The role of scintigraphy in the evaluation of brain malignancies

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Abstract

The gold standard for diagnosis of primary brain tumors is histopathological evaluation of the obtained tissue samples. Nevertheless, anatomical and functional imaging modalities have a determinative role in the precise localization and characterization of these lesions. In this review we focus on the clinical applications and future potentials of nuclear medicine procedures. Several single photon emission tomography (SPET) tracers such as thallium-201 chloride ($^{201}TlCl_2$), technetium-99m (^{99m}Tc) methoxyisobutylisonitrile (MIBI), ^{99m}Tc-tetrofosmin (TF) and 3-[iodine-123] iodo-α-methyl-L-tyrosine (^{123}I-IMT) have been utilized in the diagnosis of brain tumors. Positron emission tomography (PET) alone or fused with computed tomography (CT), are widely acceptable methods in oncology, at present and for the future.

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Introduction

Brain tumors may be primary or metastatic. A variety of signs and symptoms although non specific, may lead to suspect a brain tumor. Differential diagnosis includes a number of non-oncologic causes [1]. The goal standard for the diagnosis of brain tumors is the histopathology of the tissue samples obtained either surgically or by stereotactic biopsy [2].

Diagnostic modalities are often used to assist diagnosis; moreover they offer additional information of the tumor characteristics and biological properties. Anatomical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are better suited for defining of the exact size and location of the mass, along with the assessment on invasion of the surrounding tissues [1, 2]. Positron emission tomography (PET) seems to be a promising imaging modality for the detection and assessment of brain masses [1, 2]. Functional imaging techniques, namely nuclear medicine procedures and the recently developed MRI equipments are used to assist in defining the metabolic activity of these tumors [1, 2].

Studies have demonstrated several applications for the radionuclide brain imaging including tumor delineation, grading and prognosis, response to treatment and follow-up along with the discrimination of radionecrosis from recurrence [2].

Single photon emission tomography (SPET) using thallium-201 chloride ($^{201}TlCl_2$) or technetium-99m (^{99m}Tc) methoxyisobutylisonitrile (MIBI) has been widely accepted as a reliable method for detecting malignant tumors and recurrences. Recently it has been suggested that ^{99m}Tc-tetrofosmin (TF) may be an accurate scintigraphic variant for brain tumor imaging [2-4]. Research has focused on the role of 3-[iodine-123] iodo-α- methyl-L-tyrosine (^{123}I-IMT), a synthetic amino acid analog, which is strongly taken up by brain tumors [2, 4]. In this article, we review the current data and future prospects on the role of scintigraphy in the diagnosis and follow up of patients with brain tumors.

The role of SPET in brain tumors

Nuclear medicine imaging, given the wide availability of radiotracers, plays a major role in the diagnosis and the follow up of patients with brain tumors. The broad availability, especially for PET and SPET cameras, the continuous improvement of their software and the recent development of hybrid systems (SPET/CT and PET/CT) further improve diagnostic accuracy [5, 6].

Thallium-201 chloride

Thallium-201 chloride ($^{201}TlCl_2$) has been used in myocardial scintigraphy, in lung carcinoma [7, 8] and also in brain tumors [7]. This radiopharmaceutical behaves biologically similar to potassium; however multiple factors are involved in its uptake by brain tumors such as regional blood flow, blood brain barrier (BBB) permeability, tumor viability and type, sodium-potassium ATPase system, co-transport system and calcium ion channel system [3, 7]. The combination of these mechanisms explains the substantial uptake of $^{201}TlCl_2$ in viable cerebral tumors. Its accumulation in normal tissues is minimal and almost non in necrotic or non-active tissues [3, 7].

Early scanning (20-60min p.i) has been recommended as the preferable imaging time. However delayed images (2-3h p.i) may additionally provide an enhanced lesion-to-background ratio [3]. Moreover $^{201}TlCl_2$ showed slower washout from malignant tumors compared to benign ones [3].

In a population of 90 patients with supratentorial brain tumors, the overall sensitivity and specificity of $^{201}TlCl_2$ in detecting the lesion has been evaluated to be 71.7% and 80.9% respectively [2]. It provides high sensitivity in malignant gliomas and meningiomas, intermediate for posterior fossa tumors and low for pituitary, brainstem and low grade tumors. Small size lesions (<2cm), centrally located or adjacent to areas of physiological tracer uptake, such as the choroid plexus, can not be easily detected [3].

Besides the qualitative, quantitative assessment of $^{201}TlCl_2$ uptake by brain tumors, using the regions of interest (ROI) method, can correctly distinguish low from high grade tumors and malignant from benign lesions. In such cases a ROI is first drawn around the lesion in the scan-slice showing maximal activity and a similar ROI is drawn in the contralateral hemisphere and finally the tumor-to-normal (T/N) brain uptake ratio, namely the $^{201}TlCl_2$ uptake index (UI), is determined [4, 7].

Others compared three different methods for calculating the $^{201}TlCl_2$ UI and concluded that the method using the ratio of average counts along with the use of attenuation correction is the most reproductive one [7].

Several studies have focused on the role of the different uptake indices [3, 4, 7]. Using 1.5 as a threshold for the UI, one can correctly identify the high grade lesions and the low grade tumors with increased biologic malignancy or anaplastic transformation [4, 7].

