Review Article

Biological principles and clinical application of positron emission tomography-tracers in prostate cancer: a review

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A B S T R A C T

Prostate carcinoma is the most common malignancy in men and the second cause of death by cancer in the western world. Currently, prostate carcinoma's diagnosis is achieved by transrectal ultrasound-guided biopsy (gold-standard), usually requested after an elevation of prostate specific antigen (PSA) levels or an abnormal digital rectal exam or transrectal ultrasound. Nevertheless, this diagnosis sequence sometimes presents with significant limitations. Therefore, there is a need of a diagnosis modality that improves the tumor detection rates and that offers information for its accurate staging, allowing the treatment's planning and administration. Molecular imaging by the means of positron emission tomography uses radiopharmaceuticals labeled with positron-emitting radioisotopes to detect metabolic changes that might be suggestive of cancer tissue. Recently, this technique has suffered a huge dynamic development, and researchers have been working on novel radiotracers agents to improve accuracy in targeting and detecting prostate tumors. On this review, it is highlighted that the most promising positron emission tomography-tracers that will, in a near future, not only improve diagnostic abilities for prostate carcinoma but also open new possibilities for theranostic approaches to treat this malignancy at a world level.

1. Introduction

Positron emission tomography (PET) is a highly regarded image technique that uses a vast number of radiopharmaceuticals marked with radioactive isotopes, capable of detecting molecular alterations suggestive of tumor tissues, and it can be addressed to a variety of molecular targets such as glycose metabolism, fatty acids metabolism, amino acids metabolism, prostate-specific membrane antigen (PSMA), androgens receptors, and osteoblastic bone activity.

Currently, the biomarker 2-deoxy-2-^{18}F-FDG-PET is the most widely used in molecular imaging; however, it presents with various limitations regarding prostate cancer. According to these, new markers have been studied to potentiate the efficacy of this imaging method, for diagnosis and staging of prostate cancer, namely in the evaluation of the tumor extension (confined to the prostate gland, lymph node disease, and distance metastasis). As a noninvasive and full body exam, with huge potential to evaluate the tumor burden, evaluate the therapeutic response, and characterize the disease activity, PET will allow the development of personalized therapeutic strategies aiming the maximum benefit of the patient, while decreasing the side-effects and associated morbidity.

2. Methods

For this review, an extensive literature research was held using mainly the PubMED, ScienceDirect, and ResearchGate. The publications were selected by the relevance of its content, and the most recent studies were given preference. The guidelines of the European Association of Urology were also reviewed at www.uroweb.org, for evaluation of the current methods for diagnosis and staging of prostate carcinoma.

3. Results

3.1. Prostate-specific membrane antigen positron emission tomography/CT

(1) Biological principles

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In the last few years, the PSMA has been a target of interest in imaging diagnosis and therapeutic matters. As a transmembrane receptor, it has an internal domain, which function is still unclear, and an external domain with enzymatic functions, acting as the main target of PET markers[1]. Despite its name, PSMA can be produced by a variety of tumors such as bladder, pancreas, lungs, and kidneys and, on normal tissue, such as salivary and lacrimal glands, epididymis, ovarian, and proximal renal tubules and on the astrocytes of the central nervous system[2]. However, it is on the prostatic tumors that PSMA displays a stronger expression (100- to 1000-fold that in normal cells), namely in more aggressive tumors and in metastatic disease and tumor recurrence, turning it an interesting target for imaging and therapeutic tools and allowing this "image and treat" strategy to become a major approach to patients with prostatic cancer.

2) ^{68}Ga PSMA: diagnosis potential

The ^{68}Ga-PSMA-HBED-CC PSMA (^{68}Ga PSMA) ligand is a small antagonist molecule of PSMA, developed in Europe and studied and used by a variety of world imaging centers, that by binding to its receptor emits radiation allowing its visualization on PET. This compound presents with a fast cellular internalization and a high tumor-cell accumulation. It presents with physiologic accumulation in salivary and lacrimal glands, liver, spleen, small bowel, and urinary tract[2].

