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Seminars in
NUCLEAR
MEDICINE

Molecular Imaging of Recurrent and Metastatic Prostate Cancer

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Although bone-scanning agents remain important for the detection of bone metastasis, the most common site of distant disease in prostate cancer, novel molecular imaging techniques are entering into clinical practice that provide new opportunities to both detect and characterize sites of involvement by prostate cancer, particularly in the setting of recurrent or advanced metastatic disease based on biochemical, clinical or imaging criteria. These approaches can define disease burden, guide locoregional salvage therapies, and select and monitor systemic treatment. While a wide array of tracers is available, the clinical role of broad classes of agents will be reviewed. An exciting and emerging role of molecular imaging is its use in selecting patients for radionuclide therapy.
Semin Nucl Med 49:280-293

Historical Context

Molecular imaging techniques have been integral to the management of patients with advanced prostate cancer for several decades. From the late 1960s until the late 1980s, the primary clinical indications for molecular imaging were the presymptomatic detection of skeletal metastatic disease and assessment of pain syndromes potentially caused by skeletal metastases. These evaluations relied upon detection of osteoblastic activity on whole-body bone scanning (WBBS), providing prognostic information[1] or guiding palliative radiotherapy. Subsequently, WBBS was used in patients with pain from widespread skeletal involvement for application of palliative treatments with bone-seeking radionuclides such as ^{89}Strontium[2] and ^{153}Samarium EDTMP.[3] This remains an important indication in the era of ^{223}Radium therapy.[4]

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The availability of prostate-specific antigen (PSA) testing since the 1980s has allowed early identification of patients in whom radical prostatectomy or definitive radiotherapy had failed to eradicate disease, offering the prospect of salvage therapy for residual or recurrent disease. In this setting, the primary imperative was to detect patients whose prostate cancer had spread beyond the intended locoregional treatment field in order to prevent futile procedures that may have significant morbidity.[5] Despite being deemed suitable for salvage treatment by conventional imaging, many of these men still progress to symptomatic metastatic disease and death from prostate cancer. However, since the lag time to symptoms averages almost a decade and the overall risk of cancer-specific death at 15 years is low,[6] the patient benefits of salvage therapies with curative intent remain unclear.[7]

Despite contemporaneous advances in CT and MRI technology, the accuracy of these anatomical tests for delineating sites of recurrent prostate cancer remained suboptimal, particularly in the clinical context of low PSA values.[8] Widely used contemporary molecular imaging studies were similarly limited with WBBS[9] and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)[10] demonstrating very low negative predictive values, particularly in the setting of early biochemical failure. Accordingly, there was a clear opportunity for imaging approaches with higher sensitivity.

 https://doi.org/10.1053/j.semnuclmed.2019.02.005
0001-2998/

Overview of Molecular Imaging Probes for Recurrent Prostate Cancer

The need for better biomarkers for guiding management of patients with recurrent prostate cancer stimulated efforts to develop and validate alternatives to WBBS and FDG-PET. Table 1 contains an illustrative list of radiotracers that have been investigated in prostate cancer. A detailed review of the characteristics and development of these agents is found elsewhere in this edition of *Seminars in Nuclear Medicine* (Insert Ref. from current issue).

A discussion of the role of each of these individual molecular imaging agents in recurrent prostate cancer is beyond the scope of this review and, therefore, we will emphasize molecular imaging agents that have progressed beyond the preclinical stage with sufficient published information to warrant making reasonable judgments about their clinical relevance in management decision-making in patients with recurrent or advanced metastatic prostate cancer. From this perspective, literature pertaining to ^{11}C methionine, ^{18}F-FSPG, and ^{18}F-FLT will not be discussed. Small studies using ^{18}F-FMISO PET have suggested that hypoxia is prevalent in primary prostate cancer,[11] but this was not confirmed in a histologically validated study using ^{18}F-FAZA PET.[12] Although potentially relevant to the efficacy of salvage radiotherapy and as a potential predictor of metastatic behavior,[13] the clinical implications of hypoxia imaging have not been sufficiently studied in recurrent prostate cancer to warrant further discussion.

While there are potential differences in biodistribution that could influence sensitivity or specificity, ^{11}C and ^{18}F variants and minor structural differences between molecular probes of a particular category will not be separately discussed unless clinically relevant. Thus, ^{11}C-choline, ^{18}F-fluoromethylcholine, and ^{18}F-fluoroethylcholine will be discussed under the single category of "choline" tracers with the understanding that, where available, ^{18}F ligands are usually more suited to routine clinical application than ^{11}C biosimilars due to a more favorable half-life. Similarly, evidence indicates that ^{11}C-acetate provides very similar information to ^{11}C-choline,[14] so this tracer will not be discussed separately, especially in view its limited availability.

A range of molecular probes and scanning techniques are available for detecting osteoblastic reactions to skeletal prostate carcinoma metastases. Planar WBBS with single photon tracers is less accurate than WBBS with single photon emission tomography (SPECT), and the greatest accuracy is achieved with ^{18}F NaF PET imaging.[15] Nevertheless, clinical trial guidelines[16] generally regard these different techniques as a single entity. For the sake of brevity, this practice will also be adopted in this manuscript.

With respect to agents directed to prostate-specific membrane antigen (PSMA), despite being an approved agent by the United States Food and Drug Administration (FDA), ^{111}Indium capromab pendetide will not be discussed owing

Table 1 Some Molecular Imaging Agents for Prostate Cancer Evaluation

Oncological Target	Positron Examples	Single Photon Examples
Tumor metabolism		
Glucose	^{18}F FDG	
Amino Acid	^{11}C Methionine	
	^{18}F Fluciclovine	
Nucleic Acid	^{18}F FLT	
Sterol synthesis	^{11}C and ^{18}F Choline	
Fatty Acid	^{11}C Acetate	
Oxygen	^{18}F MISO	
	^{18}F FAZA	
Glutathione	^{18}F FSPG	
Tumor receptors		
Androgen	^{18}F FDHT	
Bombesin	^{68}Ga RM2	^{99m}Tc Demobesin 4
Tumor antigens		
PSMA small molecule	^{68}Ga PSMA-11	^{99m}Tc-MIP-1040
	^{68}Ga PSMA I&T	^{99m}Tc PSMA I&S
	^{18}F DCFBC	^{123}I-MIP-1072
	^{18}F DCFPyL	
	^{18}F PSMA-1007	
	^{124}I-MIP-1095	
PSMA antibody	^{89}Z-anti-PSMA minibody	^{111}I Capromab Pendetide
	^{89}Z-J591	^{111}In-radiolabeled anti-PSMA Nanobody
Tumor environment		
Osteoblastic response	^{18}F NaF	^{99m}Tc MDP, HDP
	^{68}Ga DOTA-zoledronate	

