Review Article

Clinical implications of PET/CT in prostate cancer management

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Abstract: Several imaging modalities exist for the investigation of prostate cancer (PCa). From ultrasound to computed tomography (CT) and magnetic resonance imaging (MRI), the role of imaging in detecting lesion foci, staging, and localizing disease after biochemical recurrence (BCR) is expanding. However, many of the conventional imaging modalities are suboptimal, particularly in the detection of metastasis. Positron emission tomography (PET) has recently emerged as a promising tool in PCa management. The ability to develop radiolabeled tracers for functional imaging based on characteristics of PCa cells can potentially provide more insight into management by utilizing key features of those cells, such as metabolic activity, increased proliferation, and receptor expression. 18-flurodeoxyglucose (FDG) is one of the earliest tracers used in PET imaging that takes advantage of increased metabolism of glucose. Its role in PCa has been somewhat limited due to poor resolution and confounders including noise resulting from the proximity of the prostate to the bladder. Choline, a precursor molecule for a major component of the cell membrane, phosphatidylcholine, shows increased uptake in cells with rapid proliferation. When compared to metabolic based imaging techniques with FDG, choline PET/CT was superior. Nevertheless, choline PET/CT was not equivocal to MRI in detection of local disease, but was superior to conventional imaging in localizing metastasis and lymph node metastasis (LNM). Fluciclovine is another novel marker that utilizes the increased proliferation seen in tumor cells. Studies have shown it to be superior to choline PET/CT in PCa management, particularly in patients with BCR. As with choline PET/CT, studies that have assessed the impact of fluciclovine on clinical practice have highlighted the impact of these new tracers on clinical decision making. Most recently, the newest molecular probe targeting prostate specific membrane antigen (PSMA) was developed. It offers higher detection rates compared to choline PET/CT and conventional imaging modalities and has shown promise in LNM and BCR. With the wide range of available PET tracers, this review aims to highlight the role of each in lesion foci detection, primary staging, disease recurrence and explore the potential clinical impact.

Keywords: Prostate cancer (PCa); imaging; positron emission tomography (PET); computed tomography (CT)

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Introduction

Prostate cancer (PCa) is the most common solid neoplasm and third leading cause of death in men in the United States (1). Currently, imaging of the prostate is indicated for primary diagnosis, staging, and detection of biochemical recurrence (BCR) depending on the clinical stage of the disease. There exist several tools for evaluating clinical and pathological parameters, including prostate-specific antigen

(PSA), PSA doubling time, Gleason score, and lymph node invasion; however, all fall short of accurately localizing the site of disease. Moreover, given that about 50% of patients treated with radical prostatectomy (2) or external-beam radiotherapy (3) experience BCR, an effective tool needs to accurately capture and characterize the disease in these patients. Thus, there needs to be improved strategies for localizing disease foci within the prostate, accurately staging and capturing patients with metastasis, localization of new disease foci after BCR as well as monitoring treatment response based on tumor characteristics.

Current conventional imaging modalities, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), are all being used for many facets of PCa management, including diagnosis and localization, whole-gland and focal therapy, staging, active surveillance, and recurrence monitoring (4). Despite the move toward molecular diagnostics, our clinical imaging paradigms for diagnosing cancer and for monitoring cancer therapy have largely remained anatomically dependent rather than taking advantage of tumor cellular or molecular behavior. Transrectal US enables the quantification of the prostate size and demonstration of zonal anatomy, with malignant lesions typically appearing hypoechoic. While this modality has advantages including ease of use, lack of radiation, and relatively cheap cost, it does have major spatial resolution limitations making its utility in accurate malignant lesion detection and well as extra-capsular extension of the PCa and seminal vesicle invasion limited (5). CT is widely used for the diagnosis and follow-up of most other cancers; however, it has a limited role in PCa given its poor soft-tissue contrast resolution (6). Thus, in parallel with bone scans, the leading role of CT remains in detection of bony involvement and nodal staging, but again the clinician is challenged with this tools inability to differentiate whether lymph nodes are simply reactive or contain malignant deposits. MRI overcomes resolution limitations and provides information regarding prostatic architecture and anatomy and gives insights into potential malignant transformation via parameters such as diffusion restriction. It has better soft-tissue resolution which enables for more accurate staging and lesion detection. Despite so, this modality is very expensive and not ideal for real time imaging, with many benign lesions having signal patterns that mimic those of malignant ones (7).

There also exists a significant need in appropriately identifying and assessing patients with advanced PCa. These patients who have failed curative and androgen deprivation therapies often suffer from the inability of CT or MRI to correctly identify lesions below a threshold of 8–10 mm (8). Additionally, the utility of bone scans in metastasis is difficult given that malignant lytic bone lesions have scarce uptake and degenerative bone changes are often mistaken for spread of primary disease (9).