Afshar-Oromeih et al[3] evaluated 319 patients with this agent, including patients with primary disease, biochemical recurrence, and metastatic disease. [68]Ga PSMA identified at least one malignant lesion in 83% of the patients, and the uptake by tumor cells correlated positively with the PSA value and the androgen deprivation therapy. On a lesion-based analysis, the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were 76.6%, 100%, 91.4%, and 100%, respectively.

Eiber et al[4] studied retrospectively 248 men with biochemical recurrence after radical prostatectomy and supported the high detection rate of ^{68}Ga PSMA, identifying a malignant lesion in 89.5% of the patients. It also confirmed the correlation between higher detection rates and increasing PSA level. Furthermore, they found that ^{68}Ga PSMA detected pathologic lesions that conventional TC could not in 33% of the patients. However, the limitation of this study relies on the fact that histological confirmation was only available for 37% of the cases. When the histological confirmation was available, it was verified a considerable number of false-negative results for this imaging method.

[68]Ga PSMA also demonstrated promising results in tumor staging and therapy planning. In a retrospective study by Sterzing et al[5], 57 patients, who were candidates for radiotherapy (15 with primary diagnosis and 42 with recurrent disease), were evaluated by ^{68}Ga PSMA PET/TC and conventional TC. It was registered a higher detection rate for ^{68}Ga PSMA PET/TC than for conventional TC (59.6% vs 21.1%). Therefore, the TNM classification of 29 patients was modified after evaluation by ^{68}Ga PSMA PET/TC and, consequently, the initial therapeutic scheme.

These data were also supported by a recent systematic review and meta-analysis including 1309 patients, either studied for primary staging or for biochemical recurrence detection. Aiming for identification of predictors of positive ^{68}Ga PSMA PET and accessing the true sensitivity and specificity of ^{68}Ga PSMA PET-positive lesions confirmed by histopathology, Perera et al[6] established the role of pre-PET PSA levels and PSA doubling-time (PSAdt) as risk factors for a positive imaging. It was reported an overall percentage of positive ^{68}Ga PSMA PET among patients of 40% for primary staging and 76% for biochemical recurrence. Positive scans for biochemical recurrence patients were increased for progressively higher pre-PET PSA

levels: estimated positivity was 42% for PSA<0.2ng/ml, 58% for 0.2-0.99ng/ml, 76% for 1.00-1.99ng/ml, and 95% for >2.00ng/ml PSA subgroup. On the other hand, a shorter PSAdt was associated with a higher probability of a positive PET-scan (pooled positivity of 64% for PSAdt $\geq$6 mo and 92% for PSAdt <6 mo). On per-patient analysis, the summary sensitivity and specificity were both 86%; as for a per-lesion analysis, the summary sensitivity and specificity were 80% and 97%, respectively. The results of this study highlighted the promising detection rates for ^{68}Ga PSMA PET in prostate cancer patients with low PSAdt or PSA levels.

The proPSMA study[7], a promising multicenter, prospective, randomized study also aims to access the impact of PSMA PET/CT as either a first- or second-line imaging modality. Contemplating an innovative design, a total of 200 patients with high-risk prostate cancer will be selected from 10 centers. These patients will be submitted to imaging evaluation either by conventional imaging modalities or by PSMA PET/CT to detect nodal or distant metastatic disease. The authors project that this study will provide solid high-quality data that may establish whether the PSMA PET/CT should replace conventional imaging in the primary staging of high-risk patients or whether it should be useful only to provide additional clinical information in selected cases. The study also pledges to access the economic benefits of incorporating the PSMA PET/CT in the management algorithm and also establish a direct comparison between this modality and whole-body magnetic resonance imaging, using a subset of 50 patients. Whatever new data this study brings, it sure will heavily contribute to the modern literature and may even have a significative impact in changing the conventional investigation paradigm of PCa.

Regardless, as a novel modality, there is an increasing and significant need for further clinical data as for larger and retrospective single-institutional studies.

3) ^{177}Lu-PSMA: therapeutic agent

Developed by a German research center, PSMA-DKFZ-617 ligand labeled with [177]Lu (^{177}Lu-PSMA) is a theragnostic agent for PCa, which presents very promising results in reducing PSA levels and with minimum side-effects.