Researchers also focused on the utility of $^{201}TlCl_2$ retention indices, in addition to the $^{201}TlCl_2$ UI [9]. They are appropriate for tumor differentiation, particularly when hypervascular meningiomas are involved. *^{201}Tl retention index (RI) A: AvLd/AvLe and ^{201}Tl RI B: MxLd/ MxLe, where AvLe and MxLe are average and maximum early counts for lesions and AvLd and MxLd are average and maximum delayed counts for lesions.* A threshold RI A set at 0.8 shows a sensitivity of 81.8% and a specificity of 68.8% for the differentiation between high grade gliomas and meningiomas (P<0.0005) [9].

The aim of several groups has been to evaluate the response to treatment in patients with brain tumors [10-14]. They compared the changes in tumor size measured by MRI with the changes in tumor activity measured by scintigraphy in patients receiving stereotactic irradiation (STI). A significant correlation between the ratio of $^{201}TlCl_2$ index within 1 week of STI and the ratio of tumor size 1-2 months after STI has been demonstrated. The researchers confirmed the important role of $^{201}TlCl_2$ imaging as an early indicator of response in patients being treated with STI [10].

Others studied by SPET the contribution of $^{201}TlCl_2$ to the assessment of chemotherapy follow up. The volume and intensity responses demonstrated by scintigraphy were more pronounced and preceded the response of conventional radiation techniques. Moreover they suggested that $^{201}TlCl_2$-SPET may have an additional prognostic role since patients with a negative scintigraphic study after the completion of treatment showed a prolonged disease-free interval [11, 12].

Others assessed the prognostic role of $^{201}TlCl_2$-SPET in patients with recurrent gliomas. Thallium-201 chloride seemed to be a more accurate predictor of survival and response to chemotherapy than conventional CT or MRI. The absence of intensity response after two courses of chemotherapy was inversely related to overall survival and indicated poor outcome [13].

The role of $^{201}TlCl_2$-SPET in the treatment follow-up, using the tumor uptake volume (TUV) as a measurement of metabolically active tumor tissue, has also been evaluated. Using a threshold value of 10ml, researchers could correctly identify patients with progressive disease, treatment failure and reduced survival time [14]. Moreover scintigraphic findings seemed to precede the anatomical responses of CT [14].

The accuracy of $^{201}TlCl_2$ in differentiating radiation induced necrosis from tumor recurrence in gliomas has also been examined [15-17]. Conventional CT and MRI are routinely unable to distinguish between these entities, since they both often reveal edema, mass effect and abnormal contrast enhancement [15].

A recent study focused on the value of $^{201}TlCl_2$-SPET in clinicopathology follow-up and decision on treatment management of 19 patients with high grade gliomas. Using histology or clinical course as the gold standard, the sensitivity and specificity of scintigraphy in differentiating tumor recurrence from radiation necrosis was 84% and 100%, respectively. The examination with MRI came short of diagnostic accuracy reporting a sensitivity of 65% and specificity of 75% [15].

Quantitative evaluation of tracer uptake has been also utilized for the discrimination of glioma recurrence from necrosis. A $^{201}TlCl_2$ tumor-to-scalp uptake ratio greater than 3.5 most probably indicates tumor recurrence while a ratio of less than 1.1 is probably associated with radionecrosis [3]. The aid of ^{99m}Tc hexamethylpropylene amine oxime (HMPAO) tumor-to-cerebellar uptake ratio is mandatory for lesions with $^{201}TlCl_2$ uptake ratios between 1.1 to 3.4 [3]. A ^{99m}Tc-HMPAO ratio less than 0.5 is highly suggestive of necrosis while a ratio more than 0.5 indicates recurrence [3].

Recently a systematic review has been published of the diagnostic accuracy of $^{201}TlCl_2$-SPET in identifying recurrence and its differentiation from radiation necrosis. The results of eight studies, which included both high grade and low grade gliomas, were analyzed. The authors concluded that $^{201}TlCl_2$-SPET provides an accurate scintigraphic method for the diagnosis of recurrence in patients treated with radiotherapy [16].

The important role of $^{201}TlCl_2$-SPET in identifying tumor recurrence in cases of low grade gliomas has been also evaluated. The early detection of low grade gliomas recurrence is of utmost importance since they have a better theoretical prognosis than high grade type gliomas [17]. Using a $^{201}TlCl_2$ UI with a cut off value of 1.25, the sensitivity and specificity obtained, after studying 84 patients, was 90% and 80%, respectively. On the contrary, the diagnostic accuracy of neurostructural imaging, namely CT and MRI, was lower, with a sensitivity of 63% and specificity of 59% [17].

Despite the aforementioned favorable results of $^{201}TlCl_2$, main points such as high cost, radiation dosimetry and technical problems, contribute to limitation of its use.

Technetium-99m-MIBI

Technetium-99m-MIBI is a lipophilic cationic complex, initially designed for myocardial perfusion imaging. However it has been recently found to have also tumor-imaging capabilities. The disruption of BBB in

combination with the cationic charge and lipophilic character of ^{99m}Tc-MIBI, its large negative transmembrane potential, higher metabolic activity and mitochondrial density are probably the factors involved in the uptake of the tracer by the malignant tumor cells [3, 18].

Technetium-99m-MIBI is taken up by normal choroid plexus, scalp and the pituitary gland [18, 19]. The physical characteristics, the low cost, the wide availability and the low radiation dosimetry constitute major advantages of ^{99m}Tc-MIBI [19, 20].

