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Basic principles and oncological applications of the ^{18}F-FDG PET/CT

Princípios básicos e aplicações oncológicas do PET-CT/^{18}F-FDG

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ABSTRACT: Positron Emission Tomography/Computed Tomography represents a technological leap for Nuclear Medicine and particularly for Oncology, as it is able to differentiate between benign and malignant changes based on semiquantitative data from the metabolism of radiopharmaceuticals by body tissues. The present work aimed to perform a narrative review of the main contemporary bibliographical surveys about the physical principles of ^{18}F-FDG PET/CT, their applications in Oncology and the technological advances of this methodology. This work was elaborated based on articles obtained from databases PubMed, SciELO and Microsoft Academic Search, with descriptors related to PET/CT and Oncology. The reviewed articles show that ^{18}F-FDG PET/CT is an important technique for obtaining morphofunctional images of the patient's body with great applicability in Oncology. The ^{18}F-FDG PET/CT is recommended in cases of identification and follow-up of tumor staging, monitoring therapeutic results against cancer and target planning in radiotherapy treatments. Furthermore, the development of more efficient mathematical algorithms and radiation detection systems in ^{18}F-FDG PET/CT improves image quality and reduces examination time.

Keywords: Positron emission tomography computed tomography. Fluorodeoxyglucose F18; Medical oncology.

RESUMO: A Tomografia por Emissão de Pósitron/Tomografia Computadorizada representa um grande salto tecnológico para a Medicina Nuclear e particularmente, para a Oncologia, visto que é capaz de distinguir alterações benignas e malignas com base em dados semiquantitativos da metabolização de radiofármacos pelos tecidos corporais. Este trabalho teve como objetivo realizar uma revisão narrativa dos principais levantamentos bibliográficos contemporâneos acerca dos princípios físicos da PET-CT/^{18}F-FDG, suas aplicações na Oncologia e os avanços tecnológicos desta metodologia. Este trabalho foi elaborado com base em artigos obtidos de bancos de dados como PubMed, SciELO e *Microsoft Academic Search*, com descritores relacionados a PET-CT/^{18}F-FDG e a Oncologia. A partir dos artigos analisados, observa-se que a PET-CT/^{18}F-FDG é uma importante técnica para a obtenção de imagens morfofuncionais do corpo do paciente com sensibilidade e especificidade, muitas vezes, superiores aos métodos convencionais de diagnóstico por imagem. Dessa forma, a PET-CT/^{18}F-FDG é recomendada nos casos de identificação e acompanhamento do estadiamento tumoral, monitoramento da taxa de resposta das terapias oncológicas e planejamento do alvo em tratamentos radioterápicos. Ainda, o desenvolvimento de algoritmos matemáticos e de sistemas de detecção de radiação mais eficientes na PET-CT/^{18}F-FDG melhoram a qualidade da imagem e reduzem o tempo de exame.

Descritores: Tomografia computadorizada com tomografia por emissão de pósitron; Fluordesoxiglucose F18; Oncologia.

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INTRODUCTION

The increasingly rapid evolution of Nuclear Medicine and the incorporation of new technologies that allow the advent of more sensitive and less invasive equipment contribute significantly to radiodiagnosis. In this context, the emergence of hybrid equipment had a major impact on diagnostic imaging. These devices have a high standard of diagnosis and are able to merge the functional images with the anatomical images through overlay software. Currently, the most accepted and used technology in clinical practice is composed of an integrated Positron Emission Tomography (PET) system with Computed Tomography (CT), providing greater ease in differentiating between physiological and pathological tissues[1].

PET/CT is an extremely important diagnostic tool for several areas of medicine, including Oncology. This technology has revolutionized the therapeutic approach to cancer in recent years, contributing to the choice of the most effective treatment for the patient and prognosis[2]. The evolution of PET/CT was accompanied by the development of several radiotracers, such as ^{18}Fluordesoxyglucose (^{18}F-FDG). ^{18}F-FDG PET/CT has established itself as a standard methodology in the study of lymphomas[3], however, currently its application in Oncology goes further, being used in staging, evaluation of therapeutic results and radiotherapy planning for other types of cancers. Thus, this work aims to address the physical principles of ^{18}F-FDG PET/CT and discuss its importance in oncopathological diagnosis, tumor staging, monitoring of therapeutic results and planning of radiotherapy treatment, as well as presenting some recent technological advances this methodology.

