Review Article

# Positron emission tomography in prostate cancer: An update on state of the art

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## ABSTRACT

Prostate cancer (PCa), one of the most common cancers in males, is a topic of active interest in imaging research. Positron emission tomography/computed tomography (PET/CT) and PET/magnetic resonance imaging (PET/MRI) have enabled the combination of morphologic and functional imaging with the promise of providing better information in guiding therapy. $^{18}$F-fluorodeoxyglucose, the workhorse radiopharmaceutical in PET imaging, has not found preference in PCa since these tumors show poor glucose uptake and can be obscured by the normal urinary excretion of the radiotracer. Hence, the last two decades have seen the development of multiple newer radiotracers and better optimization of the technical aspects of PET imaging. The combination of functional imaging and MRI holds great promise. We searched PubMed, Scopus, and Google Scholar for peer-reviewed literature concerning the advances and newer developments in the imaging of PCa between the years 2005 and 2017. This review aims at summarizing current evidence on the role of PET imaging in PCa and its impact on the diagnosis, staging, prognostication, response assessment, and restaging of this malignancy.

## INTRODUCTION

Prostate cancer (PCa) is an active field in imaging research, and many modalities have been evaluated in the past few decades in the detection, characterization, and staging of PCa. Metabolic imaging with PET has been evaluated in its ability to outperform the conventional imaging modalities. With the advent of hybrid positron emission tomography/computed tomography (PET/CT) and PET/magnetic resonance imaging (PET/MRI), morphologic and functional imaging have been combined with the promise of providing better information in guiding therapy. A search was made in PubMed, Scopus, and Google Scholar for peer-reviewed literature concerning the above topic between the years 2005 and 2017. This review aims at summarizing the current evidence on PET imaging in PCa and its impact on the diagnosis, staging, prognostication, response assessment, and restaging of this malignancy.

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## SUMMARY OF RADIOTRACERS

PET using $^{18}$F-fluorodeoxyglucose (FDG), the workhorse radiopharmaceutical in PET, has not found preference in PCa since these tumors show poor glucose uptake. Often, there is significant overlap in the standardized uptake values (SUV) of the normal prostate gland, benign hyperplasia, scar tissue, and PCa.[1] Furthermore, the normal urinary excretion of the radiotracer may obscure pathologic uptake, which makes the detection and characterization of organ-confined disease and pelvic lymph nodes difficult. FDG PET was observed to least impact the clinical management of PCa as compared to other malignancies.[2] Currently, the limited role of FDG PET is in the workup of high-grade, castrate-resistant PCa.



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Even in this regard, it has been superceded by the newer, alternative radiotracers. Fatty acid oxidation, rather than glycolysis, is the dominant metabolic pathway in PCa. In addition, during cell membrane turnover, carbon and choline uptake are increased in PCa.[3] Hence, acetate and choline radiolabeled with $^{11}C$ or $^{18}F$ have been favored in PCa. These radiotracers also have little urinary excretion resulting in lesser obscuration of the prostatic bed. Of late, much attention has been on developing radiotracer ligands targeted at the prostate-specific membrane antigen (PSMA), a cell-surface protein whose expression is more specific to prostate than other tissues. The PSMA-ligand complex is readily internalized and released into the cytoplasm of PCa cells, which makes PSMA an attractive target for both diagnostic imaging and therapy. Other newer radiotracers being evaluated include synthetic amino acid analogs, bombesin analogs, and androgen receptor (AR) ligands. A detailed discussion of the above-mentioned radiotracers and their applications is given below.

## DIAGNOSIS, LOCALIZATION, AND T-STAGING OF PRIMARY PROSTATE CANCER

The current guidelines recommend systematic transrectal ultrasound (TRUS)-guided systematic biopsy in patients who present with high prostate-specific antigen (PSA) levels. Once histopathologic confirmation is obtained, risk stratification is done based on the digital rectal examination findings, PSA level, and Gleason score. Patients with intermediate- to high-risk PCa undergo metastatic workup including CT or MRI of the chest and abdomen as well as bone scintigraphy. In patients with high suspicion of PCa in whom histologic findings are negative, multiparametric MRI (mp-MRI) is an accurate and recommended imaging modality for the detection and localization of primary PCa. Beyond recommendations, there is strong evidence to support the routine usage of mp-MRI following the detection of high PSA values on screening. Biopsy of the MRI-visible lesion has been found to be a better alternative to systematic TRUS-guided biopsy.[4] MRI fares similar to sextant biopsy in intraprostatic localization of the cancer and is better for lesions of the prostate apex.[5] MRI is also the gold standard in the T-staging of primary PCa, the results being better with the utilization of an endorectal coil.[6]