DCFBC, *N*-[*N*-[(*S*)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine; FAZA, fluoro-azomycin arabinoside; FDHT, 16-beta-fluoro-5-alpha-dihydrotestosterone; FLT, fluoro-L-tyrosine; FSPG, (*S*)-4-(3-fluoropropyl)-L-glutamic acid; MISO, fluoro-misonidazole; NaF, sodium fluoride; PSMA, prostate specific membrane antigen (see reviews for detailed structures of PSMA-11, PSMA I&T, PSMA-1007, PSMA I&S, MIP-1095, MIP-1040 and MIP-1072); RM2, DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2.

to its limited sensitivity for disease localization, which is related to the intracellular location of the targeted PSMA epitope.[17] Similarly, while a monoclonal antibody to PSMA, J591, is being investigated as a therapeutic agent due to its low salivary gland uptake,[18] its long circulating half-life does not favor routine clinical imaging. However, a version labeled with ^{89}Zirconium[19] may be helpful for prospective dosimetry estimation prior to radioligand therapy. Further, of small molecule (SM) inhibitors of the PSMA enzymatic site via the Glutamate-Urea-Lysine motif, ^{18}F DCFBC has substantially delayed blood clearance and relatively low uptake at sites of known prostate cancer[20] and, therefore, will not be reviewed. At the current time, other agents of this class appear to provide very similar diagnostic clinical information.[21,22] Accordingly, standardized reporting guidelines have been prepared for this class of agents with directions regarding adjustments required to reporting thresholds when using individual agents.[23] These agents will be referred to collectively as SM PSMA PET tracers. Human data related to SM PSMA PET tracers targeting the enzymatic site through other chemical motifs[24] as well as preclinical studies using new molecular PSMA probes with modified pharmacokinetic behavior[25,26] or are combined with other functional targeting moieties[27] show promise but there are insufficient clinical data to assess their clinical utility in this setting. SM PSMA probes labeled with single photon emitters[28,29] will be addressed separately to SM PSMA PET tracers given somewhat different sensitivities for disease detection and the potential clinical implications thereof. The discussion of molecular imaging probes for Gastrin Releasing Peptide receptor (GRPr) expression will be restricted to ^{68}Ga Rm2, as this is the agent with the most published data in relation to recurrent prostate cancer.

Molecular Imaging Probes in the Spectrum of Recurrent Prostate Cancer

Any discussion of clinical relevance of molecular imaging probes must be cognizant of the wide spectrum of disease states represented by the term "recurrent prostate cancer," which influences the potential role for particular molecular imaging probes to contribute incremental information that is of benefit to patients. From this perspective, this discussion about the relevance of molecular imaging biomarkers to patient management will focus on three broad categories of recurrent prostate cancer:

(i) biochemical recurrence (BCR)
(ii) noncastrate progression
(iii) castrate-resistant metastatic disease

Use of Molecular Imaging Probes in Biochemical Recurrence (BCR)

As mentioned previously, therapeutic decision-making in this group of patients is difficult because they are asymptomatic and have a high probability of survival even if no treatment is instigated.[6] Nevertheless, European[30] and US (https://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf) management guidelines currently favor the application of "salvage" locoregional ablative therapies with curative intent in patients at risk of eventual progression and death from prostate cancer. Ideally, salvage therapy should be precisely targeted to actual sites of recurrent cancer by highly accurate imaging, while patients found to have disease outside clinically feasible treatment fields could avoid costly therapeutic interventions that may do more harm than good.

Despite these considerations, best-practice guidelines suggest that salvage therapy should be guided by a priori probability estimates of the location of recurrent prostate cancer rather than the use of molecular imaging probes. This advice is particularly strong for patients with BCR at a PSA level <1 ng/mL, where the salvage therapy outcomes are maximal. Several potential reasons exist for this lack of acceptance of the patient benefits of imaging biomarkers in BCR. Firstly, available imaging biomarkers may truly not offer patients significant benefits. Secondly, the evidence supporting the patient benefits of imaging-directed salvage treatments may be insufficiently developed to warrant a positive recommendation for their use. Thirdly, the process of guideline formulation may be lagging a rapid accumulation of evidence that new molecular imaging methods are fit for purpose, particularly if driven by clinicians with limited experience of these new techniques. Finally, the benchmarks used to judge the patient benefits of imaging biomarkers may unreasonably stringent. We will examine each if these impediments to the more routine application of molecular imaging biomarkers for therapeutic decision-making in patients with BCR.

Is There a Lack of Suitable Imaging Biomarkers for Beneficially Guiding BCR Salvage Treatments, Especially at Very Low PSA Levels?

The perfect imaging biomarker neither exists nor is ever likely to exist for this clinical indication from the perspective that even histopathology can fail to detect all sites of micrometastatic disease and local tumor invasion.[31] However, imaging biomarkers that reproducibly achieve near-perfect specificity (ie, that have extremely low false-positive rates) with even moderate sensitivity could direct patients away local therapies with minimal risk of depriving them of potentially curative attempts at total disease ablation.

A wealth of evidence indicates that ultrasound, CT, MRI, bone scanning and FDG-PET/CT lack incremental benefit in this clinical indication, especially since the incremental costs for imaging are high and disease detection rates are low, even in patients with PSA levels substantially greater (5-10 ng/mL) than the currently accepted ideal upper limits for instituting salvage curative-intent treatments. One large randomized clinical trial in this setting with median follow-up of 13 years showed CT and bone scan to have an ultimate negative predictive value of just 22%.[32] Unsurprisingly, the addition of systemic therapy in the face of such high rates of micro-

metastatic disease was of strong benefit beyond local pelvic salvage RT. Long-term follow-up of molecular imaging agents tested in prospective trials in this setting are yet to be reported. As detailed below, there is, however, now abundant evidence that several molecular imaging approaches, particularly including SM PSMA PET/CT, are fit-for-purpose as techniques for disease detection in the context of BCR.

Based on available evidence, FDA has approved ^{11}C-choline for use with PET imaging in "*patients with suspected prostate cancer recurrence (based on elevated PSA levels following initial therapy) and noninformative bone scintigraphy, CT or MRI. C-11 choline may help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation.* The evidence-base related to the diagnostic accuracy of choline PET in biochemical has accumulated over more than a decade. Several systematic reviews have been published[33-36] with common conclusions that choline PET imaging is safe and has a very high specificity and as well as acceptable sensitivity. However, many of the included studies reported on patients with imaging undertaken at PSA levels significantly higher than those currently recommended for instituting salvage radiotherapy. In their systematic review, Fanti et al[34] calculated a pooled sensitivity of 61% (95% confidence intervals [CI] 40%-80%) but specificity of 97% (95% CI 87-99%) from six studies with 491 participants that were suitable for analysis. In general, the evidence indicates that lower PSA levels and particularly slow PSA kinetics reduces the detection rate of choline PET, with mixed findings about the effects of androgen-deprivation therapy (ADT) on disease detection rates. To test the boundaries of utility for choline PET in BCR, Castellucci et al[37] examined 102 patients with PSA elevations between 0.2 and 1.5 ng/mL and found in a detection rate of 29%. Initial positive nodal status and PSA doubling-time (DT) were found to be the only variables predicting scan positivity on multivariate analysis, suggesting benefit only in the patients with the highest risk of disease.