METHOD

This work is a narrative review developed through the search for scientific articles from June to July 2019. The articles selected and analyzed according to the title and summary were obtained from databases such as PubMed, SciELO and Microsoft Academic Search, in English and Portuguese, with no publication date limit. As inclusion criteria, original articles or case reports that addressed the physical principles of ^{18}F-FDG PET/CT and its role in tumor staging, monitoring of therapeutic results against cancer and planning of radiotherapy treatment were used, as well as works whose addressed the main technological advances of ^{18}F-FDG PET/CT.

DISCUSSION

Basic physical principles of ^{18}F-FDG PET/CT

Despite being interconnected, PET/CT is an equipment composed of functionally independent devices. Obtaining functional images of the organism by PET is only possible due to the administration of a positron-emitting radiopharmaceutical. The positron is the positively charged electron, or also called the electron antiparticle, emitted by some radionuclides through a process called beta decay. Among positron emitters, carbon-11 (^{11}C), nitrogen-13 (^{13}N), oxygen-15 (^{15}O) and fluorine-18 (^{18}F) are the most common radionuclides in Nuclear Medicine[4].

However, radionuclides themselves do not have chemical characteristics that favor their application in biological systems, requiring association with drugs. A very common association occurs between ^{18}F and a glucose analog called 2-deoxy-glucose (2-DG), giving rise to 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) or also called fluordesoxyglucose[5]. Although there are other radiopharmaceuticals that can be used in PET and PET/CT, ^{18}F-FDG has gained greater prominence mainly in oncological studies, since malignant neoplastic cells have high glycolytic rates, superior to the adjacent healthy tissues[6].

PET imaging is based on electronic coincidence detection. After the administration of the radiopharmaceutical into the patient's body, the emitted positrons interacts with the atomic electrons and annihilates, resulting in two photons with energy of 511 keV in opposite directions. These photons are captured by detectors consisting of scintillation crystals based on bismuth germinate (BGO), lutetium oxy-orthosilicate (LSO) or gadolinium silicate (GSO), coupled to photomultipliers present in the PET apparatus that convert the photons into signals electrical. Subsequently, mathematical reconstruction algorithms create three-dimensional images, showing the place of annihilation[7].

One of the greatest advances in Nuclear Medicine came after the association of PET with computed tomography (PET/CT). Unlike PET, CT obtains anatomical images of the body, whose acquisition occurs through the differential attenuation measure of X-ray beams by body tissues in the patient's transversal plane and computational reconstruction of the data obtained. When the X-ray beams transmitted by the patient's body reach the radiation detectors present in the equipment, the intensity of the generated signal is proportional to the incident radiation and the computer performs the correction and reconstruction of the image[8].

Although PET/CT is composed of hybrid equipment, the images are obtained separately and merged into a single exam, providing anatomical identification of the information obtained by PET. This technology makes data analysis more satisfactory, with reduced examination time and a wealth of details[9]. Through the image obtained from ^{18}F-FDG PET/CT it is possible to carry out a semi-quantitative analysis of the metabolism of radiopharmaceutical by the human body. For this, the

determination of the standard uptake value becomes one of the main parameters analyzed in oncology. Basically, the SUV calculation considers the activity of an area of interest in relation to that contained throughout the patient's body. In oncological studies, the maximum SUV value (SUV_{max}) is adopted, which refers to the region with the highest radiopharmaceutical uptake by the injury. Thus, $SUV(_{max})$ values have become one of the main parameters of analysis in PET/CT exams in several oncological studies[10].

^{18}F-FDG PET/CT *in tumor staging*

Tumor staging reflects the extent and identification of the disease in the patient's body, these findings being of great relevance for the prognosis and the choice of the best medical treatment. Computed Tomography and Nuclear Magnetic Resonance (NMR) are imaging methods routinely used to assess staging in various types of cancers, however, they have limitations because they are based on only anatomical and morphological analyzes[11]. In this context, PET-CT associated with ^{18}F-FDG corresponds to a tool superior to conventional methods, contributing decisively to the detection of tumors and their metastases[12].

