PET Imaging for Prostate Cancer

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KEYWORDS

• Fluciclovine • Prostate-specific membrane antigen • PET imaging • Prostate cancer • Biochemical recurrence • Theranostics

KEY POINTS

- ^{18}F-fluciclovine and prostate-specific membrane antigen (PSMA) PET/CT have demonstrated high positive predictive value in detecting extraprostatic malignancy in patients with biochemical recurrence with diagnostic performance exceeding that of conventional imaging.
- Although ^{18}F-fluciclovine is not FDA approved for use in initial staging, both ^{18}F-fluciclovine and PSMA PET/CT may help identify patients with occult metastasis who may not benefit from curative surgery in primary prostate cancer.
- Early data indicate that the use of ^{18}F-fluciclovine and PSMA PET improves patient outcomes.
- ^{18}F-fluciclovine excels in local disease detection because of limited urinary excretion, whereas PSMA has superior performance in extraprostatic disease detection.
- PSMA PET can serve as a means of selection for treatment with PSMA radioligand therapy.

INTRODUCTION

The role of PET imaging with ^{11}C-choline and ^{18}F-fluciclovine in evaluating patients with prostate cancer (PCa) has become more important over the years and has been incorporated into the NCCN guidelines. A new generation of PET radiotracers targeting the prostate-specific membrane antigen (PSMA) is widely used outside the United States to evaluate patients with primary PCa and PCa recurrence.

CHOLINE PET

Choline is a component of phosphatidylcholine incorporated into the cell membrane. The enzyme choline kinase is upregulated in many cancers, including PCa.[1] In September 2012, ^{11}C-choline was FDA approved for PET imaging of patients with suspected PCa recurrence. Choline radiotracers have been mostly replaced by PSMA PET worldwide and are not widely available in the United States compared with the FDA-approved synthetic amino acid PET radiotracer ^{18}F-fluciclovine.

^{18}F-FLUCICLOVINE PET

Pathophysiology and Biodistribution

^{18}F-fluciclovine is a fluorinated synthetic amino acid PET tracer approved by the FDA for imaging of patients with suspected PCa recurrence after prior treatment. In PCa cells, amino acid transport is significantly upregulated.[2] ^{18}F-fluciclovine physiologic activity is most intense in the pancreas and liver.[3] Variable mild to moderate physiologic uptake is seen in salivary glands, pituitary, adrenals, muscle, esophagus, bowel, and bone marrow;

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^{18}F-fluciclovine has greater heterogeneity than seen with ^{18}F-fluorodeoxyglucose (FDG). Mild uptake is noted within the blood pool and brain parenchyma. ^{18}F-fluciclovine is only minimally excreted by the kidneys with little to no resulting bladder activity, though a minority of patients may exhibit an early excretion pattern.[3]

Normal Variants/Pitfalls

^{18}F-fluciclovine is not prostate specific, as other benign and malignant neoplasia have upregulated amino acid metabolism and may have increased ^{18}F-fluciclovine uptake, such as lung, breast, and gynecologic cancers as well as meningioma and osteoid osteoma.[4,5] It is not uncommon to have mild to moderate symmetric ^{18}F-fluciclovine benign activity in inguinal, distal external iliac, and axillary nodes. Periurethral tissue may have mild to moderate activity, and therefore, sagittal images can help differentiate physiologic uptake from recurrence at the vesicourethral anastomosis. The early appearance of bladder or ureteral activity may mimic tumor or abnormal lymph nodes, respectively.[6]

Degenerative uptake is less intense and less commonly described than with FDG PET. Though amino acid imaging demonstrates less inflammatory uptake than FDG, amino acid transport also occurs in benign inflammation, and therefore fluciclovine uptake not specific to malignancy can occur.[3] For bone lesions, uptake is typically more intense with lytic or mixed sclerotic lesions. Indolent, dense sclerotic lesions may have little or no ^{18}F-fluciclovine uptake. Occasional ^{18}F-fluciclovine uptake seen in isolated red marrow in the pelvis or proximal femurs may stimulate metastasis. In these cases, bone-specific MR imaging, skeletal scintigraphy with agents such as sodium ^{18}F-fluoride or ^{99m}Tc-methylene diphosphate, or biopsy may be required.[7]

Patient Preparation and Imaging Protocol

Patient preparation and imaging protocol for ^{18}F-fluciclovine PET have been described in detail.[7,8] In brief, the patient is advised to fast (except for medications) for 4 hours and avoid excessive physical activity starting 24 hours before the scan. If possible, patients should refrain from voiding 15 to 30 minutes before the study to mitigate early urine tracer excretion.

PET images should start at 4 minutes (3–5 min) postinjection of 10 mCi (370 MBq) ^{18}F-fluciclovine as an IV bolus. As the dynamic tracer washout is relatively fast, it is important not to delay the start of the PET images. The CT can be acquired within the 4-minute interval between ^{18}F-fluciclovine injection and PET acquisition. CT images with IV contrast should be performed after the PET, as the IV contrast may act as a diuretic and increase early urinary excretion.

Image Interpretation

^{18}F-fluciclovine image interpretation is based on the uptake compared with defined background regions such as bone marrow and blood pool.[7,9] Typical PCa recurrence patterns should be kept in mind when interpreting ^{18}F-fluciclovine PET.[7,10] Overall, any lesion with increased uptake equal to or higher than bone marrow (level of normal L3 vertebrae) should be considered suspicious for malignancy. Lesions smaller than 1 cm may demonstrate lower activity due to partial volume artifact, and therefore the threshold for positivity is lower. Hence, subcentimeter structures should be considered suspicious when uptake is significantly above the adjacent visualized blood pool uptake and approaches the bone marrow uptake.[7,9] For bone lesions, focal activity should be clearly seen on the maximum intensity projection (MIP) image.

Primary Disease and Staging

Neither characterization of the primary lesion nor initial staging are FDA-approved indications for ^{18}F-fluciclovine. While primary malignant lesions have higher uptake versus normal prostate tissue, there is a significant overlap in uptake between PCa and nonmalignant processes such as benign prostatic hypertrophy.[11,12] Multiple studies have demonstrated a correlation between Gleason grade and ^{18}F-fluciclovine uptake.[11–15] Approximately 28% of patients are undergraded on biopsy compared with prostatectomy.[16] The possibility of using ^{18}F-fluciclovine to help direct biopsy to more aggressive occult lesions, especially with the addition of multiparametric PET/MR to refine characterization, is intriguing.