Significant management change consequent upon the incremental diagnostic yield of choline PET has also been reported but not necessarily in the population in whom empiric salvage therapy is recommended. For example, Ceci et al analyzed data in 150 patients with BCR after radical primary therapy with a mean PSA 4.3 ± 5.5 ng/mL.[38] Intended treatments (prostate bed radiotherapy in 95 patients and palliative ADT in 55 patients) were altered in 47% of cases on the basis of PET/CT findings. Importantly, 13 (14%) of the patients planned for salvage prostate bed radiotherapy avoided this treatment because distant metastases were detected. There is also evidence that therapies directed by choline PET/CT findings can have a beneficial impact on patient outcome. Ost et al reported the results of a randomized phase II trial of patients with BCR and three or less extracranial metastases detected by choline PET.[39] The investigational cohort received metastasis-directed therapy (either surgery or stereotactic radiotherapy) and the control group underwent surveillance. The time to ADT commencement (based on symptoms, or evidence of progression) was 21 months in the metastasis-directed therapy group compared to 13 months in the control arm (hazard ratio 0.60, 80% CI: 0.4-0.9; $P = 0.11$), but without quality of life or clinical event difference as yet. Several other less rigorously controlled studies addressing the effects of radiation treatment intensification at sites of recurrent tumor detected by choline PET also suggest a favorable outcome to the treatment modifications implemented with low incidence of adverse effects.[40-42] All of these findings require corroboration in prospective trials with validated clinical endpoints.

The European Medicines Agency (EMA) and FDA have approved ^{18}F-fluciclovine PET for use in patients with BCR. The FDA indication is for "*PET imaging in men with suspected prostate cancer recurrence based on elevated blood PSA levels following prior treatment.*" Accordingly, fluciclovine PET imaging has been applied to investigation of human prostate cancer for more than a decade. Evidence of its diagnostic performance includes a pivotal clinical trial involving 128 studies in 115 patients with BCR and negative bone scans.[43] Histologic validation of positive PET findings was established in 96.1% of patients. In the prostate/bed, fluciclovine PET had 90.2% sensitivity but only 40.0% specificity, whereas for the presence or absence of extraprostatic disease, fluciclovine PET had 55.0% sensitivity and 96.7% specificity. More recently, a multi-institution study of 596 BCR patients using fluciclovine PET reported metastatic involvement outside the pelvis in 155 scans (26%).[44] The overall detection rate was 68%. Even in the PSA range of 0.79 ng/mL or less, the detection rate was 41%, including distant metastases in 19% of scans. A further prospective European trial in 100 patients with BCR who had choline PET and fluciclovine PET studies within a 1-week interval,[45] the authors concluded that there was a small but significant diagnostic advantage in favor of fluciclovine, with increased sensitivity of fluciclovine demonstrated in patients with PSA level of <1 ng/mL. These results were supported by a study by Andriole et al, which reported on 213 evaluable patients with BCR and median PSA of 1 ng/mL.[46] Overall, 122 (57%) patients had fluciclovine-avid lesions, while 126 (59%) patients had management change, of which 98 were major.

Although not currently approved by either the EMA or FDA, the identification of PSMA as a frequently expressed cellular cell surface marker of prostate cancer, with generally higher expression in more aggressive primary tumors, metastases and castrate-resistant tumors,[47] stimulated the development of a wide range of radiolabeled molecular probes suitable for PET imaging, as discussed elsewhere in this issue of *Seminars in Nuclear Medicine* [insert reference from current issue]. There has been rapid progress toward validating this class of molecular imaging agents as biomarkers for guiding therapeutic decision-making in patients with BCR.[48]

Early human experience with these agents indicated a high potential for clinical utility in BCR.[49] The intensity of PET scan uptake of this class of molecular probes has been shown to correlate strongly with immunohistochemical analysis of PSMA-expression in resected prostate cancer specimens.[50] A strong association was also demonstrated between higher prostate cancer detection rates and higher PSA levels but there was inconsistent association with PSA dynamics (unlike choline PET), Gleason score or ADT in studies from different

institutions.[51] These early validation studies consistently indicated that detection of sites of disease recurrence could be achieved in 30%-50% of patients with PSA values <0.5 ng/mL, and generally in more than 70% of case with PSA levels greater than 1 ng/mL, as well as consistently documenting the ability of the molecular imaging assessment to demonstrate tumor deposits where no abnormality could be discerned on morphologic imaging.[52,53] An important pathologically validated study, which included detailed examination of resected lymph nodes containing prostate cancer, demonstrated a high sensitivity of PSMA PET imaging with tumor deposits in scan-negative nodes having a median short access diameter of only 1.3 mm compared to 5.5 mm in scan-positive nodes.[54] These findings explain the incremental sensitivity of PSMA PET over strict, size-based criteria for identification of lymphadenopathy used with anatomical imaging.

Several studies have addressed differences in detection capacity for SM PSMA PET in different categories of BCR. Ceci et al reported on 332 patients with PSA <2 ng/mL (median 0.84 ng/mL) examined with PSMA PET[55]: 45 (13%) with persistent PSA elevation following radical prostatectomy, 149 (45%) with first time BCR, and 138 with PSA increase after prior salvage or hormonal therapy. Detection rates in these groups were 65%, 46%, and 59%, respectively. Correlative imaging was negative at 83% sites of disease detected by SM PSMA PET. Schmidt-Hegemann et al also analyzed SM PSMA PET detection rates in patients with biochemical persistence after radical surgery ($n = 60$) separately from those with biochemical recurrence ($n = 49$).[56] The authors reported PET-positivity in 75% of patients with persistence and 55% of patients with recurrence, yielding overall detection rates of 33%, 42%, and 69% at PSA levels of <0.2 ng/mL, 0.2-0.5 ng/mL, and 0.5-1 ng/mL, respectively. Overall, 14.7% of patients had extra pelvic disease sites identified and radiation treatment plans required modification in 57% based on SM PSMA PET findings. Emmett et al evaluated men with BCR with PSA levels between 0.5 and 1.0 ng/mL.[57] Outcomes following treatment were assessed with the authors concluding that SM PSMA PET is independently predictive of treatment response to SRT and stratifies men into a high treatment response to SRT (negative or fossa-confined PSMA) versus men with poor response to SRT (nodes or distant-disease PSMA). In particular, a negative SM PSMA PET result predicted a high response to salvage fossa radiotherapy. This most likely reflects the impact of low tumor burden or the presence of tumors close to urinary activity that are not visualized well on PSMA PET/CT, supporting the contention that macroscopic disease detected by SM PSMA PET/CT is clinically significant and less likely to be controlled by locoregional therapies than microscopic disease below the limits of detection by imaging.[58]

