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GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Novel Imaging in Detection of Metastatic Prostate Cancer

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Abstract

Purpose of Review This review aims to highlight the limitations of current standard-of-care prostate cancer (PCa) imaging and discuss novel clinical imaging in advanced disease.

Recent Findings PCa staging through imaging is important for proper selections in clinical treatment. Traditional imaging techniques for metastatic disease (i.e., computed tomography [CT], magnetic resonance imaging [MRI], and radionuclide bone scan) have suboptimal performance in early recurrent or metastatic disease. Novel positron emission tomography agents including radiolabeled prostate specific membrane antigen (PSMA), choline, and anti-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) have demonstrated improved sensitivity and specificity in initial staging and early biochemical recurrence (BCR).

Summary Conventional imaging modalities for PCa incompletely characterize disease burden. The development of new PET tracers in combination with CT and MRI offers superior anatomic localization and biologic correlation of tumor sites, which enhance providers' abilities to make appropriate decisions regarding treatment.

Keywords Prostate cancer · Novel prostate cancer imaging · PET agents · PSMA · Choline · Fluciclovine

Introduction

Prostate cancer is a common malignancy that accounts for nearly 5% of all annual cancer deaths in the USA [1]. There are several imaging modalities available for staging patients who are diagnosed with prostate cancer, both in the initial and recurrent settings. This review article will explore those imaging techniques and their strengths and limitations regarding the detection of metastases.

Initial Staging

Computed tomography (CT) scans of the chest, abdomen, and pelvis are considered standard of care for initial staging of many solid tumors, as computed tomography is a widely available non-invasive diagnostic tool. For patients with prostate cancer and a predicted risk of > 10% lymph node (LN) involvement, the National Comprehensive Cancer Network (NCCN) guidelines recommend pelvic imaging with or without abdominal imaging [2]. The benefit of identifying men who harbor nodal or distant metastases should be weighed against the potential drawbacks of computed tomography imaging. Abdominal CT scans have been reported to have the greatest number of incidental findings among all imaging modalities [3]. Judicious selection of patients for whom CT scans should be ordered has therefore been examined. One recent study found that the American Urological Association (AUA) Best Practice recommendations for obtaining CT scans, including Gleason Score ≥ 8, PSA > 20 or T3 or greater disease, resulted in a sensitivity and specificity of 87.3% and 82.6%, respectively, for recommending imaging among patients with positive studies [4]. It is also important to consider that CT scans may result in understaging nodal involvement. The highest positive predictive value for CT scan identification of nodal involvement is for a LN > 1.5 cm. However, studies have shown that nearly one in three normal-sized pelvic lymph nodes have micro-metastases [5] and, in a large series, fewer than one in six positive lymph nodes detected on pelvic lymph node dissection (PLND) were detected on CT [6]. Despite these limitations, CT remains a common imaging

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device used to assess distant spread of prostate cancer. While it has limited sensitivity for detecting nodal metastases, it provides utility for assessing visceral cancer deposits and bony metastases.

The gold standard imaging modality used to detect and follow bone metastases is the technetium-99m bone scan. The predominantly osteoblastic nature of > 80% of prostate cancer bone metastases facilitates detection on bone scintigraphy through the osteoblastic repair process incorporating technetium instead of calcium [7]. Acceptable sensitivity levels for prostate cancer bone metastasis detection have been reported ranging from 62 to 89% by various studies [8–11]. However, the specificity is much lower than that, as increased technetium uptake can be observed in many other osteoblastic processes such as bone fractures or degenerative joint disease, Paget's disease, and inflammatory processes [12–14]. Therefore, improvements to imaging bone disease have been investigated.