Technetium-99m-MIBI SPET imaging can be used as a guide for grading malignancies and predicting their clinical aggressiveness [18, 19].

It can also assist in the diagnosis of malignant transformation of low grade to high grade gliomas. Moreover the intensity of tracer accumulation corresponds with the histological pattern of the tumor and the point of highest malignancy [18].

Quantitative assessment using the ROI method, similarly to $^{201}TlCl_2$ imaging, can be performed. The ^{99m}Tc-MIBI UI of early (20-30min p.i) and delayed (3-4h p.i) imaging can be obtained as well as the RI (ratio of delayed to early UI) [18, 21, 22]. The former index is in correlation with the patient survival rate, namely the higher the UI the less the survival rate, however the latter index is not statistically significant [18, 21]. Moreover the RI of ^{99m}Tc-MIBI was significantly lower (0.47 ± 0.01) than that of $^{201}TlCl_2$ (0.89 ± 0.19) in metastatic brain lesions but not in malignant gliomas [22].

Apart from the diagnosis of the primary brain tumor, ^{99m}Tc-MIBI has been reported useful in detecting the presence of bone metastases from brain tumors [20].

Research groups evaluated and compared the usefulness of ^{99m}Tc-MIBI and $^{201}TlCl_2$ -SPET in patients with malignant brain tumors. The results in terms of tumor detectability were similar, still the determination of tumor boundaries was better and the UI was higher with ^{99m}Tc-MIBI [23]. Additionally the difference of the ^{99m}Tc-MIBI SPET RI between glioblastoma multiforme and metastatic brain tumor was significant i.e 1.85 ± 0.43 and 0.99 ± 0.65 respectively [23]. Both radiopharmaceuticals seemed of similar usefulness for the prediction of histological diagnosis; however the combined indices of $^{201}TlCl_2$ / ^{99m}Tc-MIBI may contribute further to the discrimination between the different types of malignant brain tumors [23].

Others have focused on the role of ^{99m}Tc-MIBI in differentiating neoplastic from nonneoplastic intracranial hemorrhage. Neoplastic intracranial hematomas revealed high tracer UI while low grade or non neoplastic lesions showed low or no tracer accumulation [24]. The authors suggested that the BBB disruption combined to the presence of metabolically active neoplastic cells constitute the possible mechanisms of localization in neoplastic hematomas. The lack of metabolically active neoplastic cells can explain the low or absent tracer accumulation in non neoplastic hematomas [24].

The utility of ^{99m}Tc-MIBI as a proliferation marker in gliomas has also been investigated. Researchers evaluated the degree of tracer uptake to the proliferation potential of gliomas, estimated by the monoclonal antibody to Ki-67 antigen (MIB-1) staining method. A significant correlation between ^{99m}Tc-MIBI T/N uptake ratio and the presence of positive nuclear area for MIB-1 was found, whereas for $^{201}TlCl_2$ this correlation was little weaker [25].

Recently, ^{99m}Tc-MIBI was characterized as a substrate for the P-glycoprotein (P-gp), encoded by the multi-drug resistance (MDR-1) gene [18, 26, 27]. P-glycoprotein acts as an efflux transporter of several antineoplastic agents, resulting in drug resistance to tumor cell [18, 28, 29]. Tracer uptake by metabolically active tumor cells in early scanning combined with rapid washout of ^{99m}Tc-MIBI is indicative of the presence of P-gp [28, 29]. High levels of P-gp are significantly associated with disease progression, poor prognosis and necessitate the induction of MDR-1 reversing agents in the study protocol [28, 29]. However others demonstrated that its presence does not seem to be the main cause of chemoresistance in gliomas, since the P-gp level is inversely proportional to the degree of malignancy [18, 22].

The aim of several groups has been to evaluate the role of ^{99m}Tc-MIBI as a detector of tumor recurrence after radiotherapy [30-33]. Conventional CT and MRI have a limited role in differentiating tumor relapse from necrosis; however scintigraphy reveals better results [18, 30-33]. According to others, sensitivity and specificity are high, with no false positive or false negative findings [30]. In a study conducted on 105 patients, authors reported that ^{99m}Tc-MIBI-SPET has a sensitivity of 88%, specificity of 92%, accuracy of 89%, PPV of 98% and NPV of 63%. The combination of SPET and CT findings revealed higher parameters with the exception of specificity which dropped to 75% [31].

A comparative study published in 2002 demonstrated that the high UI indicates recurrence, yet the lower background activity is the possible explanation for the higher UI of ^{99m}Tc-MIBI compared to $^{201}TlCl_2$ [32]. A more recent study, performed on 81 patients, revealed separate results for low and high grade gliomas, namely sensitivity for tumor recurrence 91% and 89% respectively, specificity 100% and 83% and accuracy 95% and 87% respectively [33]. The authors attributed the three false positive results to an inflammatory reaction following the recent radiotherapy and the three false negative to an intact BBB or the presence of P-gp [33]. Other factors that may be involved in false negative imaging results might be the small size of the tumor or the concomitance of a large cystic or necrotic tissue within the brain tumor [34].

