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PET–CT with (68 Ga)Gallium-Labeled PSMA Ligand for the Diagnosis of Prostate Cancer: Clinical Applications and Protocols

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Abstract The detection of lesions in the context of biochemical recurrence of prostate cancer is a major challenge for all imaging modalities. Recently, the prostate-specific membrane antigen (PSMA) is recognized as a novel target for the PET–CT (positron emission tomography–computed tomography) imaging of prostate cancer with the tracer ^{68}Ga-PSMA (^{68}Gallium-labelled PSMA), mainly in the detection of relapses and metastasis. PSMA PET–CT imaging shows high tracer uptake at the sites of primary tumor and lymph node, and bone metastasis in direct correlation with aggressiveness and Gleason scores. PSMA PET–CT seems to be a highly accurate imaging tool for restaging of prostate cancer patients with biochemical recurrence, and it proved to be clearly superior in detecting prostate cancer lesions at low PSA levels when compared to other methods.

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Introduction

Prostate cancer is the most common neoplasm in men. In absolute terms, it is the sixth most common type of cancer in the world and most prevalent in men. In the United States, 220,800 new cases of prostate cancer were estimated in the year 2015. It is the second leading cause of tumor with the highest estimate of death, surpassed only by lung cancer and bronchus [1].

Most prostate tumors consist of localized neoplasia, which exhibit slow growth rate and require high potential for cure. However, it is necessary to have sufficiently accurate methods for diagnosis, detection of local recurrence, and lymph node involvement, which entails a more difficult task for most conventional imaging methods.

There are great expectations for new radiopharmaceuticals emitting positrons to optimize the primary stage, local recurrence detection, metastasis, and to predict the level of seriousness of the disease. The prostate-specific membrane antigen (PSMA) is a marker of prostate cancer, and since its expression is increased in the presence of metastasis and tumor recurrence [2], it may represent an important diagnostic and therapy tool in treating these patients.

Biodistribution and Pathological Concentration in Prostate Cancer

PSMA is a type II cell surface transmembrane glycoprotein with intracellular and extracellular components that are present in normal prostate tissue, but entailing much larger

expression (100–1000 times) in primary cancer and the metastatic lesions [3]. It can also be found outside the prostate gland, as in the neovasculature of many solid tumors [4], in the kidney, in some subtypes of bladder carcinoma [5], pancreas, lung tumors, and schwannomas [6]. A low level of expression is demonstrated in the small intestine, proximal tubule kidney, salivary glands, and brain.

The normal biodistribution of PET–CT with ^{68}Ga-PSMA consists of intense uptake in kidneys and in the salivary glands, as well as moderate absorption in lacrimal glands, liver and spleen, and, of a lesser magnitude, in the gastrointestinal tract [7•] (Fig. 1). PSMA is concentrated especially in the proximal small intestine; however, there may be uptake in other intestinal segments. The absorption in the colon reflects the PSMA expression in colonic crypts in populations of neuroendocrine cells or in areas of physiological regeneration [8]. Usually, no activity is evidenced by the gall bladder and bile ducts.

It is also possible to observe concentration of the radiopharmaceutical in the nasal mucosa, which can be explained by PSMA expression in tissue regeneration zones or by a blood pool effect.

PSMA uptake in the celiac ganglion should be carefully assessed, as it is usually related to physiological concentration and can be mistaken with secondary neoplastic involvement [9•].

A study carried out by Oromieh et al. [7•] has measured the average and maximum values of SUV (SUV_{mean}/SUV_{max}) in the brain, lacrimal glands, parotid, submandibular glands, lungs, blood, mediastinum, liver, spleen, head of pancreas, intestines, and kidneys at 1 and 3 h after injection. The average SUV values showed less variability than the maximum values. However, the study itself proposes the use of the maximum SUV value due to its greater reproducibility between researchers. It was also possible to observe that malignant suspicious lesions showed excellent contrast in images taken after 1 h of injection, even at low levels of prostate-specific antigen (PSA).

In prostate tumor, PSMA expression generally increases with the increase in Gleason scale [10], and hence, the study with ^{68}Ga-PSMA may prove to be helpful to facilitate the assessment of metastasis and/or malignant transformation of prostatic tissue. There is an increase in PSMA expression in advanced stages and in the lesions resistant to hormonal castration. Several studies have reported that the PSMA expression levels increase according to the tumor stage and tumor level [8].