The side-effects and the tumor response for the ^{177}Lu-PSMA therapy were evaluated by Ahmadzadehfar et al[8] in 22 patients presenting progressive prostate cancer with long distance metastasis, resistant to hormonal and chemotherapy. The patients received two cycles of therapy. Eight weeks after de first cycle, 79.1% presented decreasing levels of PSA. Reduction of PSA levels were also registered in 68.2% patients 8 weeks after the second cycle of therapy. Only two cases of severe grade 3 anemia were registered, without any other signs of hematological or renal toxicity. Overall, 70% of patients experienced a decrease in the PSA value, allowing the authors to conclude that ^{177}Lu-PSMA is a valuable and safe therapy option for metastatic prostate cancer, with a low toxicity profile.

Rahbar et al[9] reached the same conclusions in a retrospective study by evaluating the tumor response and the patients' tolerance to a single dose ^{177}Lu-PSMA therapy in 74 patients. Eight weeks after the therapy session, 47 (64%) patients presented with a reduction in PSA level, noting a decrease over 50% in 23 patients. As for side-effects, seven patients developed transitory dry mouth, and some experienced mild thrombocytopenia. These results highlighted the potential of ^{177}Lu-PSMA as a selective therapy option well tolerated by patients and with a significant impact on the PSA levels.

Nevertheless, now bigger studies evaluating the side-effects and the tumor response to the administration of multiple cycles of ^{177}Lu-PSMA therapy were required.

3.2. $^{11}C/^{18}F$-Choline PET/TC

(1) Biological principles

Choline is a precursor of the phospholipids present in the cellular membrane. It is used to synthesize phosphatidylcholine, the main phospholipid in the cellular membrane. The first step of this metabolic pathway consists on the phosphorylation of choline into phosphocholine by the choline kinase, an enzyme overexpressed by PCa. As a result, there is a higher endogenous production of choline and a greater intracellular uptake by prostatic tumor cells[10]. Physiologically, this biomarker's uptake occurs on salivary glands, liver, renal parenchyma, pancreas, spleen, bone marrow, and muscles[11].

Choline can be labeled with carbon-11 (^{11}C) or fluorine-18 (^{18}F). ^{18}F-choline presents as a major advantage; its higher half-life time in comparison to ^{11}C allows its utilization in facilities located far away from the production center. Besides, ^{11}C-Choline presents pancreatic excretion, while ^{18}F-Choline is excreted in the urinary tract[1].

(2) Primary disease

The performance of this biomarker in diagnosing localized disease is usually limited by the physiological uptake in prostatic conditions other than cancer (as in benign prostatic hyperplasia), leading to a decreased capability in differing benign from malignant disease[1].

Farsad et al[12] evaluated the potential of ^{11}C-choline for the detection of localized primary PCa in 36 patients, with confirmation by histopathological analysis. It reported a sensitivity, specificity, accuracy, PPV, and negative predictive value (NPV) of 66%, 81%, 71%, 87%, and 55%, respectively. These results demonstrated that even though ^{11}C-choline PET/TC is capable of reliably identifying a high number of malignant lesions, it still presented a significant number of false-negative results because of the undifferentiated uptake of the biomarker in benign prostatic conditions. Therefore, the authors considered the routine use of this biomarker was not justified.

(3) Staging

Currently, the utility of ^{18}F-choline PET/TC in stratifying and staging of patients with PCa, namely in the evaluation of disease's extent, such as localized disease, lymph node involvement, and distance metastasis, is well documented. This modality may also play an important role on the identification of biopsies' sites by detecting the areas with higher biomarker uptake, representing higher malignant probability[13].

In a prospective study that included 111 candidates for radical prostatectomy with moderate and high risk PCa, sensitivity, specificity, PPV, and NPV of 66%, 96%, 82% and 92%, respectively, was reported for ^{18}F-choline PET/TC in detecting lymph node invasion. Overall, these results promoted a modification in the therapy plan of 15% of patients. Schiavina et al[14] evaluated 57 patients for the same purposes, reporting a sensitivity, specificity, PPV, NPV, and an accuracy of 60%,97%,90%, 87%, and 87%, respectively.