A multicenter Phase 2 trial for initial staging of primary PCa with ^{18}F-fluciclovine PET/CT in 28 patients reported sensitivity and specificity of 66.7% and 86.4%, respectively, for extraprostatic nodal disease.[17] Another study of 28 patients with high-risk PCa in patients who underwent ^{18}F-fluciclovine PET/MR imaging before surgery reported patient-based and region-based sensitivity of 40% and 30%, respectively, with 100% specificity for the detection of regional lymph node metastases with a higher PPV of PET versus MR imaging alone.[18]

A prospective study using ^{18}F-fluciclovine PET for preoperative staging in patients with intermediate-risk to high-risk primary PCa of 57 patients who subsequently underwent robotic

radical prostatectomy with extended pelvic lymph node dissection reported a sensitivity and specificity for malignant nodal detection of 55.3% and 84.8% per patient, respectively, and 54.8% and 96.4% per region, respectively.[19] The sensitivity was significantly higher than conventional imaging both on a patient-based (55.3% vs 33.3%, $P<.01$) and region-based (54.8% vs 19.4%, $P<.01$) analysis with similar high specificity. Metastasis detection correlates to the size of metastatic deposits within lymph nodes and overall metastatic burden.[18,19] Hence, ^{18}F-fluciclovine PET can be useful to guide lymph node dissection because of its high specificity and to help identify patients with occult metastasis who may not benefit from curative surgery.

Recurrence/Restaging

^{18}F-fluciclovine PET/CT demonstrated promising initial results in detecting malignancy in patients with biochemical recurrence (BCR).[20] In a prospective clinical trial in which there was a 96.1% level of histologic proof, the detection rate was related to the prostate-specific antigen (PSA) level: 37.5% at a PSA of less than 1 ng/mL, 77.8% at 1 to 2 ng/mL, 91.7% at >2 to 5 ng/mL, and 83.3% at greater than 5 ng/mL, which was significantly better than CT.[21] The sensitivity and specificity in the treated prostate or prostate bed were 90.2% and 40.0%, respectively; sensitivity and specificity for extraprostatic disease were 55.0% and 96.7%, respectively. Confounding uptake due to inflammation or prostatic hypertrophy was likely responsible for the lower specificity in the treated prostate.[22] A subsequent study using ^{18}F-fluciclovine-guided transrectal ultrasound-guided biopsies reported that using a higher threshold of intensity minimizes false-positive results in the treated prostate.[23] A multisite study of 596 patients reported a sensitivity of 88.1%, specificity of 32.6%, and PPV of 71.8% for local recurrence.[24] Thus, histologic confirmation of findings in the treated prostate is recommended, yet there is high specificity for extraprostatic disease detection mirrored by the multisite study that reported a PPV of 92.3%.[24]

In the prospective multicenter intention-to-treat LOCATE trial enrolling 213 patients with BCR, detection rate varied with PSA level: 31%, 79%, and 81% with a PSA (ng/mL) of 0 to 0.5, greater than 1.0, and greater than 2.0, respectively. A postscan change in management occurred in 59% of patients.[25] The FALCON prospective trial enrolled 104 patients and reported a 64% change in management with detection rates of 29.5% and 93% in PSAs of less than and greater than 2.0 ng/mL, respectively.[26] Interestingly, there was a 28.9% patient-level detection rate with PSA less than 0.5 ng/ml. A retrospective report of 152 patients from clinically performed ^{18}F-fluciclovine PET/CT demonstrated positivity rates of 58%, 87%, 100%, and 92% for PSA (ng/mL) levels of less than 1, 1 to 2, 2 to 5, and greater than 5, respectively.[27]

A final analysis of patients from a randomized prospective trial of 165 patients (NCT01666808) in a postprostatectomy setting with BCR reported a 35.4% change in therapy approach in patients who underwent standard of care imaging (abdominopelvic CT or MR imaging) followed by ^{18}F-fluciclovine PET/CT.[28] Upon examining outcomes from salvage radiotherapy planning with standard imaging only versus those whose planning was based on the additional ^{18}F-fluciclovine PET/CT, a significant improvement in failure-free survival at 3 years (75.5% vs 63.0; $P = .003$) and 4 years (75.5% vs 51.2%; $P<.001$) was reported. A second similar randomized clinical trial (NCT03762759) will compare ^{18}F-fluciclovine and ^{68}Ga-PSMA in patients with BCR postprostatectomy.

The detection of recurrent disease at low PSA levels has assumed importance as salvage radiotherapy is being offered at increasingly lower PSA levels. The reported detection rate of ^{18}F-fluciclovine at low PSA levels has varied widely. In the randomized salvage therapy outcomes trial above, there was a 72% detection rate with PSA less than 1 ng/mL while Wang and coworkers reported a 33% detection rate at this level.[29,30] Others have reported values in between 46.4% and 58% for PSA< or $\leq$1 ng/mL.[27,31] These differences in detection rates are likely related to specifics of trial populations, such as aggressiveness of disease.

Therapy Response Assessment with ^{18}F-Fluciclovine PET

Preliminary studies suggested that ^{18}F-fluciclovine could be used to assess response to therapy.[32,33] A small prospective study of patients with primary PCa undergoing androgen-deprivation therapy (ADT) reported a significant decrease in standardized uptake values (ie, SUVmax) of detected local and metastatic lesions on a subsequent PET/MR imaging scan.[33] A second small retrospective study in patients with BCR found a correlation between PSA and the number of lesions to findings on post-therapy PET/CT scans.[32] However, this needs to be further evaluated in larger prospective clinical trials.

