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Special collaboration

Importance of ^{68}Ga-PSMA PET/CT in hospital practice. View of the radiation oncologist☆

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ABSTRACT

Radiotherapy is a treatment with curative intent, both in patients with primary diagnosis of prostate cancer (PCa) and in patients presenting with biochemical recurrence after radical prostatectomy (RP). Moreover, the use of stereotactic body radiotherapy (SBRT) as a metastasis directed therapy in patients with oligometastatic PCa has significantly increased in the recent years. Conventional imaging techniques, including transrectal ultrasound, computed tomography, morphologic magnetic resonance and bone scintigraphy have traditionally played a minor role in all those clinical scenarios due to its low diagnostic accuracy. The recent development of the PET radiotracer ^{68}Ga-PSMA binding to the prostate specific membrane antigen (PSMA), a transmembrane glycoprotein overexpressed in PCa cells, has shown promising results. Detection rates for PCa lesions are higher than CT and higher than the best technique available, the PET/CT with choline. Its superiority has been demonstrated even at very low PSA levels (<1 ng/ml). This increase in diagnostic accuracy represents a potential impact on patient management, especially in radiotherapy. Even if this imaging technique is already available for routine clinical practice in some European countries, in Spain, unfortunately, there is very limited access. In this review, we analyze the main studies that investigate the usefulness of ^{68}Ga-PSMA PET/CT in patients with PCa and its potential impact on radiotherapy treatments. In addition, we compared the ^{68}Ga-PSMA PET/CT, with the multiparametric magnetic resonance imaging (mpMRI) and the PET/CT with choline, in the different clinical scenarios.

PET/TC con ^{68}Ga-PSMA, importancia en la práctica hospitalaria. Visión del oncólogo radioterápico

Palabras clave:
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Cáncer de próstata
PET-Colina
RM Multiparamétrica
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RESUMEN

La radioterapia es un tratamiento curativo indicado en pacientes con cáncer de próstata (CaP) primario y en aquellos con recurrencia bioquímica tras prostatectomía radical (PR). Además, recientemente, ha habido un aumento en el uso de técnicas de alta precisión como la radioterapia estereotáctica fraccionada corporal (SBRT) para tratar un número limitado de metástasis en pacientes con CaP oligometastásico. Las pruebas de imagen convencional (ecografía transrectal, tomografía computerizada (TC), resonancia magnética morfológica y gammagrafía ósea) tienen un papel menor en estos escenarios, debido a su bajo rendimiento diagnóstico. Recientemente, se ha desarrollado el radiotrazador ^{68}Ga-PSMA, para la tomografía por emisión de positrones (PET), que es un ligando del antígeno de membrana especifico de próstata (PSMA), una proteína transmembrana sobrexpresada en las células del CaP. Sus resultados son prometedores, con tasas de detección de lesiones tumorales mayores que la TC y mayor que la mejor técnica disponible actualmente,

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la PET con Colina. Su superioridad es más evidente en pacientes con valores bajos de PSA (<1 ng/ml). Esta mejora en el rendimiento diagnóstico representa un potencial impacto en el manejo terapéutico, especialmente en radioterapia. A pesar de que la prueba ya está disponible en la práctica clínica diaria de otros países europeos, en España su uso es muy limitado. En esta revisión, analizamos los principales estudios que investigan la utilidad de la PET/TC con ^{68}Ga-PSMA en pacientes con CaP y su potencial impacto en los tratamientos de radioterapia. Además, comparamos la PET/TC con PSMA, con la resonancia magnética multiparamétrica (RMmp) y la PET/TC con Colina, en los distintos escenarios clínicos.

Introduction

Radiotherapy is a curative treatment which is indicated in both patients with primary prostate cancer (PC) and in those with biochemical relapse following radical prostatectomy (RP).[1] In the last years there has been an increase in the use of high precision techniques such as fractionated stereotactic body radiation therapy (SBRT) for treating a limited number of metastases in patients with oligometastatic PC.[2] The success of treatment planning with radiotherapy requires imaging techniques with a high sensitivity and specificity for diagnosis. Positron emission tomography/computerized tomography (PET/CT) with ^{68}Gallium prostate-specific membrane antigen (^{68}Ga-PSMA) is a molecular imaging technique based on the detection of overexpression of the PSMA in PC. In recent years this technique, together with multiparametric magnetic resonance imaging (mpMRI), has shown to be the best technique to detect recurrence following RP, especially in patients with low prostate specific antigen (PSA) levels (<1 ng/mL).[3,4] In these patients the use of ^{68}Ga-PSMA prior to rescue radiotherapy can modify the planning of radiotherapy treatment in up to 19% of patients.[5] In patients with oligometastasis and a favorable prognosis, this radiotracer allows the administration of therapies aimed at metastases.[2] Finally, ^{68}Ga-PSMA PET/CT also seems to play an important role in the initial staging of PC prior to curative treatment.[6]This review analyzes the most relevant evidence regarding the impact of ^{68}Ga-PSMA PET/CT on radiotherapy treatment of patients with PC. We also compare the utility of PET/CT with PSMA with mpMRI and PET/CT with choline in different clinical scenarios.

