REVIEW ARTICLE

Radiotracers Used in Nuclear Medicine for Prostate Cancer Diagnosis and Follow-Up

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Abstract  Prostate cancer is the most common cause of cancer in males worldwide. Currently, imaging in prostate cancer has acquired great importance in staging, re-staging, treatment selection, and recurrence assessment. Molecular imaging with positron-emission tomography has enabled a personalized approach for these purposes. In addition to these clinical needs, there are growing perspectives and a challenge for new molecular imaging techniques, not only to detect metastatic disease, but also to provide relevant information on tumor biology and prognosis, and one of the greatest challenges for non-radioisotope imaging techniques is the ability to detect recurrence in patients with low levels of prostate-specific antigen. (creativecommons.org/licenses/by-nc-nd/4.0/).

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INTRODUCTION

According to GLOBOCAN 2012 data, 14,016 patients are diagnosed with prostate cancer (PC) every year in Mexico, which represents 9.5% of all newly diagnosed tumors in the country, with this malignancy occupying the first place among males and females. In males, it is at first place, with 21.4% of all newly diagnosed tumors\(^1\).

Imaging plays an important role in PC, including accurate evaluation of disease extension, assessment of the site of recurrence, and monitoring of treatment response. Nuclear medicine imaging techniques are among the most novel results of investigations associated with image acquisition in PC, which enables better assessment than a few years ago\(^2\).

Several radiotracers for scintigraphy plus single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) are currently commercially available in our country and many others are under investigation.

The purpose of the present review is to offer a current summarized perspective on the different radiotracer options used in nuclear medicine, both for scintigraphy and PET/CT, but especially on the usefulness of each one of them according to the patient’s clinical scenario.

RADIOTRACERS USED FOR SCINTIGRAPHY PLUS SPECT/CT

99mTc-MDP

Bone scintigraphy with 99mTc-radiolabelled bisphosphonates is perhaps one of the most widely performed studies in nuclear medicine with the purpose to detect bone metastases. Osteoblasts form the osteoid matrix that subsequently will be mineralized by hydroxyapatite crystals. 99mTc-MDP (methylene diphosphonate) binds to hydroxyapatite crystals by chemo-adsorption proportionally to two situations: blood flow and osteoblastic activity\(^6\).

According to the National Comprehensive Cancer Network (NCCN), bone scintigraphy is indicated in patients with prostate-specific antigen (PSA) levels ≥ 20 ng/ml, Gleason ≥ 8, T3, T4, or T2 if PSA > 10 ng/ml, or if there are symptoms present\(^8\). It is a highly sensitive method to detect bone metastases, especially osteoblastic. It can also be used to assess treatment response, although not semi-quantitatively as in the case of PET/CT\(^9\).

One of the greatest advantages of bone scintigraphy is that it requires a minimum of 5% bone turnover rate to be able to detect a lesion, whereas with anatomic studies such as X-ray, a minimum of 40-50% turnover is required for lesions to be visualized. This feature provides elevated sensitivity for the detection of bone metastases, which can be as high as 96.9%\(^10\). However, the greatest disadvantage of this study is its low specificity, which can range from 41 to 57%\(^10,11\). For this reason, hybrid equipment (SPECT/CT) allows for such specificity to be improved by merging the findings with a CT study, with up to 82% specificity being attained (Fig. 1)\(^11\).

99mTc-PSMA

The prostate-specific membrane antigen (PSMA) is a full-membrane, type II glycoprotein that was identified as a homolog of type I folate hydrolase protein. In the central nervous system, it cleaves the NAAG (N-acetyl-1-aspartyl-1-glutamate) neurotransmitter into NAA (N-acetyl-aspartate) and glutamate. In malignant tissues, PSMA has been shown to be strongly expressed in the stroma adjacent to the neo-vasculature of multiple solid tumors\(^12\-15\).

In PC, overexpression is associated with tumor grade, aneuploidy, and biochemical recurrence. An important characteristic of this radiotracer is that it is overexpressed when tumors become androgen-independent\(^9\).

The availability of gamma cameras and hybrid equipment at different hospital centers in comparison with PET/CT equipment remains centralized; for this reason, labeling this novel agent with a more available radionuclide such as 99mTc has been attempted.