PROSTATE-SPECIFIC MEMBRANE ANTIGEN-TARGETED PET

Introduction to Prostate-Specific Membrane Antigen-Targeted PET

PSMA radiotracers are widely used throughout the world for PCa imaging and therapy. PSMA is a type II transmembrane glycoprotein with folate hydrolase activity and an extracellular domain that includes the enzyme active site.[34] Expression of PSMA is seen in approximately 95% of PCa tumors.[35] At the histologic level, aggressive and advanced PCa shows increased levels of PSMA expression.[36] The accessibility of the active site to high-affinity ligands, combined with rapid internalization of PSMA from the cell surface, allows for high-contrast imaging.[37]

Early in the clinical adoption of PSMA PET agents, ^{68}Ga-labeled radiotracers proliferated because of several factors including facile synthesis and the ability to make such compounds without access to a cyclotron. ^{68}Ga-PSMA-HBED-CC, later more commonly known as ^{68}Ga-PSMA-11 or simply ^{68}Ga-PSMA, became the dominant agent in the field.[38] However, parallel to the development of ^{68}Ga-labeled radiotracers, PSMA-targeted agents labeled with fluorine-18 were also being explored, initially ^{18}F-DCFBC[39] and other first-generation compounds, and later more widely used radiotracers such as ^{18}F-DCFPyL,[40] ^{18}F-PSMA-1007, and ^{18}F-rhPSMA-7.[41,42]

Patient Preparation and Imaging Protocol

Patient preparation and imaging protocol for PSMA-directed imaging PET were previously described.[43,44] Patients do not fast and are encouraged to be well hydrated. Voiding before imaging may decrease the frequency of halo artifacts. The dose range from 1.8 to 2.2 MBq (0.05–0.06 mCi) per kilogram for ^{68}Ga-labeled PSMA radiotracers,[43] and 200 to 370 MBq (5–10 mCi) for the ^{18}F-labeled counterparts.[44] After bolus injection, an uptake time of 1 h is recommended, although delayed acquisition or the use of furosemide may improve lesion detection.[45] Field of view includes the base of the skull to midthigh with 3 to 4 min per bed position and images.[43]

Normal Variants/Pitfalls

For most PSMA radiotracers, biodistribution includes the lacrimal glands, salivary glands, liver, spleen, kidneys, small bowel, ganglia, and urinary tract due to renal excretion.[43] There are some variations among radiotracers. ^{18}F-DCFPyL has higher hepatic uptake than ^{68}Ga-PSMA-11, whereas ^{68}Ga-PSMA-11 has increased accumulation in the kidneys.[46] ^{18}F-PSMA-1007 has less renal excretion, which can increase the lesion detection rate for small pelvic lymph node lesions or local recurrence.[41] With increasing clinical availability of PSMA-directed imaging, the number of reported pitfalls is steadily increasing (**Fig. 1**). Multiple benign pathologies with increased PSMA expression can be misinterpreted as malignant, for example, sympathetic ganglia,[47] benign tumors (meningioma, schwannoma), soft tissue lesions (desmoid tumors, myxoma), or lung lesions (sarcoidosis, tuberculosis, or anthracosilicosis). Nonprostatic malignant tumors, however, may also have substantial PSMA expression; these include medullary thyroid carcinoma, renal cell carcinoma, breast cancer, and lung cancer.[48]

Interpretative Criteria

Multiple standardized frameworks for image interpretation have been introduced for PSMA PET. For instance, Eiber and coworkers recently introduced the "PROMISE" system, which is based on a molecular imaging TNM classification (''miTNM,'' version 1.0). Using the "miPSMA expression score," different uptake levels are considered relative to normal uptake in the blood pool, liver, and parotid glands. The local tumor is classified, which refers to extent and organ confinement ranging from "miT0" to "miT4". In addition, a sextant segmentation of the prostate is used for intraprostatic tumor extension. Pelvic lymph node lesions are categorized (from "miN0" to "miN1b"). Last, the extrapelvic nodes ("miM1a") and distant metastases ("miM1b" referring to bone or "miM1c" to other organ involvement) are also evaluated.[49] In a prospective trial applying PROMISE to ^{68}Ga-PSMA-11 PET/CT in 635 men afflicted with PCa, interreader reproducibility was substantial, with a Fleiss κ of 0.65 to 0.78.[50] Also providing reliable standards in PSMA PET/CT interpretation, the PSMA Reporting and Data System (RADS) framework has been recently introduced. In brief, a 5-point scale is applied to a maximum of 5 target lesions, with increasing numbers indicating a higher likelihood of malignancy. PSMA-RADS ranges from 1 = no evidence of disease and definitively benign to 5 = high certainty that prostate carcinoma is present and refers to the site of disease and the intensity of radiotracer uptake. Depending on the derived RADS score, PSMA-RADS also triggers further clinical workup—for example, by recommending biopsy or follow-up imaging. Taken together, this framework should increase the level of reader confidence, should facilitate communication with other specialists, and may guide the reader in determining