One such innovation is use of single positron emission computerized tomography (SPECT), which allows for cross-sectional visualization of tracer uptake compared to restricted planar views provided by the traditional bone scan. However, the resolution of SPECT is still quite limited, making accurate anatomic localization challenging [7, 15, 16]. The added value of SPECT in bone scans reduces false positives and equivocal findings, thus resulting in downstaging. In one study, the addition of SPECT resulted in downstaging of more than one third of prostate cancer patients [17], and in another study, the number of equivocal bone scan findings was greatly decreased from 61% to just 8% with the addition of SPECT [18]. Despite these improvements, barriers remain to more widespread implementation of SPECT due to cost burden and technical requirements.

A widely available nuclear medicine study used for imaging solid tumors is FDG-PET/CT. However, FDG-PET/CT is rarely used for staging prostate cancer, and the American College of Radiology (ACR) Appropriateness Criteria recommends against it except for follow-up in patients with metastatic prostate cancer treated by systemic therapy [19]. FDG-PET/CT is relatively poor at detecting osseous metastases compared to standard bone scans and MRI [20, 21]. However, as prostate cancer becomes more advanced or transforms to aggressive variants such as neuroendocrine type, there may be higher glucose metabolism that may make FDG-PET/CT useful (Fig. 1) [19]. It is not recommended in the routine setting, however, as there is relatively low glycolytic activity in early prostate cancer. If patients undergo FDG-PET/CT scans for other reasons and incidental uptake in the prostate is found, however, additional characterization using multiparametric MRI may be useful [22]. Other PET agents have been explored extensively for identifying prostate cancer metastases and are later discussed in this article.

The increasing prominence of multiparametric prostate MRI has established its important role in the initial radiologic evaluation of patients with clinical suspicion of prostate cancer. It is very helpful for defining the extent of local disease, T staging, detection of extracapsular extension, and seminal vesicle invasion. Its role in the detection of nodal or distant metastases is less well defined. However, the utility of MRI for nodal and metastatic staging has been evaluated using MR lymphography and whole-body MRI, respectively.

MR lymphography involves the use of iron oxide particles which are preferentially taken up by normal macrophages in lymph nodes, resulting in a hypointense appearance on MRI. Tumor-containing lymph nodes do not take up the iron particles, resulting in preservation of signal on MRI. MR lymphography has been shown to have a higher sensitivity for prostate cancer lymph node detection compared to MRI (86–90% vs 35–46%) and CT (59% vs 42%) and comparable specificity to MRI [23]. However, the use of MR lymphography in clinical practice is limited by inaccessibility of iron oxide compounds, which are currently only available under a European license (Ferumoxtran-10) or as an off-label use of a drug approved for iron-deficiency anemia (Ferumoxytol). Although Ferumoxytol has been shown to have a strong safety profile [24] and the feasibility of lymph node mapping using Ferumoxytol intraprostatic injections has been established in a study of non-human primates [25], further work remains to investigate clinical applications for MR lymphography.

Whole body MRI may aid in the detection of bone metastases through the presence of abnormal bone marrow signal suggestive of tumor infiltration. This represents a particularly attractive option for patients who are already undergoing multiparametric prostate MRI. Due to advances in technology, it is now possible to perform whole body MRI in less than 30 min [7]. Moreover, MRI has been shown to outperform bone scan in terms of higher sensitivity and specificity of prostate metastatic detection (97 and 95% for MRI, respectively, compared to 79 and 82% for bone scan on a recent meta-analysis) [10]. MRI has also been reported to have higher accuracy for the detection of visceral metastases compared to FDG-PET/CT imaging. Although its diagnostic capability has been shown, MRI is not routinely used in this setting due to concerns regarding incidental findings, cost, and time limitations [7]. There may also be challenges in terms of resource allocation at various clinical centers, with MRI scans reserved for scenarios in which the clinical question can only be addressed with MRI.

