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The Role of Positron Emission Tomography-Computed Tomography/Magnetic Resonance Imaging in Modern Medicine

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ABSTRACT

Positron emission tomography (PET) has been utilized in numerous aspects of medicine since its introduction and development in 1970s. There has been a rapid improvement in imaging techniques and radiotracers in the last decade, which have enhanced the quality of PET in different biomedical research domains and patient care settings. In this editorial we will discuss applications of PET-computed tomography (CT)/magnetic resonance imaging (MRI) as well as other radiotracers in different variety of malignant and non-malignant diseases such as cardiovascular, central nervous system, inflammatory and systemic diseases and review new concepts applicable to this imaging modality.

1. Introduction

Since the introduction of Positron Emission Tomography (PET) and 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG) in the 1970s as a molecular imaging technique and the expansion of its applicability in humans in 1976 by administration of FDG to humans by Alavi et al. [1], PET imaging has been utilized in the management of a wide range of diseases. Specifically, the last decade has witnessed a rapid expansion of PET utilization in many centers around the world [2, 3]. Advances in imaging systems such as implementation of PET/computed tomography (CT) time of flight [4, 5] and hybrid PET/magnetic resonance imaging (MRI) machines [6] as well as an expanding number of radiotracers such as radiolabeled nanoparticles (NPs), sodium ^{18}F-fluoride (Na^{18}F) [7] and ^{18}F-fluorodihydroxyphenylalanine (FDOPA) [8] among others, are increasing the application of this technique in different biomedical research domains and in different levels of patient care.

Despite the emergence of newly synthesized radiotracers, FDG still remains the most widely used radiotracer owing to its unique capabilities [2]. Due to structural similarities to glucose, FDG enters the cell using glucose transporters, but is not used as a substrate for glycolytic metabolism and cannot leave the cell. Therefore net accumulation of FDG occurs inside the metabolically active cells, such as malignant or activated macrophages. These factors make FDG an outstanding marker for tracing glucose metabolism as an illustration of tissue molecular behaviors (Figure 1) [9].

In this editorial we will review applications of FDG-PET as well as some other less commonly used radiotracers in a wide variety of malignant and non-malignant diseases including cardiovascular, central nervous system, inflammatory, infectious and systemic disorders. In addition to FDG, we will briefly discuss new concepts applicable to this imaging modality and the emerging role of PET-CT/MRI in medicine.

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2. Neoplastic Disease

With the introduction of FDG as a marker of malignancy and disease activity, FDG-PET has been extensively used for the diagnosis, staging, treatment, restaging, treatment monitoring and follow up of cancer patients [10-14]. Sensitivity and specificity of this functional imaging method has been reported to be 84% and 88%, respectively [15]. This performance has improved further by combining FDG-PET with CT scanning, which allows exact localization of the cancerous lesions [16-18]. The excellent diagnostic value of whole body FDG-PET for detection of regional and distant metastases has been discussed in several systematic reviews and meta-analyses [19-22]. It has been shown that preoperative PET can reduce unnecessary surgery in the newly diagnosed lung cancer patients [23]. Also, it has been shown that FDG-PET allows accurate staging and optimal management of non-small cell lung cancer patients, and provides prognostic value in this disease [24]. Results from the study of national oncologic PET registry have demonstrated change in the cancer management by physicians in many patients. Following availability of PET scan results, physicians decided to change their choice of imaging tool (53%), ongoing treatment (41%) and biopsy and watching (6%) during this trial. Their management plan changed more frequently if they noted poor prognosis based on PET compared to those, which revealed no change or improvement (78% vs. 40%). These changes were more toward continuing/starting treatments than stopping the treatments (28.3% vs. 8.2%) [25-27].

The radiotracer 3'- deoxy-3'- [^{18}F] fluorothymidine (FLT) has been used for imaging various malignancies [28] as a marker of cell proliferation. One of the potential advantages of this tracer is that it is somewhat specific for cell proliferation for malignant diseases. FDOPA is another radiotracer that targets dopamine receptors and is used for detecting neuroendocrine tumors and diagnosing movement disorders [29-31]. Gallium 68 with a half-life of 86 minutes is another widely used radiotracer. ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) somatostatin receptor scintigraphy PET imaging has been used to target somatostatin receptors in neuroendocrine or other tumors that express high number of these receptors [32-36]. Radiolabeled choline-based imaging tracers have been used in urogenital diseases. Choline is an essential phospholipid component of cell membranes and is increased with activity of choline kinase enzyme in prostate cancer. ^{11}C-Choline and ^{18}F-Choline have shown to be beneficial in restaging and further treatment of patients with prostate cancer [37].