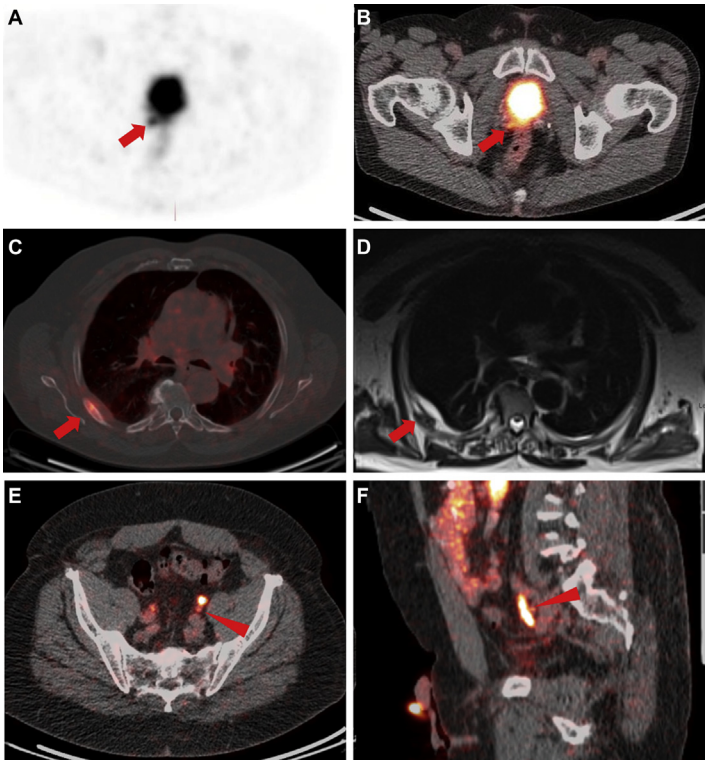

Fig. 1. (*A*) (PET axial) (*B*) (axial fused PET-CT) 51-year-old man postprostatectomy with positive margin (Gleason 3 + 4 = 7). PSA at time of ^{11}Ga-PSMA PET was 0.23 ng/mL. Uptake in right lateral surgical margin (*arrows*) obscured by intense bladder activity. Patient underwent EBRT to prostate bed with ADT with subsequent PSA less than 0.01 ng/ml. (*C*) (PET/CT fused axial) 65-year-old man postprostatectomy presented with PSA of 0.03 ng/mL. ^{11}Ga-PSMA images demonstrate abnormal uptake in the right fifth rib with sclerosis and new soft tissue thickening (*arrow*). The patient denies trauma. An MR image (*D* axial T2 HASTE) showed a characteristic healing fracture (*arrows*). (*E*) PET/CT fused axial and (*F*) sagittal images demonstrate abnormal uptake in a left external iliac lymph node measuring 0.6 × 0.5 cm behind and obscured by intense left ureteral activity (*arrowheads*).

whether radioligand therapy for PCa should be recommended.[51] In a prospective setting enrolling 50 ^{18}F-DCFPyL PET/CTs, the interobserver agreement rate using PSMA-RADS was excellent.[52]

Prostate-Specific Membrane Antigen-Targeted PET in Primary Prostate Cancer and Initial Staging

Identification of primary PCa is ongoing research with PSMA PET. An early study with the first-generation agent ^{18}F-DCFBC noted that PET had an improved specificity for high-grade disease than MR imaging, although with a lower sensitivity.[53] Other studies have been more promising. Eiber and colleagues found that ^{68}Ga-PSMA-11 PET had a significantly higher area under the receiver-operating-characteristic curve (AUC, 0.83) than multiparametric MR imaging (0.73).[54] The combination of both modalities led to the highest AUC (0.88).[54] Similarly, Hicks and colleagues found that ^{68}Ga-PSMA-11 PET/MR imaging sensitivity was superior to multiparametric MR imaging at the anatomic-region level.[55] These findings suggest that PSMA PET may be appropriate to incorporate into biopsy planning.[56]

PSMA PET is a useful staging modality for patients at risk of occult locoregional nodal involvement or distant metastatic disease. In single-center retrospective[57] and prospective studies in men with intermediate-risk or high-risk PCa,[58] PSMA PET has demonstrated moderate sensitivity and very high specificity for identifying pelvic lymph node involvement. The first published study on this topic reported a relatively low patient-level sensitivity of 33.3%,[57] which is in line with larger multicenter trials, such as OSPREY (sensitivity 30.6%–41.9% among three readers)[59] or a study with ^{68}Ga-PSMA-11 that reported sensitivity of 40%.[60] The apparently low sensitivity of PSMA PET in multicenter trials suggests that there may be heterogeneity between centers and that care will need to be taken in translating PSMA PET beyond large tertiary care medical centers with specific expertise.

PSMA PET can predict biochemical persistence (BCP) after radical prostatectomy with lymph node dissection. Van Leeuwen and colleagues found that BCP was noted in 50% of men in whom lymph node involvement was seen on PSMA PET and confirmed histologically, whereas only 16.7% BCP was noted in men with lymph node involvement histologically but not identified on PSMA PET.[61]

The recently published proPSMA trial found that PSMA PET outperformed conventional imaging for the systemic staging of men with high-risk PCa.[62] Therefore, despite limitations in sensitivity, PSMA PET may become a clinical standard for staging patients being considered for curative-intent local therapy.

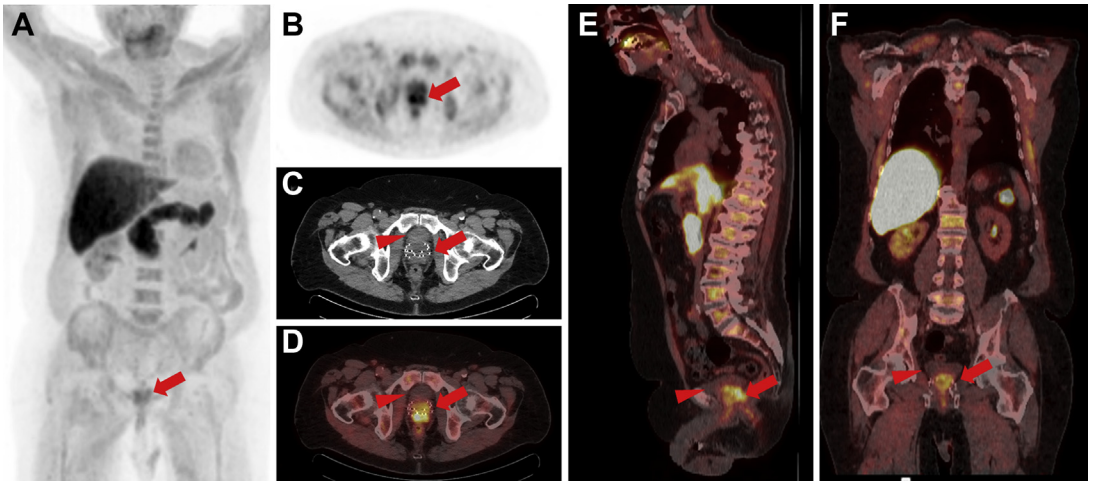

Fig. 2. A 72-year-old-man with biochemical recurrence of PCa with PSA 4 ng/mL after prior brachytherapy (initial PSA of 11 ng/mL). ^{18}F-fluciclovine PET/CT images (*A*) MIP, (*B*) axial PET, (*C*) axial CT, (*D*) axial PET/CT, (*E*) sagittal PET/CT (*F*), and coronal PET/CT images demonstrate increased tracer uptake within the prostate extending to the seminal vesicles (*arrows*). A prostate biopsy confirmed the presence of recurrent disease. Compared with ^{68}Ga-PSMA-11 or ^{18}F-PSMA- DCFPyL PET tracers, ^{18}F-fluciclovine urine washout to the bladder is usually mild (*arrowheads*), improving the evaluation of local recurrence.