Both the metastatic lesions and the recurrent lesions of prostate cancer present excellent contrast if compared to the background radiation, which contributes to the increase in the detection rate of suspect lesions, even with low levels of PSA. Some authors believe that the detection rate increases with the increase in PSA level and the tumor size; however, it is noted that even small lymph nodes metastasis presents optimum contrast. In addition, ^{68}Ga-PSMA can detect undifferentiated prostate carcinoma lesions, i.e., tumors which produce minimum levels of PSA, despite multiple metastasis and low initial Gleason score [7•].

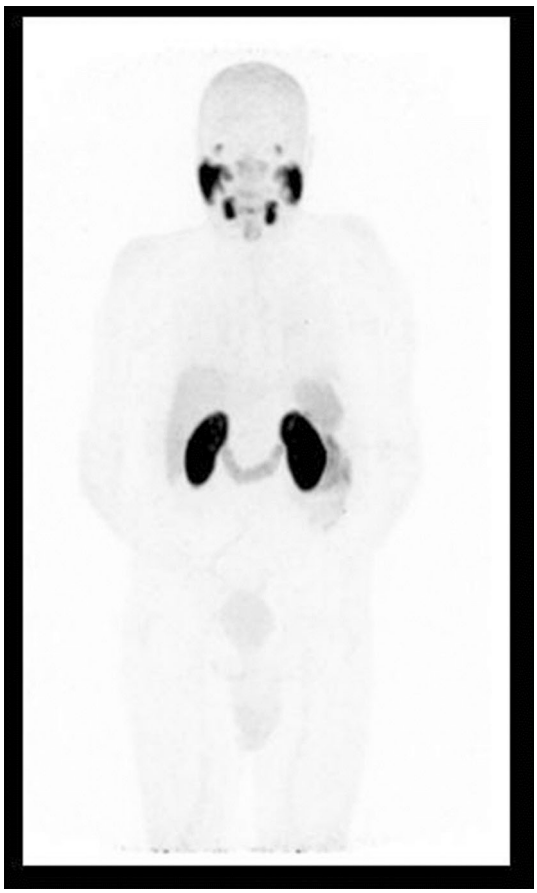

Fig. 1 Normal biodistribution of ^{68}Ga-PSMA showing intense uptake in kidneys and in salivary glands, moderate level in lacrimal glands, liver and spleen, and, of a lesser magnitude, in the gastrointestinal tract, especially the proximal small intestine

Patients presenting PSA < 1.0 ng/mL may present negative PET–CT PSMA. However, some studies have showed that even with PSA below such level, the positivity rate was about 50 % [11].

Image Protocol

^{68}Ga-PSMA solution should be introduced to patients as intravenous *bolus*, whose average activity is 2 MBq/kg [12•]. Fast or any other kind of preparation is not necessary.

There are differences between the image protocols, especially when it comes to the first images. The first

images of the pelvic region can be taken 5 min post-injection (early images), in order to minimize the artefactual effect caused by radiopharmaceutical accumulation in the urinary bladder, which could affect the assessment of possible uptake lesions in the pelvic region [13].

The capture of delayed images until 3 h after the radiopharmaceutical injection and the use of diuretics can avoid interference of the urinary bladder activity, optimizing the analysis of lymph nodes metastasis or other adjacent lesions.

Firstly, computed tomography (CT) is obtained 60 min after the radiotracer injection [14], with low-dose protocol and with or without the use of iodinated contrast [12•]. When iodinated contrast is used, the images are obtained preferably in the portal phase (around 40–80 s after intravenous injection of iodinated contrast [14]), followed by PET screening, covering the surface from the skull to the proximal third of the lower limbs.

Comparing the high-dose CT with the use of iodinated contrast, the low-dose CT has been shown to be sufficient for anatomical localization and characterization of lesions with concentration of ^{68}Ga-PSMA [14].

Late PET images with 2, 3, or 4 h after injection can also be obtained in order to assess the possibility of increase in the concentration of the radiopharmaceutical in the target lesions. However, PET–CT with ^{68}Ga-PSMA performed 60 min later has become a standard procedure, according to the literature published to date, since there is still a small number of statistically reliable publications regarding images obtained at different times. A more detailed analysis is needed with a greater number of patients in order to demonstrate the importance of images at different times after injection of the radiopharmaceutical, including the early images [14].

