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Comparison of ^{18}F-FDG, ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 in PET for prostate cancer

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ABSTRACT

Prostate cancer is the second most incident neoplasm in men, except for non-melanoma skin cancer, and has the second highest mortality rate in Brazil. Early diagnosis increases the chances of cure and enables a less aggressive treatment for the patient. Nuclear Medicine presents effective alternatives for prostate cancer diagnosis, such as Positron Emission Tomography (PET) or PET and Computed Tomography (PET/CT) imaging. The aim of this study is to compare the advantages and disadvantages of the radiopharmaceuticals ^{18}F-FDG, ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 used for PET or PET/CT in the diagnosis of this type of cancer. Compared to ^{18}F-FDG, ^{68}Ga-PSMA-11 has some advantages such as its availability by means of generators, the independent production of a cyclotron facility and its theranostic potential. The disadvantages compared to ^{18}F-FDG are the scalability of ^{18}F-FDG production compared to limited generator production. Despite its favorable characteristics, the radiopharmaceutical ^{18}F-FDG has limitations in the diagnosis of some types of tumors, such as prostate cancer. The recently studied radiopharmaceutical ^{18}F-PSMA-1007 has shown potential in the identification of small lesions in cases of prostate cancer and local recurrence. All the favorable and unfavorable aspects of these three radiopharmaceuticals are presented in this work.

Keywords: **prostate cancer, Positron Emission Tomography ,^{18}F-FDG, ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007**

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1. INTRODUCTION

Cancer is one of the main causes of mortality worldwide and is considered a global public health problem that has been generating a high economic and psychosocial burden [1].

The number of new cancer cases is directly related to the Human Development Index (HDI), and the number of cancer cases in countries with low and medium HDI, such as Brazil, is even more exacerbated [2, 3].

The Global Cancer Observatory (GLOBOCAN) provides updated estimates of the number of new cancer cases worldwide. In the year 2020 the number of cancer cases was 19.3 million, and the number of deaths was approximately 10 million people [1].

Due to the coronavirus pandemic (COVID-19) access to health services has been reduced, by the closure of many of these services, affecting the number of cancer diagnoses and treatments in the year 2020, this may increase the number of cases diagnosed in advanced stages in the coming years and consequently there will be an increase in the mortality rate [4].

Through the statistics and data provided by the National Cancer Institute (INCA) on the estimated number of cancer cases in Brazil for the triennium 2020-2022, it is estimated that 625 thousand new cases of cancer will occur, and the neoplasms that will most affect men with the exception of non-melanoma skin cancer, will be respectively: prostate (29.2%), colon and rectum (9.1%), lung (7.9%), stomach (5.9%) and oral cavity (5.0%); for women with the exception of non-melanoma skin cancer, breast (29.7%), colon and rectum (9.2%), cervix (7.5%), lung (5.6%) and thyroid (5.4%) cancers will have the highest incidence [5].

This work will focus on prostate cancer, because it is the fifth most recurrent neoplasm in the world and the second most incident in men. It is known that early diagnosis increases the chances of cure and enables a less aggressive treatment for the patient [6].

The Ministry of Health currently does not recommend national programs for prostate cancer screening in the country. There is guidance for performing exams such as rectal touch and Prostatic Specific Antigen (PSA) [7]. Nuclear medicine presents effective alternatives for prostate cancer diagnosis, such as Positron Emission Tomography (PET) or PET and Computed Tomography (PET/CT) imaging.

This work will focus on the radiopharmaceuticals ^{18}F-FDG and ^{68}Ga-PSMA-11, which are the most widely used in routine PET/CT scans in nuclear medicine. The recently developed radiopharmaceutical ^{18}F-PSMA-1007 has been generating interest for production and commercialization in Brazil for use in PET/CT will also be addressed. The objective of this work is to compare the use of these radiopharmaceuticals in the diagnosis of prostate cancer by means of PET scans, addressing their advantages and disadvantages.

2. MATERIALS AND METHODS

The methodology used in this work consisted of a survey of data in the literature, comparing the advantages and disadvantages of the radiopharmaceuticals ^{18}F-FDG, ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 for the prostate cancer with PET and PET/CT.

The results obtained are presented in the next item of this work.

3. RESULTS AND DISCUSSION

The radiopharmaceutical ^{68}Ga-PSMA-11 has limitations such as its shorter half-life and the limited number of doses produced when compared with ^{18}F-FDG that can be produced in scale and has a longer half-life, making it possible to transport it to locations far from the production center [8]. In the year 2016 the Heidelberg University Hospital in Germany developed the radiopharmaceutical ^{18}F-PSMA-1007, that shows potential for use in PET for prostate cancer, in the same year ^{18}F-PSMA-1007 was granted a patent by the German cancer research center ABX Advanced Biochemical Compounds, with the registration of the ^{18}F-PSMA-1007 patent, the radiopharmaceutical production centers had their production limited, which affected the studies and research published [9].