Many of the limitations presented regarding these modalities can be overcome by positron emission tomography (PET). PET is a functional imaging modality that utilizes intravenous injected radiolabeled tracers within the prostate that are then visualized using gamma cameras. The uses of PET imaging in medicine are evolving and it is commonly used in PCa for the staging, evaluation of BCR after radiotherapy, and metastatic involvement. Its value in the initial diagnosis of PCa however is limited (10). PET/CT is typically not considered useful in studies that do not stratify patients based on risk, but it does have some advantages. PET imaging critically highlights the metabolic, molecular, or cellular activity of prostate cells and is used in conjunction with anatomical imaging in the form of PET/MRI or PET/CT. For example, this can be particularly useful in lymph node metastasis (LNM) because PET/CT is able to highlight which nodes are metabolically active outside the standard active pelvic lymph node dissection. The utility of PET/CT can vary greatly depending on the different methods used for PET imaging and choice of radiolabeled tracers that can target different biological process such as cellular metabolism, proliferation, and receptor binding allow for different evaluations.

Recently, exciting techniques utilizing PET in combination with CT have emerged for not only PCa staging and assessment of metastatic involvement, but also diagnosis and treatment response. With the advent of nuclear tracers, PET allows for the ability to map changes in function and metabolism rather than anatomy only (11). And while it is relatively expensive, given its high sensitivity and specificity, it has been proven to be cost effective in the management of other cancers. Thus, the added functional component of PET in addition to CT has opened many avenues for the management of PCa. The goal of this review article is to discuss and evaluate the important evolving role of multimodality imaging in relation to PCa staging, recurrence and its clinical impact. The review is organized based on the choice of major PET imaging tracers used to image PCa based on tumor behavior. Subsections within a specific modality discuss the various imaging techniques involved. Emphasis is made not only on the imaging techniques but also on the biological and

functional characteristics of tumors that rationalize the use of these imaging methods.

Evidence acquisition

This search identified key articles using MEDLINE search of the English literature was conducted from inception to April 2018 using the following primary search strings: 'prostate cancer', 'imaging', 'positron emission tomography', 'PET', 'PET/CT'. Additional secondary strings included 'metabolic imaging', 'FDG', 'fluciclovine', 'choline', 'acetate', and 'PSMA'.

Metabolic activity-based PET imaging

18-flurodeoxyglucose (FDG)

Local detection and primary staging/recurrent disease

Cancer cells rewire their metabolic pathways to promote growth, proliferation and survival. A common feature to maintain this dynamic process is increased glucose metabolism and uptake to maximize energy production and allow for malignant cell turnover. This phenomenon is explained by the Warburg effect, which postulates that cancer cells will have increased glucose uptake to accommodate for rapid proliferation. This precisely serves as the foundation for FDG, a biologic analogue of glucose, that is taken up in cells with increased glucose consumption. Thus, cancer cells will be enhanced with FDG and can be functionally imaged using PET/CT. However, recent studies have found that FDG is not suitable for PCa given the relative proximity of the prostate to the bladder, which confounds the uptake reading (12,13). Furthermore, the weak glucose metabolism of PCa cells makes it difficult to appreciate tumor cells from benign tissue or inflammatory insults to the prostate such as prostatitis (14).

These disadvantages were highlighted by a study performed by Yang and his colleagues which showed that FDG uptake was positive in only 20% of malignant prostatic lesions and the remaining were benign (15). However, in LNM, FDG PET/CT may provide diagnostic value given its reported non-inferior ability to detect pelvic LNM. Chang *et al.* found FDG PET/CT to have a sensitivity, specificity, PPV, and NPV of 75%, 100%, 100%, and 67.7%, respectively, for detecting metastatic pelvic lymph nodes (16).

Clinical impact

Given the emergence of novel prostate specific radiotracers that will be discussed over the course of this review, which are more specific and sensitivity in both primary tumor detection, staging, recurrence, and treatment monitoring, FDG PET/CT appears to have little clinical implication and added value to conventional imaging techniques.

Increased proliferation-based PET imaging

^{11}C-choline and ^{18}F-fluorocholine (^{18}F-FCH)

^{11}C-choline, a precursor molecule for a major component of the cell membrane, phosphatidylcholine, has been the most extensively studied tracer for the detection of PCa. As tumor cells divide and proliferate, choline is actively incorporated into the new cell membranes (17). Likewise, choline analogues such as ^{18}F-FCH have been utilized in a similar fashion (18). When compared to metabolic based imaging techniques with FDG, both ^{11}C-choline and ^{18}F-FCH were superior (18). However, between the two choline-based tracers, there are advantages and limitations that make their utility cumbersome at times. ^{11}C-choline takes advantage of having a lower urinary excretion rate, which favors the analyses of the prostate bed, but is actively hindered by having a relatively short half-life ($t_{1/2}$ =20 min) compared to its choline counterpart, ^{18}F-FCH (19). Thus, procedures using ^{11}C-choline requires faster procedures that must be performed within the first minute after intravenous administration. In the absence of urinary activity, local relapse may be more easily diagnosed with radio-fluorinated compounds because of favorable tumor-to-background ratio. Nevertheless, given this, a disadvantage of ^{11}C-choline comes in high false negative results in bone metastases, which do not show a significant lesion-to-background ratio only until a few minutes after intravenous injection. Conversely, ^{18}F-FCH has a longer half-life making it possible to not only use it in PET centers without on-site cyclotron, but also overcomes the low urinary excretion limitation of ^{11}C-choline (20). ^{18}F-FCH allows for more delayed scans which improves the diagnostic capabilities of PET imaging in lymph node and skeletal involvement. For this review, both isotypes will be referred to as choline PET/CT imaging.