Biochemical Recurrence (BCR)

In the recurrent setting, bone scans are most helpful for evaluating patients with very high PSA values in which bony metastases are suspected. However, the yield from

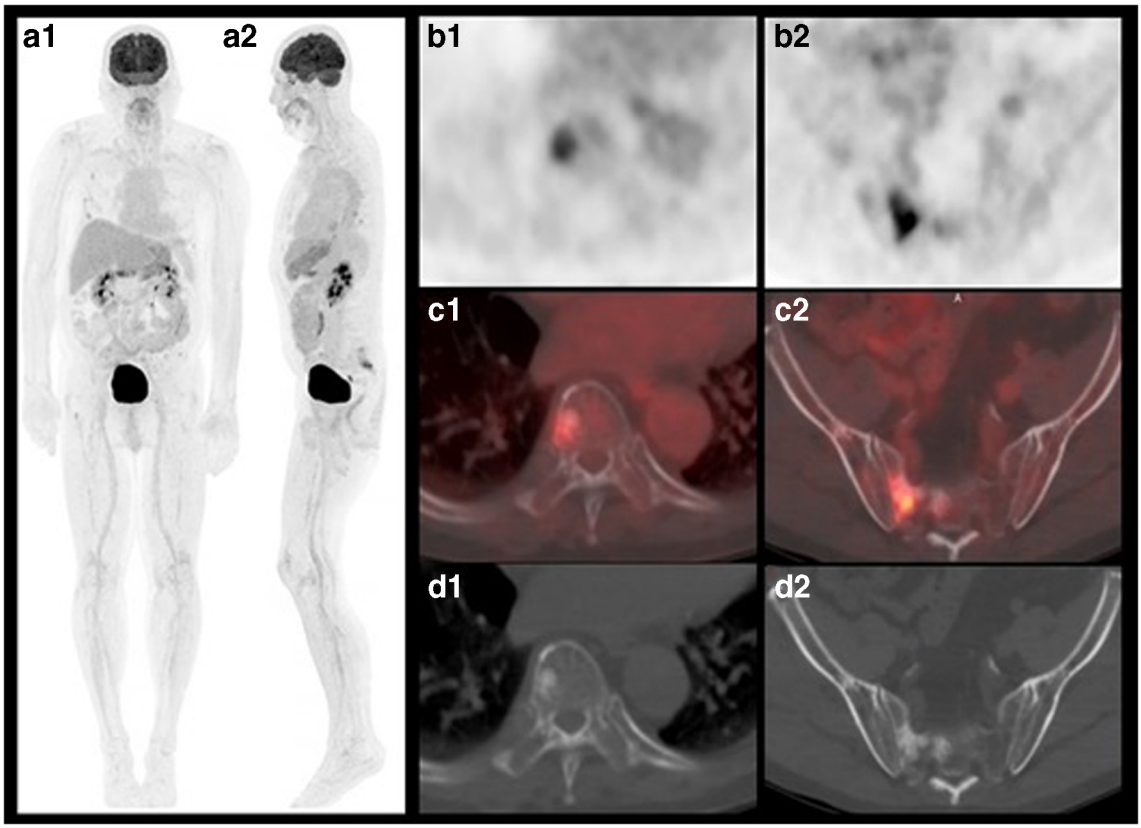

Fig. 1 Sixty-nine-year-old male with metastatic PCa on androgen deprivation therapy. Maximal intensity projection (A1, A2), axial PET (B1, B2), axial fused PET/CT (C1, C2), and axial CT (D1, D2) images demonstrates FDG-avid sclerotic bone lesions in the right T8 vertebra body and sacrum

bone scans has been very low, < 5%, even in a group of post-prostatectomy patients with high PSA levels between 40 and 45 ng/mL [26]. Instead, bone scans can be very helpful for following the response to treatment over time [27]. Therefore, a bone scan should be considered for patients who have very high post-treatment PSA values or who present with new sites of bone pain concerning for osseous metastases.

MRI offers one of the most helpful assessments for prostate cancer recurrence. Dynamic contrast enhanced (DCE) MRI is the most helpful sequence for the detection of local recurrence prostate cancer. One meta-analysis indicated a sensitivity of 90% and specificity of 81% for the detection of locally recurrent prostate cancer after initial treatment with radiation therapy [28]. In terms of evaluating for metastatic disease, whole body MRI and MR lymphography could be considered, though these modalities have not been specifically studied in the recurrent setting. NCCN guidelines recommend evaluating for progressive disease in patients who are post-definitive therapy and should include chest imaging with chest X-ray or CT scan, bone imaging, and cross-sectional imaging of the abdomen and pelvis with either CT or MRI [2]. The guidelines indicate that PET/CT imaging with specialized agents such as C-11 choline, F-18 fluciclovine, or F-18 sodium fluoride can be considered as well, to be discussed further in this review article.

