Is there still a place for SPET in the era of PET brain imaging?

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Abstract

Although positron emission tomography (PET) may be credited with providing the impetus for the new clinical interest in functional neuroimaging and currently is an increasingly important imaging tool for noninvasive assessment of brain tumors, single-photon emission tomography (SPET) has offered an alternative technique with the relative advantages of lower price and wide availability. Brain SPET has been proven useful in the differentiation of tumor recurrence from radiation necrosis, in the non-invasive assessment of gliomas and meningiomas aggressiveness, in differentiating neoplastic from non neoplastic intracerebral haemorrhage, in monitoring treatment response and estimating patients' prognosis. Thus, SPET may still have a role in the diagnosis and characterization of brain tumors. Future comparative studies between SPET and PET or latest magnetic resonance based neuroimaging techniques are warranted.

Introduction

At present positron emission tomography (PET) constitutes the most sophisticated modality of nuclear medicine imaging for brain tumor evaluation. Starting with fluorine-18 fluorodesoxyglucose (^{18}F-FDG), for oncological use and using other more advanced PET tracers, PET has proved useful, in patients with brain lesions. Nevertheless, PET has some disadvantages like the high cost of maintaining PET instrumentation and that some tracers better applied for the detection of brain lesions require an on-site cyclotron. Single-photon emission tomography (SPET) has also been used for brain tumor imaging. This modality has the advantages of wider availability and lower cost; however its lower resolution of about 1cm as compared to about half of it for PET is a limitation [1].

Single photon emission tomography-PET/CT and MRI

Various SPET traces have been used for brain tumor evaluation. Thallium-201 (^{201}Tl), one of the first tracers studied, proved useful for the differentiation of tumor recurrence from radiation necrosis and its uptake correlated with glioma aggressiveness [2, 3]. Technetium-99m labeled compounds have also been studied. They were proven advantageous over ^{201}Tl, due to their optimal 140keV γ-rays energy and higher photon flux resulting in improved spatial resolution, less radiation burden to the patient and excellent availability. Technetium-99m-hexakis-2-methoxy isobutyl isonitrile (^{99m}Tc-sestamibi) has been extensively evaluated in brain tumor imaging, especially for the differentiation of glioma recurrence from radiation necrosis, for the non invasive assessment of glioma proliferation index and for the detection of neoplastic intracerebral hemorrhage [4-6]. Nevertheless, ^{99m}Tc-sestamibi uptake has been proven *in vitro* and *in vivo* to be inversely correlated with glioma's multidrug resistance phenotype, thus its uptake might be low in high grade gliomas [7, 8].

Over the last 8 years we have evaluated ^{99m}Tc-tetrofosmin (^{99m}Tc-TF), a SPET tracer, for brain tumor imaging [9-17]. This radiopharmaceutical is a lipophilic cationic diphosphine, routinely used for myocardial perfusion imaging. Its uptake mechanism bears similarities to ^{99m}Tc-sestamibi, as it depends mainly on regional blood flow and cell membrane permeability. This radiopharmaceutical enters cells mainly via passive transport, driven by the negative potential of the intact cell membrane, localizes mostly within the cytosol, while a fraction of it passes into mitochondria. Contrary to ^{99m}Tc-sestamibi, ^{99m}Tc-TF accumulation is not influenced by the multidrug resistance phenotype of gliomas, thus is superior for brain tumor imaging [9]. Using a semiquantitative method of image analysis, by calculating the lesion-to-normal (L/N) uptake ratio, we have found that SPET with ^{99m}Tc-TF could distinguish radiation necrosis from tumor recurrence with an optimal cut-off value of 4.7 [10]. Recently, we have also compared ^{99m}Tc-TF brain SPET, with the diffusion tensor and dynamic susceptibility contrast perfusion magnetic resonance imaging (MRI) metrics, for the detection of recurrent tumors. In a group of 21 patients suspicious of glioma recurrence we found that both imaging modalities had the same efficacy [unpublished data]. Furthermore, ^{99m}Tc-TF brain SPET showed promise for the differentiation of neoplastic from non-neoplastic intracerebral hemorrhage, whereas its uptake correlated with glioma and meningioma aggressiveness as assessed by MIB-1 immunohistochemistry and flow cytomemtry [11-14]. MIB-1 is a monoclonal antibody that

