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THE SITUATION OF THE BRAZILIAN RADIOPHARMACY SCENARIO FOR DIAGNOSIS, TREATMENT AND STAGING OF PROSTATE CANCER

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ABSTRACT

Cancer is one of the biggest public health concerns in the world. In Brazil, itis the second largest cause of mortality in Brazil, according to the National Cancer Institute (INCA). The prostate cancer accounted for approximately 68.2 thousand new cases in the biennium 2018-2019. The diagnosis and response to treatment in prostate cancer is a significant challenge faced by oncologists and radiologists worldwide. The determination of this pathology and its stages can be confirmed by rectal examination, PSA dosage, abdominal and transretal ultrasonography, biopsy, magnetic resonance imaging (MRI), and nuclear medicine. However, even with complementary methods of PSA levels associated with advances in ultrasound and MRI technologies, the medical images have their limitations regarding diagnosis, staging, and prognosis. Both radiological imaging and PSA levels evaluation methods show high percentage of false positives and negatives during the screening due the confounding effects of benign prostatic hyperplasia and prostatitis. Therefore, other more specific and less invasive diagnostic methods such as PET/CT (positron emission tomography/computed tomography) and more recently, PET/MRI, are proposed. Such technologies bring molecular imaging as an essential tool in the diagnosis and staging of prostate cancer. In nuclear medicine, ^{11}C-Choline and ^{18}F-FCH radiopharmaceuticals were the gold-standard for several years for prostate cancer evaluation. Nowadays, the state-of-the-art worldwide for such purpose uses short-lived radiopharmaceuticals with greater effectiveness, i.e., ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007, ^{18}F-DCPL, among others. The objective of this work was to present the Brazilian scenario in industrial-scale production and the use of radiopharmaceuticals for diagnosis and staging of the prostate cancer. As a result, we found that only ^{68}Ga-PSMA-11 produced by ^{68}Ge/^{68}Ga generators with Good Manufacturing Practice (GMP) certificate is available in the Brazilian scenario.Unfortunately, we did not find reports of industrial-scale production of^{68}Ga-PSMA-11 by 68Ga production with cyclotrons,^{18}F-FACBC, Al^{18}F-PSMA-11, ^{18}F-PSMA-1007, ^{18}F-DCPyL, and ^{64}Cu-PSMA-617. To our knowledge, there is no cyclotron facility producing neither ^{68}Ga-PSMA-11 nor 18F-based radiopharmaceuticals for prostate cancer in Brazil. Our work encourages the Brazilian cyclotrons facilities to put strengthin production, development and distribution of such radiopharmaceuticals for diagnostic and therapy.

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INTRODUCTION

Cancer is one of the biggest public health concernsworldwide, responsible for one in eight deaths, which is higher than AIDS, tuberculosis, and malaria combined (Santos, 2018). In Brazil, cancer is ranked as the second-largest cause of mortality in Brazil. The South and Southeast regions together hold 56% of the estimated new cases of cancer inthe country, according to the INCA. The prostate cancer accounted for approximately 68.2 thousand new cases in the biennium 2018-2019 (INCA, 2017). The prostate is an exclusive gland with a fluid secretory

function, present in men. In general, the dimensions of the prostate are 3 cm long, 4 cm wide and 2 cm deep anteroposterior - classically referred to as "walnut" size. The average weight of a prostate gland at 20 years-old is 20g, and there is a growth of 0.4g/year starting from the age of 30 years (BERMAN, 2012). The prostatic fluid has basic pH, which is important to the process of vaginal alkalization and delivering the milky appearance of the semen and distinctive odor. Besides, it alkalizes the seminal fluid, improving sperm motility (HALL, 2011). The prostate cancer is characterized by its overgrowth, with a consequent decrease in the caliber and intensity of the urinary stream (CHAPPELL, 2005). Different ethnicities have an unusual incidence of prostate cancer. This is obviously due to genetics, but also to other factors such as lifestyle, environment, and diet, among many others that may increase the known risk factors. About ethnicity, for example, African descendants are more likely to develop prostate cancer, followed by Caucasians, Latins, Asians and Native American descendants (Goeckeler, 1984). Regarding the age, prostate cancer is also a classic tumor in elderly men. Only 2% of the cases occur in men younger than 50 years. The mean age of the patients with prostate cancer is 68 years old (Andrey Biff Sarris, 2018).