Novel Functional and Targeted Imaging Modalities

Identification of prostate cancer (PCa) metastases could profoundly influence treatment. Unfortunately, conventional imaging cannot reliably provide this information, especially in the early biochemical recurrence (BCR) setting in patients with low PSA values. Because of this, many efforts have been made to develop novel functional and targeted imaging agents that exhibit both high sensitivity and specificity for detecting metastatic PCa. The advent of novel PET agents in the imaging of prostate cancer has led to a high volume of research which will be the focus of this review. PET in combination with MR or CT (hybrid imaging) is highly sensitive and specific. Currently, ^{18}F-fludeoxyglucose (^{18}F-FDG) is the most commonly used radiotracer in oncologic staging, but other PET tracers have been studied for lymph node evaluation in PCa patients due to FDG PET/CT's poor sensitivity in evaluating LN metastases [29]. One study of 41 patients undergoing FDG PET/CT prior to radical prostatectomy for PCa treatment

revealed a sensitivity of 27% for LN metastases [30]. Several novel PET agents including radiolabeled choline, prostate specific membrane antigen (PSMA), and anti-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) are among some of the most promising novel PET agents for the detection of metastatic PCa in initial and recurrent staging. Before implementing novel imaging technology into routine clinical practice, the accuracy of these radiotracers must be determined. Multiple groups have evaluated these novel imaging agents in patients at risk for developing regional and distant metastases.

Choline

Choline is a water-soluble nutrient that is incorporated into cell membranes as phosphatidylcholine. Radiolabeled choline therefore is found in proliferating cells, such as cancer and inflammation [31]. Choline can be radiolabeled with ^{11}C, which has a half-life of 20 min and thus is limited to institutions with on-site cyclotrons. Preclinical data suggests that choline metabolism is altered in PCa cells, where increased choline concentrations are found in human PCa cells derived from metastases [32]. A meta-analysis by Fanti et al. examined 12 studies consisting of 1270 participants that investigated the accuracy in detecting PCa recurrence sites with corresponding histopathologic lesion confirmation. In this setting, the detection rate for localized recurrence was found to be 36%, while bone metastases detection rate was 25% [33]. ^{11}C-choline thus demonstrates moderate detection capabilities in recurrent LNs and distant bone metastases, while also posing production issues for medical centers. Altogether, this makes ^{11}C-choline challenging for many institutions to use.

Alternatively, ^{18}F-choline has a longer half-life than ^{11}C-choline (110 min vs 20 min), but it demonstrates more urinary excretion and higher background signal [29]. A meta-analysis by Evangelista et al. included 10 studies evaluating the performance of ^{18}F-fluoromethylcholine PET/CT in the detection of LN disease at initial staging in PCa patients. The pooled sensitivity and specificity were 49.2% and 95%, respectively [34].

In addition to radiolabeled choline, ^{11}C-acetate has been studied for the staging of PCa. This agent has a relatively low false positive rate and modest sensitivity. A meta-analysis of ^{11}C-acetate PET/CT for preoperative staging found a sensitivity, specificity, positive predictive value, and negative predictive value of 68.0%, 78.1%, 48.6%, and 88.9%, respectively [35]. Similar to ^{11}C-choline, ^{11}C-acetate has a short half-life and thus is impractical for most health care settings. Thus, ^{11}C-acetate does not demonstrate clear advantages for metastatic staging of PCa.