Evidence has also accumulated to demonstrate the high sensitivity of SM PSMA PET/CT compared to other molecular imaging techniques. On direct comparison in BCR patients, additional sites of disease were identified in up to 54% of patients on SM PSMA PET and this test was very rarely false negative at sites reported as tumor on choline PET.[59,60] The diagnostic performance of SM PSMA PET was found to be near perfect in patients with BCR in comparison with conventional bone scanning and across the spectrum of prostate cancer presentations with 17.6% of affected bone regions being recognized only by PET. Conversely, only 1.2% of positive regions were detected by WBBS while remaining unrecognized by PET.[61]

Studies of SM PSMA PET in the setting of BCR have also addressed more focused questions about therapeutic decision-making, particularly in the setting of early BCR. In a prospective study of 270 patients with BCR and PSA <1 ng/mL (median 0.48 ng/mL) being planned for salvage radiotherapy, post hoc analysis by Calais et al found 132 (49%) patients had a positive PET scan.[62] Fifty-two patients (19%) had at least one site of presumed disease that would not been included in consensus-designated clinical treatment volumes, of which 33 were extrapelvic (12%) and 19 pelvic (7%). Farolfi et al reported on 119 patients with BCR and PSA levels 0.2-0.5 ng/mL (median 0.32 ng/mL).[63] SM PSMA PET was positive in 41 patients (34%) with 25 patients (20%) having extrapelvic disease. Intended radiotherapy plans were modified in 88% of patients. In 164 patients with BCR and PSA levels <1 ng/mL, Emmett et al found SM PSMA PET detected disease in 102 (62%) with 23 (14%) cases of metastatic disease outside the pelvis.[57] Supporting these findings, a systematic review of management change related to SM PSMA PET,[64] including 15 studies (1163 patients, 1057 with BCR) described a pooled proportion of management changes of 54% (95% CI 47%-60%). A subsequent Australian prospective study,[65] supported these data with 192 of 312 BCR (62%) patients with median PSA level 1.1 ng/mL having management change related to SM PSMA PET scan findings.

Based on some of these studies and others, a compendium of evidence, mostly composed of retrospective single-institution exploratory data, supports the potential for this class of molecular probes to contribute to the care of patients with BCR.[14] Identification of abnormal patterns of PSMA PET uptake that reflect benign pathology or malignancy other than prostate cancer have been identified[66] and codified.[67-69] In parallel, expert procedure guidelines have been published[70] and reporting reproducibility has been demonstrated.[71] Methods to deal with potential false-positive results related to urinary excretion of some agents have also been published, including use of CT-urography[72,73] and early dynamic or delayed imaging[74] to improve diagnostic accuracy in the vicinity of the ureters, bladder base and urethra. Along with promulgation of standardized reporting schema[23,69] PSMA PET/CT is now widely accepted by the clinical community and was recently endorsed as the preferred advanced imaging technique for assessment of BCR.[75]

SM PSMA single photon tracers have also been developed and entered clinical trials. Phase 0/1 clinical trials of several agents labeled with ^{123}I[29] and ^{99m}Tc[76] identified their capability for detecting metastatic prostate cancer in soft tissues and bone, including subcentimeter lymph nodes sites. As ^{99m}Tc-MIP-1404 had the most promising biodistribution characteristics, this agent was taken forward to a phase II study in patients undergoing radical prostatectomy with extended lymph node dissection to correlate imaging with histopathology.[77] Schmidkonz et al subsequently reported on the diagnostic performance of ^{99m}Tc-MIP1404-scintigraphy in 225 patients with

biochemical relapse of prostate cancer[78] with quantitative analysis of the SPECT/CT data in a subset of 125 patients. Follow-up reports of subsequent therapeutic interventions were available for 139 (59%) patients. Positive sites were detected in 77% of all patients: 56 local recurrences in the prostate, 105 metastases in lymph nodes, and 76 bone or visceral metastatic sites. Detection rates were 90% at PSA levels at or above 2 ng/mL and 47% below 1 ng/mL. Total tumor uptake was significantly higher in patients with higher Gleason scores or on androgen deprivation therapy. Based on ^{99m}Tc-MIP-1404-imaging and other information, an interdisciplinary tumor board review recommended changes to treatment plans in 74% (104/139) of those patients for whom the necessary documentation was available. Thus, although less extensive than the information available for SM PSMA PET agents, the close similarity of imaging characteristics suggests that SM single photon PSMA molecular imaging techniques will also have significant clinical utility with respect to treatment planning in patients with BCR.

Evidence has recently emerged pertaining to a further application of SM single photon PSMA agents known as Radio-Guided Surgery, where preoperative administration of the molecular imaging agent is followed by surgery that is aided by use of a gamma probe in a manner analogous to sentinel lymph node localization. For example, Maurer et al retrospectively analyzed 31 consecutive patients with BCR after radical prostatectomy and localization of recurrent prostate cancer on SM PSMA PET/CT imaging who underwent ^{99m}Tc-PSMA Radio-Guided Surgery.[79] All lesions visualized on preoperative PET could be removed with a PSA reduction below 0.2 ng/mL in 65% of patients, including 42% of patients who remained biochemical recurrence-free after a median follow-up of 13.8 (range: 4.6-18.3) months.

To our knowledge, assessment of androgen receptor expression with ^{18}F-FDHT PET scanning has not been explored in BCR but, given the rapid metabolism and blood pool retention of radioactive metabolites found with this molecular probe, it seems unlikely to be suited to the sensitive detection of disease that is required for this indication. More promisingly, GRPr receptors are known to be overexpressed in prostate cancers including metastases and in patients treated by ADT. Receptor density has been shown to be higher in well-differentiated tumor types.[80] ^{68}Ga-RM2 is a GRPr antagonist peptide that has been investigated as a diagnostic agent in several small studies of patients with BCR.[81,82] On the basis of this limited published evidence, a role for molecular imaging of BCR using GRPr targeting probes such as ^{68}Ga-RM2 PET has not been established in patients with recurrent prostate cancer but further study is warranted and human results of molecular probes designed to target both overexpressed GRPr and PSMA[27] being awaited with great interest.

In summary, the evidence relating the use of choline, ^{18}F-fluciclovine and SM PSMA PET scanning in BCR is consistent and refutes the suggestion that there is a lack of suitable molecular imaging probes to detect disease in patients with low PSA BCR who fulfill current criteria for salvage locoregional therapies. In particular, SM PSMA PET has a very low rate of false positives when reported by experienced physicians who understand the uptake patterns of potentially confounding pathologies. Imaging interpretation is highly reproducible and although disease detection is somewhat reduced at PSA levels less than 1 ng/mL, detection rates are still approximately 50% with approximately 20% of patients overall having disease sites detected that are either extrapelvic, or outside empirically guided radiotherapy pelvic treatment volumes. Anatomical imaging and WBBS are more commonly negative than positive at sites of PSMA-detected disease. Choline PET has been proven to be less sensitive and specific than SM PSMA PET, but as yet there is insufficient evidence to judge the relative diagnostic potential of SM PSMA and ^{18}F-fluciclovine PET/CT. Both appear to have clinical utility, but it seems probable that the higher signal to noise ratio (SNR) provided by SM PSMA PET will lead to diagnostic accuracy improvements. Most importantly, SM PSMA PET has a high management impact in BCR patients with 15%-20% of patients avoiding radiotherapy that would otherwise neglect sites of disease. Intensification of local therapy on the basis of positive identification of tumor location requires prospective evaluation since the lure of this apparently more sensitive imaging will be diluted if the negative predictive value remains nontrivial.