detects the Ki-67 antigen. Ki-67 is a cellular marker for proliferation. In glioblastoma, which is the most aggressive and most often found primary brain tumor, preoperative ^{99m}Tc-TF uptake could predict patient's survival [15]. Finally, ^{99m}Tc-TF could provide an insight into the nature, benign or malignant, of a single brain lesion [16, 17]. This is important for the patients' management since a single lesion, detected by conventional MRI, may be: (a) cerebral abscess, (b) metastasis, (c) glioma, (d) subacute infarct, (e) tumefactive multiple sclerosis or (f) lymphoma. In a study of 106 patients with brain tumors that were treated surgically, we performed preoperative ^{99m}Tc-TF brain SPET and found a significant difference between low-grade gliomas and high-grade gliomas with a 2.8 optimum cut-off value. When we compared low and high-grade gliomas with intra axial non-neoplastic lesions, the difference in ^{99m}Tc-TF uptake was still statistically significant. In the same study there was also statistically significant difference between low-grade gliomas and non-neoplastic lesions [17]. Thus, one may suggest that SPET with ^{99m}Tc-TF constitutes an imaging modality that can provide important information for the proper patients' management, having the advantages of lower cost and wider availability as compared to ^{18}F-FDG-PET studies. Nevertheless, as mentioned above, SPET has an inferior resolution and poorer quantitative properties as compared to PET scanners. Furthermore, combining PET and computed tomography (CT) has the potential to improve localization of lesions and reduce the overall scanning time.

Fluorine-18-FDG PET/CT was shown to be superior to conventional MRI for the detection of glioma recurrence [18]. Others, in a study of 90 patients with histopathologically diagnosed glioma and suspicion of recurrence clinically or on MRI, found ^{99m}Tc-glucoheptonate SPET to be superior to ^{18}F-FDG PET/CT [19]. Others have recently evaluated by ^{11}C-methionine (^{11}C-MET) and ^{18}F-FDG PET-CT, thirty-seven patients with a history of treated primary brain tumors referred for suspected recurrence. The authors found that ^{11}C-MET was superior to^{18}F-FDG because of higher sensitivity and better intraobserver agreement. One of the advantages of ^{11}C-MET is the markedly lower background activity in normal gray and white matter, but the requirement for an on-site cyclotron due to the short half-life of ^{11}C (20min) is its main limitation [20].

Apart from the nuclear medicine modalities, the latest MR techniques, namely diffusion, perfusion and spectroscopy, are also essential for the evaluation of patients with brain tumors. Magnetic resonance spectroscopy evaluates tumor malignancy based on the levels of metabolites such as N-acetylaspartate (NAA), choline (Cho), creatine (Cr), lactate (Lac), myo-Inositol (ml), glycine (gly) and the ratios of Cho/NAA and Cho/Cr [21-23]. Perfusion MRI measures the vascularity within brain lesions by measuring the relative cerebral blood volume (rCBV). Measurements of rCBV have been shown to correlate reliably with tumor grade and increased tumor vascularity [22-24]. Furthermore, diffusion imaging evaluates the rate of microscopic diffusion of free water molecules within tissues and the magnitude of diffusion is quantified by the apparent diffusion coefficient (ADC). Ratios of ADC have been shown to correlate with glioma aggressiveness [22]. Others compared MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from post treatment effects and found perfusion MR and multivoxel MR spectroscopy to have similar diagnostic performances. Both MR perfusion and spectroscopy were superior to MR diffusion [25].

In conclusion, SPET may still have a role in the diagnosis and characterization of brain tumors, although the plethora of latest imaging techniques. Comparative studies between SPET and PET/CT or latest MR based neuroimaging techniques are warranted.

The authors declare that they have no conflicts of interest.

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Hippocrates from his statue in the Archeological Museum of his birthplace, the island of Kos, in the Aegean.