^{18}F-FACBC

Fluciclovine, also known as Axumin®, or ^{18}F-FACBC is a synthetic l-leucine analog that demonstrates uptake in PCa [36]. ASCT2 is an important amino acid transporter of glutamine, which is an essential tumor nutrient and has been implicated in cancer signaling pathways. ASCT2 is the main transporter of ^{18}F-FACBC as well, and it is transported similarly to glutamine [37]. Unlike glutamine, ^{18}F-FACBC is not metabolized in the cell, which leads to its intracellular accumulation in PCa cells and at sites of rapid amino acid metabolism like the liver and pancreas [38]. One of the advantages of ^{18}F-FACBC is its lack of physiologic activity in the urinary tract, which improves visualization of small lesions of disease relapse in the region [39, 40].

A meta-analysis by Ren et al. included 6 studies with 251 patients in the setting of biochemical recurrence. The pooled sensitivity and specificity on a per-patient analysis was 87% and 55%, respectively [40]. These results do not include two more recent publications evaluating the operational characteristics of ^{18}F-FACBC. Schuster et al. and Odewole et al. reported specificities of extraprostatic lesions of 97% and 100% in patients with recurrent PCa [41, 42]. ^{18}F-FACBC has been recently approved by the US FDA for the detection of recurrent disease; however, it suffers from high false positive rates that could result in incorrectly upstaging the disease. The utility of this agent may need to be considered in the context of the newer PSMA-based PET agents despite its good performance [7].

PSMA Targeting Agents

PSMA is a transmembrane protein that is highly overexpressed in PCa cells [43]. Increased PSMA expression is evident in the majority of prostate tumors even when PSA staining is weak and also when the cells become castrate-resistant [44, 45]. The recent development of small-molecule inhibitors (i.e., ^{68}Ga-PSMA-11 and ^{18}F-labeled PSMA agents) that target the active substrate recognition site of PSMA has improved upon the previously developed targeted antibodies, due to their decreased half-life and lower background-to-tumor noise.

The most commonly used PSMA agent in PET imaging is ^{68}Ga-PSMA-11, which is internalized and accumulates in high levels, including in small metastases [46]. In the recurrent setting, Afshar–Oromieh et al. retrospectively analyzed 42 patients with histologically proven PCa. They found ^{68}Ga-PSMA PET/CT had a lesion-based sensitivity, specificity, NPV, and PPV of 76.6%, 100%, 91.4%, and 100%, respectively [47•]. Hijazi et al. was the first group to evaluate pelvic extended lymph node dissection (pLND) in oligometastatic PCa detected by ^{68}Ga-PSMA PET/CT [48]. Among 35 PCa

patients who underwent ^{68}Ga-PSMA PET/CT in the BCR setting ($n = 23$) or before primary therapy of high-risk PCa ($n = 12$), the group performed pLND in 17 men with nodal oligometastatic PCa. A per node sensitivity, specificity, PPV, and NPV were found to be 94%, 99%, 89%, and 99.5%, respectively. A systematic review by Perera et al. evaluated 16 articles including 1309 patients [49]. They found a sensitivity and specificity of 86% for both, on a per-patient analysis. On a per-lesion basis, they revealed a summary sensitivity and specificity of 80% and 97%, respectively.