Table 1 presents the advantages and Table 2 presents disadvantages of using the ^{18}F-FDG radiopharmaceutical, which is the most widely used in PET in Brazil.

Table 1 - Advantages of the radiopharmaceutical ^{18}F-FDG.

Advantages
It is the most widely used in diagnostic PET imaging in oncology, because glucose metabolism is elevated in tumor cells
Its half-life of 109.7 min enables full body imaging
Despite its lower efficiency in diagnosing prostate cancer, studies show that ^{18}F-FDG can influence the clinical management of patients with this type of cancer (from no treatment to treatment in 25% of the cases after PET scanning with ^{18}F-FDG)
In patients diagnosed with bone metastasis ^{18}F-FDG can distinguish metabolically active from inactive lesions
PET with ^{18}F-FDG may be useful for staging advanced prostate cancer in patients with high PSA levels (despite treatment) and in patients without any treatment

Source: According to references [10,11,12,13,14,15,16].

Table 2 - Disadvantages of the radiopharmaceutical ^{18}F-FDG

Disadvantages
Its accuracy in detecting prostate cancer is lower, due to the low metabolic rate of this type of tumor and its excretion through the urinary tract
Excretion through the urinary tract affects the identification of lesions in this region due to the proximity of the prostate to the bladder
Prostate cancer tumor cells have a low glucose metabolism, which makes it difficult to evaluate tumor cells from benign tissue or inflammatory lesions in the prostate (prostatitis)
Low sensitivity in the identification of bone and pelvic lymph node metastasis
PET with ^{18}F-FDG is not useful in the evaluation of advanced prostate cancer in patients who are on treatment and have a low PSA level
False positive result may occur in cases of prostatitis
High uptake in inflammatory cells and healthy organs, which can lead to false-positive results

Source: According to references [10,11,12,13,14,15,16].

Table 3 presents the advantages and Table 4 the disadvantages of using the radiopharmaceutical ^{68}Ga-PSMA-11 only in the diagnosis of prostate cancer through PET and PET/CT. In Brazil, this radiopharmaceutical has been used since 2015.

Table 3 - Advantages of radiopharmaceutical ^{68}Ga-PSMA-11

Advantages
When compared with conventional imaging techniques, PET/CT with ^{68}Ga-PSMA-11 has a superior result in detecting cases of biochemical recurrence of prostate cancer
The use of this radiopharmaceutical has a significant impact on the clinical management of patients with prostate cancer, as well as in cases of biochemical recurrence and pre-surgical staging
In advanced stage or metastatic patients, PET/CT with ^{68}Ga-PSMA-11 has a high detection rate - 84% impacting clinical management by 61%.
In patients who have an elevated PSA level even after treatment, PET/CT with ^{68}Ga-PSMA-11 may assist in a change in treatment strategy
High benefit in the diagnosis of high-risk patients according to the D'Amico classification (PSA >20 ng/ml)

Source: According to references [17, 18, 19, 20, 21].

Table 4 - Disadvantages of radiopharmaceutical ^{68}Ga-PSMA-11

Disadvantages
Daily production limit, affecting the number of exams performed
High bladder activity and urinary excretion
Low image resolution due to the high energy of the emitted positron
Little benefit in diagnosing patients at low to intermediate risk according to the D'Amico classification (PSA <10 ng/ml to 20 ng/ml)

Source: According to references [17, 18, 19, 20, 21].

Table 5 presents the advantages and Table 6 the disadvantages of the radiopharmaceutical ^{18}F-PSMA-1007 which has favorable characteristics for use in PET for the diagnosis and staging of prostate cancer.

Table 5 - Advantages of radiopharmaceutical ^{18}F-PSMA-1007

Advantages
Low accumulation in the urinary system, facilitating the identification of small lesions in the pelvis and cases of local recurrence
Excellent image quality
Large-scale production, enabling the care of a large number of patients in clinical practice
High capacity to identify benign lesions in lymph nodes and bone lesions

Source: According to references [9, 20, 22, 23, 24].

Table 6 - Disadvantages of radiopharmaceutical ^{18}F-PSMA-1007

Disadvantages
High liver fundus, which can be a disadvantage in advanced stages of the disease (detection of liver damage)
Patent registration (limiting its production); reducing published studies and research
Less published data compared with ^{68}Ga-PSMA-11 and ^{18}F-FDG

Source: According to references [9, 20, 22, 23, 24].

A 2018 study looked at the clinical impacts of using ^{68}Ga -PSMA-11 in PET/CT for patients in biochemical recurrence of prostate cancer. It was concluded in this study that 39% of patients had their clinical treatment changed after PET/CT scans with this radiopharmaceutical. The changes occurred mainly in patients who had elevated PSA levels and in patients treated with radiotherapy instead of radical prostatectomy [25].

Another study, which also analyzed the clinical impact and changes in treatment of patients in biochemical recurrence of prostate cancer, after the use of ^{68}Ga-PSMA-11 in PET/CT. Significant changes occurred in the treatment of 53% of patients after this scan was performed, the changes were from focal to systemic treatment, changes in systemic treatment, among others [17].