Local detection and primary staging

Most studies that have investigated the role of choline PET/CT for initial staging were performed in intermediate to high-risk patients. The limitations of choline-based PET/CT radiotracers in local detection of primary disease

have been well documented. For PCa nodules greater than 5 millimeters, choline PET/CT has a respectable sensitivity of 83%; however, in lesions that are smaller than this cutoff, sensitivity drops to an abysmal 4% (21). Moreover, this same study demonstrates that choline PET/CT did not have any role in extraprostatic extension detection, with a sensitivity of 22% compared to 63% for multiparametric MRI (mpMRI). These findings were confirmed in two other studies that also showed choline PET/CT to be inferior to mpMRI in terms of extraprostatic involvement (22,23). In semi-quantitative analysis using maximum standardized uptake value, choline PET/CT is unable to distinguish malignant from benign tissue (24). For nodal metastatic disease, the reported sensitivities of choline PET/CT has been varying. In one study, the sensitivity for choline PET/CT on primary staging was poor, with a high false-negative rate that was attributed to less than 5 millimeter spatial resolution (25,26). In larger studies, patients with high D'Amico risk PCa and larger LNM greater than 5 millimeters, sensitivity of LNM was 45% and specificity of 96%, with ^{18}F-FCH, which was superior to CT scans (27). Despite so, the results were unclear as to benefits over diffusion weighted MRI (DWIMRI). Pinaquy *et al.* showed a clear advantage of using choline PET/CT over MRI, with a sensitivity of 56% compared to 17% for DWIMRI, but the authors did admit that despite its excellent performance that it cannot replace MRI (22).

Bone involvement at initial diagnosis is uncommon, but is dependent on numerous biochemical and pathological variables (28). While the advantages of choline PET/CT in restaging are well documented, the same does not always apply in initial staging. For the detection of bony involvement, choline PET/CT has been shown to be effective and accurate with data suggesting superiority over conventional imaging techniques, especially 99m Tc-MDP bone scintigraphy. In a study by Beheshti *et al.*, which included only patients at initial staging that were intermediate to high risk, bone metastasis was detected in 10% of the 132-patient cohort with a mean PSA of 27 ng/mL, noting that it may always be useful preoperatively to exclude distant metastasis (27). Numerous other studies have also shown choline PET/CT to be consistently superior to bone scans in the detection of bone metastases (29,30); however, another study noted it to be inferior to 18F-NaF (31).

Recurrent disease

The limitations of choline PET/CT to detect local lesions extends to detection of local relapsing lesions. This modality is only able to capture 54–73% of lesions upon BCR (32-34). Compared to mpMRI, choline PET/CT was inferior, with mpMRI able to detect local recurrence in 36.1% compared to 1.6% with choline PET/CT (34). However, in detection of LNM, choline PET/CT was superior, while both modalities performed excellent in pelvic bone metastasis. In another study by Reske *et al.*, focal increase in ^{11}C-choline uptake reliably predicted relapse after radical prostatectomy, properly identifying 71% of patients (34). Choline PET/CT was shown to detect LNM and distant lesions with a pooled sensitivity of 61% and specificity of 97% in a recent comprehensive meta-analysis of 29 studies whereby all studies had a high degree of consistency (35). Compared to FDG-PET, choline PET was consistency more accurate, with diagnostic yield incrementally increasing with PSA values greater than 1.9 ng/mL, despite FDG having better correlation with Gleason score (36). In another comparative study, choline PET/CT was superior to FDG-PET, detecting 47% of patients with abnormal focal disease compared to 27% (18). This study also showed that ^{11}C-choline PET/CT picked up additional anatomical sites with pathological uptake, i.e., pelvis, retroperitoneal lymph nodes, prostate bed, and bones.

An early study in 2008 assessing the correlation of PSA with choline PET/CT in BCR by Krause *et al.* reported a dose-dependent relationship between the two with positive detection rate of 36% for PSA less than 1 ng/mL, 43% for PSA between 1 and 2 ng/mL and 62% for PSA between 2 and 3 ng/mL (37). Years later, Giovacchini *et al.* demonstrated in a study with over triple the sample size that choline PET/CT had a detection rate of 45%, with PSA being the most single positive predictor of a positive choline PET scan (38).