Technetium-99m-MIBI plays an important role in separating brain tumor recurrence from radiation induced necrosis, yet MR spectroscopy (MRS) seems to gain ground in providing with sufficient information for this problematic issue [35]. A recent study, performed on 30 glioma patients, compared the data of both diagnostic modalities to histologic findings and reported values of sensitivity of 90%, specificity of 100%, accuracy of 93%, NPV of 83% and PPV of 100% for either method. Combined use of both methods seemed to provide higher parameters, namely sensitivity of 95%, specificity of 100%, accuracy of 96%, NPV of 90.9% and PPV of 100% [35].

Many groups of researchers have assessed the role of ^{99m}Tc-MIBI as an indicator of response to chemotherapy [36-38]. The persistence of high ^{99m}Tc-MIBI T/N uptake ratio during or after chemotherapy is compatible to poor prognosis [36]. An UI higher than 2 is considered abnormal and indicates disease progression [36, 37]. Researchers studied 30 patients and observed a significant correlation (97%) between the scintigraphic findings of treatment response and the MRI findings [37]. Scintigraphic changes appeared either simultaneously with radiologic changes or even earlier, at an average of 4 months [37].

The prognostic role of ^{99m}Tc-MIBI in high grade glioma patients after the end of chemotherapy and radiotherapy has been also evaluated [38]. Considering the tumor as a sphere and using 3 slides, the metabolic tumor volume (MTV) was calculated. The first assessment was performed within 10 days after the completion of the therapeutic protocol. Metabolic tumor volume higher than 32 cm^3 indicated poor survival rate, while MTV<32 cm^3 a fair survival rate [38].

At present, data concerning SPET guided target volume delineation for high grade gliomas are limited. The effect that ^{99m}Tc-MIBI-SPET and MRI fusion may have on treatment planning has been evaluated. Using the gross tumor volume (GTV), researchers have highlighted that a larger GTV was detected by SPET than by MRI. The discrepancy was more striking in patients who had surgical resection of the tumor before receiving radiotherapy [39]. These confirm published results about the role of scintigraphic imaging in modifying actual target volume and treatment planning [40-42]. The combination of ^{99m}Tc-MIBI and MRI data seems to be a more appropriate approach for the delineation of target volume than MRI data alone [39-42].

Technetium-99- tetrofosmin

Technetium-99m-TF is a lipophilic cationic tracer, initially used for myocardial perfusion imaging. Recent data have indicated its role as a tumor-seeking agent. This radiopharmaceutical shares many properties with ^{99m}Tc-MIBI, including the uptake mechanism in neoplastic cells [2, 43, 44]. Preliminary results have highlighted its utility in brain tumors [43, 44].

Researchers confirmed the role of ^{99m}Tc-TF-SPET in the diagnosis of brain neoplasms, defined the best imaging time and compared its results to those of $^{201}TlCl_2$ imaging. The UI was calculated in the 20, 40 and 120min scan. Since the UI values were much the same, early imaging was recommended [45]. Although the agreement among $^{201}TlCl_2$ and ^{99m}Tc-TF examinations was significant, the image quality, the contrast and the definition of tumor margins obtained by ^{99m}Tc-TF were superior to those of $^{201}TlCl_2$ [45]. The utility of hybrid SPET/CT in imaging brain tumors has been also evaluated. Its diagnostic accuracy was superior to SPET alone, particularly for paraventricular lesions or tumors contiguous to areas of physiological ^{99m}Tc-TF uptake [5, 6].

Besides tumor imaging, ^{99m}Tc-TF-SPET has been proven to be a useful radiopharmaceutical for non-invasive grading. A striking difference between the ^{99m}Tc-TF UI in low grade and high grade gliomas was revealed, which was not the case for $^{201}TlCl_2$, ^{99m}Tc-MIBI and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) [44]. We recently studied the value of ^{99m}Tc-TF in 15 patients with brain tumors and yielded higher UI (mean range 5.6-62.6) in high grade (Fig. 1) compared to those with low grade tumors (<3.77) (Fig. 2) [unpublished data]. Along with the aforementioned, our department compared the role of ^{99m}Tc-TF in the non-invasive grading to MRI perfusion weighted imaging (PWI) using the biopsy results as the gold standard. Initial evidence demonstrated significant correlation between the two diagnostic modalities (Fig. 3). These are preliminary unpublished results of an ongoing study.