None of the PET tracers are currently recommended for the primary staging and localization of PCa due to their low sensitivity and specificity.[7,8] Martorana *et al*. compared choline PET with sextant biopsy and concluded that the sensitivity for localization with PET/CT was reduced to 4% for nodules <5 mm as against 83% for larger nodules. Sensitivity for the assessment of extraprostatic extension was also lower than MRI.[9] Souvatzoglou *et al*. observed that the tumor configuration on histopathology influenced tumor detection and localization on choline PET with "rind-like" carcinomas being frequently missed. Furthermore, differentiation of PCa from benign hyperplasia and prostatitis based on $SUV_{max}$ values lacked specificity.[10,11] Choline PET may have a diagnostic role in the setting of high clinical suspicion and repeatedly negative biopsies.[7] Most studies show lack of significant correlation for tumor uptake on choline PET (as measured by $SUV_{max}$) with tumor aggressiveness, grade, proliferation indices, and PSA values.[12,13] $^{11}C$-acetate has also limited accuracy in the diagnosis, localization and prediction of aggressiveness in PCa.[14] In the local staging of PCa, detection of extracapsular extension, and seminal vesicle invasion, mp-MRI has consistently fared better than choline or acetate PET, which are known to understage the local extent of the tumor.[9] As such, PET is not recommended in making management decisions, especially with regard to performing nerve-sparing radical prostatectomy (RP).

## LYMPH NODE STAGING

Currently, pelvic lymph node dissection (PLND) is the gold standard for detection of nodal metastasis in patients with moderate- to high-risk PCa. Size and morphologic criteria used in conventional CT and MRI lack sensitivity in identifying metastasis, especially in normal caliber nodes. The detection rate has improved with the usage of diffusion-weighted imaging (DWI) and lymph node-specific contrast agents; however, significant overlap is frequent in the apparent diffusion coefficient values of normal and metastatic lymph nodes. Multiple studies have evaluated choline PET and observed moderate sensitivity and high specificity in detecting metastatic nodal disease, especially for nodes larger than 5 mm. In a systematic review of 10 studies involving 441 patients, Evangelista *et al*. observed a pooled sensitivity of 49% and specificity of 95%, with $^{11}C$-choline PET faring better than $^{18}F$-choline PET. Beheshti *et al*. observed that the majority of false-negative nodes were smaller than 5 mm, which highlights the high frequency with which micrometastases are missed.[15] Another study observed a detection rate of 0% for modal micrometastases (<2 mm) and 30% for nodes measuring 2–5 mm.[16] The same reason could also explain the lower performance of PET in detecting nodal metastasis in high-risk PCa as against intermediate-risk cancer.[17] Few studies which compared nodal detection with DWI and choline PET showed similar sensitivity for both modalities, but specificity was higher for choline PET.[18,19] Findings for $^{11}C$-acetate PET were similar to that of choline PET.[20,21] PET is not currently recommended for routine clinical use in nodal assessment irrespective of the risk category and is unlikely to replace PLND.[8]

## METASTATIC WORKUP

Conventionally, bone scan is used to detect and quantify the burden of metastasis in the skeleton, which is the most common site for extranodal metastasis in PCa. However, both $^{18}F$-choline PET and $^{18}F$-NaF PET, which reflect increased osteoblastic activity, have been more sensitive and

specific than bone scan and $^{18}$F-FDG PET in the detection of bony metastasis in primary cancer as well as biochemical recurrence. In addition, $^{18}$F-choline PET has better detection rate than bone scan for early bone metastases while they are still limited to the marrow.[22] In a series of 38 patients, both $^{18}$F-choline PET and $^{18}$F-NaF PET showed similar diagnostic performance; however, $^{18}$F-choline PET altered the management in two patients through early detection of metastasis.[23] Two other studies observed $^{18}$F-choline PET to be more sensitive than $^{18}$F-NaF PET.[24,25] Langsteger *et al*. observed that in patients with suspected biochemical recurrence, $^{18}$F-choline PET was more specific than $^{18}$F-NaF PET in the detection of metastasis.[26] These authors recommend $^{18}$F-choline PET for early detection of metastasis and $^{18}$F-NaF PET as a second agent in evaluating suspicious sclerotic $^{18}$F-choline PET-negative lesions.