Clinical Applications of PET–CT PSMA, and Comparative Assessment of PET–CT Results with Other Imaging and Perspective Methods

Primary Diagnosis of Prostate Cancer

The transrectal biopsy of prostate neoplasia is guided by ultrasound (US) directed systematically in different segments of the gland without the direction of a focal lesion. This technique has low sensitivity for cancer detection, since random samples may miss lesions (especially previous injuries) or present a few fragments of the damage, only by detecting the low-level portion [15], without clinical significance, but that requires follow-up and repeat biopsy.

Biopsy guided by MRI is more accurate in detecting the lesion, however, the procedure requires the use of specialized expensive materials, and extended time in the room. Recently, promising results have been published with the use of image fusion platforms using MRI and US for biopsies of specific prostate lesions. To date, there are a limited number of prospective studies evaluating the cancer detection rates with the US–MRI image fusion platforms. Although the merger of US–MRI images has proven to be of value in patients with previous negative biopsies, the general use of this technique in the diagnosis of prostate cancer should only be carried out after some critical analysis. There is a need for more prospective studies to assess and validate the technique [16].

Some prostate neoplastic lesions are not detected by MRI; in these patients it is paramount that further assessment through molecular imaging with PET–CT be carried out [17]. Some studies have shown good PET–MRI results in directing biopsies of neoplastic lesions in the prostate. Eiber et al. assessed 53 patients and compared the diagnostic performance of ^{68}Ga-PSMA HBED-CC with PET–MRI for primary prostate cancer location with multiparametric magnetic resonance imaging (mpMRI) and PET alone. MpMRI, PET, and PET–MRI have detected cancer in 66, 92 and 98 % of patients, respectively. The study, therefore, has concluded that PET–MRI PSMA increases accuracy for localization of prostate cancer if compared to mpMRI and PET alone [18].

In the assessment of primary prostate tumor, ^{18}F-FDG has low sensitivity in the detection and, thus, few practical application. Most tumors are well differentiated and indolent or intermediate, and, therefore, have low attraction to glucose. Moreover, urinary excretion of ^{18}F-FDG with accumulation in the bladder and ureters renders it difficult to assess the prostatic bed and regional lymph nodes [19]. In some specific scenarios, such as in the case of highly aggressive tumors with Gleason score 9–10 and PSA above 20.0 ng/ml, PET–CT could be indicated.

Primary Staging of Prostate Cancer

In the primary stage, ^{68}Ga-PSMA showed increased specificity and sensitivity in detecting lymph node, bone and visceral metastasis, compared to the methods of conventional imaging (CT, MRI, and bone scintigraphy) in patients with prostate cancer whose primary risk was intermediate or high. A retrospective analysis of 130 patients with intermediate to high risk prostate cancer, who underwent radical prostatectomy with lymphadenectomy, showed sensitivity and specificity of ^{68}Ga-PSMA at 65.9 and 98.9 %, respectively, in lymph node staging [20].

PET–CT with FDG also does not contribute to the primary staging because it has low sensitivity in assessing regional lymph nodes due to low uptake, but this fact is also related to urinary activity. Moreover, metastatic

osteoblastic lesions cannot likewise present radiopharmaceutical uptake [19].

Staging of Recurrent Prostate Cancer

Despite the need for further studies in order to obtain a more accurate assessment as to their possible indications, most scientific papers highlight PET–CT with ^{68}Ga-PSMA as a promising imaging method in assessing the restaging of prostate cancer with biochemical recurrence. Detection of recurrence even in early stage is possible, also taking into account the low levels of PSA (<0.5 ng/mL) [5, 14]. It is worth highlighting that the increase in PSA levels may precede clinically detectable recurrence in months or years (Fig. 2).

PET–CT with ^{68}Ga-PSMA may show suspicious lesions with high rates of sensitivity and specificity, and sharp contrast as regards the areas of physiological uptake [5, 14], clearly showing to be better than the conventional imaging methods, especially in assessing lymph node involvement (Fig. 3).