^{18}F-FDG PET/CT has become one of the main clinical indications for the staging of Hodgkin's and non-Hodgkin's lymphomas, being considered a standard methodology for defining the therapeutic conduct of lymphomas due to its high sensitivity and specificity of diagnosis[13], in addition to better cost-efectiveness[14]. When incorporated into clinical practice, ^{18}F-FDG PET/CT changes the disease staging in a decisive way, as noted by Bednaruk-Młyński et al[15], in which the technique changed the stage of Hodgkin's lymphoma in up to 34% of patients, reflecting a change in cancer treatment in 21% of cases. More expressive results were observed in the study by Ahmed et al.[16], in which the technique altered clinical staging in 53% of patients diagnosed with lymphoma. Still, in the case of extranodal lymphomas, ^{18}F-FDG PET/CT is effective in detecting bone, splenic and bone marrow lesions[17], being able to replace conventional methods of detecting spinal cord injuries, such as biopsies[18].

In several cancer studies, the use of ^{18}F-FDG PET/CT significantly increases the detection of disease expansion through metastasis. In a study carried out by Zhou et al.[19] this methodology demonstrated a sensitivity above 90% in the detection of nodal metastases in people with non-small cell lung cancer, the combination of SUV_{max} with the tumor dimensions being extremely relevant for metastasis prediction in these patients. In patients with breast cancer, Abo-Sheisha et al.[20] showed similar results in the detection of secondary tumor sites by ^{18}F-FDG PET/CT (sensitivity of 97%), contrary to the data obtained by radiography and chest tomography , which had a sensitivity of 75%. Still, in a retrospective study conducted by Al-Muqbel[21], the information originated from PET/CT was not limited to the sensitivity of the method alone, the data obtained allowed us to conclude that bone marrow metastasis is an initial stage of secondary bone tumors in patients with breast cancer.

In some cases, the site of metastasis is unclear and the tumor is classified as a primary cancer of unknown origin (CPD). In this scenario, the ^{18}F-FDG PET/CT test proved to be highly efficient, as it has a sensitivity and specificity above 70% for the detection of primary sites in metastatic patients[22]. Noij et al.[23] obtained even more expressive data, in which the SUV_{max} quantitative information indicated sensitivity above 80% and specificity of 93% in the detection of primary head and neck cancer of unknown origin in patients with cervical metastases.

In addition to the identification of the primary tumor, ^{18}F-FDG PET/CT has the great advantage of providing the physician with changes in the conduct of therapeutic procedures. According to Lowe et al.[24], the findings of tumor staging by ^{18}F-FDG PET/CT altered the surgical treatment plan in 22% of patients diagnosed with head and neck squamous cell carcinoma. Tumor staging of ^{18}F-FDG PET/CT also contributes to the reduction of unnecessary surgeries, such as thoracotomies linked to lung injuries[25] or exploratory laparotomies in patients diagnosed with stomach cancer[26], among others.

PET-CT / ^{18}F-FDG in monitoring therapeutic results against cancer

The analysis of the therapeutic response against cancer is fundamental for the patient's prognosis. In 2000, a guide was created with several criteria to evaluate the efficiency of new anti-tumor treatments against solid tumors, called RECIST, which use morphological parameters to measure tumor reduction and disease progression[27]. In 2009, RECIST underwent a reformulation and, in addition to the morphological imaging methods already contained in this guide, the interpretation of the PET and PET/CT findings associated with the ^{18}FDG was included, giving rise to the term PERCIST[28]. Since then, ^{18}F-FDG PET/CT has become a great marker of effective therapeutic response, because, although widely used, anatomical imaging methods have significant limitations to monitor tumor reduction[29], since the tumor size changes more slowly compared to cell metabolism[30].

As it is a functional method based on the metabolization of ^{18}F-FDG inside cells, the results of ^{18}F-FDG PET/CT reflect the response rate of oncological therapies. Many chemotherapeutic agents act directly or indirectly, inhibiting the glycolytic metabolism of neoplastic cells[31]. Thus, in effective therapies against cancer, tumor cells reduce glucose uptake and, consequently, ^{18}F-FDG uptake. These changes in tumor metabolism can help with more appropriate therapeutic measures and even predict tumor recurrences[32].