## BIOCHEMICAL RECURRENCE

Biochemical recurrence precedes the clinical manifestations of disease recurrence. Early identification of local recurrence enables salvage surgery or radiation therapy (RT) and improves survival, whereas the presence of nodal or distant recurrence has guarded prognosis. "PSA only" relapse is defined as raised PSA values in the absence of conventional imaging evidence of local, nodal, or systemic recurrence. Choline PET has been extensively evaluated in the biochemical recurrence of PCa after RP or RT. $^{11}$C, $^{18}$F-choline PET and $^{11}$C-acetate PET have high diagnostic performance in restaging PCa in the event of biochemical recurrence.[27,28] Evangelista *et al*. noted pooled sensitivity and specificity of 85.6/92.6%, 75.4/82%, and 100/81.1% for recurrence in all sites, prostatic bed, and lymph nodes, respectively.[29] The performance is better with older age, advanced stage, higher grade of the tumor (as quantified by Gleason score), and higher PSA scores. Giovacchini *et al*. observed that the percentage of positive $^{11}$C-choline PET scans was 19% for PSA of 0.2–1 ng/mL, 46% for PSA of 1–3 ng/mL, and 82% for PSA of >3 ng/mL.[30] Similar observations were also made for $^{11}$C-choline PET and $^{11}$C-acetate PET.[31,32] Castelluci observed increased detection rate with increasing PSA velocity and decreasing PSA doubling time.[33] One study concluded higher performance for choline PET as against FDG PET in detecting recurrence; however, the correlation with Gleason score was better for FDG PET.[34]

Mp-MRI with endorectal coil fares better in the detection of prostatic bed recurrence, whereas choline PET is better in the detection of nodal and bony metastasis.[35,36] Hence, both MRI and PET have a complimentary role in detecting biochemical recurrence.[37,38] The demonstration of local or pelvic nodal disease in patients with biochemical recurrence can alter the management by increasing the field and dose of salvage RT. Multiple authors have reported the utility of choline PET in planning RT, and thereby enabling better locoregional control.[39,40]

## ASSESSMENT OF THERAPEUTIC RESPONSE

Many authors have confirmed the utility of both $^{11}$C and $^{18}$F-choline PET in predicting early therapeutic response to antiandrogen therapy.[41,42] The findings were concordant with a decline in PSA levels. According to De Giorgi *et al*., PET was the only predictor of progression-free survival and overall survival in metastatic castrate-resistant tumors treated with abiraterone whereas a decline in PSA did not.[43] Ceci *et al*. observed that an increase in PET uptake after docetaxel chemotherapy in castrate-resistant cancer indicated disease progression despite a decline in PSA values.[44]

## PROGNOSTICATION

PET has been found to be a useful marker of prognosis in patients with PCa. Kwee *et al*. noted that the measurement of overall metastatic burden using volumetric measurement of tumor metabolic activity on $^{18}$F-choline PET/CT can predict survival in castrate-resistant PCa.[45] Similar findings have been observed for $^{11}$C-choline PET and $^{11}$C-acetate PET.[46,47]

## PROSTATE-SPECIFIC MEMBRANE ANTIGEN POSITRON EMISSION TOMOGRAPHY: THE NEW PROMISE

PSMA is a cell surface protein whose expression is more specific to prostate than other tissues. Neoplastic transformation in prostate further increases the luminal surface expression of PSMA. The ratio of membranous and cytoplasmic PSMA increases with higher Gleason score and androgen resistance. Hence, PSMA expression shows a positive correlation with tumor aggressiveness, metastatic disease, and castrate resistance.[48] The PSMA-ligand complex is readily internalized and released into the cytoplasm of PCa cells, which makes PSMA an attractive target for both diagnostic imaging and therapy.

Active research has been undertaken in developing high-affinity, small-molecule ligands (inhibitors/antibodies) to PSMA. Antibodies are less preferred since they have long-circulating half-life with high nonspecific background activity. Till date, only one radiolabeled anti-PSMA antibody (ProstaScint® SPECT) has been approved by the FDA. PSMA inhibitors, on the other hand, have higher affinity, the maximum being for urea-based ligands. The most widely used PSMA ligand is the inhibitor HBED-CC, which forms a thermodynamically stable complex with $^{68}$Ga and shows high affinity for PCa with rapid clearance from nontarget tissues.