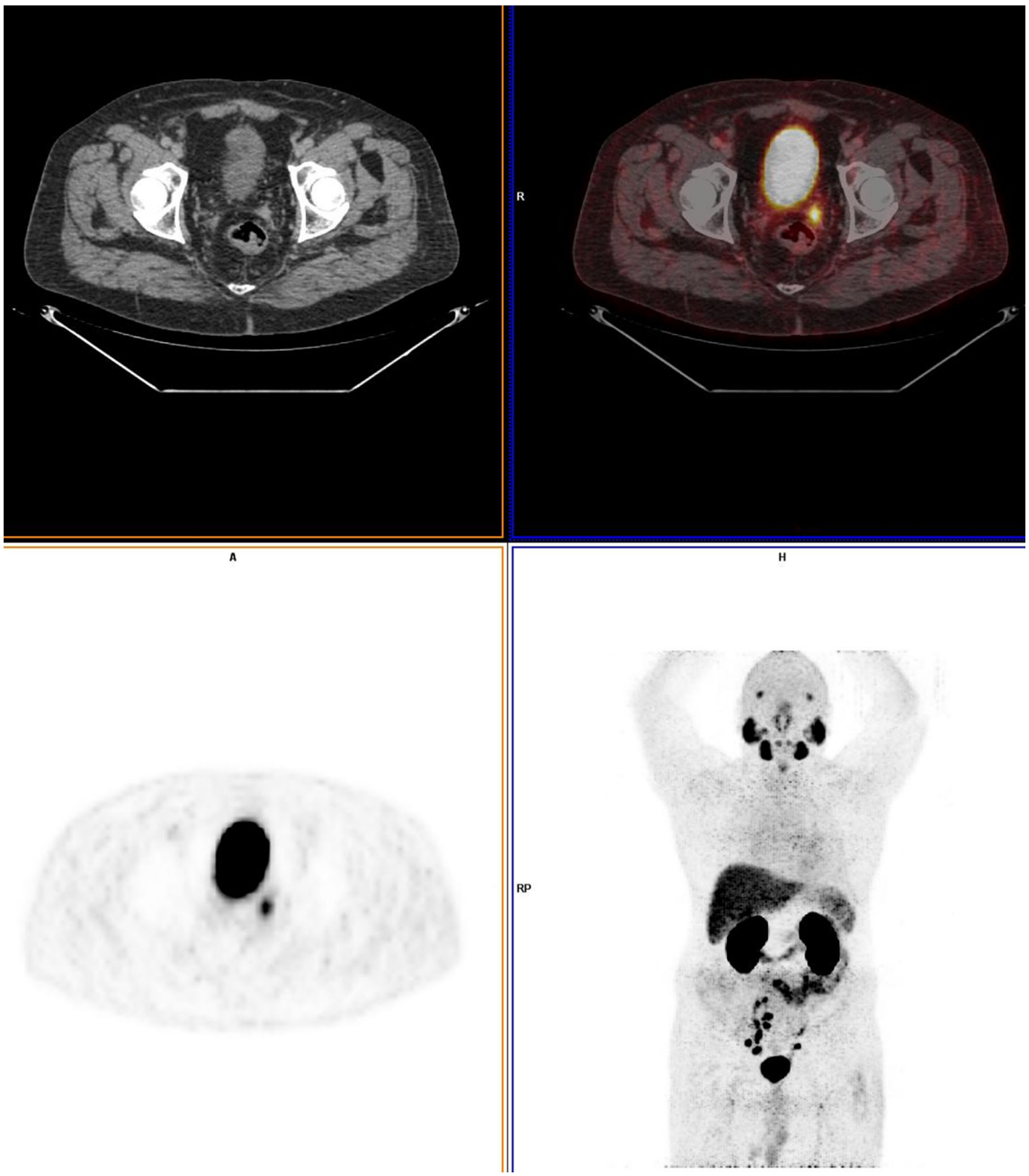

Fig. 2 Set of images of a 68-year-old patient with status after radical prostatectomy and PSA value of 36.0 ng/mL. Tissue formation identified in the paramedian position on the left of the seminal vesicles, measuring 1.5 cm, showing radiopharmaceutical uptake (SUVmax = 11.5)