Clinical impact

While demonstrating a technique to be accurate does not always change clinical management, a few studies have attempted to evaluate the clinical impact of adopting choline PET/CT in everyday practice and generally have similar conclusions regarding its utility. Overall, studies agree that the use of choline PET/CT is beneficial for patient management; however, there exists confounders including the baseline for assessing change and the discrepancies in criteria classifications. At Zurich University Hospital, Soyka *et al.* designed a retrospective study of 156 patients with a mean Gleason score of 6.9 at diagnosis that received their initial treatment with radical prostatectomy (110 patients), radiotherapy (39 patients), or combined prostatectomy

and radiotherapy (7 patients) (39). Questionnaires for each choline PET/CT examination were sent to the referring physician 14 to 64 months after imaging. The referring physician was asked to make a therapeutic plan based on results from ^{18}F-FCH and then report what they would have done had they not had this information. The group demonstrated that treatment plan was changed in 48% of patients due to findings obtained after ^{18}F-FCH. Of these patients, 22% were changed from palliative support to intent for curative treatment and 11% from curative to palliative. In 5%, treatment plan was changed to another strategy and 17 patients remained on the current treatment plan. A major limitation however was the retrospective design by nature and that no comparisons to other imaging modalities were made.

Another retrospective study investigated the clinical impact of choline PET/CT on treatment management in 150 patients with recurrent PCa after radical therapy (40). The intended treatment before ^{11}C-choline PET/CT was salvage radiotherapy of the prostatic bed in 63% of patients and palliative androgen deprivation therapy in remaining 37%. The group found change in therapy in 47% of patients, with 18% having major clinical impact. Again, this study was retrospective and did not compare PET/CT with other modalities. Results from both these studies indicate that larger, prospective studies may be warranted.

Fluciclovine (^{18}F-FACBC)

1-amino-3-fluorine ^{18}F-flurocyclobutane-1-carboxylic acid/fluciclovine, fluciclovine, is a synthetic diagnostic amino acid analogue that also takes advantage of prostate adenocarcinoma cell's amino acid transport system and increased energy demand. It differs from choline in that kidney uptake of fluciclovine is negligible and has no activity in the urinary tract. It also has low brain uptake compared to FDG, which is advantageous in brain metastasis identification. Like ^{18}F-FCH, fluciclovine has a long half-life eliminating the need for an onsite cyclotron.

Local detection and primary staging

One major limitation of fluciclovine is its non-specific uptake, often making it difficult to differentiate from benign prostatic inflammation. Thus, fluciclovine PET/CT performs poorly in primary PCa detection, having sensitivity and specificity inferior to mpMRI, rendering it an insufficient modality for initial local tumor detection (41). This study by Turkbey *et al.* also mentioned that fluciclovine PET/CT uptake was similar in patients with BPH, making it non-specific for PCa. In a multisite study assessing the efficacy and safety of fluciclovine PET/CT to assess diagnostic performance, the detection rate was 67.7% with 38.7% at the prostate bed level and 32.6% in the pelvic lymph nodes (42). The ability to detect metastatic involvement outside of the pelvis was 26.2% with an overall detection rate of 41.4% in the lowest quartile of patients with higher rates as PSA increases.

Recurrent disease

Fluciclovine PET/CT has proven efficacy in detection of recurrent PCa in patients with BCR. In 93 patients with BCR enrolled in a prospective clinical trial, Schuster *et al.* found a sensitivity of 90.2% and specificity of 40%, respectively, while recurrence in the prostatic fossa had a slightly lower sensitivity. Specificity in nodal disease was 55% and 96.7% in distal metastasis (43). Detection rates with this modality exceeded that of receptor targeted imaging PET (43,44), which will be discussed later in this review. Another group found that fluciclovine PET/CT was superior and possibly an alternative to choline PET/CT in the setting of BCR given its lower false negative and false positive rates (45). A prospective trial confirmed these results, demonstrating that the main benefits of fluciclovine PET/CT are related to technical and practical advantages over choline PET/CT, primarily its lower background activity in the abdomen and pelvis as well as longer half-life (46).

Clinical impact

Like choline PET/CT, fluciclovine PET/CT changed treatment management in 40% of patients (45). Given this impact, in 2016 the United States Food and Drug Administration approved fluciclovine PET tracers to be used for the detection of PCa in the setting of BCR. Given the limited studies assessing the clinical impact of this tracer due to its recent approval, it is widely believed that given its efficacy at lower PSA thresholds that it will in fact have a bigger impact clinically moving forward.

Receptor targeted PET imaging

Prostate specific membrane antigen (PSMA)

Over 90% of PCa overexpress PSMA, which can be actively targeted by ^{68}Ga-PSMA PET/CT imaging. PSMA is a transmembrane glycoprotein found on the prostatic epithelium. Dysplastic transformation of prostate tissue

causes the transfer of PSMA from the apical to luminal membrane surface of the gland ducts (47). As proliferation of tumor cells increases, the ratio of PSMA to the truncated form, PSM', increases in favor of PSMA and this ratio has been positively associated tumor aggressiveness markers such as Gleason score (48). The overexpression of PSMA in PCa makes it an interesting target for molecular imaging, with normal tissue having almost no expression of this molecule further enhancing delineation between malignant and healthy tissue (42,47,49).