In local detection, PSMA PET is less accurate than mp-MRI but fares better than choline PET due to more specific uptake, especially in high-grade, clinically significant PCa. Utilization of hybrid PSMA PET/mp-MRI increases the diagnostic

confidence of suspicious lesions on MRI and potentially guides fusion biopsy better, especially in patients with previously negative biopsies where intratumoral hemorrhage could confound the mp-MRI findings [Figure 1]. PSMA has better sensitivity in picking up nodal as well as distant metastasis than choline or acetate PET [Figures 2 and 3].[49] Thus, the combination of mp-MRI with PSMA PET has the potential to serve as the single comprehensive staging modality in intermediate- to high-risk PCa. However, majority of the experience with PSMA PET has been in assessing tumor recurrence. Eiber *et al*. observed a detection rate of 89.5% for $^{68}$Ga-PSMA PET in a large series of 248 patients who underwent RP and had biochemical recurrence. The detection rate was highest for PSA levels >2 ng/mL and higher PSA velocity.[50] $^{68}$Ga-PSMA PET has been more sensitive than choline PET in the detection of local as well as distant recurrence in both post-RP and post-RT patients.[50,51] This is particularly true in the phase of early rise of PSA (0.5–1 ng/mL), where choline PET was rarely positive.[52]

Recently, $^{18}$F-radiolabeled DCFBC and DCFPyLis, two small-molecule high-affinity PSMA ligands, have been used in the evaluation of PCa. Utilization of $^{18}$F over $^{68}$Ga improves the image quality and provides higher tracer activity.[17] $^{18}$F-DCFPyLis has more accuracy than $^{68}$Ga-PSMA PET and is better for small PCa.[53] $^{18}$F-DCFPyLis has more rapid plasma clearance and attains a better tumor-to-background signal ratio than $^{18}$F-DCFBC PET.[54] In a study by Rowe *et al.,* $^{18}$F DCFBC was more specific in the detection of clinically relevant higher grade (Gleason score 8 and 9) and larger volume (>1 mL) lesions despite MRI having higher sensitivity for the detection of primary PCa. Thus, in future, $^{18}$F DCFBC may play an adjunct role to mp-MRI in the detection of clinically significant PCa.[55] $^{18}$F-DCFBC PET has also been found to be moderately sensitive, however the detection rate is dependent on the PSA levels.[56] A study comparing the new PSMA ligand $^{18}$F-DCFBC with $^{18}$F-NaF PET, showed lower sensitivity for $^{18}$F-DCFBC PET as well as a discordance in the pattern of tracer uptake. This has been attributed to the distinct mechanisms of uptake for the two tracers.[57] More recently, $^{68}$Ga-PSMA PET has been found to be useful in predicting early therapeutic response.[58] Of late, two ligands – PSMA-I and T and PSMA-DKFZ-617 – have been found to have high specificity for PCa and are being evaluated as theragnostic agents with applications in both diagnostic imaging ($^{68}$Ga) and radionuclide therapy ($^{177}$ Lu) of metastatic castrate-resistant PCa.[59]

## NEWER, ALTERNATIVE TRACERS

Since virtually all PCas are dependent on androgen and express receptors for it, attempt was made to do androgen receptor (AR) imaging using the radiolabeled AR ligand, $^{18}$F-FDHT. FDHT PET showed similar uptake and retention pattern as bone scan and FDG PET in a study which included metastatic PCa.[60] The observation of reduced uptake after antiandrogen therapy could promote its utilization in monitoring therapeutic response. Positive FDHT PET was associated with higher PSA levels and tumor burden.[61] Chen *et al*. noted overexpression of AR in castrate-resistant tumors, which suggests their continued role in tumor growth even after acquisition of androgen resistance.[62] Fox *et al*. suggested imaging to evaluate the activation of glycolysis pathway using FDG PET and androgen signaling pathway using FDHT PET in castrate-resistant tumors and classified them into "AR predominant," "glycolysis predominant," and "AR/glycolysis concordant" categories. Such evaluation was hypothesized to have prognostic and therapeutic implications.[63]