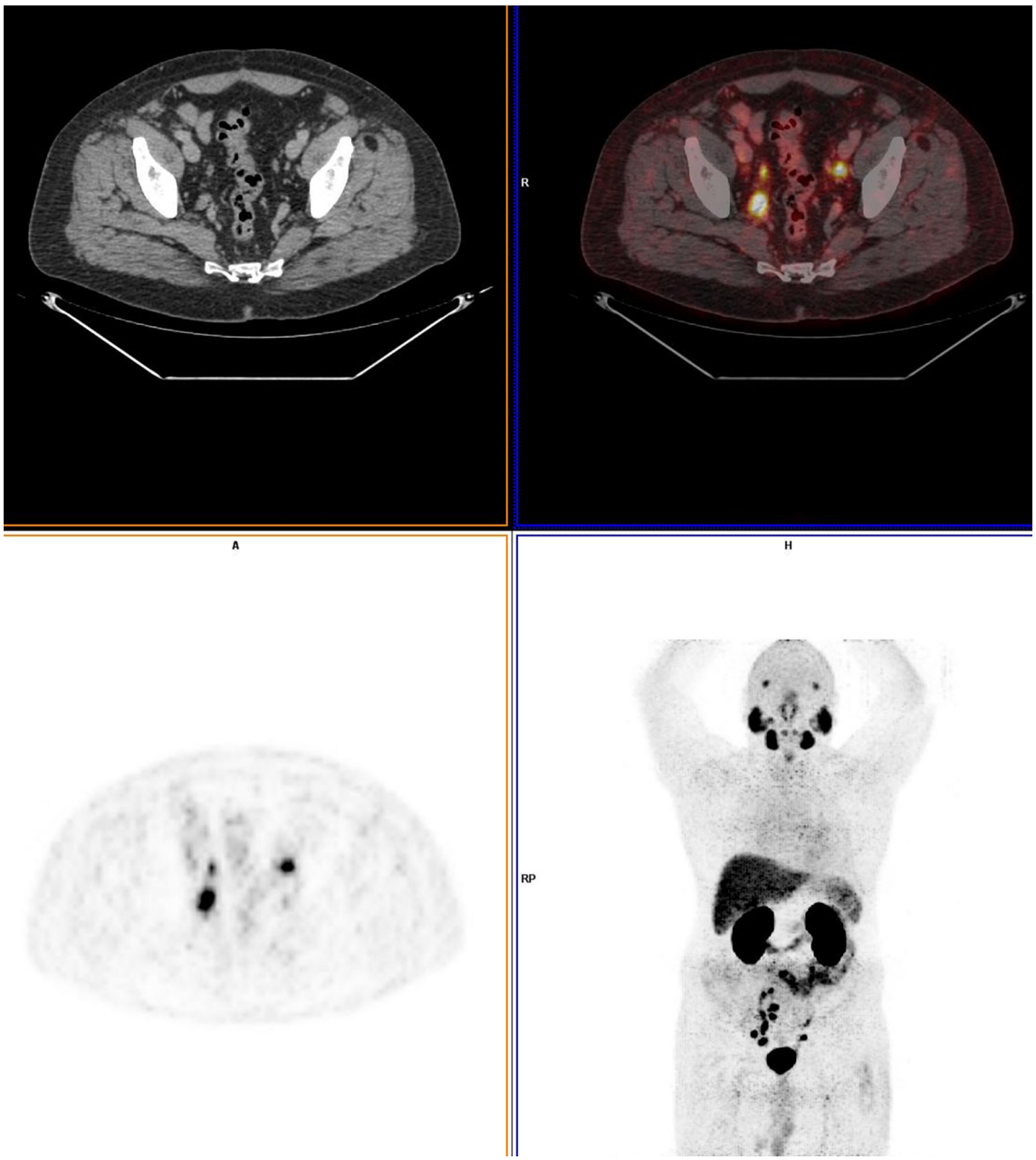

Fig. 3 CT images reveals subcentimetric lymph nodes with corresponding PET and fused PET–CT images showing intense uptake (SUVmax = 18.2), with high lesion-to-background ratio. Whole-body maximum-intensity projection displays right common iliac, right internal iliac, and left external iliac lymph node metastasis with PSMA uptake

The PSMA expression does not seem to significantly change with hormone therapy. It may represent a useful marker of response/control in patients using anti-androgenic drugs.

Rescue radiotherapy in patients with recurrence after radical prostatectomy is more efficient for serum PSA values at <0.5 ng/ml [21]. Thus, radiation therapy should be started as soon as possible. The conventional bone scan scintigraphy and CT have low detection rates of metastatic lesions in biochemical recurrence after curative treatment. So these studies are recommended for symptomatic patients or those who have PSA levels at >10 ng/mL [22] (Fig. 4).