More recently, ^{18}F-labeled agents have been developed with the hope of creating a PSMA agent that exhibits advantages over ^{68}Ga agents with respect to production amount, availability, clinical utility, and image resolution. Pomper et al. developed the first and second generations of the ^{18}F-PSMA radiotracer, ^{18}F-DCFBC and ^{18}F-DCFPyl, respectively [50, 51]. In a prospective trial of 16 patients with new or progressive metastatic disease, there was a 92% sensitivity for adenopathy using ^{18}F-DCFBC PET/CT [52]. The subsequently improved radiotracer,^{18}F-DCFPyl, shows promise in the early BCR setting compared to conventional imaging and other new PET agents. A recent prospective study included 22 patients with documented BCR after local therapy with negative standard conventional imaging [53]. Patients underwent whole body ^{18}F-DCFPyl PET/CT and multiparametric MRI (mpMRI). In the 19 patients (86.3%) with at least one positive ^{18}F-DCFPyl-avid lesion, there were 53 lesions identified: 9 in the prostate bed, 36 lymph nodes, and 8 distant sites. The detection rates were 80%, 50%, 100%, and 90.9% for PSA levels of > 0.2 to < 0.5, > 0.5 to 1.0, > 1 to 2.0, and ≥ 2.0 ng/mL, respectively. The ^{18}F-DCFPyl-PET and mpMRI findings were concordant for 11 lesions (20.7%), while ^{18}F-DCFPyl solely detected an additional 42 lesions (79.2%), 16 located outside the mpMRI field of view (Fig. 2). ^{18}F-DCFPyl-PET has strong performance in the early BCR setting even in patients with no lesions seen on conventional imaging, but there is still room for improvement when PSA values are less than 1.0 ng/mL. Finally, numerous efforts have been made to develop subsequent ^{18}F-labeled PSMA radiotracers that hope to provide improved clinical utility and signal-to-noise resolution [54–56].

Comparison Studies Between Choline, ^{18}F-FACBC, and PSMA in the BCR Setting

PCa recurrence after initial treatment is most commonly detected by a rising serum PSA. Although very low PSA levels can be detected (< 1 ng/mL) with current assays, PSA detection cannot localize where the PCa recurrence is in the body (i.e., local, regional, or distant). Additionally, morphological imaging methods exhibit significant limitations. Sensitivity ranges between 25 and 54% for the detection of local recurrence by transrectal ultrasound or CT, which is moderately improved using functional MR imaging techniques [57]. Due to the current lack of imaging modalities that contain both combined high sensitivity and specificity in the biochemical recurrence setting, many patients are staged incorrectly resulting in inappropriate treatment [7]. Fortunately, novel emerging PET radiotracers have shown thus far to perform better than the current standard-of-care imaging modalities. The three PET radiotracers that exhibit the most promise in the future of PCa imaging in the recurrence setting are ^{11}C/^{18}F-choline, ^{68}Ga/^{18}F-PSMA, and ^{18}F-FACBC.

The PCa specific PET (pcPET) agent systematic review by Evans et al. examined 20 clinical studies investigating radiolabeled choline, PSMA, and ^{18}F-FACBC PET/CT positivity in the BCR setting [58]. They found that among BCR patients with PSA < 1.0, PSMA was more sensitive than choline or ^{18}F-FACBC. The percent of men with PSA levels < 1.0 and a positive PET ranged from 21–41%, 7–44%, and 29–67% for ^{18}F-FACBC, choline, and PSMA, respectively. These PET sensitivities compare favorably to conventional imaging sensitivities at this low PSA level.

A prospective study by Nanni et al. analyzed 89 BCR patients after radical prostatectomy who underwent ^{11}C-choline and ^{18}F-FACBC PET/CT within 1 week of each other and were off hormonal therapy at the time of the scans. Categorizing patients by PSA level (< 1 ng/mL 28 patients, 1 to < 2 ng/mL 28 patients, 2 to < 3 ng/mL 11 patients, and ≥ 3 ng/mL 22 patients), the number (percent) of patients with true positive findings were generally higher with ^{18}F-FACBC than with ^{11}C-choline: six patients (21%) and four patients (14%), eight patients (29%) and eight patients (29%), five patients (45%) and four patients (36%), and 13 patients (59%) and 11 patients (50%), respectively.