The diagnosis and response to treatment is a significant challenge faced by oncologists and radiologists worldwide. Genetic influences, sexual history, exposure to pathogens, industrial chemicals, urbanization, eating habits, hormonal metabolism, besides age and lifestyle, are postulated factors in the induction of the disease (Abouassaly, 2012). The diagnosis of this pathology and its stages can be confirmed by rectal examination, PSA dosage, abdominal and transrectal ultrasonography, biopsy, magnetic resonance imaging, and nuclear medicine.However, even with complementary methods of PSA levels associated with significant advances in ultrasound and MRI, the medical images have their limitations with diagnosis, staging, and prognosis. Conventional radiological imaging and PSA level evaluation is likely to present limited accuracy and specificity during the screening. It occurs because of the confounding effects of benign prostatic hyperplasia and prostatitis (Tonon, 2009). Therefore, specific and less invasive diagnostic methods, such as PET/CT and PET/MRI can support nuclear physicians. Hence, it brings molecular imaging as an essential tool in the diagnosis and staging of the disease of prostate cancer (Jeffrey, 2015). In nuclear medicine, ^{11}C-Choline and ^{18}F-FCH radiopharmaceuticals were the gold-standard for several years for the detection of prostate cancer. Currently, the state-of-the-art worldwide for this purpose are theshort-lived radiopharmaceuticals with greater effectiveness, i.e., ^{68}Ga-PSMA-11 (Hoffmann, 2018), ^{18}F-FACBC (Trover, 1995), Al^{18}F-PSMA-11 (OKA, 2007), ^{18}F-PSMA-1007 (Frederik, 2016) and ^{18}F-DCPL (Szabo, 2015). In this aspect, the objective of this work was to present the Brazilian scenario in industrial-scale production-level and the use of radiopharmaceuticals for diagnosis and staging of prostate cancer.

METHODOLOGY

A narrative literature review was performed using PUBMED database. A survey of the radiopharmaceuticals for prostate cancer diagnosis and staging using PET was performed using the following terms: "Brazilian nuclear medicine", "radiopharmaceuticals for prostate cancer", “Production of ^{18}F-PSMA-11 in Brazil”, “Production of ^{68}Ga-PSMA-11 in Brazil”, “Production of ^{18}F-FACBC in Brazil”, “Production of Al^{18}F-PSMA-11 in Brazil, “^{18}F-PSMA-1007 in Brazil” and “^{18}F-DCPyL production in Brazil”.

RESULTS

The first use of radioisotopes in Brazil and Latin America occurred in mid-1949 with the foundation of the Laboratory of Isotopes at the Faculty of Medicine of the University of São Paulo. It was possible after World War II due to a large task-force that was established to spread the peaceful use of nuclear energy. This project was called "atoms for peace" and was funded by some US-owned institutions in partnership with the US government.Followingthe Laboratory of Isotopes of the Faculty, a nuclear medicine clinic was organized in the Radiotherapy Service of the Hospital das Clínicas in 1954. The first application of radioactive iodine in the thyroid gland in Brazil hasstartedin this clinic (Santos, 2011). Nowadays, the clinic has become the Nuclear Medicine Service of the Radiology Institute of the Hospital das Clínicas of the School of Medicine of the University of São Paulo. In 70 years of nuclear medicine in the country, several advances have been achieved; however, there are lots of challenges in the way to surpass.The modernity of the diagnostics and treatments bring significant therapeutic advances and help the patient's journey against the prostate cancer. Furthermore, the treatments are not fully fundedbythe Brazilian Single Health System (SHS).The nuclear medicine has changed the history of several diseases, but it is still underused in Brazil. It has grown as a medical diagnostic tool and one need to join, by encouraging multicentric scientific research in the country and expanded access to the specialty through public health system. Currently, there are 434 nuclear medicine clinics in the country. This amount is insufficient for the Brazilian population. The countryranks the 25th position in the number of exams performed per year compared to other countries.