However, there are no reported studies in the literature reflecting the sensitivity and specificity since it is still under investigation, although the results so far are highly promising, even comparable to those with 68Ga-PSMA (Fig. 2).

99mTc-Bombesin

Gastrin-releasing peptide receptors (GRPR) are G protein-coupled receptors that are overexpressed in many solid tumors, including PC. Bombesin is a 14-amino acid peptide that binds with high affinity to GRPR. Some studies have demonstrated that GRPR expression depends on the Gleason score in such a way that the higher the Gleason score, the lower the expression of these receptors will be\(^7,18\).

Only a few authors have reported on the safety and efficacy of radiolabeled bombesin analogs in PC, with a strong correlation being found with GRPR expression in patients with PC and in patients without the disease.
F. O. García-Pérez, S. S. Medina Ornelas, et al. demonstrated high affinity of the radiotracer in the primary tumor in 8/10 patients, and lymph node involvement in three patients.

De Vincentis, et al. studied 14 patients with suspected PC, and found true-positives in 12 of them with confirmed histology, and true-negatives in the rest, with similar results to Scopinaro’s findings in terms of lymph node involvement.

Other studies show similar results as well as the same limitations in bone metastasis visualization since this agent has poor sensitivity for the detection of metastatic bone involvement, owing to the fact that the GRPR expression pattern in PC bone metastasis is different to that found in the primary tumor or lymph node involvement (Fig. 3).

Radiotracers using GRPR-antagonist agents have been recently found to be superior to those using agonists. Most recent investigations have focused on these agents for PET/CT, but marked with radionuclides such as 68Ga and 64Cu.

RADIOTRACERS EMPLOYED FOR PET/CT

18F-NaF

Sodium fluoride (NaF) is a radiotracer with similar properties to 99mTc-MDP, but minimal binding to proteins, rapid first-step extraction, and higher clearance from soft tissue, which allows twofold higher bone uptake, thus attaining a better target/background ratio. After chemo-adsorption onto the hydroxyapatite crystals, the 18F ion is rapidly exchanged for the hydroxyl ion (OH) on the hydroxyapatite matrix surface to form fluorapatite, with this incorporation being slow.

The 18F-NaF uptake, the same as 99mTc-MDP, is conditioned by blood flow and bone remodeling, and uptake indicates osteoblastic activity by identifying reactive changes on the underlying involved bone area. However, abnormal uptake is not a phenomenon exclusive to metastases since any process with increased bone remodeling can display abnormal uptake, including trauma, arthritis, metabolic bone disease, osteomyelitis, surgical procedures at the bone level, and even visceral calcification.

Several studies have compared the sensitivity and specificity of 99mTc-MDP with regard to 18F-NaF, with superiority of the latter being demonstrated for the detection of blastic-type metastatic bone disease (Fig. 4), with a sensitivity of 86.7-100% and specificity of 44-88.6%, and there are even some reports that show a specificity close to 100%.
Perhaps the greatest disadvantage of the study is the higher exposure to radiation, since total effective dose for PET/CT with 10 mCi (370 MBq) of 18F-NaF ranges from 8.9-12.1 mSv, in comparison with approximately 5.3-7.4 mSv for SPECT with 25 mCi (925 MBq) of 99mTc-MDP 31,33.

11C-Choline/18F-FCH

Choline (CH) can be labeled both with Fluor-18 (18F) and carbon-11 (11C). It enters into the cell by means of choline transporters and is the precursor for phospholipid biosynthesis, which is the main component of the cell membrane 30.

Some tumors, particularly the prostatic tumor, show an increase in cell membrane synthesis as a consequence of uncontrolled cell proliferation, which is driven by choline kinase overexpression. This enzyme catalyzes choline phosphorylation to form phosphorylcholine, followed by the generation of phosphatidylcholine on tumor cell membrane. Choline uptake in PC appears to be affected by hypoxia, but it may not be correlated with cell proliferation 30.

The usefulness of this agent is wide, and it ranges from detection to recurrence assessment 31.