A prospective study by Morigi et al. compared ^{18}F-fluoromethylcholine with ^{68}Ga-PSMA PET/CT in patients not on systemic therapy with rising PSA after definitive treatment [59]. Thirty-eight men underwent both ^{68}Ga-PSMA and ^{18}F-fluoromethylcholine PET/CT in addition to diagnostic CT. Of the patients enrolled, 34 underwent radical prostatectomy and 4 underwent radiation therapy. Twelve men underwent salvage radiation therapy after primary radical prostatectomy. With a mean PSA level of 1.74, 26 of the 34 (68%) patients had at least one positive PET scan. Of the 26 positive scans, 14 (54%) were positive with ^{68}Ga-PSMA alone, 11 (26%) were positive on both PET scans, and only 1 (4%) was positive on ^{18}F-fluoromethylcholine alone. When PSA was below 0.5 ng/mL, the detection rate was 50% for ^{68}Ga-PSMA versus 12.5% for ^{18}F-fluoromethylcholine. This prospective study showed that in patients with biochemical failure and low PSA level, ^{68}Ga-PSMA demonstrates a significantly higher detection rate than ^{18}F-fluoromethylcholine. Overall, PSMA appears to have the highest detection rate among

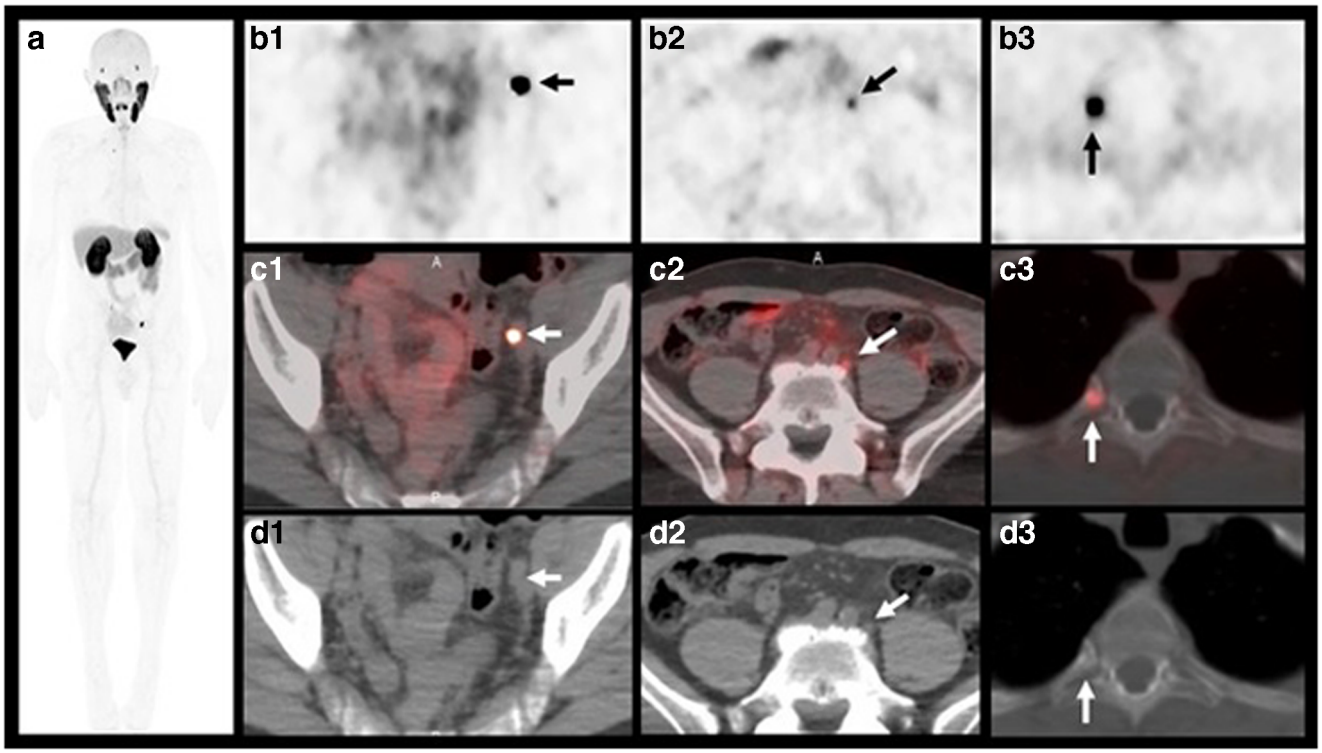

Fig. 2 Sixty-four-year-old male with rising PSA (1.42 ng/mL) after 8 years post-prostatectomy for prostate cancer, Gleason 7 (4 + 3), T3aNoMx. Maximal intensity projection (A), axial PET (B1, B2, B3), axial fused PET/CT (C1, C2, C3), and axial CT (D1, D2, D3) images demonstrate two DCFPyl-avid left iliac lymph nodes measuring 6 and 4 mm and a small DCFPyl-avid sclerotic bone lesion at the posterior right 4th rib