3. Cardiovascular Disease

Cardiovascular disorders are the leading causes of death and morbidity in the industrialized societies. In recent years, investigators are rapidly shifting from diagnosis of atherosclerosis by conventional tools such as CT, MRI and angiography to detecting disease activity at molecular and cellular levels. This approach will allow prevention in early stages, and therefore, significantly reduce mortality and morbidity as well as health service costs. Clinicians presently employ ultrasonography, CT, and MRI to detect the presence or degree of arterial stenosis. However, these techniques are limited in their ability to detect inflammatory plaque while 70% of ruptures occur in plaques that have less than 50% stenosis. Thus, an ideal imaging modality should be able to detect the vulnerable/culprit atherosclerotic plaques. FDG-PET/CT holds the greatest potential for this purpose [38]. Using this method we are able to visualize the ongoing activity of atherosclerotic plaques and follow their response to therapy and even stratify patients into different risk groups [39-41]. Even after clinical diagnosis of atherosclerosis and myocardial infarction, FDG-PET could help physicians to determine myocardial tissue viability and whether the patients would benefit from revascularization interventions [42, 43].

Another promising radiotracer for cardiovascular disease is radioactive Na^{18}F, which exchanges with the hydroxyl group on hydroxyapatite of bone tissue and is an ideal tracer for early detection and quantification of active calcification and molecular changes in atherosclerotic plaque [44]. PET/CT imaging using Na^{18}F is a non-invasive imaging method for identification of calcification in atherosclerotic plaques and valvular structures of patients with coronary artery disease and aortic stenosis, respectively. Recent studies have suggested the ability of Na^{18}F to detect and localize high-risk and rupture prone atherosclerotic plaques [45].

Another radiotracer with potential for cardiovascular diseases is ^{18}F-labeled mannose (2-deoxy-2-[(^{18})F]fluoro-D-mannose) for detection of atherosclerotic plaque, which has been hypothesized to have considerable number of receptors in high-risk atherosclerotic plaques and is an isomer of FDG. This radiotracer might open new horizons in cardiovascular imaging [46].

4. Neurologic Disease

The central nervous system is an important domain for FDG-PET imaging, which can be used to assess neurologic and psychiatric disorders. Currently, the main focus of FDG-PET is on clinical assessment of brain tumors, seizure disorders, dementia and Parkinson's disease (PD). However, newly adopted quantitative methods may open new horizons in this field. Differentiation of tumor grade of malignant gliomas is one of the many indications of FDG-PET because of its specific patterns of glucose uptake in this cancer [47]. Contrast enhanced MRI, has an excellent spatial resolution, which makes it the current diagnostic standard for surgical management of central nervous system tumors. However, this modality cannot differentiate recurrent tumors from radiation necrosis or non-neoplastic lesions due to its inability to assess disease activity [47].

FDA approved the application of FDG-PET in the assessment of seizure disorder in 1994, enabling localization of active seizure site with increased cerebral glucose metabolism and hypo-metabolism in interictal states. Pre-surgical assessment of temporal lobe epilepsy using FDG-PET has been beneficial and Willmann et al. in their meta-analysis have shown its superiority over MRI and electroencephalography [48].

FDG-PET has been successfully employed to diagnose Alzheimer's disease (AD) with high accuracy. The classical pattern of hypo-metabolism in the temporoparietal lobes of the brain has been shown in these patients [49]. Recently, imaging probes targeting amyloid beta deposits, a pepide waste product mostly seen in brains of AD patients, have been introduced to the literature. Pittsburgh compound B (C11-PiB) was the first radiopharmaceutical for imaging of amyloid plaques. ^{18}F-florbetapir was another radiotracer, which was approved specifically for AD. However, there are still controversies regarding amyloid imaging [50, 51]. Other applications of FDG-PET/CT include discrimination of PD from essential tremor [52], differentiation and treatment response assessment of posttraumatic stress disorder [53], obsessive-compulsive disorder [54], schizophrenia [55], depression [56] and bipolar disorder [57] and tinnitus [58].