^{18}F-choline PET/TC also demonstrated promising results in detecting osseous metastasis. Since ^{18}F-choline does not accumulate in bone degenerative diseases, it is able to reliably distinguish malignant osseous lesions from degenerative conditions. With a feasible ability in early detecting intramedullary metastasis, this imaging method presents potential to act as an alternative option to bone scintigraphy (BS)[15]. Two literature reviews[15,16] compared the performance of ^{18}F-choline PET/TC, ^{18}F-sodium fluoride (NaF) PET/TC, and BS for detection of osseous metastasis with similar outcomes. Both PET modalities revealed a higher sensitivity and specificity than BS. ^{18}F-choline PET/TC revealed a higher specificity and a lower sensitivity than ^{18}F-NaF PET/TC for detection of malignant osseous lesions.

(4) Biochemical recurrence

On September of 2012, the Food and Drug Administration approved the clinical usage of ^{11}C-choline PET/TC for imaging evaluation of patients with suspected biochemical recurrence of PCa, a condition defined as an increase on PSA serum levels after radical prostatectomy.

A literature review by Guttilla et al[17] including 1555 patients with biochemical recurrence of PCa revealed a sensitivity of 86% and a specificity of 93% for detection of recurrent disease in all sites evaluated (prostatic bed, lymph nodes, and bone). ^{11}C-choline PET/TC had a better performance on the lymph node disease's detection, revealing a sensitivity of 100% and a specificity of 82%.

Androgen deprivation therapy (ADT) is a systemic therapy often used on patients with recurrent disease. Fuccio et al[18] evaluated the effect that this kind of therapy had on choline's uptake by tumor cells and concluded that it had a negative impact on ^{11}C-choline PET/TC detection rates, as it decreased the accumulation of choline in tumor tissue.

Several studies also supported the use of ^{11}C-choline PET/TC as a prognostic indicator in biochemical recurrence after radical prostatectomy. Giovacchini et al[19] verified that patients with ^{11}C-choline PET/TC positive scans presented a lower overall survival compared with patients with negative scans (4.1 years vs 7.9 years).

3.3. ^{11}C-acetate PET/TC

(1) Biological principles

Acetate is a natural precursor of fatty acids. Prostatic tumor cells present an overexpression of fatty acid synthase, an enzyme responsible for turning acetate into fatty acids for further incorporation in cellular membrane. This allows ^{11}C-acetate to be used for evaluation of patients with PCa[1]. This biomarker presents a physiological uptake in pancreas, salivary glands, liver, spleen, and bowel. Its excretion is majorly by the respiratory system and not by the urinary tract, which acts as an advantage since pelvic disease could be confounded if there was radioactive urine in the bladder[11].

2) Primary disease

Like $^{11}C/^{18}F$-choline, this biomarker does not reveal a great performance in detecting localized disease, for the same reasons. Mena et al[20] evaluated 39 patients for detection of localized PCa, using ^{11}C-acetate PET/TC. A sensitivity and a specificity of 61.6% and 80%, respectively, and a high rate of false-positive results was registered because this biomarker also presented a high uptake by benign prostatic conditions, such as prostatic benign hyperplasia. Mohsen et al[21] reviewed 24 studies focusing on the performance of ^{11}C-acetate PET/TC in detecting primary PCa and demonstrated a sensitivity and a specificity of 75% and 76%, respectively. The authors noted that patients with prostatic benign hyperplasia also showed increased ^{11}C-acetate uptake, and this biomarker's ability to detect small sized lesions was poor.

(3) Lymph node and distance metastasis

Candidates for radical prostatectomy are usually submitted to imaging evaluation by TC or magnetic resonance imaging for lymph node staging to evaluate the need for lymph node dissection.

However, none of these modalities are sensitive enough to detect lymph node metastasis, unless the nodes are enlarged[11].