The evaluation of ^{18}F-FDG uptake by PET/CT examination helps to identify patients who are responsive or not to anti-cancer treatments. In a prospective study, Zhao et al.[33] used the results of ^{18}F-FDG PET/CT to assess the response of patients with lung adenocarcinoma to chemoradiotherapy (CRT). In this case, the researchers observed a complete or partial response in 57.1% of post-CRT patients when applying the PERCIST criteria, contrary to 42.9% of the RECIST. Based on these data, ^{18}F-FDG PET/CT can be an important methodology for changing dosages and incorporating therapeutic reinforcements in future decisions. According to Vlenterie et al.[34], the PET/CT findings associated with PERCIST identified that 25% of patients with metastatic soft tissue sarcoma were not responsive to the two-week treatment with Pazopanib, suggesting ^{18}F-FDG PET/CT as an early biomarker to predict disease progression.

On the other hand, the analysis of the efficiency of the therapeutic response by the RECIST and PERCIST criteria may be inconsistent with each other. In a comparison between these two criteria, Sager et al.[35] showed that the metabolic findings of PET/CT were less efficient than the morphological results of CT and NMR in patients with hepatocellular carcinoma treated with yttrium-90 microspheres, however, were most significant for the treatment of colorectal cancer metastases. Similarly, other studies show that, despite being divergent in some cases, RECIST and PERCIST are important criteria for predicting the response of cancer to immunotherapeutic treatments[36].

Although the RECIST and PERCIST recommendations are comprehensive for the most varied types of cancer, specific criteria have been formulated for hematological cancers, such as lymphomas. These criteria are described in the international guidelines of Lugano, previously called Deauville[37,38], from which ^{18}F-FDG PET/CT can predict the early response to treatments for lymphomas and assist in defining the best therapeutic strategy. In addition, the persistence of ^{18}F-FDG uptake at the end of cancer treatment is associated with therapeutic failure and the high probability of lymphoma recurrence[39,40].

In addition to its importance in assessing the antitumor response of clinically approved therapies, the 18F-FDG uptake data are also relevant for the development of new therapeutic alternatives against cancer. In a study by Collantes et al.[41], model mice for osteosarcoma were treated with VCN-01 oncolytic adenovirus and the SUV_{max} values for ^{18}F-FDG showed high sensitivity of PET in the study of tumor growth reduction after treatment with the virus. In another study, carried out by Wang et al.[42], the reduction of ^{18}F-FDG uptake in mice treated with phosphatidylinositol 3-kinase inhibitor (PI3K) demonstrated the therapeutic efficiency of this substance against bone metastases from lung cancer.

^{18}F-FDG PET/CT *in planning radiotherapy treatment*

Radiotherapy is a powerful tool in the treatment of cancer patients, and the emergence of more accurate diagnostic modalities that assist in planning radiotherapy procedures is essential. In recent years, advances in imaging methods have been decisive for radiotherapy and the use of ^{18}F-FDG PET/CT is increasingly common in this context[43]. From the morphological and metabolic data obtained with this technique, it is possible to change the indication for radiotherapy, as well as the dosimetry for each patient[44,45].

One of the crucial points before undergoing radiotherapy is to identify and differentiate the tumor area from the adjacent healthy tissue[46]. Although CT is the gold standard in the tumor design, the data obtained by this technique may not efficiently define the limits of the lesion, which is why algorithms capable of combining PET images with those of CT[47] are used. In this case, the determination of tumor volumes is a central task in radiotherapy planning, highlighting the visible tumor volume, the target clinical volume and the target planning volume, whose acronyms are GTV, CTV, PTV, respectively: Gross Tumor Volume, Clinical Target Volume and Planning Target Volume)[46]. These volumes can be better delimited by means of the ^{18}F-FDG uptake data by cancer[48-49].

In a study evaluating the impact of ^{18}F-FDG PET/CT on radiotherapy planning for patients with non-small cell lung cancer, Zheng et al.[50] demonstrated that the merging of PET images with CT had altered GTV by 60% of patients when compared only to computed tomography. Similar data were obtained by Lee et al.[51], who observed a reduction in GTV based on ^{18}F-FDG PET/CT data in six of the ten patients analyzed with thoracic lymphoma. In another study, Yaraghi et al.[52] observed that in 40% of lung cancer patients, the comparison of $GTV_{PET/CT}$ and GTV_{CT} values showed tumor volume differences greater than 25%. Similarly, in the work of Dębiec et al.[53], $GTV_{PET/CT}$ was superior in 54% of patients with gastric cancer, reaching a value of approximately 49.7 cm^3 more than GTV_{CT}. Thus, assessing GTV changes can reduce interobserver variability in radiotherapy planning[48].