^{18}F-choline does not have the ability to identify small lesions, especially in patients with serum PSA values at <2 ng/mL [23], and therefore is not generally recommended in the initial stages of recurrence.

Afshar-Oromieh et al. analyzed 78 lesions characteristic of prostate cancer using ^{68}Ga-PSMA, compared to 56 lesions that were detected in patients undergoing PET–CT

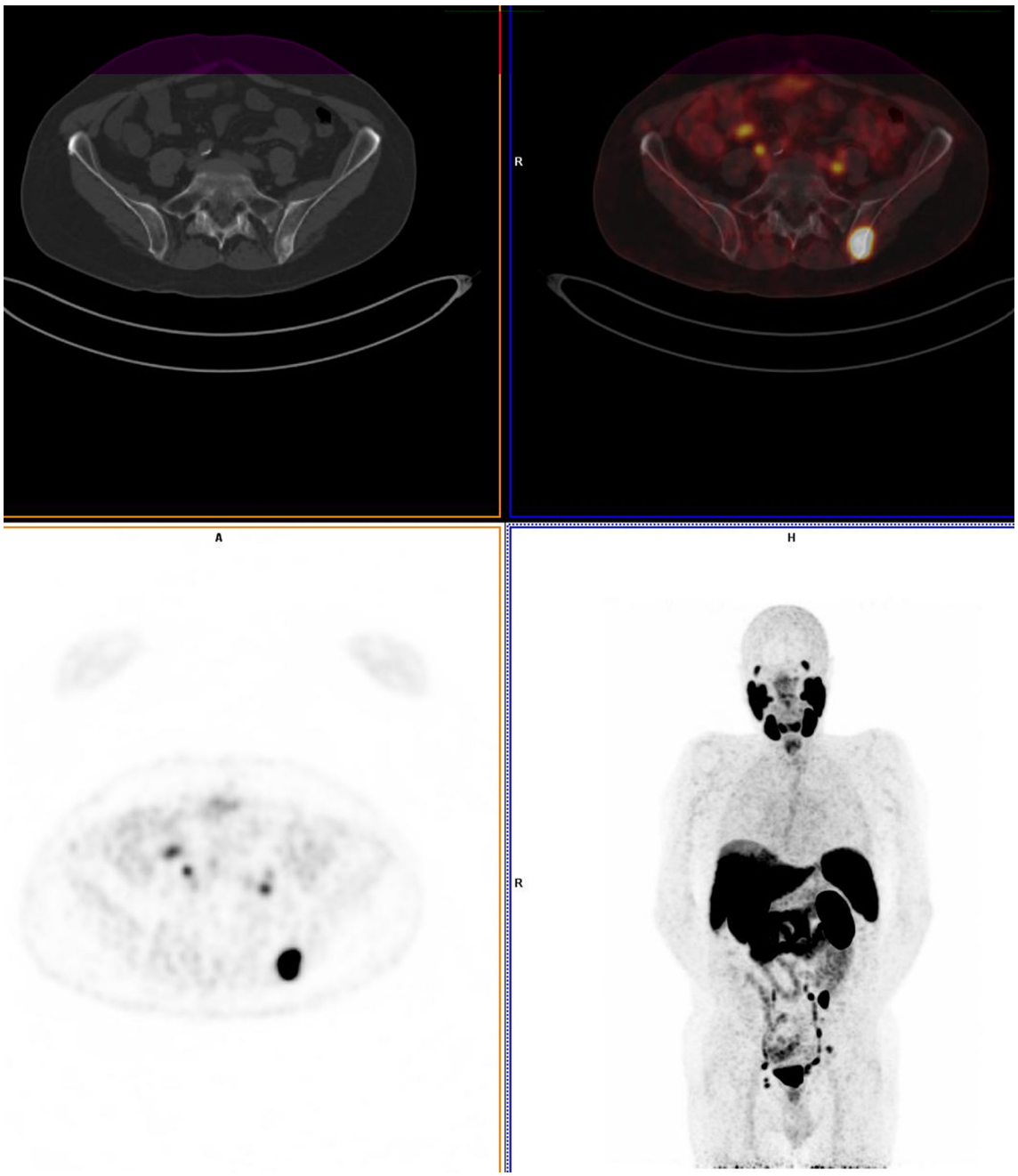

Fig. 4 CT images of a 73-year-old man, with a PSA value of 4.7 ng/ml, showing a sclerotic lesion in the posterior left iliac bone, with an intense ^{68}Ga-PSMA uptake in PET–CT (SUVmax = 20.9)