Schumacher et al[22] assessed the performance of ^{11}C-acetate PET/TC on detecting lymph node invasion in 19 patients before prostatectomy. The imaging results were subsequently compared with the surgery and histopathological findings. On a lesion-based analysis, this biomarker revealed a sensitivity, specificity, PPV, and NPV of 62%, 89%, 62%, and 89%, respectively. ^{11}C-acetate performance was limited in detecting small-sized lesions and the exact metastatic location, leading to false-positive and false-negative results on one third of the patients. In a 107 patients study, ^{11}C-acetate PET/TC detected either lymph node or distance metastasis in 33.6% of patients with important influence on staging and treatment planning[23].

(4) Biochemical recurrence

The performance of ^{11}C-acetate PET/TC on the identification of recurrence sites was assessed by several studies. Mohsen et al[21] review reported a low sensitivity (64%) and a high specificity (93%). In a retrospective study including 123 patients with suspicion of biochemical recurrence of PCa, ^{11}C-acetate identified recurrence in prostatic bed, lymph nodes, or osseous metastasis in 82 of them (66.7%). PET-positive patients were associated to higher PSA levels than PET-negative subjects and to higher Gleason scores[24]. These results underlined the potential utility of ^{11}C-acetate as a prognosis and tumor aggressiveness indicator in patients with recurrent disease.

3.4. ^{18}F-FACBC PET/TC (Fluciclovine)

1) Biological principles

Amino acids also demonstrated potential to be used in molecular imaging of PCa patients because their metabolism and transport are increased in this cancer.

^{18}F-FACB (anti-1-amino-3-18F-fluorocyvlobutane-1-carboxilix acid) or Fluciclovine is a synthetic leucine analog that showed promising results in PCa imaging because it is not metabolized or incorporated in proteins. Its physiological absorption is higher not only on the pancreas but also on the liver, bone marrow, salivary glands, lymphoid tissue, and hypophysis. This radiopharmaceutical also presents with low cerebral activity and minimal urinary excretion, allowing a perfect visualization on imaging evaluation of the brain, retroperitoneum, and pelvis[1].

2) Localized disease

The evaluation of primary disease with ^{18}F-FACBC shares the same limitation as acetate and choline: the low specific uptake by prostatic tumor cells. In a prospective study, 21 men were evaluated by ^{18}F-FACBC PET/CT and by multiparametric magnetic resonance, previously to prostatectomy. It was verified that fluciclovine uptake by tumor cells was higher than on normal prostatic tissue; however, patients with benign prostatic hyperplasia also presented with an increased uptake, leading to an elevated number of false-positives. The sensitivity and specificity for fluciclovine-PET/CT was 67% and 66%, respectively, and for RMNmp, 73% and 79%, respectively[25].

3) Biochemical recurrence

Fluciclovine's main role could be on the evaluation of patients with recurrent prostate cancer, because FDA recently approved its use for studying this group of subjects.

In a clinical trial[26], 93 patients with recurrent prostatic disease were evaluated by fluciclovine PET/CT for detection of prostatic and extra prostatic tumor masses. On the evaluation of the confined disease, fluciclovine revealed a sensitivity of 90.2%, a specificity of 40%, an acuity of 73.6%, a PPV of 75.3%, and a NPV of 66.7%. On the other hand, on assessment of extra prostatic disease, the values of sensitivity, specificity, acuity, PPV, and NPV were 55%, 96.7%, 72.9%, 95.7%, and 61.7%, respectively. A meta-analysis including 251 patients showed similar results with a sensitivity of 87% and a specificity of 66%[27]. Nanni et al[28] showed that fluciclovine's performance outruns that of choline, having detected a higher number of true-positive and true-negative lesions on prostatic bed, lymph nodes, and bone.

As other biomarkers, one of the possible applications of fluciclovine is its incorporation on the US-guided biopsy system. Combining molecular imaging with ultrasound, the detection rate of prostatic tumor by directed biopsy could be certainly improved[29].

Based on the results of several studies, it is plausible that fluciclovine would be more useful for the detection of recurrent disease and high-risk primary prostatic tumor staging than for primary disease's detection and characterization.

3.5. ^{18}F-fluoro-5alfa-dihidrotestosterone PET/TC

1) Biological principles

Androgens play an important role on the pathogenesis of prostatic cancer, since there is a high expression of androgen receptors in all disease's stages. Dihidrotestosterone, a testosterone derivate, is a natural ligand of these receptors. This way, a biomarker that gauge the molecular route of dihydrotestosterone could be useful for the imaging evaluation of the prostatic tumor.