Prostate-Specific Membrane Antigen-Targeted PET for Recurrence, Restaging, and Metastatic Disease

The most widely studied aspect of PSMA PET imaging is detection efficiency in recurrent disease, as identifying the site of recurrence influences the approach to salvage therapy.[63] Early studies on PSMA PET in the recurrence population varied in the reported detection efficiencies, which may have been due in part to the retrospective nature of many of the studies and differences in the degree of inclusion of patients with visible lesions on conventional imaging.[37] However, the limitations from early studies have begun to be addressed by improved study designs. For example, Fendler and colleagues reported in a two-center prospective trial that sites of PCa were localized in 75% of men with recurrent disease and that the PPV of PSMA PET findings was 0.84 on a per-patient basis with histologic validation.[50] Another recent prospective study that specifically excluded patients with evidence of disease on conventional imaging found a detection rate of 67.7%.[64] Although detection efficiency generally tracks with serum PSA level,[37] the rates of lesion localization are still moderate at low PSAs, and there are no current recommendations to exclude patients from imaging based on PSA level.

Phillips and colleagues reported the results of the ORIOLE trial, in which patients were randomized to either stereotactic ablative body radiation (SABR) or observation for oligometastatic disease identified on conventional imaging. SABR improved progression-free survival, particularly in a post hoc analysis that showed that inclusion of all PSMA-positive sites of disease in the treatment plan was beneficial.[65] We can expect that the high sensitivity of PSMA PET will popularize metastasis-directed therapy in oligometastatic patients.

Therapy Response Assessment with Prostate-Specific Membrane Antigen-Targeted PET

There is a complex interplay between androgen signaling and PSMA expression, making interpretation of response assessment difficult. Hope and coworkers demonstrated that short-term ADT led to a flare phenomenon with increased uptake in known lesions and the appearance of new lesions.[66] Longer-term ADT generally leads to decreased conspicuity of lesions.[67] The initiation of second-generation anti-androgen therapy can also confuse patterns of changes in uptake on PSMA PET.[68] Due to the apparent complexity of response assessment with PSMA PET, interest has arisen in developing response criteria.[69] However, prospective data are needed to evaluate systemic therapy effects on PSMA expression.

Prostate-Specific Membrane Antigen Ligands Versus ^{18}F-Fluciclovine

^{18}F-fluciclovine is a metabolic radiotracer, whereas PSMA is targeted to receptors. Thus, each radiotracer reflects a different aspect of PCa biology. Intrapatient comparisons of ^{18}F-fluciclovine and ^{68}Ga-PSMA-11 reported superior performance for ^{68}GA-PSMA-11 in detecting

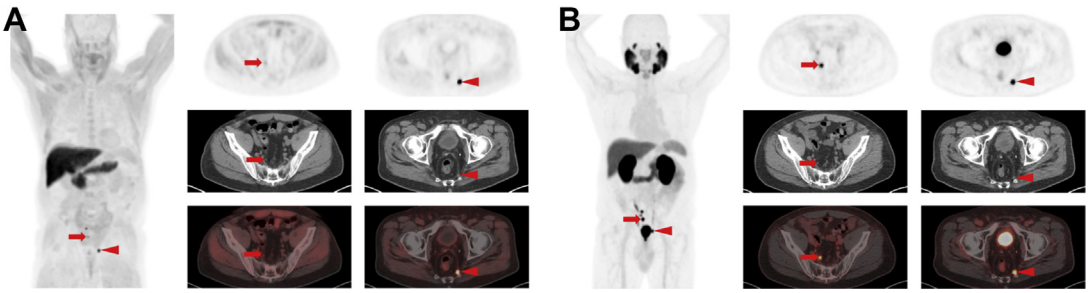

Fig. 3. A 74-year-old man with biochemical recurrence of PCa after radical prostatectomy. (*A*) ^{18}F-fluciclovine PET whole-body MIP image showing multiple radiotracer-avid pelvic lymph nodes as well as axial PET (*top row*), CT (*middle row*), and PET/CT (*bottom row*) images. (*B*) PSMA-targeted ^{18}F-DCFPyL PET whole-body MIP image showing multiple radiotracer-avid pelvic lymph nodes as well as axial PET (*top row*), CT (*middle row*), and PET/CT (*bottom row*) images. Although some lesions are more conspicuous with the PSMA agent (*red arrows*), it also has high urinary excretion that obscures lesions in some images, such as on the MIP (*red arrowheads*). This patient was imaged on the CONDOR clinical trial protocol (NCT03739684).

metastatic lymph nodes and skeletal disease, particularly for patients with PSAs less than 2 ng/mL.[70,71] For detecting local recurrence, ^{18}F-fluciclovine is reported to be superior to ^{68}Ga-PSMA-11 because of much lower urinary excretion, which could interfere with the detection of recurrence adjacent to the bladder (**Figs. 2** and **3**).

^{18}F-fluciclovine is FDA approved for the detection of recurrent PCa and is widely commercially available.[68] Ga-PSMA-11 is now FDA approved for patients with suspected PCa metastasis who are potentially curable by surgery or radiation therapy (primary PCa) and for patients with suspected PCa recurrence based on elevated PSA. The approval is specific to the University of California, Los Angeles, and the University of California, San Francisco. More recently, 18F-DCFPyL PET was approved by the FDA for commercial use in the United States for patients with prostate cancer. Other PSMA radiotracers, including fluorinated variants, are expected to gain FDA approval in the near future. With time, it is expected that PSMA-based radiotracers will assume a dominant role, though fluciclovine may be of value in the definition of local recurrence and with PSMA-negative or equivocal lesions. As noted above, flare has been reported with PSMA radiotracers post initiation of ADT. More study is needed to determine which radiotracer may be useful in posttherapy monitoring and under which circumstances.

For patients with a more extensive disease burden, PSMA PET can serve as a means of selection for treatment with PSMA radioligand therapy (PRLT), **Fig. 4**. PRLT appears to be effective with limited toxicities[72] and is expected to move toward regulatory approval in the future.