novel PET tracers in the BCR setting; however, sensitivity is still lower than desired in the very early stage of BCR.

Novel PET Imaging During Hormone Therapy

PCa patients at risk of or who currently have metastatic disease are commonly administered systemic anti-androgen therapies to suppress and prevent the growth of extraprostatic disease. Concerns about imaging performance arise while patients are administered anti-androgen therapies.

Preclinical data have shown that anti-neoplastic treatment of PCa cells results in alterations of energy metabolism and choline metabolism [60]. In parallel with this finding, experienced centers have found that after administration of systemic therapy to patients with $^{11}C/^{18}F$-choline PET-positive lymph nodes, these nodes are no longer choline-avid [58]. Conversely, PSMA expression has been shown to increase when treated with anti-androgen therapy and as tumor grade and castrate resistance increases [45, 61]. Additionally, PSMA overexpression in PCa cells has been found to be 100 to 1000 times that of normal tissue expression [62]. A retrospective review by Afshar-Oromieh et al. tested these preclinical findings in the clinic by evaluating 1704 patients who underwent ^{68}Ga-PSMA-11 PET/CT. Of 306 patients scanned at least twice, 10 had started and continued ADT with a continuous clinical response between the two PSMA scans. Among these 10 patients, 31 PCa lesions were visible before ADT initiation. However, during ongoing ADT, only 14 lesions were visible in 8 of the 10 patients. The average tracer uptake values decreased in 71% and increased in 12.9% of the lesions. These results suggest that long-term ADT reduces the visibility of castration-sensitive PCa on PSMA PET/CT and that patients should undergo PSMA PET/CT before initiating ADT [63•]. Further preclinical and clinical investigations of PSMA expression under androgen deprivation and in castrate resistant cells are important for the management of patients in these clinical scenarios.

Impact of Novel Imaging on Management of Prostate Cancer Patients

Novel PET tracers are increasingly being implemented into clinical practice, with the literature reporting high rates of detection of PCa even at low PSA levels. However, as any new imaging modality comes along, it is important to understand the clinical impact of these developments. There have been several small size, mainly retrospective, single-

institution studies that have evaluated the clinical impact of using ^{68}Ga-PSMA PET/CT in patients with PCa [64–66].

A prospective, multicenter study among four Australian imaging centers assessed whether ^{68}Ga-PSMA PET/CT affects management intent in patients with primary and recurrent PCa [67]. The study included 431 patients with PCa, 25% being staged for high-risk primary disease, and 75% being staged for BCR. Investigators found that ^{68}Ga-PSMA PET/CT led to a change in planned management in 51% of patients, with the impact being greater in the group of patients with biochemical failure (62% change in management intent) than in patients undergoing primary staging (21% change). These findings demonstrate the high clinical impact of ^{68}Ga-PSMA/PET on the management of PCa patients.

Conclusion

Appropriate treatment of PCa depends on accurate staging of localized versus metastatic disease. Emerging imaging techniques such as MR lymphography, whole-body MRI, and novel PET radiopharmaceuticals appear to perform superiorly to conventional imaging techniques in the primary and recurrence settings. In the era of ultrasensitive PSA detection in the scenario of BCR, there is a greater demand for more sensitive and specific imaging at very low PSA levels. PSMA PET appears to have the highest sensitivity at very low PSA levels, but sensitivity at PSA levels < 0.5 ng/mL still needs improvement. Future efforts need to be made to further develop imaging modalities with improved performance in the very early stage of BCR.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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