The molecular agent ^{18}F-fluoro-5alfa-dihidrotestosterone (^{18}F-FDHT) binds with high affinity to the androgen receptor, showing the localization of prostatic tumor cells who present a high expression of these receptors[1].

2) Clinical application

Aiming to evaluate the ability of this biomarker on the detection of prostatic tumor, Larson et al[30] compared the detection rates of ^{18}F-FDHT and ^{18}F-FDG in seven patients with progressive metastatic disease. A total of 59 tumor lesions were identified on this group by conventional imaging, and of those, the ^{18}F-FDG identified 57 (97%), while ^{18}F-FDHT identified 46 (78%). This study established the viability of ^{18}F-FDHT for the identification of tumor cells and allowed the analysis of the androgen receptor expression, with possible impact on the clinical approach of these patients.

This biomarker's ability on the identification of tumor cells with increased expression of androgen receptors was found useful on the therapeutic approach of patients with prostate cancer. In a clinical trial by Rathkopf et al[31], the efficacy of ARN-509, a second generation anti-androgen with therapeutic potential for castration resistant prostate cancer, was studied. On this study, ^{18}F-FDHT PET/TC was used to quantify the binding of this pharmaceutical to the androgen receptors, allowing the evaluation of tumor response rate to treatment.

Finally, the potential utility of this biomarker on the prognosis evaluation of patients with castration-resistant prostatic cancer was also established by Vargas et al[32] in which 38 patients with bone metastasis were studied, and it was verified that a higher uptake of ^{18}F-FDHT by these lesions was associated with a lower survival rate.

3.6. ^{18}F-sodium fluoride PET/TC

(1) Biological principles

Physiologically, NaF allows the detection of osteoblastic activity by binding to bone formation sites, presenting with an increased bone turnover. It is usually applied on bone metastasis management, on the evaluation of tumor response to therapy, and on the clarification of bone abnormalities found by other imaging modalities[15].

(2) Clinical application

Owing to its physiological characteristics, the main role of ^{18}F-NaF is on the evaluation of bone metastasis in PCa patients. Poulsen et al[33] compared the performances of ^{18}F-NaF, ^{18}F-choline, and BS on the detection of spinal column metastasis. A higher sensitivity and a lower specificity for NaF in comparison to ^{18}F-choline (93% vs 85% and 54% vs 91%, respectively) was registered. The main cause for NaF low specificity was the high uptake of this biomarker in degenerative and inflammatory bone lesions, showing an important limitation of this compound as it leads to a high number of false-positive findings. At last, both PET modalities revealed a better performance than BS, in means of sensitivity, accuracy, PPV, and NPV.

Furthermore, another possible application for ^{18}F-NaF PET/TC may be in the evaluation of prognosis and tumor response to systemic therapies. Etchebehere et al[34] found that the uptake of NaF by tumor cells was related to the lesions' volume and that both parameters acted as independent indicators for overall survival in patients under systemic therapy with ^{223}Ra.

4. Discussion

The molecular imaging radiotracers reviewed in this literature research target the diverse biological activity and metabolic changes presented by the PCa. Understanding the processes of tumor growth is the key to an optimized selection of the most suitable molecular imaging modality to be adopted in the common clinical practice.

On Table 1, there is a summarized list of the most important advantages and the significant limitations of each PET-tracer reviewed in this article.

Molecular imaging by PET/CT has at its disposal several radiotracers that target the tumor's biological activity. Although it demonstrates a limited performance on the initial diagnosis of PCa, it still has the potential to play a major role on the identification of biochemical recurrence and of lymph node or distance metastasis and on the development of personalized therapeutic strategies.

Currently, choline PET/CT is already used in several centers for detection and identification of recurrent disease when the conventional imaging methods reveal inconclusive findings. PSMA PET/CT also presents a huge potential to be added to common clinical practice diagrams, as it offers a promising "image and treat" approach, allowing the detection of tumor lesions, and simultaneously acting as a focal therapy option on patients with refractory PCa, with a clear impact on PSA levels and with minimal side-effects.