The active binding sites of PSMA have been extensively investigated (50). It has been recently found that urea-based ligands have a high affinity and specificity for androgen sensitive prostate adenocarcinoma cells making them an ideal radiotracer for PCa cell detection (51). The PSMA-ligand complex is also rapidly internalized after binding via clathrin coated pits and endosome accumulation, which leads to enhanced retention—a feature that is important for both image quality and therapeutic efficacy (52). Additionally, their relatively rapid clearance makes them ideal agents for PSMA targeting and PCa localization (51).

Local detection and primary staging

^{68}Ga-PSMA PET/CT has been investigated for its potential in staging of primary PCa. ^{68}Ga-PSMA PET/CT has been shown to be superior to standard imaging modalities, such as CT (53), with studies showing higher rates of detection compared to CT alone, especially in detection of metastatic disease (54). Compared of the standard method of intra-prostatic tumor localization, PSMA-PET/CT appears to be highly correlated with mpMRI in terms of tumor allocation in patients with a high pre-test probability for large tumors (55). In studies comparing the two modalities head to head, ^{68}Ga-PSMA-11 PET/CT appears to be superior. The sensitivities and specificities for mpMRI were 58% and 82%, respectively while in ^{68}Ga-PSMA-11 PET/CT they were 64% and 94% (56). Perhaps the greatest evidence highlighting the potential role of ^{68}Ga-PSMA PET/CT in primary staging was an Australian prospective multicenter study whereby scans of 431 patients with PCa from four centers had pre- and post-^{68}Ga-PSMA management plans completed (57). The study found that in these patient ^{68}Ga-PSMA PET/CT revealed unsuspected disease in the prostate of 27% of patients exemplifying the ability of ^{68}Ga-PSMA PET/CT to detect previously unsuspected disease and changed management of patients imaged with this technique.

However, a major limitation to this modality revolves around the fact that up to 10% of PCa do not overexpress PSMA (58); thus, in those PSMA-negative patients, ^{68}Ga-PSMA PET/CT is ineffective. With this consideration, ^{68}Ga-PSMA PET/CT outperformed traditional staging via conventional imaging modalities (59), with the ability to detect benign prostatic epithelium and primary cancer in all cases and lymph node metastases in 98% of cases (60). While PSMA expression is less in bony tissue compared to that of prostate and lymph, skeletal involvement was still superior to conventional imaging modalities (59). Another added benefit of ^{68}Ga-PSMA-11 PET/CT is its ability to detect distal soft tissue metastasis including brain and visceral lesions, which are often missed (61).

The ability of ^{68}Ga-PSMA PET/CT to localized prostate lesions and surrounding tissue at initial diagnosis was further evaluated in a study by Fendler *et al.* (62). In a cohort of 21 patients, PSMA scanning had a sensitivity of 67%, a specificity of 92%, an accuracy of 72%, a PPV of 97% and an NPV of 42%, all of which were significantly higher than mpMRI (62). The ability of PSMA PET/CT to detect LNM is still under investigation, but Budäus and his group have shown in a cohort of 30 patients that LNM detection is relatively poor with 33.3% sensitivity; however, this was a retrospective study with low incidence of LNM (8.7%) (63). Conversely, optimal sensitivity and specificity was observed in a study by Maurer *et al.* in which 130 patients were assessed for the presence of LNM where the sensitivity, specificity and accuracy of PSMA PET was 65.9%, 98.9% and 88.5%, and those of morphological imaging were 43.9%, 85.4% and 72.3%, respectively (58). van Leeuwen's group confirmed these results in a cohort of 30 moderate to high-risk PCa patients which showed that PSMA PET/CT had a sensitivity of 64%, specificity was 95%, the PPV was 88%, and the NPV was 82% (64). In an LN region-based analysis, the sensitivity was 56%, specificity was 98%, PPV was 90% and NPV was 94%, while the reported mean size of missed LNMs was 2.7 mm. The size of the LNM appeared to be an important determinant of PET positivity, with high sensitivities ranging between 66–88% were reported with increasing LNM size (53). Overall, ^{68}Ga-PSMA-11 PET/CT was consistently found to outperform MRI and CT for primary tumor localization and LNM detection.