Nuclear medicine is not efficiently provided to the Brazilian population, especially by patients of the Brazilian Single Health System (SHS) due to the costs of examination. As a comparison, Canada performs 64.6 examinations per 1000 inhabitants/year,whilst Brazil makes only 2.5 in the same scale showing the need to spread the medical specialty in the country.More than 82% of the nuclear medicine procedures, which are funded by SHS, are performed in private clinics and hospitals. Only 6% of the country's nuclear medicine clinics are public (free costs for the patient). The high cost of nuclear medicine equipment, such as the SPECT (single photon emission computed tomography), PET/CT, PET/RM, reinforce this scenario. As a consequence of the price of the imaging equipment and the difficulty in obtaining the radiopharmaceuticals, only 23 are funded by SHS, out of 40 in the available portfolio in Brazil (Pozzo, 2014). The bureaucratic and financial issues that the medical specialty encounters reflect in the Brazilian scenario for the production and use of radiopharmaceuticals. The problematic situation of the Nuclear and Energy Research Institute (IPEN), the leading supplier for conventionalnuclear medicine, shows the current scenario of radiopharmaceutical production in Brazil.In May 2018, IPEN was prohibitedby ANVISA (Agency of Public Health Vigilance) to produce 16 radiopharmaceuticals. The agency stated that the number of employees and, mainly the production structure, was inadequate.The difficulties presented by IPEN, clearly reflect the challenges that every PET

radiopharmaceutical producers face in Brazil. The worse scenario is likely for private units due to the depreciation of the Brazilian currency against the US Dollar (CIEPLINSKI, 2018).It is noteworthy to say that 100% of the raw essentialmaterials for the ^{18}F-FDGproduction, the most important radiopharmaceutical, comes from abroad, and the trade balance has not favored Brazil in the last years. Thus, these difficulties increase the examination costs, reducing their accessibility, and hampering the growth of nuclear medicine in Brazil. Furthermore, the Dollar currency is much higher than the Brazilian, which directly impacts the importation of technology and, consequently, the production of new radiopharmaceuticals.

The radiopharmaceutical production in Brazil also faces several bureaucracies to obtain the legal licenses to produce the already-approved compounds worldwide institutions such as the FDA (Food and Drug Administration) in the USA (United States of America). These difficulties derive from the high cost of imported raw materials, patents, and the non-availability of precursors to Latin America.Due to everything that has been reported so far, it is notorious to say that there is a huge delay ofavailability of a new radiopharmaceutical between the world scenario and Brazil. The production of radioisotopes in Brazil began in 1963. However, in the world, radioisotopes were already produced since the discovery of artificial radioactivity by Irene and Joulie Curie in 1935 (Gilmer, 2011). For ^{18}F-FDG, the lag was much higher. The time interval between the first synthesis in the world and Brazil was approximately 30 years. In the staging of prostate cancer, nuclear medicine in Brazil had only a complementary role due to the technology and the radiopharmaceutical available until 1997. At that time, the specialty only monitored the evolution of bone metastases arising from prostate cancer. Furthermore, it was not possible to evaluate the stages before neoplasia. This type of follow-up was performed with SPECT using ^{99m}Tc-MDP(^{99m}Tecneo-methyl diphosphonate). Unlike the world scenario in the same year, brain tumor images were already acquired using PET scanners with the ^{11}C-Choline(Kosaka, 1997). In the palliative treatment therapy of pain due to the metastases, the delayof the availability of radiopharmaceuticalsbetween the world and Brazil would not be different.