Table 1
Advantages and limitations of each PET-tracer

PET/CT	Advantages	Limitations
PSMA	• High sensitivity, specificity, and accuracy for detection of primary PCa, lymph node, distance and visceral metastasis, and of biochemical recurrence • Low rate of false-positive and false-negative results • Positive correlation with increased PSA levels and tumor aggressiveness • Useful in treatment planning • ^{177}Lu-PSMA acts as a therapeutic agent, with impact in decreasing PSA levels, well tolerated by patients and presents a low toxicity profile	• Expensive equipment • Patients are exposed to radiation • Weak reproducibility at a community hospital because of the need of equipment and geographic proximity with isotopes production centers
Choline	• High sensitivity and specificity for identification of lymph node and bone metastasis • Approved by the FDA for detection of biochemical recurrence • Effective in the evaluation of disease's extent and its staging • Capable of guiding biopsies to sites with greater disease's probability • Prognostic value, positive scans are associated with lower overall survival • Can be labeled with higher half-life isotopes (^{18}F)	• Limited impact for detection of primary PCa because of tracer accumulation in benign conditions (Benign Prostatic Hyperplasia) • ADT decreases choline uptake by tumor cells, with impact on the detection rate in this group of patients
Acetate	• Moderate sensitivity and high specificity for detection of lymph node and distance metastasis and biochemical recurrence • Does not present urinary excretion, avoiding false-positive results in the evaluation of pelvic disease • Positive scans are associated with higher PSA levels and Gleason scores, acting as a prognostic indicator	• Limited impact for detection of primary PCa because of tracer accumulation in benign conditions (Benign Prostatic Hyperplasia) • Low detection rates for small-sized lesions • Labeled with a low half-life isotope (^{11}C)
FACBC	• Moderate sensitivity and high specificity for detection of biochemical recurrence • Approved by the FDA for detection of biochemical recurrence • Capability for guiding biopsies • Presents with minimal urinary excretion, allowing an optimal visualization of the pelvis	• Limited impact for detection of primary PCa because of tracer accumulation in benign conditions (Benign Prostatic Hyperplasia)
FDHT	• Viability for detection of localized PCa and bone metastasis • Allows quantification of increased expression of androgen receptors, with impact on the therapeutic approach and on the evaluation of tumor response to treatment • Acts as a prognostic indicator, and increased uptake in malignant lesions is associated with a lower overall survival	• Lower sensitivity, specificity, and accuracy compared with other imaging modalities
NaF	• Highly sensitive for bone metastasis' detection • Better performance than BS in detecting bone metastasis • Allows evaluation of tumor response to systemic therapy in patients with castration-resistant PCa • Increased uptake in large metastatic bone lesions, acting as a prognostic indicator • Allows clarification of bone abnormalities found by other imaging modalities	• Poor specificity for detection of bone metastasis when compared with other PET-tracers (ex. choline PET/CT) • False-positive results by tracer's uptake in degenerative and inflammatory bone lesions

BS, bone scintigraphy; FDHT, fluoro-5alfa-dihidrotestosterone; FDA, Food and Drug Administration; FACBC, anti-1-amino-3-18F-fluorocyvlobutane-1-carboxilix acid; NaF, sodium fluoride; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

5. Conclusion

The constant technological development and the arising clinical data may assign these innovative molecular imaging radiotracers a major role in prostate carcinoma's management, initial diagnosis, staging and identification of lymph nodes and distance metastasis, therapy planning and administration, and in prognosis evaluation.

To further incorporate these promising molecular imaging modalities in the common clinical practice, the perpetuation of scientific investigation is now required, with the elaboration of larger prospective and comparative studies and with the constant actualization and reflection on the achieved results, so that standardized protocols can be created to uniform the evaluation and the interpretation of the collected images. If this is assured, then we will be one step further to the optimization and personalization of prostate cancer imaging and treatment, with obvious impact on decreasing this malignancy's prevalence and associated morbidity and mortality.

Conflict of interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2018.12.003.

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