The evidence pertaining to recurrence localization with SM PSMA scintigraphy is emerging but appears promising albeit within the limits imposed by current imaging equipment resolution.[83] The use of these molecular imaging probes to guide surgical resection appears compelling but ultimately may have greater clinical utility in primary surgical treatment.

Is the Lack of Guideline Endorsement for Newer Molecular Imaging Probes Primarily due to Delays Incorporating Compelling Evidence?

The Advanced Prostate Cancer Consensus of 2017[7] addressed the role of "advanced imaging" with an overview that *"bone scintigraphy and CT have significant limitations in detecting metastases as well as monitoring response to treatment but remain the standard of care in most settings."* With particular reference to patients with BCR, it is noted that the use of next-generation imaging modalities has led to identification of metastatic foci at lower PSA levels but concluded, *"as of now there are no prospective data to show that earlier detection of metastatic disease with next-generation imaging results in meaningful long-term clinical improvement."* Although this forum included imaging experts, they were not giving voting privileges. Conversely, a recent consensus meeting that included both expert clinicians involved in the care of prostate cancer and imaging experts favored the use of SM PSMA PET tracers in this situation.[75] While some delay is inevitable between the publication of new practice-changing evidence and its alignment with clinical consensus and incorporation into authoritative clinical guidelines, based on the evidence presented above, it seems that there is a lack of current alignment between the opinions of those with experience of these techniques and the wider urological community, which may be negatively influenced by considerations of restricted availability and reimbursement.

Are the Benchmarks for Guideline Endorsement of New Molecular Imaging Probes Inappropriately Stringent?

There has been a regrettable failure of the molecular imaging community to generate prospective data on the diagnostic performance of SM PSMA PET from the outset. Nevertheless, subsequent pathologically controlled comparisons allow confidence that metastatic sites reported on PET are associated with a very low false-positive rate. Therefore, it is reasonable to conclude that there is minimal risk that patients who do not receive "salvage" locoregional therapies on the basis of PSMA PET positivity will be inappropriately denied the putative benefits of such treatments. As such, there is no novelty in the notion that patients should not be exposed to interventions that do more harm than good. In this context, BCR patients benefit immediately from avoiding the adverse impact of potentially morbid treatments[5] that cannot achieve total disease ablation because tumor is located outside the treatment field. An arbitrary value judgment is required to decide the frequency at which incremental detection of tumor outside locoregional treatment fields can be deemed to represent clinical utility and offer meaningful patient benefit by molecular imaging approaches. Current guidelines recommend that pelvic lymph node dissection should be undertaken in patients with >2%-5% risk of pelvic nodal metastases. These recommendations have been adopted on the basis of retrospective poorly controlled series with no supporting high-quality randomized trial data demonstrating "fitness for purpose" by way of long-term improvement in oncological outcomes. This procedure involves at least some additional cost and morbidity. By comparison, SM PSMA PET involves minimal patient inconvenience and some additional cost but is safe and fit for purpose because it reliably detects sites of metastatic disease at a rate that is dependent to a great extent on the level of PSA, albeit without correlative histopathologic status, but in the order of at least 10%-20% of cases. Perhaps a 5% probability threshold for detecting treatment defining sites of metastatic involvement with SM PSMA PET is also not an unreasonable benchmark, even in the absence of randomized trial data.

Molecular Imaging of Advanced Prostate Cancer

Providing definitive guidance about the role of molecular imaging for guiding therapeutic decisions in advanced prostate cancer is complicated by several factors. The grouping includes a wide range of disease and clinical states and, even within each broad grouping, there is considerable heterogeneity with respect to molecular origins, pathologic types, and associated clinical behavior which ultimately impact individual patient outcomes. Collectively, this disease category incorporates patients in whom locoregional treatments are no longer able to offer the prospect of cure and, therefore, generally require consideration of systemic therapies with aim of prolonging survival or managing symptoms. Additionally, over the past decade several life-extending systemic therapies beyond castration have been identified, but with ongoing uncertainty about their optimal timing and sequencing.[84]

At present, the standard of care for imaging of these patients remains CT and WBBS but clinical evidence in several advanced disease states is challenging this standard. Firstly, based on the current imaging standard, patients treated with "nonmetastatic" but rapidly progressive castrate-resistant prostate cancer (CRPC) based on PSA DT were shown to have improved outcomes with potent antiandrogen therapy using apalutamide or enzalutamide compared to standard therapy,[85,86] suggesting the presence of occult metastatic disease. It is likely these patients would have had high rates of disease apparent on novel molecular imaging and that the arbitrary description of "nonmetastatic" CRPC disease is primarily a reflection of the poor sensitivity of conventional imaging. Further confounding matters in these men is the notion of "oligometastatic" disease, typically defined as comprising ≤3-5 metastases. Although not universally accepted,[87] the proposition has been made that meaningful patient benefits can accrue when low-volume metastatic disease is targeted with locally ablative rather than systemic therapy.[39] If this rationale for local targeting of all active disease is to be optimal, the negative predictive value of the imaging used to select men for this approach will be critical in its success.

With this perspective, our review will emphasize areas of high confidence about the role of molecular imaging within current management paradigms for patients with advanced prostate cancer, especially in relation to newer molecular probes. We will also explore evidence where unique information provided by molecular imaging could lead to better patient management but sound conclusions about patient benefits of applying molecular imaging are not possible.

Clinical Indications in Advanced Recurrent Prostate Cancer Management for Which Confident Judgments Can Be Made About the Role of Molecular Imaging

Assessment of Skeletal Metastatic Burden and Response to Therapy

As noted above, despite known limitations in its accuracy, WBBS remains the standard of care for assessing the degree of skeletal involvement and its response to therapy at all phases of advanced prostate cancer. As we will discuss, its exact role is dependent on the clinical context.

Pain in patients with both castrate-naïve and CRPC is most commonly due to skeletal involvement. Accordingly, molecular imaging approaches that are WBBS scanning has high clinical utility but the increased accuracy of ^{18}F NaF PET requires emphasis when considering the optimal approach.[88] The reduced sensitivity of SM PSMA PET in late-stage, metastatic CRPC (mCRPC) suggests alternative molecular imaging assessments, such as ^{18}F NaF PET,[89] may have greater utility for establishing skeletal metastatic disease as the cause of symptoms, with SM PSMA PET better suited to assessing the potential for PSMA-based radionuclide therapy. MRI is also accurate for assessing

patients with back pain and in this setting is probably the imaging investigation of choice due to its ability to diagnose nonmetastatic causes of pain, and to also spinal cord jeopardy.