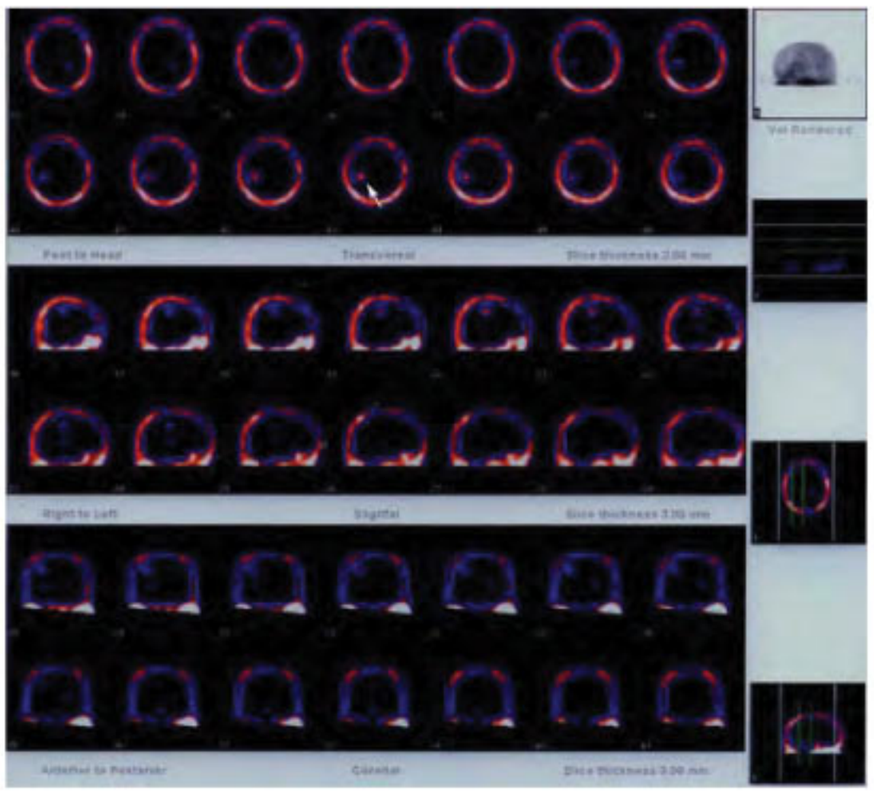

Figure 1. A 40 years old male with grade III astrocytoma . The lesion displays intense ^{99m}Tc-tetrofosmin uptake on SPET scintigraphy (arrow). The tracer uptake index (UI) obtained was 39.1.

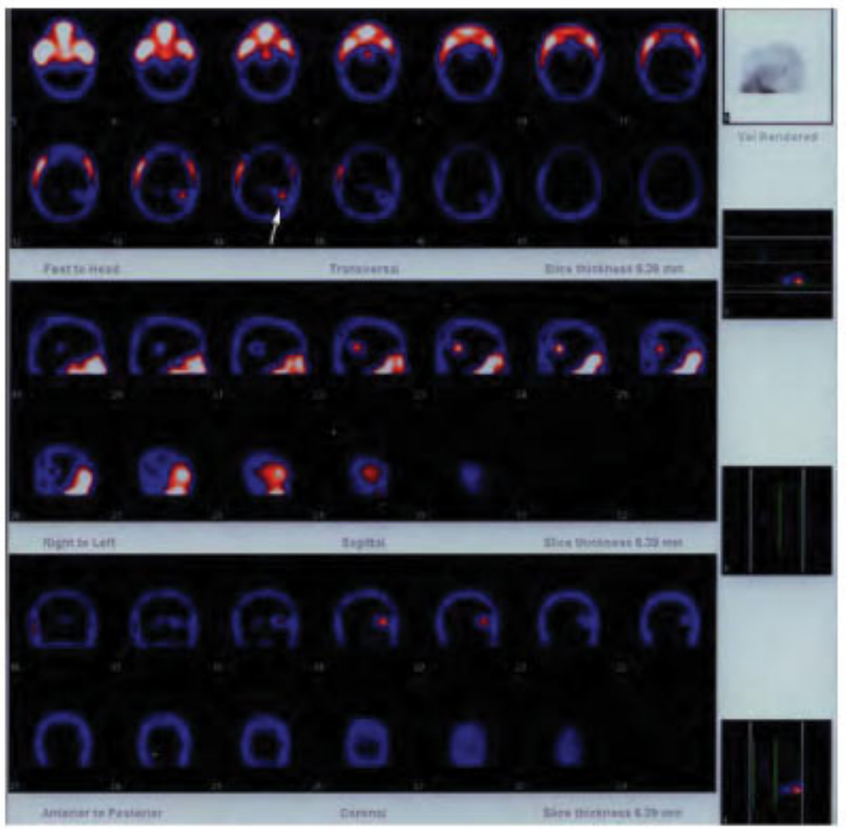

Figure 2. A 35 years old woman with grade II astrocytoma. The lesion displays fair ^{99m}Tc-tetrofosmin uptake on SPET scintigraphy (arrow). The tracer UI obtained was 3.1.

The role of ^{99m}Tc-TF-SPET as a contributor to patients' prognosis has been assessed. It has been suggested that it can distinguish tumor recurrence from radiation necrosis [46-48]. The UI in necrosis was lower than in recurrence, moreover the threshold value of 4.7 seemed to be the most accurate [46, 48]. Despite the aforementioned data, this radiopharmaceutical has been proven inappropriate for the detection of recurrence of tumors of the posterior fossa. The presence of P-gp, the small size of the lesions or the coexistence of gliosis may explain these unfavorable results [49].

Additional prognostic information was obtained in gliomas and meningiomas [50-53]. As a prognostic parameter the correlation between the ^{99m}Tc-TF uptake and the proliferation potential, estimated by the MIB-1 staining method, was considered. In patients with gliomas there was a significant agreement between radiotracer uptake and Ki-67 expression [50]. A study, using DNA flow cytometry as an indicator of tumor proliferation, revealed a direct relation between tracer accumulation and the percentage of tumor cells on the S-phase cell cycle [51]. Similar results were initially obtained for meningiomas [52, 53]. These results seem

to suggest that ^{99m}Tc-TF-SPET could be used to non-invasively assess gliomas and meningiomas proliferation.

Reliant on the basic assumption of tracer uptake by viable tumor cells, in contrast to hemorrhage, ^{99m}Tc-TF scintigraphy constitutes a useful approach in differentiating neoplastic from nonneoplastic intracranial hemorrhage [54].