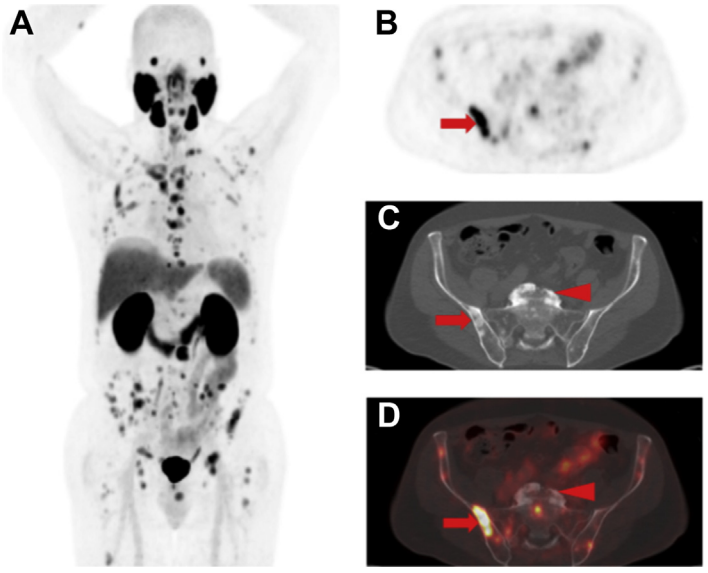

Fig. 4. An 86-year-old man with extensive bone metastatic PCa. (*A*) MIP, (*B*) axial PET, (*C*) axial CT, and (*D*) axial PET/CT images from a PSMA-targeted ^{18}F-DCFPyL scan showing extensive abnormal uptake in the visualized skeleton. Note the intense uptake in sclerotic lesions consistent with bone metastases (*red arrows*), whereas there is no uptake in degenerative sclerosis (*red arrowheads*).

CLINICS CARE POINTS

- 18F-fluciclovine and PSMA PET/CT are highly useful in detecting prostate cancer recurrence and metastases.
- Low urinary activity is an advantage for 18F-fluciclovine in detecting local recurrence, while high affinity and low background are advantages for PSMA in detecting extra-prostatic disease.
- 18F-fluciclovine PET is FDA approved for patients with biochemical recurrence, yet early data also suggest the benefit of evaluating for occult metastases in patients with higher-risk primary prostate cancer.
- The FDA recently approved the clinical use of 68Ga-PSMA-11 and 18F-DCFPyL for patients with primary and recurrent prostate cancer. It is expected that those PSMA-based radiotracers will become more predominant, with 18F-fluciclovine reserved for niche situations such as PSMA negative disease.
- PSMA PET radiotracers can be used for selecting patients for PSMA radioligand therapy (PRLT).

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REFERENCES

1. Zheng QH, Gardner TA, Raikwar S, et al. [11C] Choline as a PET biomarker for assessment of prostate cancer tumor models. Bioorg Med Chem 2004; 12(11):2887–93.
2. Fuchs BC, Bode BP. Amino acid transporters ASCT2 and LAT1 in cancer: partners in crime? Semin Cancer Biol 2005;15(4):254–66.
3. Schuster DM, Nanni C, Fanti S, et al. Anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid: physiologic uptake patterns, incidental findings, and variants that may simulate disease. J Nucl Med 2014;55:1986–92.
4. Savir-Baruch B, Zanoni L, Schuster DM. Imaging of Prostate Cancer Using Fluciclovine. Urol Clin North Am 2018;45(3):489–502.
5. Tade F, Buehner T, Potkol R, et al. Feasibility of Fluciclovine PET-CT Imaging of Endometrial, Cervical, and Ovarian Cancers: Preliminary Findings. J Nucl Med 2019;60(supplement 1):558.
6. Lovrec P, Schuster DM, Wagner RH, et al. Characterizing and Mitigating Bladder Radioactivity on (18)F-Fluciclovine PET/CT. J Nucl Med Technol 2020; 48(1):24–9.
7. Savir-Baruch B, Banks KP, McConathy JE, et al. ACR-ACNM Practice Parameter for the Performance of Fluorine-18 Fluciclovine-PET/CT for Recurrent Prostate Cancer. Clin Nucl Med 2018;43(12):909–17.
8. Tade FI, Sajdak RA, Gabriel M, et al. Best practices for ^{18}F-Fluciclovine PET/CT imaging of recurrent prostate cancer: a guide for technologists. J Nucl Med Technol 2019;47(4):282–7.
9. Nanni C, Zanoni L, Bach-Gansmo T, et al. [(18)F]Fluciclovine PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging-version 1.0. Eur J Nucl Med Mol Imaging 2020;47(3):579–91.
10. Barbosa FG, Queiroz MA, Nunes RF, et al. Revisiting prostate cancer recurrence with PSMA PET: atlas of typical and atypical patterns of spread. Radiographics 2019;39(1):186–212.
11. Schuster DM, Taleghani PA, Nieh PT, et al. Characterization of primary prostate carcinoma by anti-1-amino-2-[(18)F] -fluorocyclobutane-1-carboxylic acid (anti-3-[(18)F] FACBC) uptake. Am J Nucl Med Mol Imaging 2013;3(1):85–96.
12. Turkbey B, Mena E, Shih J, et al. Localized prostate cancer detection with 18F FACBC PET/CT: comparison with MR imaging and histopathologic analysis. Radiology 2014;270(3):849–56.
13. Elschot M, Selnæs KM, Sandsmark E, et al. A PET/MRI study towards finding the optimal [(18)F]Fluciclovine PET protocol for detection and characterisation of primary prostate cancer. Eur J Nucl Med Mol Imaging 2017;44(4):695–703.
14. Jambor I, Kuisma A, Kähkönen E, et al. Prospective evaluation of (18)F-FACBC PET/CT and PET/MRI versus multiparametric MRI in intermediate- to high-risk prostate cancer patients (FLUCIPRO trial). Eur J Nucl Med Mol Imaging 2018;45(3): 355–64.
15. Kendall JJAA, Abiodun-Ojo OA, Alemozaffar M, et al. Fluciclovine detection of primary prostate cancer at the sextant level and correlation of SUVmax with Gleason grades. Oral Presentation presented at RSNA; 2020. Virtual.