While indicating the likely presence of metastatic disease after definitive treatment, progressive PSA elevation contributes no localizing information, so whether disease is oligometastatic or widely disseminated can only be defined by imaging. More accurate techniques than CT and WBBS are required to appropriately make this distinction. Addition of SPECT and low-dose correlative CT to molecular imaging with traditional WBBS significantly improves detection accuracy and localization, but further improvements are seen with ^{18}F NaF PET/CT.[15] Recent data suggest that SM PSMA PET/CT is very close in diagnostic performance to[18] F NaF PET with both tests having superior diagnostic performance to diffusion-weighted whole-body MRI in a prospective study of 68 patients with BCR.[90] Nevertheless, SM PSMA PET/CT imaging seems to be the best choice for defining oligometastatic disease and for targeting local ablative treatments given its ability to assess both bone and soft tissue disease sites.

A great deal of research and development effort is being expended to refine and simplify the predictive and prognostic use of molecular imaging biomarkers to select patients for radionuclide therapy. The field of "theranostics" is evolving field in nuclear medicine and aims to prospectively identify patients who will not respond to therapy due to an absolute or relative lack of the molecular target. While identifying patients who might respond to treatment by virtue of high target expression, ideally, through prospective dosimetry, the results of therapy in patients who are suitable for treatment could also be maximized.

For several decades, beta-emitting molecular entities that concentrate in bone in proportion to regional osteoblastic activity (^{89}Srontium chloride, ^{153}Samarium EDTMP, and ^{188}Rhenium HEDP) have been used to successfully palliate castrate-resistant patients with painful skeletal metastases.[4] More recently ^{223}Radium dichloride, an alpha-emitting bone-seeking radiopharmaceutical, has been shown to prolong overall survival (OS) along with a reduction in the time to new skeletal-related events.[91] Demonstration of increased osteoblastic activity at sites of metastatic skeletal involvement is pivotal to the successful application of these treatments and bone scanning is an essential predictive biomarker in this context. Control of skeletal disease is potentially important since semiquantitative indices of skeletal metastatic disease have been related to prognosis by a number of authors, as are skeletal-related events. The bone scan index (BSI) represents the percentage of the entire skeleton volume affected by tumor on conventional WBBS, which can now be calculated using automated software technique. A recent meta-analysis of this technique, including 14 high-quality studies involving a total of 1295 patients with castrate-naïve and mCRPC, indicated that high baseline BSI and an increase in BSI on treatment (ΔBSI) were significantly predictive of poor OS.[92] Baseline BSI was also significantly related to cancer-specific survival. In a prospective study of patients with advanced prostate cancer using ^{18}F NaF PET/CT, Apolo et al studied 30 patients with and 30 patients without skeletal metastases on conventional bone scan at baseline and during a 12-month follow-up period.[93] The baseline number of malignant lesions and changes in standardized uptake value (SUV) on follow-up ^{18}F NaF PET/CT significantly correlated with clinical benefit and OS. ^{18}F NaF PET/CT also detected more bone metastases than WBBS and provided earlier detection of new bone disease in high-risk patients, potentially identifying patients more likely to benefit from radionuclide therapy than from external beam treatment of oligometastatic disease.

Recently the theranostic paradigm has also been applied to the treatment of patients with mCRPC who are otherwise refractory to multiple other classes of therapy. Significant responses have been demonstrated to a variety of radionuclide therapeutic agents including ^{131}I MIP-1095,[94] ^{177}Lu DOTA-PSMA-617,[95] [(177)Lu-PSMA-617 radionuclide treatment in patients with mCRPC (LuPSMA trial): a single-center, single-arm, phase 2 study.],[96] ^{225}Ac DOTA PSMA-617[97] and ^{177}Lu J591.[98] These therapeutic applications have been guided by the use of a "diagnostic pair" that provides assessment of PSMA expression at sites of prostate cancer metastases. Hofman et al[95] took the additional step of using molecular imaging with FDG-PET/CT in all patients being screened for therapy with ^{177}Lu DOTA-PSMA-617 in appreciation that heavily pretreated mCRPC can be associated with rapidly proliferating tumors that lack PSMA expression and have low PSA secretion. Histopathologically, these features are often reflective of neuroendocrine differentiation.[99] In their trial, 13 of 43 patients screened were not treated with the investigational radionuclide therapy because of low PSMA expression or discordant lack of PSMA uptake at sites of FDG-avid metastatic disease. Perhaps by excluding such patients, the results of this approach were notable for high proportion (57%) of patients achieving >50% PSA decrease, measurable tumor responses in 82% of evaluable patients, meaningful improvements in pain severity and low rate of adverse events particularly grade 3 or 4 toxicity felt likely to be due to the treatment. A subsequent report of the outcomes of patients who had screening failure in the initial and expansion phases of this trial demonstrated a particularly poor survival.[100] As separately reported, an additional component of this trial was quantitative SPECT/CT at multiple time intervals following administration of ^{177}Lu DOTA PSMA-617 patients to assess radiation dose delivered to tumor sites and off-target organs.[101] The mean "whole-body" tumor dose with patients achieving greater than 50% PSA decrease was significantly higher than for those who did not (14.1 Gy vs 9.6 Gy; $P < 0.01$), suggesting that prospective dosimetry may help to select patients for treatment. These data also vindicate the decision to exclude patients with low PSMA-expression.

Clinical Indications in Advanced Recurrent Prostate Cancer Management for Which Confident Judgments Cannot Be Made About the Role of Molecular Imaging

Molecular Imaging Tumor Characterization as Predictive, Prognostic or Response Biomarkers for Nonradionuclide Therapies in Advanced Recurrent Prostate Cancer

Despite being used for many decades, the role WBBS as a technique for therapeutic response assessment remains unclear. It

is nonetheless recommended in the context of clinical trials.[16] Lack of specificity and the presence of ongoing osteoblastic activity despite PSA response can complicate interpretation of results. At least the first of these concerns is partially addressed by ^{18}F NaF PET/CT. Of importance from the perspective of using ^{18}F NaF PET/CT as a prognostic, predictive and, importantly, response biomarker in patients with advanced prostate cancer, its reproducibility of has been demonstrated in a multicenter trial.[102] Quantitative measures of ^{18}F NaF PET have been assessed from the perspective of treatment response assessment. Harmon et al studied patients with mCRPC with osseous metastases with ^{18}F NaF PET/CT scans performed at baseline and after three cycles of chemotherapy ($n = 16$) or androgen receptor pathway inhibitors ($n = 40$).[103] Functional burden (SUV_{total}) assessed mid-treatment was the strongest univariable predictor of progression-free survival (PFS) (hazard ratio, 1.97; 95% CI, 1.44-2.71; $P = 0.001$). Baseline SUV_{total} and SUV_{mean} also out-performed baseline clinical markers in predicting outcome. Without larger, prospective trials, the utility of ^{18}F NaF PET/CT for therapeutic response assessment remains unclear.