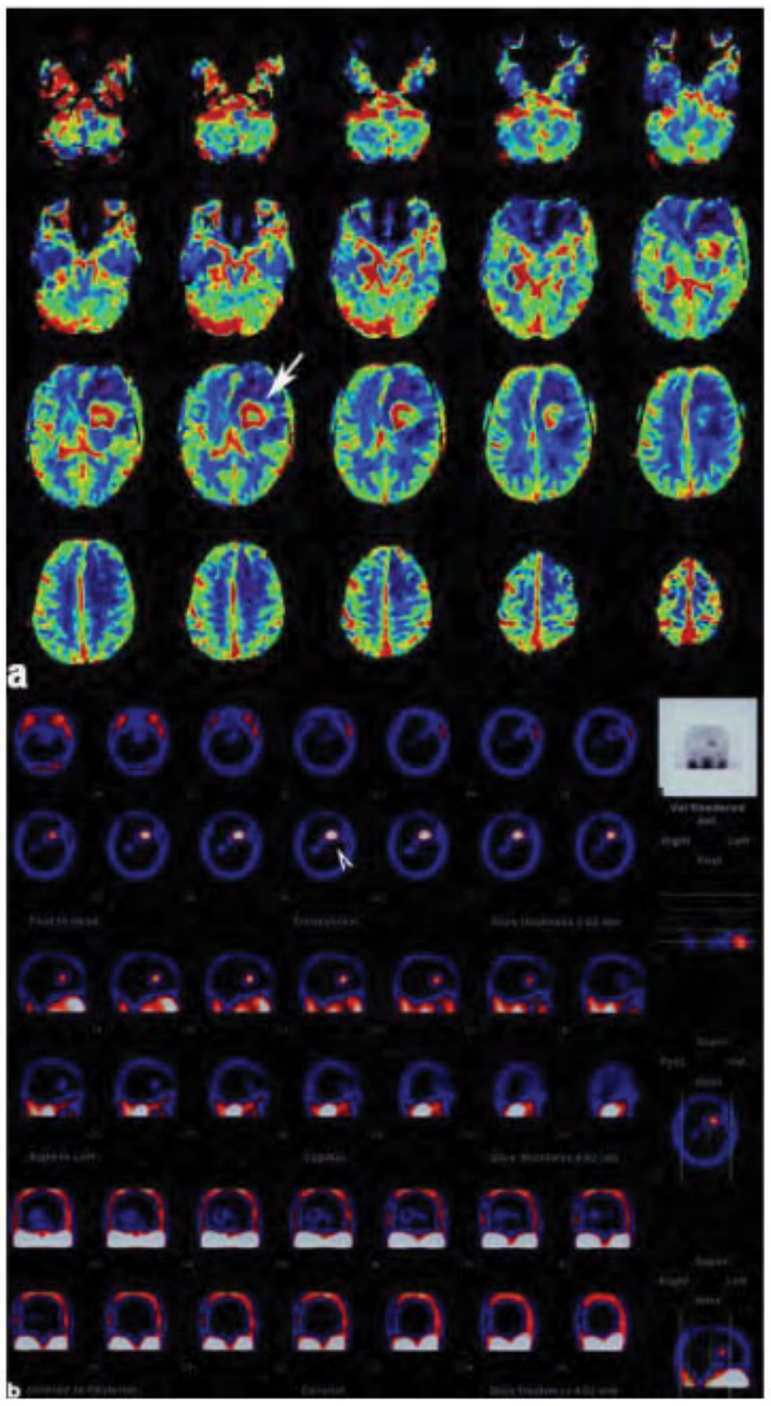

Figure 3. A 45 years old woman with glioblastoma multiforme. The lesion displays: a) elevated relative cerebral blood volume (rCBV) on colored CBV map (arrow) and b) intense ^{99m}Tc-tetrofosmin uptake on SPET scintigraphy (arrowhead). The tracer UI obtained was 42.9.

Technetium-99m-TF, similarly to ^{99m}Tc-MIBI, is a substrate for P-gp. [55, 56]. Its usefulness in predicting possible brain tumor resistance to antineoplastic agents has been suggested [55]. Recent studies have revealed that P-gp expression has less influence over ^{99m}Tc-TF uptake compared to the ^{99m}Tc-MIBI uptake [57] and suggested that the former is a more suitable radiotracer for imaging gliomas [57, 58].

3- [^{123}I]iodo- α-methyl-L-tyrosine

Iodine-123-IMT is an amino acid SPET tracer and a possible future variant to corresponding PET tracers [59, 60]. Since its initial study in the late 1980's [61], a considerable number of research groups have focused on its potential use in imaging brain tumors.

This radiopharmaceutical is taken up by a carrier-dependent active transport system in the brain, specific for large neutral amino acids [59]. Its intratumoral accumulation reflects amino acid transport and does not rely on the disruption of the BBB [59]. Moreover it is not involved in protein synthesis or in intracellular metabolism [60].

The accumulation of ^{123}I-IMT by gliomas and nonneoplastic brain lesions has been evaluated [62]. The sensitivity and specificity for differentiating high grade from low grade gliomas were 71% and 83%, respectively ($P<0.0052$). For distinguishing high grade gliomas from nonneoplastic lesions a sensitivity of 82% and a specificity of 100% were reported ($P<0.0001$); however this modality seemed inappropriate for distinguishing nonneoplastic from benign lesions ($P<0.193$).