The ^{18}F-FDG is the most used in PET/CT in oncology. Despite its favorable characteristics, this radiopharmaceutical has limitations in the diagnosis of some types of tumors, such as prostate tumors,

because of the generally low glucose uptake of cancer prostate cells, besides having a high uptake in inflammatory cells and healthy organs, which can lead to false-positive results.

A study was conducted with ^{18}F-PSMA-1007 and ^{68}Ga-PSMA-11 with the aim of comparing the accuracy of PET/CT diagnosis of patients at intermediate to high risk of prostate cancer. Both identified the dominant prostate lesions in patients with prostate cancer. However, based on visual analysis of the PET images the ^{18}F-PSMA-1007 could identify small lesions within the prostate that could lead to a false negative and identified low-grade tumors that may affect patient treatment. Comparative studies of ^{18}F-PSMA-1007 with ^{68}Ga-PSMA-11, the ^{18}F-PSMA-1007 demonstrate the potential of this radiopharmaceutical to identify low-grade lesions with clinical relevance [20].

A study of 102 patients undergoing biochemical recurrence after radical prostatectomy compared PET/CT images obtained using 18F-PSMA-1007 with images obtained using ^{68}Ga-PSMA-11. The ^{18}F-PSMA-1007 revealed five times more lesions of benign origin than the ^{68}Ga-PSMA-11, with 245 vs 52 lesions, the benign lesions were seen in lymph nodes, ganglions, and bone lesions [22].

A study comparing ^{18}F-FDG and ^{18}F-PSMA-1007 radiopharmaceuticals was performed, demonstrating that the detection rate of local lesions with ^{18}F-PSMA-1007 on PET/CT was higher than with ^{18}F-FDG, which could be explained by PSMA being a type II transmembrane glycoprotein, which is strongly overexpressed in prostate cancer cells (both in primary tumor and metastases) and low in benign prostate tissue. Another advantage is the hepatobiliary clearance of ^{18}F-PSMA-1007, while ^{18}F-FDG is excreted mainly via the urinary tract, the low activity of ^{18}F-PSMA-1007 in the urinary tract allows differentiation of primary tumor metastases and pelvic lymph nodes [26].

4. **CONCLUSION**

The radiopharmaceutical ^{68}Ga-PSMA-11 has been used in recent years in PET for the diagnosis of prostate cancer. Compared to ^{18}F-FDG, ^{68}Ga-PSMA-11 has some advantages such as its availability by means of generators, the independent production of a cyclotron facility and its theranostic potential. The disadvantages compared to ^{18}F-FDG are the scalability of ^{18}F-FDG production compared to limited generator production ; the ability to transport ^{18}F-FDG to centers farther away from the production site as the shorter half-life of ^{68}Ga limits distribution to sites closer

to the production site, favoring in house production and the longer halflife of ^{18}F allows for late imaging, which can increase the detection rate, and it is possible to increase imaging time.

The radiopharmaceutical ^{18}F-FDG is the most widely used PET/CT in oncology. Despite its favorable characteristics, this radiopharmaceutical has limitations in the diagnosis of some types of tumors, such as prostate cancer, besides having a high uptake in inflammatory cells and healthy organs, which can lead to false-positive results. Despite its lower efficiency in diagnosing prostate cancer, studies show that ^{18}F-FDG can influence the clinical management of patients with this type of cancer (from no treatment to treatment in 25% of the cases after PET scanning with ^{18}F-FDG).

In recent years several studies have demonstrated the potential of the radiopharmaceutical ^{68}Ga-PSMA-11 in the detection of relapses and metastases of prostate cancer.

The radiopharmaceutical ^{18}F-PSMA-1007 presents low accumulation in the urinary system, facilitating the identification of small lesions in the pelvis and cases of local recurrence, high capacity to identify benign lesions in lymph nodes and bone lesions. Comparative studies of ^{18}F-PSMA-1007 with ^{68}Ga-PSMA-11 demonstrate the potential of this radiopharmaceutical to identify low-grade lesions with clinical relevance.

The ^{18}F-PSMA-1007 has a higher detection rate of local lesions when compared to ^{18}F-FDG, due to PSMA being highly expressed in prostate cancer cells (both in primary tumor and metastases) and poorly expressed in benign prostate tissue. The low activity of ^{18}F-PSMA-1007 in the urinary tract allows differentiation between primary tumor metastases and pelvic lymph nodes which is an advantage over ^{18}F-FDG that is eliminated in the urinary tract.

Available scientific studies indicate that images obtained with ^{18}F-PSMA-1007 have at least the same capacity for detection of prostatic neoplastic lesions (local and distant) as those obtained with ^{68}Ga-PSMA-11.

Compared to radiopharmaceuticals ^{18}F-FDG and ^{68}Ga-PSMA-11, the literature on the use of of the radiopharmaceutical ^{18}F-PSMA-1007 in PET for prostate cancer is still limited.

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