Recurrent disease

^{68}Ga-PSMA PET/CT can effectively detect recurrence of PCa with excellent sensitivity. To obtain the best chance of cure in BCR, detection must happen at an optimal time when

PSA is low, signifying low level of cancer burden. In a cohort with mean PSA under 2 ng/mL, Afshar-Oromieh *et al.* found the sensitivity and specificity of ^{68}Ga-PSMA PET/CT in recurrence to be 76.6% and 100%, respectively in 319 patients, the largest study of patients with recurrent disease (65). In another large cohort of 248 patients with recurrent PCa with BCR, ^{68}Ga-PSMA PET/CT has a positivity rate of 89.5% with rates increasing at PSA levels between 1.0 and 2.0 ng/mL compared to 0.5 to 1.0 ng/mL (66). Moreover, the group observed that PSA at the time of the scan and PSA doubling time were associated with an increased probability of a positive PSMA PET/CT result. These results were confirmed in a meta-analysis, which reported detection rate of 76% in BCR and an improving detection rates with as PSA increased (67).

In comparison to choline PET/CT, which holds low sensitivity in patients with low PSA levels (68), ^{68}Ga-PSMA PET/CT outperformed its proliferation-based imaging counterpart (69). In another cohort of 131 PCa patients with a median PSA of 2.2 ng/mL, overall detection rate was 75% for PSMA PET/CT (70), which was higher than choline PET/CT. These results were in concordance with a study by Pfister *et al.*, who observed a sensitivity and specificity for PSMA, 87% and 93%, respectively, as compared to choline PET/CT which was 71% and 87% repetitively (71). Overall, the evidence available strongly supports the use of ^{68}Ga-PSMA-11 PET/CT for recurrence staging.

Clinical impact

While PSMA PET is still novel, a study by Roach *et al.* assessed the feasibility of this modality and its impact in a clinical setting. They utilized ^{68}Ga-PSMA-11 PET/CT in radiotherapy planning in a group of patients with either primary or recurrent PCa and found that ^{68}Ga-PSMA PET/CT resulted in a changing of planned management in 51% of patients which the greatest impact in the group with BCR. These findings were confirmed by Sterzing's group who also observed a change in management in 50.8% of patients after receiving ^{68}Ga-PSMA-11 PET/CT scans (72).

Conclusions

The field of PCa management is at a very exciting cross-road between improvements in imaging techniques and molecular tracers. PET/CT imaging proposes itself as an enticing modality for the investigation of PCa in disease detection, stating, and recurrence. The development of new radiolabeled tracers is rapid, however, PSMA based PET imaging has already proven to be superior to both choline and FDG based PET. While there is great enthusiasm surrounding PET imaging, there still needs to be more prospective trials to confirm these promising results. Ideally, well designed, homogenous studies are required to give the most accurate sensitivities and specificities as well as meaningful detection rates. In this context, this review attempts to provide a wide scope of research to be thorough and comprehensive regarding the work that has been reported by the scientific community. Although there remains much to be explored, PET/CT with different radiotracers provides a compelling and promising modality that will improve the field of PCa management.

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Footnote

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Briganti A, Karnes RJ, Gandaglia G, et al. Natural history of surgically treated high-risk prostate cancer. Urol Oncol 2015;33:163.e7-13.
3. Freedland SJ, Presti JC Jr, Amling CL, et al. Time trends in biochemical recurrence after radical prostatectomy: results of the SEARCH database. Urology 2003;61:736-41.
4. Beresford MJ, Gillatt D, Benson RJ, et al. A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. Clin Oncol (R Coll Radiol) 2010;22:46-55.
5. Hricak H, Choyke PL, Eberhardt SC, et al. Imaging prostate cancer: a multidisciplinary perspective. Radiology 2007;243:28-53.