with ^{18}F-choline, and all lesions evidenced by ^{18}F-choline were also viewed by ^{68}Ga-PSMA. For the lesions identified by PET–CT with ^{68}Ga-PSMA, maximum SUV was clearly higher in 62 of the 78 tumor lesions, and the ratio of tumor/background radiation was clearly higher in 74 of the 78 lesions when compared with ^{18}F-choline. Therefore, PET–CT with ^{68}Ga-PSMA can detect lesions characteristic of prostate cancer with higher contrast when compared to ^{18}F-choline standard, especially at low levels of PSA [24].

Eiber et al. assessed the use of ^{68}Ga-PSMA in the detection of prostate cancer in 248 patients with biochemical recurrence after radical prostatectomy, showing high detection rates even at low levels of PSA. The detection rate for PSA at $\geq$2.0 ng/ml was 97 %, for PSA between 1.0 and 2.0 ng/ml was 93 %, for PSA between 0.5

and 1.0 ng/ml was 73 %, and PSA at <0.5 ng/ml was 58 %. The detection rate reported for the ^{68}Ga-PSMA was higher than detection rates for ^{11}C and ^{18}F-choline, which showed 40–60 % for detection at levels of PSA lower than 3.0 ng/ml [13].

The use of PET–CT with FDG is limited in biochemical recurrence and will depend on PSA levels. The FDG sensitivity is higher with the increased PSA. The study may prove to be useful in patients with PSA levels at >4.0 ng/ml or in most aggressive cases when there is resistance to hormonal castration.

Other Applications

^{68}Ga-PSMA can also be used in radioguided surgery to facilitate intraoperative identification of metastatic lesions which have radiotracer concentration.

In patients with multiple metastasis at advanced stage, especially hormone resistant castration, the presence of concentration of ^{68}Ga-PSMA in lesions may indicate targeted radionuclide therapy with ^{177}Lu-PSMA. Some studies have demonstrated feasibility, safety, and efficacy of this treatment [25]. Therefore, proper selection and monitoring of patients through ^{68}Ga-PSMA PET–CT and treatment with ^{177}Lu-PSMA apply the concept of theranostics.

Conclusion

The current literature has shown that PET–CT with ^{68}Ga-PSMA is a promising tool in the assessment of patients with prostate cancer, due to the optimal target lesion/background radiation ratio and high rates of sensitivity and specificity in detecting lesions, even at low levels of PSA.

Most studies have highlighted the usefulness of PSMA PET–CT in evaluating patients with biochemical recurrence. In this situation this method clearly shows its superiority over conventional imaging methods. PET–CT with ^{68}Ga-PSMA shows good results in the initial staging and post-treatment restaging, even in the presence of antiandrogenic therapy. Moreover, this radiopharmaceutical was superior to ^{18}F-FDG and ^{18}F-choline in the same situation.

When associated with MRI, PET–CT with ^{68}Ga-PSMA can also aid in surgical planning.

Ongoing studies have shown encouraging results using PSMA labeled with lutetium-177 for the treatment of metastatic prostate cancer. However, prospective studies with larger numbers of patients are needed to assess the real impact on survival and justify their inclusion jointly with the other therapeutic options of this neoplasm.