Several investigators have examined the role of FDG with regard to prognosis in recurrent prostate cancer. In a prospective imaging trial, Meirelles et al investigated FDG-PET and WBBS prior to experimental therapies.[104] BSI and SUV on FDG-PET were recorded and patients were followed until death ($n = 36$) or for at least 5 years ($n = 7$). Prognosis correlated inversely with both SUV and BSI but only SUV was an independent factor on multivariate analysis. While promising, FDG-PET/CT is not yet widely used for baseline evaluation of prostate cancer due to perceptions of poor sensitivity and therefore availability of a baseline study for therapeutic response assessment limits the utility of this technique. Nevertheless, given the prognostic significance of high FDG-avidity, this may be an important parameter to assess when selecting the optimal systemic therapy for individual patients. In particular, spatial discordance between SM PSMA PET/CT and FDG-PET/CT distribution with FDG-avid lesions that lack PSMA expression appears to be relatively common and suggests that this component of disease may benefit from alternative therapies, which could be monitored effectively by FDG-PET/CT. In this regard, Morris et al evaluated the ability of FDG-PET to predict treatment response compared to standard response measures (PSA, bone scan and CT) in mCRPC receiving anti-microtubule chemotherapy.[105] The authors found that the average of SUV_{max} in up to five lesions at either 4 weeks or 12 weeks was predictive of clinical response. Similarly, Jadvar et al studied 87 patients with mCRPC with FDG-PET/CT prior to first or second-line therapy with respect to the correlation between survival and several semi-quantitative assessments of tumor uptake.[106] After adjusting for known clinical prognostic factors, the sum of SUV_{max} remained significant on multivariate analysis.

Being indicative of cell membrane production, which is likely to reflect active proliferation, it is reasonable to assume that choline-based tracers may provide prognostic information prior to or during treatment, particularly with respect to tumoristatic therapies. Indeed, there has been significant research into the value of choline PET as a molecular imaging biomarker with respect to prognosis and response assessment capabilities in patients with advanced prostate cancer. This data has been comprehensively discussed by Giovacchini et al.[107] Their group reported a retrospective study in 195 prostate cancer patients experiencing biochemical failure during ADT on the background of prior radical prostatectomy. The median prostate cancer-specific survival was significantly shorter in patients with positive than negative choline PET/CT (median: 11.2 years, 95% CI, 9.8-12.6 years compared to median: 16.4 years, 95% CI, 14.0-18.8 years). On multivariate analysis, statistical significance was obtained for the choline PET/CT result, PSA level, and Gleason score. The presence of uptake in bone had a worse prognosis than scans that were positive only in soft tissues. Earlier these authors had reported a similar study that included drug-naïve and drug-free patients.[108] Median prostate cancer-specific survival after prostatectomy was 14.9 years (95% CI, 9.7-20.1 years) in patients with positive choline PET/CT, while median survival was not achieved in patients with negative choline PET/CT owing to the very low prevalence of fatal events in this group. The 15-year prostate cancer-specific survival probability was significantly shorter in patients with positive than negative choline PET/CT (median: 42.4% vs 95.5%). On multivariate analysis, only choline PET/CT and Gleason score >7 predicted prostate cancer-specific survival. Kwee et al performed a study addressing the role of choline PET/CT in mCRPC patients following first- or second-line ADT and chemotherapy and found several semi-quantitative measurements from their molecular imaging analysis predicted both PSA response and OS.[109] More recently, Caroli et al reported the prognostic utility of multiple semiquantitative measures derived from choline PET/CT in patients with mCRPC previously treated with docetaxel and abiraterone ($n = 52$) or enzalutamide ($n = 42$).[110] All parameters were significant for PFS and OS in univariate analysis, but only the sum of each lesion's metabolic volume multiplied by mean SUV, which they termed total lesion activity (TLA), was significant for PFS and OS on multivariate analysis. Baseline PSA values also remained significant for OS ($P = 0.034$). Similarly, Conteduca et al analyzed mCRPC patients progressing after docetaxel, who were then treated with either abiraterone ($n = 47$) or enzalutamide ($n = 33$).[111] Androgen Receptor Copy Number (ARCN) measured from plasma samples, TLA, and metabolic tumor volume from choline PET/CT were measured at baseline. A meaningful correlation was found between ARCN gain and TLA/metabolic tumor volume compared to androgen receptor non-gained cases independent of treatment modality. Multivariate analysis revealed that only ARCN and TLA were associated with both shorter PFS and OS. Together, these studies support the prognostic value of choline PET on baseline evaluation of patients with BCR or mCRPC but whether this information can be used to beneficially influence therapeutic choices remains unclear.

With respect to acutely evaluating response to treatment, a number of studies have reported on the value of choline PET

as a response assessment biomarker in mCRPC patients. In a prospective study, Schwarzenbock et al assessed changes in choline PET SUVmax, PSA, Hounsfield units and volumes of bone, lung, lymph node metastases, and local recurrences after chemotherapy with docetaxel in such patients.[112] Quantitative changes were measured at two time points. No relationship was found between any of the cited measurements with either RECIST criteria or usual clinical criteria at either the early or late response assessments. The authors concluded that choline PET/CT seems to be of limited use for therapeutic response assessment in the context of first-line chemotherapy. Conversely, on multivariate analysis, only a positive choline PET/CT after abiraterone therapy significantly predicted progression-free survival and OS in a study by De Giorgi et al involving 43 patients with mCRPC.[113] De Giorgi et al also studied 36 mCRPC patients with choline PET/CT at baseline and after 3-6 weeks of enzalutamide therapy.[114] Using a decrease in PSA level of more than 50% to define responders, on multivariate analysis, response was predicted earlier with PET but only PSA decrease was predictive of OS. They concluded that choline does not add more information beyond that obtained from PSA. Similarly, Ceci et al used choline PET/CT to evaluate 61 metastatic CRPC patients before and after docetaxel.[115] They found that the only baseline PET/CT factor predictive of progression after docetaxel therapy was the detection of extensive (>10) bone lesions. However, they found no association between PSA response and the presence of progressive disease on early PET/CT assessment. Lee et al used choline PET/CT and semiquantitative whole-body measures of tumor volume in 42 patients before and 1-3 months after starting various treatments for mCRPC.[116] Patients with 30% or greater decline in metabolically active tumor volume exhibited significantly longer times to PSA progression (418 days vs 116 days, $P = 0.0067$) than those without. Metabolically active tumor volume response was associated with a hazard ratio of 0.246 ($P = 0.0113$) for PSA progression, which remained significant on multivariate analysis when adjusted for treatment type.