What a radiation oncologist should know about PSMA PET/CT

The PSMA is also known as glutamate carboxypeptidase II, and it is a transmembrane amino acid, glucoprotein type II, which is overexpressed in PC. The PSMA is expressed in most PCs, and its expression is increased in poorly differentiated, metastatic and castration-resistant carcinomas.[7–9] Once bound to PSMA the ligand is transported to the interior of the cell by a process of endocytosis which introduces the molecule into the interior of the cell. The exact function of the PSMA is unknown, but some studies have suggested that it may have a role in the activation of the mitogen-activated protein kinase (MAPK) pathways, conditioning resistance to apoptosis.[10] The PSMA is an attractive target for the detection, treatment and follow-up of PC because of its elevated concentrations in almost all prostate adenocarcinomas, its localization on the cell surface and its absence in the bloodstream.

The PSMA presents a lower intensity of physiologic expression in the kidney and digestive system as well as in non prostatic tumors and some benign diseases.[11–13]

The PSMA was first identified in 1987 as a target of the monoclonal antibody 7E11-C5. The first attempt to use PSMA as a target in molecular imaging was the radiotracer ProstaScint (Capromab Pendetide; EUSA Pharma, Langhorne, PA). At present, ProstaScint is practically no longer used since the antibody used binds in the intracellular epitope of PSMA, and thus, the necrotic part of the prostatic tumors is mainly detected and not the viable tumor cells, thereby reducing the sensitivity.[14] In addition, it has all the limitations of imaging with antibodies, such as an elevated circulating time or a low permeability.

Other recently developed strategies use small low molecular weight molecules also called PSMA inhibitors or PSMA ligands. These small molecules have a greater permeability in solid tumors, improving the pharmacokinetics in normal tissues and leading to an increase in the signal-to-noise ratio and facilitating the detection of very small sized lesions (4 mm of diameter). These molecules contain the three groups of carboxylic acids needed for binding to PSMA. These ligands or PSMA inhibitors were first described in 2001 by the group of Kozikowski and collaborators.[15] Since then several groups have developed small PSMA inhibitor molecules each of which is labeled with a different radioisotope (^{111}In, ^{99m}Tc, ^{18}F, ^{131}I, ^{68}Ga). The most widely used is ^{68}Ga-PSMA-HBED-CC also known as ^{68}Ga-PSMA-11.[16] This radiotracer can be synthetized in hospitals in which a ^{68}Ge/^{68}Ga generator is available. Radiolabeling is quite a simple procedure, especially since the appearance of cold kits with vials of lyophylized PSMA-11 (ANMI S.A., Belgium). The radiotracer can be obtained with these kits by simply introducing the isotope ^{68}Ga inside the vial, following the same concept as with ^{99m}Tc.

One of the limitations of the use of the isotope ^{68}Ga is its short half-life of 68 min, which complicates its distribution to hospitals without their own generator. The number of doses that can be obtained with a generator of ^{68}Ga depends on the activity of the generator, although it is true that despite having a greater activity, the number of doses obtained is very limited (for 3 or 4 patients). These limitations can be avoided by using isotopes with a longer half-life which are produced in a cyclotron as in the case of 18-Fluor (^{18}F). This radiotracer is widely used for ^{18}F-fluorodeoxyglucose (^{18}F-FDG). At present, there are basically two fluorated radiotracers under development, ^{18}F-PSMA-1007 and ^{18}F-DCFPyL, both with a similar biodistribution but with the advantage of presenting minimum physiological activity in the bladder, thereby facilitating the detection of apical prostatic lesions.[17] The choice of a PSMA radiotracer labeled with ^{68}Ga or ^{18}F depends on the national legislation for the use of ^{68}Ge/^{68}Ga generators (presently approved by the European Medicines Agency), its availability, the possibility of production and distribution of the cyclotron, the number of patients scanned per day as well as the clinical indication.

PSMA PET/CT in initial staging. Impact on primary radiotherapy treatment

The accuracy of the conventional staging techniques in PC is low, with frequent underestimation of the volume of the disease.[18–20] In addition to the advances in mpMRI for the evaluation of intraprostatic disease,[3] new molecular techniques studied in different