The increased amino acid turnover in PCa has also promoted the use of $^{18}$F-FACBC (also known as $^{18}$F-fluciclovine), a synthetic leucine analog. In one meta-analysis, $^{18}$F-FACBC had pooled sensitivity of 87% and specificity of 66% in the detection of PCa recurrence.[64] $^{18}$F-FACBC had lower detection rates of primary PCa than mp-MRI using endorectal

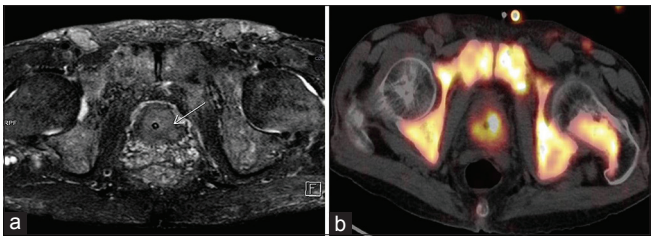


**Figure 1:** (a) Axial fat-saturated T2-weighted MR image shows hypointense nodular lesions (arrow) in the prostate base posteriorly on both sides of the midline. The pelvic bones and neck of left femur show heterogeneous signal consistent with metastasis. (b) Axial $^{68}$Ga-PSMA PET/CT image at the same level as the MRI shows marked tracer accumulation in the corresponding areas of the prostate gland, pelvic bones, and left femur

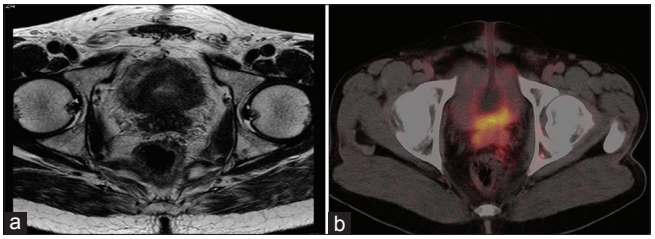


**Figure 2:** (a) Axial fat-saturated T2-weighted MR image shows hypointense prostate growth invading the bladder base as well as the seminal vesicles. (b) On axial $^{68}$Ga-PSMA PET/CT, there is significant tracer accumulation in the bladder base and seminal vesicles, confirmative of the involvement

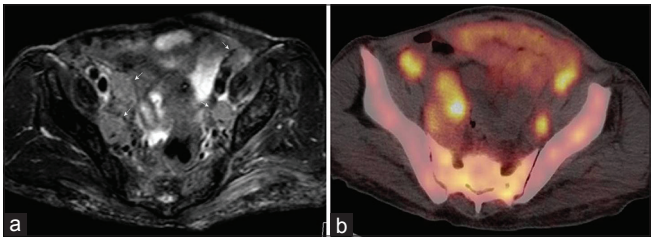


**Figure 3:** (a) Axial fat-saturated T2-weighted MR image shows multiple enlarged, homogeneously hyperintense internal and external iliac lymph nodes (arrows). (b) Axial $^{68}$Ga-PSMA PET/CT shows significant tracer accumulation in the enlarged pelvic lymph nodes

coil.[65] Lesser urinary excretion of $^{18}$F-FACBC could have advantages over choline PET, as demonstrated by Nanni *et al*. who observed better detection rates for $^{18}$F-FACBC PET over $^{11}$C choline PET at all PSA levels.[66] Among other amino acids, $^{11}$C-methionine and 5-HT PET have been explored to a lesser extent.[63] 5-HT PET uptake has been observed to be more common in high-grade PCa than low grade tumors.[67] Among nucleosides, a fluorothymidine analog, $^{18}$F-FMAU, has also been evaluated.[68]

Analogs of bombesin, which bind to gastrin-releasing peptide receptor (GRPR), have been radiolabeled with $^{68}$Ga, $^{64}$Cu, and $^{18}$F. Since GRPR expression is dense in PCa unlike benign pathologies, $^{68}$Ga-radiolabeled bombesin analogs (e.g., BAY86-7548) are extremely useful in the localization of primary PCa and metastatic lymph nodes.[69] Recently, $^{64}$Cu-uPAR PET has been introduced in PCa imaging.[70]