In 1984, Goeckeler and colleagues obtained the synthesis of a new element, the Samarium-153-ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), and found that its concentration uptakewas mainly in the bones. After several applications, it was concluded that it was a good option for alleviation of pain due to the bone metastases from prostate, breast and lung cancers. The FDA and the International Atomic Energy Agency (IAEA) approved this radio pharmaceutical after extensive study of internal dosimetry and harmful effects. It has been used to reduce the pain of bone metastases in patients with prostate, breast, and lung cancer (Goeckeler, 1984).In Brazil, Samarium was first manufactured by IPEN in 1995 and applied in several study protocols with patients with all three types of cancer. Currently, ^{153}Sm-EDTMP is less used, at the request of oncologists to reduce metastatic pain and improve the life-quality of patients who cannot achieve pain relief through opioids. In 1997, the chance of implantation of PET technology in Brazil has begunwith the possibility of supplying ^{18}F-FDG by IPEN. In the next year, the first PET/SPECT system was installed in the radioisotope service of INSTITUTO DO CORAÇÃO- INCOR and replaced by the first dedicated PET in Brazil in 2002 (Robilotta, 2006). In 2004, Brazil effectively embraced the PET technology with the use of ^{18}F-FDG for the clinical oncology, detection and evaluation of recurrences and metastases, follow-up staging, and evaluation of therapeutic procedures. However, while Brazil was crawling with ^{18}F-FDG-PET, the world scenario for the diagnosis of prostate cancer had already showed that ^{18}F-FDG did not have a significant efficiency for prostate cancer and performed tests for the diagnosis or staging of prostate cancer using the ^{11}C-Choline radiopharmaceutical (Hossein, 2011). For start, it was not possible to have another radiopharmaceutical for prostate cancer in Brazil due to the very small half-life of ^{11}C (~20 minutes) and ^{18}F-NaF (bone metastasis) was also not produced by IPEN and the Nuclear Energy Institute (IEN). With the breakdown of the monopoly (EMC–49, 2006)regarding the production of radioisotopes in 2006, there was an increase in the number of cyclotrons and PET/CT equipment in Brazil, leading to the advances of nuclear medicine technology in the country.

Between 2006 and 2012, there is an expressive amount of clinical studies, performed in patients with prostate cancer with ^{11}C-Choline, ^{18}F-FCH, ^{11}C-Acetate, and ^{18}F-Acetate. According to the PUBMED database, more than 130 articles published in the literature regarded patients in biochemical recurrence after radical prosthectomy or, less frequently, after radiotherapy. Other studies were performed on patients in the initial staging of the cancer (Giampiero, 2017). In another hand, there were no studies of production of ^{11}C-Choline, ^{18}F-FCH, ^{11}C-Acetate, and ^{18}F-Acetate, by the radiopharmaceutical production units in Brazil at the same period. The ^{11}C-choline was extremely interesting and lasted for a long period as the gold-standard for prostate cancer worldwide. However, it did not provide the desired accuracy to the diagnosis when compared to prostate-specific membrane antigen (PSMA).The PSMA is overexpressed in prostate cancer and it is found in low levels in healthy organs such as the brain, kidneys, liver, etc. Because of this, the development of small molecules inhibiting the PSMA receptor, which carries radioisotopes to the tumor and is not impaired by the microvasculature ofthe cancer, has been encouraged.Therefore, since 2010, the PSMA has started to be much more studied with the possibility of labeling with the radioisotope ^{68}Ga (Sangeeta,2010).

In 2012, the world scenario presented ^{68}Ga-PSMA-11 for the diagnosis and staging of prostate cancer, establishing it as the new gold-standard in the molecular imaging for prostate cancer. The ^{68}Ge/^{68}Ga generators with good manufacturing practice (GMP) certificates were also presented commercially. In Brazil, there were already eleven cyclotron facilities in the country and eighty PET/CT equipment. In this scenario, after six years of flexibility of the monopoly of radioisotope production by the government, the amount of ^{18}F-FDG produced in Brazil increased from 3700 GBq to approximately 22.200 GBq per year (Facure, 2012). The year of 2012 was also a historical milestone for Brazil. The first system production of ^{68}Ga-PSMA-11 was installed via ^{68}Ge/^{68}Ga generator (Patrícia Nagber, RPH Company, Internal Communication). In the following year, the IPEN initiated attempts to produce ^{18}F-Acetate on an industrial scale. However, it was not worth to commercially sellit in Brazil because of the diagnostic effectiveness of ^{68}Ga-PSMA-11, already established and proven in the world literature (Carvalho, 2012). Also in 2013, the Center for the