The precise determination of tumor extent for radiotherapy planning is of utmost importance. Several studies revealed that a larger tumor volume was detected by ^{123}I-IMT than by conventional MRI and they highlighted its mandatory use in target volume delineation [63, 41].

The role of ^{123}I-IMT in grading and patients prognosis has lead to controversy [59-60]. Kuwert et al (1997) [64] reported a strong correlation between tracer uptake and tumor proliferative activity, expressed as a Ki-67 index. The correlation between ^{123}I-IMT accumulation and cellular density, evaluated by light microscopy, was poor. The above results were confirmed by a comparative study of ^{123}I-IMT and ^{18}F-FDG-PET [65]. The authors suggested that both tracers were almost equally able to evaluate the grade of the primary tumors. On the contrary, Weber et al (2001) [66] did not report any correlation between ^{123}I-IMT uptake and tumor grading in patients with unresectable tumors. A comparative study of ^{123}I-IMT and ^{18}F-FDG-PET verified the limited correlation between histological grading and tracer uptake; however others recommended possible applications of scintitomography such as definition of tumor extent and detection of tumor recurrence [67]. Others [68] stated the higher accuracy of MRI than that of ^{123}I-IMT-SPET in the noninvasive grading of untreated gliomas. Besides, the combined use of these imaging modalities did not seem to improve the accuracy of MRI alone [68].

Several studies indicated the valuable role of ^{123}I-IMT-SPET in the follow-up of patients with brain neoplasms. Researchers studied 27 postsurgical patients who suffered from high and low grade gliomas. Using 1.8 as the threshold value of ^{123}I-IMT uptake, the sensitivity and specificity for identifying gliomas recurrence was 78% and 100%, respectively [69]. Yet another study focused on the prognostic role of ^{123}I-IMT uptake in patients with gliomas. Authors suggested that tracer uptake >1.7 after 4-6 months of tumor resection correlated with poor survival in contrast to patients with lower ^{123}I-IMT uptake ($P<0.001$). In this same study, the limited role of early postoperative MRI in radiotherapy planning, due to the unspecific contrast enhancement, has been highlighted [66]. The valuable utility of ^{123}I-IMT in the diagnosis of recurrence in patients with intracranial tumors of non-astrocytic origin has been revealed by another research group [70]. After studying 22 patients, the reported sensitivity was 81%, moreover the optimal threshold value for ^{123}I-IMT uptake defined by ROC analysis was 1.43. Yet small lesions may be missed owing to the limited spatial resolution of SPET [70]. In a recent pilot study, the usefulness of ^{123}I-IMT uptake in assessing response to radiation therapy in patients with high grade gliomas has been investigated [71]. Their results, based on a limited number of patients, indicated no significant correlation between the degree of changes in tracer uptake and patients' survival ($P=0.973$) as well as low prognostic value of ^{123}I-IMT-SPET [71].

Several studies assessed the role of ^{123}I-IMT in brain tumors relatively to other SPET or PET tracers. Researchers compared ^{123}I-IMT and ^{99m}Tc-MIBI in the follow-up of low grade astrocytomas after STI [72]. The resulting accuracy of ^{123}I-IMT for progression was superior to ^{99m}Tc-MIBI. The limited role of the latter may be attributed to the possible presence of P-gp or paraventricular location of a lesion. In another recent study ^{123}I-IMT has been compared with p-[I-123] iodo-L-phenylalanine (^{123}I IPA), a new amino acid SPET tracer [73]. Although both radiopharmaceuticals revealed equal suitability for imaging gliomas, ^{123}I-IMT showed higher UI and faster washout than ^{123}I- IPA. Therefore the authors suggested that ^{123}I-IMT is a preferable tracer in the determination of tumor extent while the application of ^{123}I-IPA in tumor treatment after labeling with ^{131}I is challenging. When compared to ^{18}F- FDG, ^{123}I-IMT should be preferred for the diagnosis of brain tumors, the delineation of the lesion and the differentiation between tumor relapses and radiation-induced necrosis. Besides ^{18}F-FDG predominated in the noninvasive grading of tumors and tumors recurrences [65, 67, 74]. In a comparative study with carbon-11 methyl-methionine (^{11}C-MET), the authors revealed sufficient intratumoral uptake of both tracers, yet the faster washout of ^{123}I-IMT was confirmed [75]. A possible explanation of that might be that ^{123}I-IMT is not involved in intracellular metabolism. In yet another study, Pauleit et al (2004) compared O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET) with ^{123}I-IMT in brain tumors. A full agreement of UI was suggested, along with a superior image quality of ^{18}F-FET [76].

Lately the interest has focused on the role of image fusion of ^{123}I-IMT-SPET with radiation modalities, regarding brain tumors. Researchers studied 45 patients with suspected relapse or residual gliomas and they concluded that image fusion with MRI reveals a positive impact on the diagnostic accuracy of positive ^{123}I-IMT scintitomography [77]. The role of image fusion is even more critical whenever nonspecific or physiological ^{123}I-IMT uptake hinders the correct diagnostic interpretation [77]. Moreover studying revealed that the determination of GTV for radiotherapy planning using amino acid PET or SPET/CT/MRI image fusion is superior to CT/MRI alone, along with an improved survival rate [78]. Recently another research group investigated 25 glioma patients and compared the role of ^{123}I-IMT and MRS in the noninvasive differentiation of tumor relapse or residue from treatment-related changes. Using 1.62 as the threshold value for ^{123}I-IMT uptake, the calculated sensitivity was 95%, specificity 100% and accuracy 96% ($P<0.0001$). The diagnostic sensitivity, specificity and accuracy of MRS were 89%, 83% and 88% respectively [79].