6. Zarzour JG, Galgano S, McConathy J, et al. Lymph node imaging in initial staging of prostate cancer: An overview and update. World J Radiol 2017;9:389-99.
7. Sosnowski R, Zagrodzka M, Borkowski T. The limitations of multiparametric magnetic resonance imaging also must be borne in mind. Cent European J Urol 2016;69:22-3.
8. Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol 2008;63:387-95.
9. Horiuchi K, Saji H, Yokoyama A. Tc(V)-DMS tumor localization mechanism: a pH-sensitive Tc(V)-DMS-enhanced target/nontarget ratio by glucose-mediated acidosis. Nucl Med Biol 1998;25:549-55.
10. Sarkar S, Das S. A Review of Imaging Methods for Prostate Cancer Detection. Biomed Eng Comput Biol 2016;7:1-15.
11. Cook GJ, Fogelman I. The role of positron emission tomography in the management of bone metastases. Cancer 2000;88:2927-33.
12. Morris MJ, Akhurst T, Osman I, et al. Fluorinated deoxyglucose positron emission tomography imaging in progressive metastatic prostate cancer. Urology 2002;59:913-8.
13. Sanz G, Robles JE, Gimenez M, et al. Positron emission tomography with 18fluorine-labelled deoxyglucose: utility in localized and advanced prostate cancer. BJU Int 1999;84:1028-31.
14. Jadvar H. Prostate cancer: PET with 18F-FDG, 18F- or 11C-acetate, and 18F- or 11C-choline. J Nucl Med 2011;52:81-9.
15. Yang Z, Hu S, Cheng J, et al. Prevalence and risk of cancer of incidental uptake in prostate identified by fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography. Clin Imaging 2014;38:470-4.
16. Chang CH, Wu HC, Tsai JJ, et al. Detecting metastatic pelvic lymph nodes by 18F-2-deoxyglucose positron emission tomography in patients with prostate-specific antigen relapse after treatment for localized prostate cancer. Urol Int 2003;70:311-5.
17. Yoshimoto M, Waki A, Yonekura Y, et al. Characterization of acetate metabolism in tumor cells in relation to cell proliferation: acetate metabolism in tumor cells. Nucl Med Biol 2001;28:117-22.
18. Picchio M, Messa C, Landoni C, et al. Value of [11C]choline-positron emission tomography for re-staging prostate cancer: a comparison with [18F] fluorodeoxyglucose-positron emission tomography. J Urol 2003;169:1337-40.
19. Cuccurullo V, Di Stasio GD, Evangelista L, et al. Biochemical and Pathophysiological Premises to Positron Emission Tomography With Choline Radiotracers. J Cell Physiol 2017;232:270-5.
20. Calabria F, Gallo G, Schillaci O, et al. Bio-Distribution, Imaging Protocols and Diagnostic Accuracy of PET with Tracers of Lipogenesis in Imaging Prostate Cancer: a Comparison between 11C-Choline, 18FFluoroethylcholine and 18F-Methylcholine. Curr Pharm Des 2015;21:4738-47.
21. Martorana G, Schiavina R, Corti B, et al. 11C-choline positron emission tomography/computerized tomography for tumor localization of primary prostate cancer in comparison with 12-core biopsy. J Urol 2006;176:954-60; discussion 960.
22. Pinaquy JB, De Clermont-Galleran H, Pasticier G, et al. Comparative effectiveness of [(18) F]-fluorocholine PET-CT and pelvic MRI with diffusion-weighted imaging for staging in patients with high-risk prostate cancer. Prostate 2015;75:323-31.
23. Watanabe H, Kanematsu M, Kondo H, et al. Preoperative detection of prostate cancer: a comparison with 11C-choline PET, 18F-fluorodeoxyglucose PET and MR imaging. J Magn Reson Imaging 2010;31:1151-6.
24. Bundschuh RA, Wendl CM, Weirich G, et al. Tumour volume delineation in prostate cancer assessed by [11C] choline PET/CT: validation with surgical specimens. Eur J Nucl Med Mol Imaging 2013;40:824-31.
25. Hacker A, Jeschke S, Leeb K, et al. Detection of pelvic lymph node metastases in patients with clinically localized prostate cancer: comparison of [18F]fluorocholine positron emission tomography-computerized tomography and laparoscopic radioisotope guided sentinel lymph node dissection. J Urol 2006;176:2014-8; discussion 2018-9.
26. Husarik DB, Miralbell R, Dubs M, et al. Evaluation of [(18) F]-choline PET/CT for staging and restaging of prostate cancer. Eur J Nucl Med Mol Imaging 2008;35:253-63.
27. Beheshti M, Imamovic L, Broinger G, et al. 18F choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. Radiology 2010;254:925-33.
28. Vali R, Loidl W, Pirich C, et al. Imaging of prostate cancer with PET/CT using (18)F-Fluorocholine. Am J Nucl Med Mol Imaging 2015;5:96-108.
29. Evangelista L, Cimitan M, Zattoni F, et al. Comparison between conventional imaging (abdominal-pelvic

computed tomography and bone scan) and [(18)F] choline positron emission tomography/computed tomography imaging for the initial staging of patients with intermediate- tohigh-risk prostate cancer: A retrospective analysis. Scand J Urol 2015;49:345-53.
30. Picchio M, Spinapolice EG, Fallanca F, et al. [11C] Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Med Mol Imaging 2012;39:13-26.
31. Kjolhede H, Ahlgren G, Almquist H, et al. Combined 18F-fluorocholine and 18F-fluoride positron emission tomography/computed tomography imaging for staging of high-risk prostate cancer. BJU Int 2012;110:1501-6.
32. Bertagna F, Abuhilal M, Bosio G, et al. Role of (1)(1) C-choline positron emission tomography/computed tomography in evaluating patients affected by prostate cancer with suspected relapse due to prostate-specific antigen elevation. Jpn J Radiol 2011;29:394-404.
33. Kitajima K, Murphy RC, Nathan MA, et al. Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. J Nucl Med 2014;55:223-32.
34. Reske SN, Blumstein NM, Glatting G. [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging 2008;35:9-17.
35. Fanti S, Minozzi S, Castellucci P, et al. PET/CT with (11)C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. Eur J Nucl Med Mol Imaging 2016;43:55-69.
36. Richter JA, Rodriguez M, Rioja J, et al. Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Mol Imaging Biol 2010;12:210-7.
37. Krause BJ, Souvatzoglou M, Tuncel M, et al. The detection rate of [11C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Eur J Nucl Med Mol Imaging 2008;35:18-23.
38. Giovacchini G, Picchio M, Coradeschi E, et al. Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 2010;37:301-9.
39. Soyka JD, Muster MA, Schmid DT, et al. Clinical impact of 18F-choline PET/CT in patients with recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2012;39:936-43.
40. Ceci F, Herrmann K, Castellucci P, et al. Impact of 11C-choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. Eur J Nucl Med Mol Imaging 2014;41:2222-31.
41. 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;270:849-56.
42. 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;197:676-83.
43. 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;191:1446-53.
44. 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;43:1773-83.
45. Nanni C, Zanoni L, Pultrone C, et al. (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging 2016;43:1601-10.
46. Wondergem M, van der Zant FM, van der Ploeg T, et al. A literature review of 18F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. Nucl Med Commun 2013;34:935-45.
47. Tuzel E, Mungan MU, Yorukoglu K, et al. Primary renal lymphoma of mucosa-associated lymphoid tissue. Urology 2003;61:463.
48. Perner S, Hofer MD, Kim R, et al. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Pathol 2007;38:696-701.
49. Silver DA, Pellicer I, Fair WR, et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res 1997;3:81-5.
50. Wang H, Byun Y, Barinka C, et al. Bioisosterism of urea-