5. Infectious and Inflammatory Disease

Inflammation and infection has become a major domain for FDG-PET/CT imaging in recent years [59]. Inflammatory cells express high levels of GLUT receptors in their cell membranes with higher affinity for glucose, and therefore, demonstrate enhanced FDG uptake in these cells in the activated state. Several inflammatory diseases have been investigated by FDG-PET including

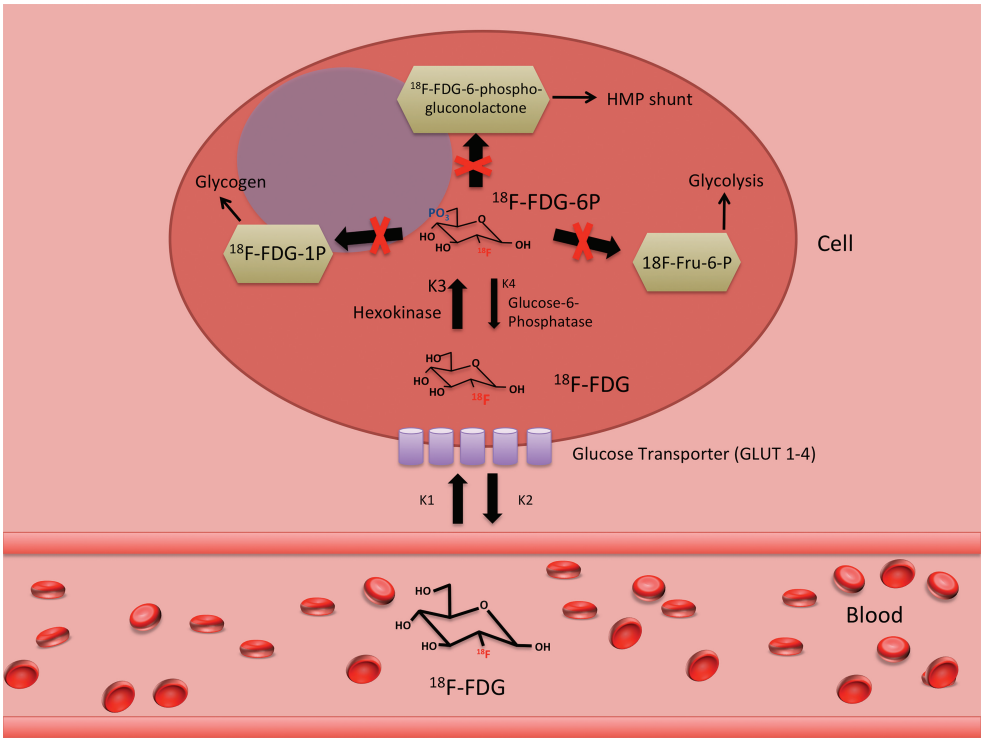

Figure 1. This figure demonstrates the steps FDG undergoes after entering the cell through glucose transporters of the cell membrane.

fever of unknown origin (FUO) [59], diabetic foot [60], vasculitis [61], sarcoidosis [62], inflammatory bowel disease (IBD) [63], rheumatoid arthritis [64], radiation induced lung inflammation and radiation pneumonitis[65], psoriasis [66] and venous thromboembolism (VTE) [67].

FUO is challenging to detect and characterize due to its diverse symptoms and etiologies and, during the last decades, has become one of the major disorders investigated by FDG-PET. Conventionally, FDG-PET is used to examine the whole body for detecting metabolically active lesions and hidden sites of infection with high sensitivity. This enables visualization of various hard-to-detect infectious conditions, including infective endocarditis, opportunistic infections in immunosuppressed patients, sepsis, occult bacteremia, and also indolent cancers. Combination of PET and CT can distinguish soft tissue infection from bone infection with high sensitivity in diabetic foot [60]. This imaging tool is beneficial in extra-pulmonary and clinically occult sarcoidosis [62]. Differentiation of HIV Differentiation of human immunodeficiency virus (HIV) associated lymphoma from HIV related reactive adenopathy is made possible by quantitative PET metabolic metrics [68].

It also provides additional information regarding extent of disease, treatment response assessment in IBD and prevents invasive diagnostic modalities [69, 70]. In recent years, the role of FDG-PET in IBD is being realized by the community. Knowledge regarding the activity and severity of inflammation in IBD would help physicians make informed decisions about treatment or follow up of these patients. Compared to standard methodologies such as colonoscopy and ultrasonography, FDG-PET has great sensitivity, specificity and accuracy in diagnosing active inflammation in children, especially in small intestine involvement [71, 72]. The same results have been noted in adults where FDG-PET has been compared to conventional and new diagnostic modalities including hydro-MRI, anti-granulocyte antibodies, and colonoscopy [63, 73, 74].

In recent years, FDG-PET imaging has been used to assess psoriasis and its systemic inflammatory and cardiovascular complications. Inflammatory sites have been shown in the skin, liver, joints, tendons and prominently in aorta. The latter findings suggest a close relationship between psoriatic skin inflammation and cardiovascular diseases [66]. FDG accumulation has been observed in rheumatoid arthritis (RA) and related complications including synovitis. Assessment of severity of synovitis, therapeutic response, cost-effectiveness, are among advantages of FDG-PET in RA [64].