## POSITRON EMISSION TOMOGRAPHY/MAGNETIC RESONANCE IMAGING

PET/MRI compares the advantages of soft-tissue contrast resolution of MRI and the metabolic imaging of PET. Both modalities have similar performance in lesion detection in studies using $^{11}$C and $^{18}$F-choline as radiotracers. However, anatomic localization of lesions was better with PET/MRI, especially for pelvic and bone lesions.[71] The maximum and mean SUV values were different for the two modalities, likely due to difference in the techniques used for attenuation correction. $^{68}$Ga-PSMA PET/MRI has been observed to be better than mp-MRI or PET alone in lesion detection and localization. However, no correlation could be observed between quantitative PET/MRI parameters and Gleason score/PSA values.[72] Due to higher contrast resolution, PET/MRI was observed to be better at lesion characterization than PET/CT.[73] Lake *et al*. evaluated the optimal MRI sequences for $^{68}$Ga-PSMA PET/MRI and found that dynamic contrast imaging was better for the detection of prostatic bed lesions and small-field-of-view T2-weighted images were better for evaluating pelvic lymph nodes.[74] MRI, especially with the use of DWI, could increase the confidence in labeling PET-positive bone lesions as metastasis especially when sclerosis is not apparent on CT. However, PET/MRI is very much naive and has the drawbacks of cost, lengthier examination times, and the need to optimize MRI attenuation correction.[75]

## CURRENT RECOMMENDATIONS

Mp-MRI has an unsurpassed role in the initial diagnosis and local staging of PCa, and none of the PET radiotracers are currently recommended for this purpose. For patients with intermediate to high-risk PCa, the European Society for Medical Oncology (ESMO; 2015) and the National Comprehensive Cancer Network (NCCN; 2016) recommend $^{11}$C-choline PET for nodal and distant metastatic workup.[76,77] $^{11}$C-choline PET is also recommended in restaging patients with biochemical recurrence after therapy. NCCN recommends $^{18}$F-NaF PET rather than conventional bone scan for the detection of skeletal metastasis. None of the other radiotracers are currently recommended for routine use in PCa. Most of the urological societies – the American Urological Association or the European Association of Urology – do not have recommendations for PET in PCa and advise bone scan for metastatic workup in intermediate- to high-risk patients. A summary of the potential applications of various PET radiotracers and the current ESMO/NCCN guidelines on their usage is provided in Table 1.

## CONCLUSION

Metabolic imaging with PET/CT and PET/MRI is advancing with newer tracers being discovered and tested. Since

**Table 1: Summary of the currently available radiotracers, their functions, potential applications, and European Society for Medical Oncology/National Comprehensive Cancer Network practice recommendations in prostate cancer**

| Tracer | Function | Potential applications | Recommendations (ESMO/NCCN) |
|---|---|---|---|
| $^{11}$C-choline | Membrane synthesis | Nodal and metastatic workup, restaging, prognostication, treatment response | Recommended for nodal and metastatic staging |
| $^{18}$F-choline | | | None |
| $^{11}$C-acetate | Fatty acid oxidation | | |
| $^{18}$F-FDG | Glucose analog | Nodal and metastatic workup, prognostication, and treatment response in high-grade, castrate-resistant PCa | None |
| $^{68}$Ga-PSMA-HBED-CC | Membrane antigen | Adjunct to mp-MRI in diagnosis (in patients with clinically significant PCa and previous negative biopsies), nodal and distant metastatic workup, treatment response | |
| $^{18}$F-DCFPyLis | | | |
| $^{18}$F-DCFBC | | | |
| PSMA-I and T | | Theranostic staging ($^{68}$Ga) and radionuclide therapy ($^{177}$Lu) of metastatic castrate-resistant PCa | |
| PSMA-DKFZ-617 | | | |
| $^{18}$F-NaF | | Detection of bony metastasis in primary PCa and biochemical recurrence | |
| $^{18}$F-FDHT | Androgen receptor | Prognostication, treatment response of metastatic castrate-resistant PCa | |

NCCN=National Comprehensive Cancer Network, ESMO=European Society for Medical Oncology, $^{18}$F-FDG=$^{18}$F-fluorodeoxyglucose, PSMA=Prostate-specific membrane antigen, PCa=Prostate cancer, MRI=Magnetic resonance imaging

mp-MRI has the advantage of better contrast resolution, combining the metabolic data of PET with MRI holds great promise; however, sufficient evidence supporting its routine use is not available at present.

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