In the evaluation of the CTV, the studies also demonstrate discrepancies between the data from the isolated tomography and the ^{18}F-FDG PET/CT. When CTV values were analyzed in patients with esophageal cancer, PET/CT findings altered tumor demarcation in the cranio-caudal direction in 61% of patients, with 11% of the volume of $CTV_{PET/CT}$ outside the area demarcated by CTV_{CT}[54]. In a study of patients with laryngopharyngeal tumors, Ligtenberg et al.[55] observed that the values of $CTV_{PET/CT}$ and CTV_{CT} were also divergent, with the clinical volume of the target being reduced in the range of 45 to 52%, depending on the methodology used.

According to PTV, it is possible to assess the planned distribution of the radiotherapy dose, with PTV_{CT} often being insufficient for this purpose. Yaraghi et al.[52] used ^{18}F-FDG PET/CT images to assess the quality of radiotherapy planning in 20 patients with lung cancer. According to the data obtained, only 43% of the tumor volumes were correctly delineated by the values of GTV_{CT} and PTV_{CT}. Still, these researchers demonstrated that in 80% of patients, radiotherapy planning based only on PTV_{CT} does not cover the volume of treatment established by PET/CT. In a similar study, Leclerc et al.[56] show that the target volume of radiotherapy was significantly reduced in ^{18}F-FDG PET/CT compared to that of computed tomography in patients with oropharyngeal cancer, resulting in a decrease in the dose of radiation in the oral cavity and parotid. When analyzing data from $GTV_{PET/CT}$ and $PTV_{PET/CT}$ in patients with lung cancer, Vojtísek et al.[57] revealed that the incorporation of these two parameters significantly reduces the exposure of the esophagus, spinal cord and heart to treatment with radiotherapy, decreasing the probability of healthy tissue complications.

Technological advances of ^{18}F-FDG PET/CT

Since the emergence of hybrid imaging diagnosis systems, several researches have been dedicated to the improvement of these Nuclear Medicine methodologies, among which the ^{18}F-FDG PET/CT stands out. Recently, Zhang et al.[58] demonstrated for the first time a PET/CT system capable of obtaining diagnostic quality images of the entire body in about 30 seconds, unlike conventional devices, whose acquisition time can reach 20 minutes. In addition, this system was the pioneer in real-time tracking of the distribution of ^{18}F-FDG throughout the body, demonstrating its applicability not only in the study of cancer, but also in inflammatory and metabolic disorders. This new technology may be important for reducing the time of anesthesia or sedation in pediatric patients, as well as for those who cannot remain idle for long periods.

Several studies have focused on increasing the performance of ^{18}F-FDG PET/CT through the development of more efficient radiation detectors. Based on Silicon photomultipliers (SiPM), Vereos PET/CT[59] technology was able to digitally count the annihilation photons, reducing analog noise and increasing the volumetric resolution and method sensitivity[60]. The introduction of SiPM-based digital detectors in PET/CT devices has also resulted in improved diagnostic parameters in other studies. In a comparative study between conventional and digital PET/CT systems, digital technology showed a 54% improvement in image quality, an increase in tumor detection in 26.5% of cancer patients and a modification of tumor staging in 32% of cases[61]. In a similar study, Van Sluis et al.[62] showed an increase in sensitivity of approximately 70% when using digital ^{18}F-FDG PET/CT. Thus, PET/CT's digital technology can be considered an evolution in molecular imaging.

CONCLUSION

PET/CT is an important radiodiagnostic technique for obtaining morphofunctional images of body structures, whose efficiency and sensitivity can complement or surpass those of conventional imaging methods. Although there are other radiotracers to be used in PET/CT, PET/CT with ^{18}F-FDG remains the most used methodology in Oncology, since it enables the identification of tumors and the monitoring of the expansion of the disease, monitoring of therapeutic results against cancer and helps in better radiotherapy planning. In addition, research has been carried out to improve PET/CT systems, reducing the examination time and increasing the quality of the images obtained. ^{18}F-FDG PET/CT consists of a relevant diagnostic imaging tool and, therefore, must be widely disseminated in public and private health systems, as the clinical benefits generated by the technique outweigh the high cost.

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