based GCPII inhibitors: Synthesis and structure-activity relationship studies. Bioorg Med Chem Lett 2010;20:392-7.
51. Eder M, Schafer M, Bauder-Wust U, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem 2012;23:688-97.
52. Rajasekaran SA, Anilkumar G, Oshima E, et al. A novel cytoplasmic tail MXXXL motif mediates the internalization of prostate-specific membrane antigen. Mol Biol Cell 2003;14:4835-45.
53. Herlemann A, Wenter V, Kretschmer A, et al. (68)Ga-PSMA Positron Emission Tomography/Computed Tomography Provides Accurate Staging of Lymph Node Regions Prior to Lymph Node Dissection in Patients with Prostate Cancer. Eur Urol 2016;70:553-7.
54. Bailey J, Piert M. Performance of (68)Ga-PSMA PET/CT for Prostate Cancer Management at Initial Staging and Time of Biochemical Recurrence. Curr Urol Rep 2017;18:84.
55. Giesel FL, Sterzing F, Schlemmer HP, et al. Intra-individual comparison of (68)Ga-PSMA-11-PET/CT and multi-parametric MR for imaging of primary prostate cancer. Eur J Nucl Med Mol Imaging 2016;43:1400-6.
56. 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;70:829-36.
57. Roach PJ, Francis R, Emmett L, et al. The Impact of (68) Ga-PSMA PET/CT on Management Intent in Prostate Cancer: Results of an Australian Prospective Multicenter Study. J Nucl Med 2018;59:82-8.
58. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. J Urol 2016;195:1436-43.
59. Kabasakal L, Demirci E, Ocak M, et al. Evaluation of PSMA PET/CT imaging using a 68Ga-HBED-CC ligand in patients with prostate cancer and the value of early pelvic imaging. Nucl Med Commun 2015;36:582-7.
60. Sweat SD, Pacelli A, Murphy GP, et al. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. Urology 1998;52:637-40.
61. Chakraborty PS, Kumar R, Tripathi M, et al. Detection of brain metastasis with 68Ga-labeled PSMA ligand PET/CT: a novel radiotracer for imaging of prostate carcinoma. Clin Nucl Med 2015;40:328-9.
62. Fendler WP, Schmidt DF, Wenter V, et al. 68Ga-PSMA PET/CT Detects the Location and Extent of Primary Prostate Cancer. J Nucl Med 2016;57:1720-5.
63. Budäus 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;69:393-6.
64. van Leeuwen PJ, Emmett L, Ho B, et al. Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. BJU Int 2017;119:209-15.
65. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42:197-209.
66. Ceci F, Uprimny C, Nilica B, et al. (68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? Eur J Nucl Med Mol Imaging 2015;42:1284-94.
67. 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;70:926-37.
68. Castellucci P, Ceci F, Graziani T, et al. Early biochemical relapse after radical prostatectomy: which prostate cancer patients may benefit from a restaging 11C-Choline PET/CT scan before salvage radiation therapy? J Nucl Med 2014;55:1424-9.
69. Morigi JJ, Stricker PD, van Leeuwen PJ, et al. Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. J Nucl Med 2015;56:1185-90.
70. Albisinni S, Artigas C, Aoun F, et al. Clinical impact of (68) Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer with rising prostate-specific antigen after treatment with curative intent: preliminary analysis of a multidisciplinary approach. BJU Int 2017;120:197-203.

71. Pfister D, Porres D, Heidenreich A, et al. Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with (68)Ga-PSMA-HBED-CC than with (18)F-Fluoroethylcholine PET/CT. Eur J Nucl Med Mol Imaging 2016;43:1410-7.

72. Sterzing F, Kratochwil C, Fiedler H, et al. (68)Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. Eur J Nucl Med Mol Imaging 2016;43:34-41.

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