Different studies have demonstrated that PET/CT with 11C-choline has a sensitivity of 55-100% and specificity of 62-86% for the detection of the primary tumor. Partly, this broad range is due to important parameters such as tumor size, grade, and location, as well as PSA level, and even when sensitivity is elevated, it can be as low as 22% in case of extension beyond the prostate 32,33.

With regard to the detection of recurrence after radical prostatectomy, international studies report a sensitivity of 64-78% and specificity of 88-90% 34,35. Detection is strongly associated with PSA levels, since higher PSA levels, PSA high velocity, or lower PSA duplication time are related to higher rates of detection. The likelihood of detection increases with PSA levels > 2.4 ng/ml, PSA duplication time < 3.4 months, or when velocity is < 1 ng/ml/year when PSA levels are < 2.4 ng/ml. For this reason, the detection rate varies even in the localization of bone metastases 34,37 (Fig. 5).

One of the greatest disadvantages of 11C-choline is its short half-life, since this is only 20-minutes long, which makes it more expensive and difficult to distribute. In view of this, it can be labeled with 18F-FCH (18F-fluoromethyl-choline), which has shown a very similar role in the detection of recurrence in comparison with 11C-choline. Pelosi, et al. reported a detection rate of 20% for 18F-FCH in patients with PSA levels < 1 ng/ml, 44% for levels of 1-5 ng/ml, and 82% for levels > 5 ng/ml, similar to findings reported by Krause, et al. for 11C-choline, with a detection rate of 36% for PSA levels < 1 ng/ml, 62% for levels of 2-3 ng/ml, and 73% for levels > 3 ng/ml 38,39.

11C-Acetate

Acetate is a molecule that rapidly enters the cell by means of monocarboxylate transporters, where it is converted into acetyl-CoA by the action of acetyl-CoA synthetase, and this way it can be incorporated into two metabolic pathways, an anabolic and a catabolic one, with the pathway depending on the cell type.

In PC tumor cells, the fatty acid synthase enzyme is overexpressed, thus converting the most part of fatty acids acetate and being incorporated in phosphatidylcholine intracellular micro-domains (anabolic pathway), which are substrates for tumor growth. Fatty acid synthase overproduction is associated with higher tumor aggressiveness. The catabolic pathway influences as well, with acetate being able to metabolize into CO2 via the Krebs cycle. Acetate is used as a substrate in some intracellular processes within the mitochondria by producing energy and in the cytosol in the synthesis of lipids 40,41.

The 11C-acetate is unable to distinguish between benign prostatic hyperplasia (BPH) and prostate cancer. Data available to date report that sensitivity and specificity with regard to detection and evaluation of lymph node involvement are quite heterogeneous, since the results of studies with larger numbers of patients range from 73-88% for sensitivity, and 29-41% for specificity in the detection of the primary tumor, whereas for lymph node staging, sensitivity ranges from 38-90% and specificity ranges from 67-96%, since the higher the PSA level is, the higher the specificity will be 42,43.

The greatest usefulness of this agent is in disease localization in case of biochemical recurrence, where the detection rate will also be highly influenced by PSA levels: using a PSA duplication velocity > 1.32 ng/ml it will have 74% sensitivity and 75% specificity, whereas an accuracy of up to 59% will be obtained in patients with PSA levels > 3 ng/ml, and it will be as low as 4% if PSA levels are lower (Fig. 6) 44,45.

18F-FDG

Cell membrane glucose transporter 1 (GLUT1) increased levels and hexokinase-mediated enzyme activity increase found in most tumors drive to intra-tumor increased metabolic activity. The GLUT1 expression is strongly upregulated in androgen-dependent and non-androgen-dependent prostate...
cells, with high levels of this transporter being found both in PC and BPH. In addition, 18F-FDG (fluorodeoxyglucose) normal urinary elimination route makes it a poorly sensitive or specific radiotracer in the detection of the primary tumor.

Some studies have demonstrated its usefulness in this scenario: in one meta-analysis of 47,925 patients who underwent PET/CT, a PC prevalence of 1.8% was demonstrated for those with uptake incidental finding; however, with the advent of other radiotracers, its indication might be assigned to other conditions.

