; **4:** 163.

Dietlein M, Kobe C, Kuhnert G et al: Comparison of [^{18}F]DCFPyL and [^{68}Ga]Ga-PSMA-HBED-CC for PSMA-PET imaging in patients with relapsed prostate cancer. Mol Imaging Biol 2015; **17:** 575.

Epstein JI, Amin MB, Beltran H et al: Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. Am J Surg Pathol 2014; **38:** 756.

Evans JD, Jethwa KR, Ost P et al: Prostate cancer–specific PET radiotracers: A review on the clinical utility in recurrent disease. Pract Radiat Oncol 2018; **8:** 28.

Fischer BM, Siegel BA, Weber WA et al: PET/CT is a cost-effective tool against cancer: synergy supersedes singularity. Eur J Nucl Med Mol Imaging 2016; **43:** 1749.

Fizazi K, Tran N, Fein L et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; **377:** 352.

Food and Drug Administration. FDA News Release, May 27, 2016. FDA approves new diagnostic imaging agent to detect recurrent prostate cancer. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503920.htm. Accessed March 20, 2018.

Gorin MA, Rowe SP, Patel HD et al: Prostate specific membrane antigen targeted 18F-DCFPyL positron emission tomography/computerized tomography for the preoperative staging of high risk prostate cancer: Results of a prospective, phase II, single center study. J Urol 2018; **199:** 126.

Gundem G, Van Loo P, Kremeyer B et al: The evolutionary history of lethal metastatic prostate cancer. Nature 2015; **520:** 353.

Harmon SA, Perk T, Lin C et al: Quantitative assessment of early [^{18}F]sodium fluoride positron emission tomography/computed tomography response to treatment in men with metastatic prostate cancer to bone. J Clin Oncol 2017; **35:** 2829.

Hoimes CJ and Kelly WK: Redefining hormone resistance in prostate cancer. Ther Adv Med Oncol 2010; **2:** 107.

James ND, de Bono JS, Spears MR et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017; **377:** 338.

Kranzbühler B, Nagel H, Becker AS et al: Clinical performance of ^{68}Ga-PSMA-11 PET/MRI for the detection of recurrent prostate cancer following radical prostatectomy. Eur J Nucl Med Mol Imaging 2018; **45:** 20.

Kurdziel KA, Shih JH, Apolo AB et al: The kinetics and reproducibility of ^{18}F-sodium fluoride for oncology using current PET camera technology. J Nucl Med 2012; **53:** 1175.

Larson SM, Morris M, Gunther I et al: Tumor localization of 16beta-18F-fluoro-5alphadihydrotestosterone versus 18F-FDG in patients with progressive, metastatic prostate cancer. J Nucl Med 2004; **45:** 366.

Lei JH, Liu LR, Wei Q et al: Androgen-deprivation therapy alone versus combined with radiation therapy or chemotherapy for nonlocalized prostate cancer: a systematic review and meta-analysis. Asian J Androl 2016; **18:** 102.

Lindenberg L, Choyke P and Dahut W: Prostate cancer imaging with novel PET tracers. Curr Urol Rep 2016; **17:** 18.

Lindenberg ML, Turkbey B, Mena E et al: Imaging locally advanced, recurrent, and metastatic prostate cancer: a review. JAMA Oncol 2017; **3:** 1415.

Maurer T, Gschwend JE, Rauscher I et al: Diagnostic efficacy of (68)gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol 2016; **195:** 1436.

Mena E, Lindenberg ML, Shih JH et al: Clinical impact of PSMA-based 18F-DCFBC PET/CT imaging in patients with biochemically recurrent prostate cancer after primary local therapy

[published online September 11, 2017]. Eur J Nucl Med Mol Imaging 2017 doi: 10.1007/s00259-017-3818-x. Accessed March 20, 2018.

Mohsen B, Giorgio T, Rasoul ZS et al: Application of C-11-acetate positron-emission tomography (PET) imaging in prostate cancer: systematic review and meta-analysis of the literature. BJU Int 2013; **112:** 1062.

Moreira DM, Howard LE, Sourbeer KN et al: Predicting time from metastasis to overall survival in castration-resistant prostate cancer: results from SEARCH. Clin Genitourin Cancer 2017; **15:** 60.

Nanni C, Zanoni L, Pultrone C et al: (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging 2016; **43:** 1601.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 1.2018. February 14, 2018. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed March 20, 2018.

Öbek C, Doğanca T, Demirci E, et al. The accuracy of ^{68}Ga-PSMA PET/CT in primary lymph node staging in high-risk prostate cancer. Eur J Nucl Med Mol Imaging 2017; **44:** 1806.

Okudaira H, Shikano N, Nishii R et al: Putative transport mechanism and intracellular fate of trans-1-amino-3-18F-fluorocyclobutanecarboxylic acid in human prostate cancer. J Nucl Med 2011; **52:** 822.

Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 2018; **36:** 446.

Perera M, Papa N, Christidis D et al: Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: A systematic review and meta-analysis. Eur Urol 2016; **70:** 926.

Rowe SP, Gage KL, Faraj SF et al: ^{18}F-DCFBC PET/CT for PSMA-based detection and characterization of primary prostate cancer. J Nucl Med 2015; **56:** 1003.

Schellhammer PF, Chodak G, Whitmore JB et al: Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial. Urology 2013; **81:** 1297.

Schuster DM, Votaw JR, Nieh PT et al: Initial experience with the radiotracer anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. J Nucl Med 2007; **48:** 56.

Smith MR, Saad F, Chowdhury S et al: Apalutamide treatment and metastasis-free survival in prostate cancer [published online February 8, 2018]. N Engl J Med doi: 10.1056/NEJMoa1715546. Accessed March 20, 2018.

Sweeney CJ, Chen YH, Carducci M et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; **373:** 737.

Talbot JN, Gligorov J, Nataf V et al: Current applications of PET imaging of sex hormone receptors with a fluorinated analogue of estradiol or of testosterone. Q J Nucl Med Mol Imaging 2015; **59:** 4.

Tombal B: Non-metastatic CRPC and asymptomatic metastatic CRPC: which treatment for which patient? Ann Oncol 2012; **23:** x251.

Udovicich C, Perera M, Hofman MS et al: 68Ga-prostate-specific membrane antigen-positron emission tomography/computed tomography in advanced prostate cancer: Current state and future trends. Prostate Int 2017; **5:** 125.

van Leeuwen PJ, Stricker P, Hruby G et al: (68) Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. BJU Int 2016; **117:** 732.

Wibmer AG, Vargas HA and Hricak H: Role of MRI in the diagnosis and management of prostate cancer. Future Oncol 2015; **11:** 2757.

Yu CY, Desai B, Ji L et al: Comparative performance of PET tracers in biochemical recurrence of prostate cancer: a critical analysis of literature. Am J Nucl Med Mol Imaging 2014; **4:** 580.