There is a growing body of evidence regarding the applicability of FDG-PET for assessment of venous vasculature for VTE [67]. One of advantages of this imaging technique is its ability to differentiate acute from chronic VTE. One of advantages of this imaging technique is its ability to differentiate acute from chronic VTE, which will guide the physician to proper treatment plan.

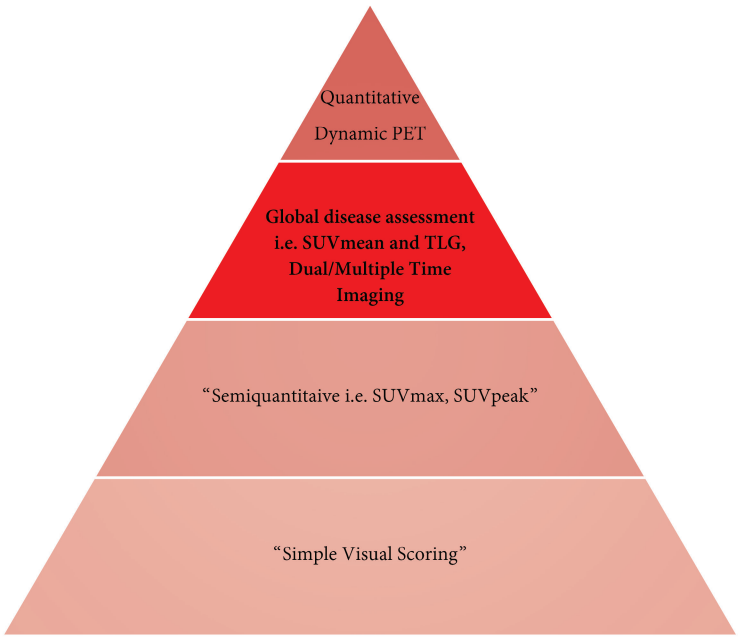

Figure 2. Hirearchial levels of PET measurement techniques.

6. Quantitative PET

In addition to qualitative interpretation by visual scoring, PET images can be assessed quantitatively by a wide range of measurements from semi-quantitative regional standardized uptake values (SUV) to global disease assessment, dual/multiple time point imaging, and using dynamic PET [63, 75, 76] (Figure 2).

7. PET/MRI

Up until recent years, PET and structural MRI images were fused electronically after being acquired separately by the respective instruments. Recently introduced devices are capable of concurrent PET and MR imaging and have overcome some of imperfections associated with the previously used method [6]. PET/MRI provides some unique advantages including high resolution soft tissue imaging, lower ionizing radiation exposure and offering a wide range of imaging protocols including diffusion-tensor imaging, diffusion-weighted imaging, MR spectroscopy, perfusion-weighted imaging and functional MR imaging [6]. Some drawbacks of MRI include motion effect and air borne artifacts affecting heart and lung imaging. Another important issue is attenuation correction for PET data based on MRI, which is not as accurate as PET/CT, especially when images include bony structures [6, 77-80]. comparative studies are needed to elucidate this modality can be of has added value over PET/CT in specific clinical settings [81].

8. Radiolabeled Nanoparticles

In recent years, NPs have been utilized for medical imaging with MRI, CT, and, to a lesser extent, with conventional nuclear medicine techniques. However, it is becoming increasingly clear that neither MRI nor CT is sensitive enough for detecting relatively limited number of signals that originate from these NPs in most organs and disease sites. In contrast, radiolabeled NPs with either single gamma emitters or positron emitting radionuclides are very encouraging for detection of inflammatory lesions in many organs. In particular, these preparations appear to have a promising role for assessing atherosclerosis in the heart and the arterial system. Further work is necessary to define the role of this new approach in medical imaging in the near future [41, 82, 83].

9. Summary

PET as a major modality in the field of molecular imaging, has revolutionized diagnosis, staging, treatment, follow up, prognostication, quantitative assessment and many other aspects of malignant, cardiovascular, inflammatory, infectious, neurologic and systemic disorders. The unique characteristics of this modality have made it an integral part of modern medicine. Combination of PET with structural imaging such as CT and MRI further enhanced the role of this modality. Discovery of new applications for existing radiotracers and the introduction of novel and new radiotracers are promoting the utility of PET imaging in many fields and open the door for further research and clinical applications that may minimize human suffering.

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