Compliance with Ethical Standards

Conflict of Interest Letícia Rigo, Daian de Bona Pessoa, Anna Carolina Borges, Pricila Gama da Cunha, and Felipe Roth Vargas each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.
2. Kabasakal L, AbuQbeitah M, Aygün A, Yeyin N, Ocak M, Demirci E, Toklu T. Pre-therapeutic dosimetry of normal organs and tissues of (177)Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(13):1976–83.
3. Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528–39.
4. Chang SS, O'Keefe DS, Bacich DJ, Reuter VE, Heston WD, Gaudin PB. Prostate-specific membrane antigen is produced in tumor-associated neovasculature. Clin Cancer Res. 1999;5:2674–81.
5. Samplaski MK, Heston W, Elson P, Magi-Galtuzzi C, Hansel DE. Folate hydrolase (prostate-specific membrane [corrected] antigen) 1 expression in bladder cancer subtypes and associated tumor neovasculature. Mod Pathol. 2011;24:1521–9.
6. Wang W, Tavora F, Sharma R, Eisenberger M, Netto GJ. PSMA expression in Schwannoma: a potential clinical mimicker of metastatic prostate carcinoma. Urol Oncol. 2009;27:525–8.
7. • Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, Holland-Letz T, Giesel FL, Kratochwil C, Haufe S, Haberkorn U, Zechmann CM. PET imaging with a [68 Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging. 2013;40(4):486–95. *The importance of this study was to establish a normal pattern of concentration of PSMA in different segments and to evaluate its applicability for tumour imaging by calculating the ratio between radiotracer uptake in tumour lesions and background.*
8. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3(1):81–5.
9. • Krohn T, Verburg FA, Pufe T, Neuhuber W, Vogg A, Heinzel A, et al. [(68)Ga]PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. Eur J Nucl Med Mol Imaging. 2015;42(2):210–4. *In this article the authors demonstrate the importance of knowledge uptake in coeliac ganglia that can mimic lymph node metastasis.*
10. Perner S, Hofer MD, Kim R, Shah RB, Li H, Moller P, Hautmann RE, Gschwend JE, Kuefer R, Rubin MA. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Pathol. 2007;38:696–701.

11. Sterzing F, Kratochwil C, Fiedler H, Katayama S, Habl G, Kopka K, Afshar-Oromieh A, Debus J, Haberkorn U, Giesel FL. ^{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(1):34–41.
12. • Afshar-Oromieh A, 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(2):197–209. *^{68}Ga-PSMA-ligand PET/CT can detect prostate cancer in a high percentage of patients with suspected neoplasm* (82.8%). *Any uptake of 68 Ga-PSMA-HBED-CC in lesions above local background is highly specific for prostate cancer and must therefore be regarded as prostate cancer unless otherwise proven. This article provides an analysis of the diagnostic value of 68 Ga-PSMA-ligand PET–CT in a large cohort and the influence of several possibly interacting variables*.
13. Eiber M, et al. Evaluation of hybrid 68 Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med. 2015;56(5):668–74.
14. Ceci F, 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(8):1284–94.
15. Dimmen M, Vlatkovic L, Hole KH, Nesland JM, Brennhovd B, Axcrona K. Transperineal prostate biopsy detects significant cancer in patients with elevated prostate-specific antigen (PSA) levels and previous negative transrectal biopsies. BJU Int. 2012;110(2 Pt 2):E69–75.
16. Gayet M, Van der Aa A, Beerlage HP, Schrier BP, Mulders PF, Wijkstra H. The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: a systematic review. BJU Int. 2016;117(3):392–400.
17. Schimmoller L, et al. MR-sequences for prostate cancer diagnostics: validation based on the PI-RADS scoring system and targeted MR-guided in-bore biopsy. Eur Radiol. 2014;24:2582–9.
18. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, Beer AJ, Wester HJ, Gschwend J, Schwaiger M, Maurer T. Simultaneous 68 Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. Eur Urol. 2016. doi:10.1016/j.eururo.2015.12.053.
19. Jadvar H. Molecular imaging of prostate cancer: PET radiotracers. AJR Am J Roentgenol. 2012;199(2):278–91.
20. Maurer T, et al. Diagnostic efficacy of 68gallium-PSMA- PET compared to conventional imaging in lymph node staging of of 130 consecutive patients with intermediate to high-risk prostate cancer. J Urol. 2015. doi:10.1016/j.juro.2015.12.025.
21. Pfister D, et al. Early salvage radiotherapy following radical prostatectomy. Eur Urol. 2014;65:1034–43.
22. Beresford MJ, Gillatt D, Benson RJ, Ajithkumar T. 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.
23. Krause BJ, et al. The detection rate of [^{11}C]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.
24. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, Holland-Letz T, Hadaschik BA, Giesel FL, Debus J, Haberkorn U. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014;41(1):11–20.
25. Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wiessalla S, Schottelius M, Mueller D, Klette I, Wester HJ. Lutetium-177 PSMA radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. J Nucl Med. 2016. doi:10.2967/jnumed.115.168443.