In the setting of biochemical recurrence, there are some studies demonstrating its usefulness. Öztürk, et al. demonstrated a sensitivity of 61.6% and specificity of 75% after definitive treatment (radical prostatectomy or radiotherapy).

In a comparative trial of 18F-FDG with 11C-choline, the combination of both radiotracers was found to increase sensitivity by up to 80% and specificity by up to 40% in patients with PSA levels > 1.9 ng/ml.

Due to the heterogeneity in these types of tumors, treatment response can sometimes be seriously compromised. After treatment, the metabolism of lesions usually decreases; however, some lesions may have their metabolism decline and others not, and in some cases even not being correlated with the biochemical response. On the other hand, it can make the management be changed in up to 35% of patients according to the National Oncology PET Registry of the USA.

The use of 18F-FDG can be useful in the detection of metastatic disease. A study conducted by Damle, et al. demonstrated 71.9% sensitivity and 100% specificity in the detection of bone metastases, which perhaps is currently the most widely accepted indication for the use of this tracer (Fig. 7), although with the use of new radiotracers it might not be the best option anymore.

68Ga-PSMA

As previously mentioned, the detection of early recurrence is one of the greatest challenges for imaging studies. The PSMA characteristics make it highly valuable by possessing the capability for early detection of progression or recurrence after androgen-deprivation therapy, even with low PSA levels (< 2 ng/ml).

In a study carried out by Afshar-Oromieh, et al., they found up to 84% of primary PC true-positives in a cohort of 37 patients, with 60% being found in patients with PSA levels < 2.2 ng/ml, whereas in those with PSA levels > 2.2 ng/ml, 100% were found.

In another study, 18F-FCH was compared with 68Ga-PSMA for restaging in patients with PSA levels ranging from 0.01 to 116 ng/ml. Lesions were detected with 68Ga-PSMA in 87% of patients, whereas lesions were detected with 18F-FCH in only 70%, with PSA levels also having an influence.

Eiber, et al., in a cohort of 245 patients with biochemical recurrence, demonstrated a detection rate of 96.8, 93.0, 72.7, and 57.9% in subjects with PSA levels > 2.1, < 2.0-1.0, < 1.0-0.5, and < 0.5-0.2 ng/ml, respectively. In this way, this radiotracer has a higher detection rate compared with other radiotracers recommended in the literature, such as 11C-choline with a detection rate of 34-88%, 18F-choline with 43-79%, and 11C-acetate with a detection rate of 59-80%.

68Ga-DOTATOC/NOC

68Ga-DOTATOC is a radiotracer with affinity to somatostatin receptors (SSTR) 2 and 5, whereas 68Ga-DOTANOC displays affinity to SSTR 2, 3, and 5, which are commonly used in PET/CT studies to characterize neuroendocrine neoplasms.
The presence of SSTR in PC is related to a phenomenon known as “neuroendocrine differentiation”, which indicates an adverse prognosis. In prostatic adenocarcinoma, an increased presence of non-androgen receptor-expressing neuroendocrine cells has been postulated to exist; therefore, they are androgen-independent so that they establish autocrine and paracrine networks to regulate growth and differentiation independently of the androgenic stimulus.55

There are not many currently existing reports demonstrating the usefulness of this radiotracer in this rather infrequent process in a large number of patients, and most publications have therefore been case reports demonstrating its usefulness, where it can be indicated in patients not responding to androgen-deprivation therapy with PSA elevation and where no disease is evidenced by other radiotracers (used in PET/CT) (Fig. 9)56,57.

**CONCLUSION**

There is substantial progress in the development and research of new radiotracers used by nuclear medicine for PC. A large volume of scientific literature has been produced over the past few years, demonstrating the potential usefulness of nuclear medicine in PC for a wide variety of indications. These advances have enabled better treatment selection for patients. Our better understanding on the early detection of local and distant recurrence is giving way to better assessment of patients with increased PSA levels after therapy, thus enabling the administration of novel therapies, including 223Ra, 177Lu-PSMA, and 225Ac.

We hope these advances in molecular imaging may contribute to increase patient's quality of life and decrease PC-related mortality.

**DECLARATION OF INTEREST**

The authors declare not having any conflicts of interests.

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