16. Chun FK, Briganti A, Shariat SF, et al. Significant upgrading affects a third of men diagnosed with prostate cancer: predictive nomogram and internal validation. BJU Int 2006;98(2):329–34.
17. Suzuki H, Jinnouchi S, Kaji Y, et al. Diagnostic performance of 18F-fluciclovine PET/CT for regional lymph node metastases in patients with primary prostate cancer: a multicenter phase II clinical trial. Jpn J Clin Oncol 2019;49(9):803–11.
18. Selnaes KM, Kruger-Stokke B, Elschot M, et al. (18) F-Fluciclovine PET/MRI for preoperative lymph node staging in high-risk prostate cancer patients. Eur Radiol 2018;28(8):3151–9.
19. Alemozaffar M, Akintayo AA, Abiodun-Ojo OA, et al. [(18)F]Fluciclovine positron emission tomography/Computerized tomography for preoperative staging in patients with intermediate to high risk primary prostate cancer. J Urol 2020;204(4):734–40.
20. Schuster DM, Votaw JR, Nieh PT, et al. Initial experience with the radiotracer anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. J Nucl Med 2007;48(1):56–63.
21. Odewole OA, Tade FI, Nieh PT, et al. Recurrent prostate cancer detection with anti-3-[(18)F]FACBC PET/CT: comparison with CT. Eur J Nucl Med Mol Imaging 2016;43(10):1773–83.
22. Schuster DM, Nieh PT, Jani AB, et al. Anti-3-[(18)F] FACBC positron emission tomography-computerized tomography and (111)In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: results of a prospective clinical trial. J Urol 2014;191(5):1446–53.
23. Abiodun-Ojo OA, Akintayo AA, Akin-Akintayo OO, et al. 18)F-Fluciclovine parameters on targeted prostate biopsy associated with true positivity in recurrent prostate cancer. J Nucl Med 2019;60(11):1531–6.
24. Bach-Gansmo T, Nanni C, Nieh PT, et al. Multisite experience of the safety, detection rate and diagnostic performance of Fluciclovine ((18)F) positron emission tomography/Computerized tomography imaging in the staging of biochemically recurrent prostate cancer. J Urol 2017;197(3 Pt 1):676–83.
25. Andriole GL, Kostakoglu L, Chau A, et al. The impact of positron emission tomography with 18F-Fluciclovine on the treatment of biochemical recurrence of prostate cancer: results from the LOCATE trial. J Urol 2019;201(2):322–31.
26. Scarsbrook AF, Bottomley D, Teoh EJ, et al. Effect of (18)F-Fluciclovine positron emission tomography on the management of patients with recurrence of prostate cancer: results from the FALCON trial. Int J Radiat Oncol Biol Phys 2020;107(2):316–24.
27. Savir-Baruch B, Lovrec P, Solanki AA, et al. Fluorine-18-Labeled Fluciclovine PET/CT in clinical practice: factors affecting the rate of detection of recurrent prostate cancer. AJR Am J Roentgenol 2019;213(4):851–8.
28. Jani AB, Schreibmann E, Goyal S, et al. Initial report of a randomized trial comparing conventional- vs conventional plus fluciclovine (18F) PET/CT imaging-guided post-prostatectomy radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2020;108(5):P1397.
29. Akin-Akintayo OO, Jani AB, Odewole O, et al. Change in salvage radiotherapy management based on guidance with FACBC (Fluciclovine) PET/CT in postprostatectomy recurrent prostate cancer. Clin Nucl Med 2017;42(1):e22–8.
30. Wang Y, Chow DZ, Ebert E, et al. Utility of (18)F-Fluciclovine PET/CT for detecting prostate cancer recurrence in patients with low (< 1 ng/mL) or very low (< 0.3 ng/mL) prostate-specific antigen levels. AJR Am J Roentgenol 2020;215(4):997–1001.
31. England JR, Paluch J, Ballas LK, et al. 18F-Fluciclovine PET/CT detection of recurrent prostate carcinoma in patients with serum PSA </= 1 ng/mL after definitive primary treatment. Clin Nucl Med 2019;44(3):e128–32.
32. Kim YPLP, Wagner RH, Gabriel MS, et al. Potential use of fluciclovine PET/CT as follow-up modality in patients with biochemically recurrent prostate cancer. Chicago: RSNA; 2019. Monday, Dec. 2 8: 55AM - 9:05AM, 2019.
33. Galgano SJ, McDonald AM, Rais-Bahrami S, et al. Utility of ^{18}F-Fluciclovine PET/MRI for staging newly diagnosed high-risk prostate cancer and evaluating response to initial androgen deprivation therapy: a prospective single-arm pilot study. AJR Am J Roentgenol 2020. [Epub ahead of print].
34. Barinka C, Rojas C, Slusher B, et al. Glutamate carboxypeptidase II in diagnosis and treatment of neurologic disorders and prostate cancer. Curr Med Chem 2012;19(6):856–70.
35. Wright GL Jr, Haley C, Beckett ML, et al. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol 1995;1(1):18–28.
36. Perner S, Hofer MD, Kim R, et al. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Pathol 2007;38(5):696–701.
37. Rowe SP, Gorin MA, Pomper MG. Imaging of prostate-specific membrane antigen with small-molecule PET radiotracers: from the bench to advanced clinical applications. Annu Rev Med 2019;70:461–77.
38. Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive (68)Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70(6):926–37.