Thus, overall, there is great heterogeneity in the data examining the use of choline PET/CT for prognostic evaluation and treatment response assessment with respect to the patient categories included, treatment types, measures of choline scan response and outcome assessments. Although there appears to be some incremental information about prognosis and treatment response obtained from choline PET, in comparison to PSA levels, the overall benefits of using this type of molecular imaging appear limited. It would seem appropriate, however, in future research to concentrate analysis on more definitive measures of patient outcome such as cancer-specific survival and OS as the comparator for molecular imaging biomarkers.

To date, minimal published data are available with respect to the value of SM PSMA PET/CT for monitoring treatment response in advanced prostate cancer. In a retrospective study, Seitz et al quantified imaging responses to docetaxel on ^{68}Ga-PSMA-11 PET and conventional CT and evaluated the correlation between these responses and PSA response in both metastatic castrate-sensitive and mCRPC patients.[117] Although, PET response rate agreed with PSA in only 9 of 16 (56%) castrate-resistant patients, the authors concluded that this might be a promising method for treatment response assessment in metastatic prostate carcinoma. The data further indicated that for different metastatic sites, the performance of SM PSMA PET in response assessment might be superior to that of the conventional CT approach and could help differentiate between progressive disease and treatment response.

Conceptually, the role of PSMA PET/CT in assessing response to ADT is complicated by preclinical data suggesting that this intervention might increase rather than decrease PSMA expression.[118] These changes may occur acutely but be subsequently associated with cell death through apoptosis and, therefore, may not necessarily parallel changes in PSA. In a small retrospective cohort looking at long-term use of ADT in patients starting and continuing ADT between sequential PSMA PET/CT studies, Afshar-Oromieh et al found that a complete PSMA PET response occurred in only 2 of 10 patients with a sustained PSA response.[119] Moreover, despite a reduction in the intensity of uptake, a third of all lesions visible at baseline remained apparent in patients despite a post-treatment PSA of 0.1 ng/mL or less. These data raise more questions about the role and optimal timing of SM PSMA PET/CT than they answer. It is possible that the authors were seeing the tail-end of a flare response or that androgen levels are still inadequate to achieve apoptosis in cells and these ongoing viable cells might be the substrate for development of subsequent resistance. Whether patients without a complete response to ADT on PSMA PET should receive second-line antiandrogen therapies or chemotherapy remains to be determined. In the first prospective trial of ^{177}Lu-PSMA therapy,[95] a complete or partial response was seen in 10% and 30% of patients, respectively, but this was lower than the rate of PSA response (57%). The prognostic value of a complete versus a partial response on post-treatment SM PSMA PET remains to be defined.

In summary, although PSMA PET generally has a high sensitivity for detecting sites of metastatic disease in advanced prostate cancer and is well-suited to quantitation at the level of individual lesions or with respect to whole body tumor burden, the independent prognostic and predictive value of this information has not been well studied in the context of therapeutic monitoring of mCRPC.

Fox et al assessed whether contemporaneous PET evaluation of androgen receptor expression using 16-beta-fluoro-5-alpha-dihydrotestosterone (FDHT) and glycolysis using FDG could identify a prognostically significant phenotype associated with castration-resistant prostate cancer.[120] Patients with mCRPC, naïve to androgen receptor signaling inhibitor drugs, had both FDHT and FDG-PET at the time of progression with selected metastases biopsied for verification. Metastases were classified according to both their FDHT and FDG imaging status. The authors concluded that heterogeneity of PET/CT imaging phenotype has clinical relevance with loss of androgen receptor expression despite ongoing glycolytic activity carrying the worst prognosis. Vargas et al recently documented the reproducibility of FDHT PET/CT

measurements in a multicenter international study, paving the way for prospective trials.[121]

Characterization of Rapidly Progressive Metastatic Castrate-Resistant Prostate Cancer With Neuroendocrine Differentiation

A subset of patients with advanced castration-resistant prostate cancer eventually evolve into an androgen receptor independent phenotype, with a clinical picture associated with the development of rapidly progressive disease involving visceral sites and androgen independence, often in the setting of a low or modestly rising serum PSA levels.[122] Biopsies performed in such patients may vary, ranging from poorly differentiated carcinomas to mixed adenocarcinoma-small cell carcinomas to pure small cell carcinomas but often express markers of neuroendocrine differentiation including synaptophysin and chromogranin-A. Molecular imaging techniques that could identify tumor sites that have developed androgen independence may impact therapeutic decision making and ultimate patient outcomes. Given the impact of somatostatin receptor imaging on management of neuroendocrine tumors of other sites, particularly using ^{68}Ga-DOTA-octreotate PET/CT,[123] it is reasonable to question whether this may also be helpful in prostate cancer with neuroendocrine features. Luboldt et al examined 20 patients with metastatic CRPC with ^{68}Ga DOTA-octreotide PET/CT but found that only 64 of 216 metastases (30%) were visible, and uptake intensity was very low compared to normal bone.[124] The authors suggested the need to explore other molecular imaging markers for neuroendocrine cells. It is possible that other tracers, particularly including FDG and choline may be superior to PSMA and somatostatin receptor ligands in this situation, but further studies are required.

Conclusion

In summary, WBBS remains the standard of care for assessing skeletal metastases at all phases of advanced disease but other agents, particularly SM PSMA, FDG, and choline PET ligands show great promise for assessing the extent of both bone and soft tissue disease as well as characterizing disease. Penetration of more sophisticated molecular imaging techniques into routine clinical practice of approaches has been slow for a variety of reasons. This is partly explained by a lack of robust evidence in a variety of clinical scenarios pertinent to the management of patients but also because of the historical primacy attached to WBBS and CT as biomarkers for stratifying patients within clinical trials. Unquestionably there will be little incentive on behalf of pharmaceutical companies to re-evaluate therapeutic interventions that have now proven been to be effective based on current selection criteria, so the use of conventional imaging will remain an integral part of therapy selection for the foreseeable future.

However, there are cogent patient and societal reasons to improve selection of treatment, particularly with respect to individualizing treatment. Future research in this area requires further, well-designed prospective studies with a clear focus on patient-important outcomes, which include not only survival but also avoidance of futile procedures and delay of the need for therapies with significant morbidity by virtue of better treatment selection or planning or, simply, by better prognostic stratification allowing an observational strategy. In parallel, evidence related to nonimaging prognostic biomarkers is also advancing[125] and, therefore, molecular imaging assessments may need to consider including these biomarkers as comparators in future trials and how these might be incorporated into diagnostic paradigm. In particular, so-called "liquid biopsy" may provide a complementary tool by which to select the need and type of imaging.[126]

We speculate that greater use of whole-body quantitation of cancer-related molecular imaging characteristics will become increasingly important for predicting prognosis and outcomes following treatment. Based on current evidence, FDG remains the leading candidate for reliable prediction of prognosis and treatment outcomes, but molecular imaging techniques that interrogate androgen signaling also hold great promise for individualizing therapeutic decision making. Importantly, molecular imaging tracers need to be considered as a means to characterize rather than simply detect sites of disease with an increasing likelihood that radionuclide therapy will be an important therapeutic option.

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