Development of Nuclear Technology (CDTN), through the Research and Production of Radiopharmaceuticals Unit (UPPR) and the Center for Molecular Imaging (CIMOL), presented the production of ^{18}F-Choline and began an study protocols in with patients from the Hospital das Clínicas of the Federal University of Minas Gerais (UFMG)and the Luxemburgo Hospital (Minas Gerais). In Brazil, the increase in the number of clinics acquiring the ^{68}Ge/68Ga system for the production of ^{68}Ga-PSMA-11 raised the interest to bring therapy with ^{223}Ra.To improve the life-quality and survival of patients with prostate cancer, the Xofigo® (radio chloride (^{223}Ra)), used to treat adults with advanced castration-resistant prostate cancer, has been released. It is a branch of prostate cancer that does not respond to treatment that reduces male hormones.Xofigo® (radio chloride (^{223}Ra)) is used only when the disease has spread to the bones. It contains the radioactive isotope ^{223}Ra that mimics the calcium found in the bones. When injected into the patient, ^{223}Ra goes into the metastases and emits short-range radiation (alpha particles) that 'destroys' tumor cells (Paul G. Kluetz, 2014).Xofigo® entered the Brazilian market on July 14, 2015, approved by ANVISA.

In 2016, a research project that implemented the production of ^{11}C-Choline for local use was performed at the radiopharmaceutical production facility in Salvador, Bahia (Fernandes, 2016). In the next year, straight-forward studies on the production and quality control of ^{177}Lu-PSMA-617 were carried out at IPEN. However, such a radiopharmaceutical is still not commercially available (Silva, 2017). The following radiopharmaceuticals are available worldwide for diagnostics, treatment and staging for prostate cancer:^{18}F-FACBC, Al^{18}F-PSMA-11, ^{18}F-PSMA-1007, ^{18}F-DCPyL, ^{64}Cu-PSMA-617 (Han, 2017), ^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617 (Maarten, 2018).Unfortunately, onecannotfind reports of industrial-scale production of the same radiopharmaceuticals for diagnostic, treatment and staging in the Brazilian literature.
In the current world scenario, there is a concern to study of the efficacy of ^{18}F-FACBC, Al^{18}F-PSMA-11, ^{18}F-PSMA-1007, and ^{18}F-DCPyL fluorinated radiopharmaceuticals, which would be the gold-standard for diagnosis and staging of prostate cancer. However, there is the challenge of putting the production route into the industrial standards to make them commercial due to the patents of ^{18}F-PSMA-1007 and ^{18}F-DCP-L. In Brazil, there were more than 40 nuclear medicine clinics that use the ^{68}Ga-PSMA-11 radiopharmaceutical system from ^{68}Ge/^{68}Ga generators and 14 cyclotrons installed. In the literature, no reports of commercial or in-house productions of ^{68}Ga or ^{18}F were found via cyclotron, specifically for the labeling of PSMA or any of the fluorinated radiopharmaceuticals: ^{18}F-FACBC, Al^{18}F-PSMA-11, ^{18}F-PSMA-1007, and ^{18}F-DCP-L.

Conclusion

We presented in this work the currently status of the Brazilian scenario of the ^{68}Ga and ^{18}F-based radiopharmaceutical production-level to provide medical diagnostic imaging and treatment of prostate cancer. We highlighted the difficulties faced by the production facilities to encounter the same level worldwide in nuclear medicine. To our knowledge, there is a time gap between the world and the Brazilian scenarios regarding radiopharmaceutical for prostate cancer. Our work encourages Brazilian cyclotrons facilities to put strength to produce and distribute radiopharmaceuticals of diagnostic and therapy for use in this continental country.

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