39. Cho SY, Gage KL, Mease RC, et al. Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. J Nucl Med 2012;53(12):1883–91.
40. Szabo Z, Mena E, Rowe SP, et al. Initial Evaluation of [(18)F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-targeted PET imaging of prostate cancer. Mol Imaging Biol 2015;17(4):565–74.
41. Giesel FL, Hadaschik B, Cardinale J, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging 2017;44(4):678–88.
42. Oh SW, Wurzer A, Teoh EJ, et al. Quantitative and qualitative analyses of biodistribution and PET image quality of a novel radiohybrid PSMA, (18)F-rhPSMA-7, in patients with prostate cancer. J Nucl Med 2020;61(5):702–9.
43. Fendler WP, Eiber M, Beheshti M, et al. 68)Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging 2017;44(6):1014–24.
44. Werner RA, Derlin T, Lapa C, et al. 18)F-Labeled, PSMA-targeted radiotracers: leveraging the advantages of radiofluorination for prostate cancer molecular imaging. Theranostics 2020;10(1):1–16.
45. Schmuck S, Nordlohne S, von Klot CA, et al. Comparison of standard and delayed imaging to improve the detection rate of [(68)Ga]PSMA I&T PET/CT in patients with biochemical recurrence or prostate-specific antigen persistence after primary therapy for prostate cancer. Eur J Nucl Med Mol Imaging 2017;44(6):960–8.
46. Ferreira G, Iravani A, Hofman MS, et al. Intra-individual comparison of (68)Ga-PSMA-11 and (18)F-DCFPyL normal-organ biodistribution. Cancer Imaging 2019;19(1):23.
47. Werner RA, Sheikhbahaei S, Jones KM, et al. Patterns of uptake of prostate-specific membrane antigen (PSMA)-targeted (18)F-DCFPyL in peripheral ganglia. Ann Nucl Med 2017;31(9):696–702.
48. Sheikhbahaei S, Werner RA, Solnes LB, et al. Prostate-Specific Membrane Antigen (PSMA)-targeted PET imaging of prostate cancer: an update on important pitfalls. Semin Nucl Med 2019;49(4):255–70.
49. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-Ligand PET/CT. J Nucl Med 2018;59(3):469–78.
50. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. JAMA Oncol 2019;5(6):856–63.
51. Rowe SP, Pienta KJ, Pomper MG, et al. Proposal for a structured reporting system for prostate-specific membrane antigen-targeted PET imaging: PSMA-RADS Version 1.0. J Nucl Med 2018;59(3):479–85.
52. Werner RA, Bundschuh RA, Bundschuh L, et al. Interobserver agreement for the standardized reporting system PSMA-RADS 1.0 on (18)F-DCFPyL PET/CT imaging. J Nucl Med 2018;59(12):1857–64.
53. Rowe SP, Gage KL, Faraj SF, et al. 1)(8)F-DCFBC PET/CT for PSMA-based detection and characterization of primary prostate cancer. J Nucl Med 2015;56(7):1003–10.
54. Eiber M, Weirich G, Holzapfel K, et al. Simultaneous (68)Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. Eur Urol 2016;70(5):829–36.
55. Hicks RM, Simko JP, Westphalen AC, et al. Diagnostic accuracy of (68)Ga-PSMA-11 PET/MRI compared with multiparametric MRI in the detection of prostate cancer. Radiology 2018;289(3):730–7.
56. Azadi J, Nguyen ML, Leroy A, et al. The emerging role of imaging in prostate cancer secondary screening: multiparametric magnetic resonance imaging and the incipient incorporation of molecular imaging. Br J Radiol 2018;91(1090):20170960.
57. Budaus L, Leyh-Bannurah SR, Salomon G, et al. Initial experience of (68)Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. Eur Urol 2016;69(3):393–6.
58. Gorin MA, Rowe SP, Patel HD, et al. Prostate Specific Membrane Antigen Targeted (18)F-DCFPyL Positron Emission Tomography/Computerized Tomography for the Preoperative Staging of High Risk Prostate Cancer: Results of a Prospective, Phase II, Single Center Study. J Urol 2018;199(1):126–32.
59. Rowe S, Gorin M, Pienta K, et al. Results from the OSPREY trial: A PrOspective Phase 2/3 Multi-Center Study of 18F-DCFPyL PET/CT Imaging in Patients with PRostate Cancer - Examination of Diagnostic AccuracY. J Nucl Med 2019;60(supplement 1):586.
60. Robertson GS, Johnson PR, Bolia A, et al. Long-term results of unilateral neck exploration for preoperatively localized nonfamilial parathyroid adenomas. Am J Surg 1996;172(4):311–4.
61. van Leeuwen PJ, Donswijk M, Nandurkar R, et al. Gallium-68-prostate-specific membrane antigen ((68)Ga-PSMA) positron emission tomography (PET)/computed tomography (CT) predicts complete biochemical response from radical prostatectomy and lymph node dissection in intermediate- and high-risk prostate cancer. BJU Int 2019;124(1):62–8.
62. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA):

a prospective, randomised, multicentre study. Lancet 2020;395(10231):1208–16.
63. Rowe SP, Macura KJ, Mena E, et al. PSMA-Based [(18)F]DCFPyL PET/CT is superior to conventional imaging for lesion detection in patients with metastatic prostate cancer. Mol Imaging Biol 2016;18(3):411–9.
64. Rowe SP, Campbell SP, Mana-Ay M, et al. Prospective Evaluation of PSMA-Targeted (18)F-DCFPyL PET/CT in Men with biochemical failure after radical prostatectomy for prostate cancer. J Nucl Med 2020;61(1):58–61.
65. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLE Phase 2 Randomized Clinical Trial. JAMA Oncol 2020;6(5):650–9.
66. Hope TA, Truillet C, Ehman EC, et al. 68Ga-PSMA-11 PET Imaging of response to androgen receptor inhibition: first human experience. J Nucl Med 2017;58(1):81–4.
67. Afshar-Oromieh A, Debus N, Uhrig M, et al. Impact of long-term androgen deprivation therapy on PSMA ligand PET/CT in patients with castration-sensitive prostate cancer. Eur J Nucl Med Mol Imaging 2018;45(12):2045–54.
68. Aggarwal R, Wei X, Kim W, et al. Heterogeneous flare in prostate-specific membrane antigen positron emission tomography tracer uptake with initiation of androgen pathway blockade in metastatic prostate cancer. Eur Urol Oncol 2018;1(1):78–82.
69. Fanti S, Hadaschik B, Herrmann K. Proposal for systemic-therapy response-assessment criteria at the time of PSMA PET/CT imaging: The PSMA PET progression criteria. J Nucl Med 2020;61(5):678–82.
70. Calais J, Ceci F, Eiber M, et al. 18)F-fluciclovine PET-CT and (68)Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 2019;20(9):1286–94.
71. Pernthaler B, Kulnik R, Gstettner C, et al. A prospective head-to-head comparison of 18F-Fluciclovine With 68Ga-PSMA-11 in biochemical recurrence of prostate cancer in PET/CT. Clin Nucl Med 2019;44(10):e566–73.
72. Hofman MS, Violet J, Hicks RJ, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19(6):825–33.