The role of PET in brain tumors

Many radiotracers have been employed with PET in the imaging evaluation of brain neoplasms. Although it has been widely use in oncology, ^{18}F-FDG possesses some diagnostic limitations in the evaluation of brain malignancies. The high rate of physiologic glucose metabolism in normal brain often encumbers the detectability of hypo- or isometabolic lesions [80]. ^{18}F-FDG uptake in low grade or recurrent high grade tumors is commonly similar to that in the white matter. The uptake in high grade tumors is generally high, however accumulation may demonstrate wide assortment [81]. Image coregistration with MRI or delayed imaging 3-8 hours after ^{18}F-FDG injection greatly improves the delineation of the lesion [82, 83].

Amino acid PET tracers are taken up by a carrier-dependent active transport system. Its intratumoral accumulation reflects amino acid transport, which has been shown to increase considerably in malignancies, yielding higher tumoral uptake than that of normal brain. ^{11}C- MET, which is the best-studied amino acid tracer, along with ^{18}F-FET and ^{18}F-fluoro-L-phenylalanine (FDOPA), constitutes the ideal agents for brain tumor imaging [80, 81].

The role of ^{18}F-FDG in differentiating tumor recurrence from radiation-induced necrosis has been studied. Essential criteria used in image interpretation are tracer uptake higher than that of the expected background along with coregistration with MRI [82]. In a series of 117 postradiotherapy patients, this approach yielded a sensitivity of 96% and a specificity of 77% in differentiating recurrent tumor from radiation-induced necrosis [84]. The faster washout of the tracer from necrotic tissue than that from relapse adds an extra potential to delayed imaging [83]. High tracer accumulation after treatment pleads for high grade tumor relapse or anaplastic transformation of previously diagnosed low grade gliomas [85]. The timing of performing the ^{18}F-FDG PET examination after the completion of radiotherapy has not been exactly determined, yet a period of more than 6 weeks has been generally recommended [86]. However a recent comparative study revealed the superiority of $^{201}TlCl_2$ over ^{18}F-FDG, especially for excluding tumor relapse [87].

Data concerning the performance of amino acid tracers in differentiating tumor relapse from radiation-induced necrosis are limited. The preliminary results revealed that they are superior to ^{18}F-FDG. Chung et al (2002) studied 45 patients with brain lesions (35 brain tumors and 10 benign lesions) using ^{11}C-MET. The sensitivity for the brain tumors in general and for gliomas (24 out of the 35 brain tumors) in particular was 89% and 92% respectively, along with the 100% specificity for all 10 benign lesions [88]. The mean UI of ^{11}C-MET was significant higher than that of ^{18}F-FDG ($P<0.0001$). ^{18}F-FET seems to have similar results to ^{11}C-MET. In a series of 53 patients, when a cut-off value of 2.0 was used for the maximum standardized uptake value (SUV) or 2.2 for the absolute maximum SUV, the accuracy reached 100% [89]. In a different study the diagnostic value of ^{18}F-FET and MRI in the diagnosis of recurrent gliomas was analysed. Using 2.2 as the cut-off value for the maximum SUV, authors obtained a sensitivity of 92.9% and specificity of 100% [90]. Sensitivity of MRI was 93.5% and specificity was 50% ($P<0.05$). Others evaluated ^{18}F-FDOPA and demonstrated low tracer uptake in normal brain, excellent contrast between lesion and background along with a sensitivity of 96% in detecting recurrence ($P<0.00001$) [91].

The role of PET in guiding biopsy has been also investigated. The combined use of ^{18}F-FDG and ^{11}C-MET was studied and the latter was shown to be a more appropriate tracer for PET guided biopsy [92]. A different research group revealed that ^{18}F- FET/MRI image fusion provides a sensitivity of 93% and specificity of 94% in identifying tumor tissue ($P<0.001$) [93]. A series of 50 patients with newly diagnosed diffuse gliomas demonstrated improved diagnostic accuracy when both ^{18}F-FET and MRS was used in differentiating neoplastic from nonneoplastic lesions (97%) than when MRS was solely used (68%) [94].

Additionally PET comprises a useful modality in delineating tumor volume for radiotherapy planning [78, 95]. Researchers evaluated 27 patients with glioblastoma multiforme who had been treated with fractionated radiotherapy and volume defined by MRI. Their results showed that ^{18}F-FDG can define unique volumes for radiation dose escalation; moreover its accumulation can predict prognosis and survival time [95]. Another study demonstrated the importance of using PET/CT/MRI image fusion when determining GTV for radiotherapy treatment along with the improvement of patient's prognosis [78]. The authors suggested that the use of image fusion in the treatment planning offers significant survival benefit in comparison to patients treated based on MRI/CT alone (median survival, 9 v 5 months: P= 0.03) [78].

Recently the application of 3-deoxy-3-[^{18}F] fluorothymidine (FLT) in investigating brain tumors and in predicting treatment response has been evaluated [96-98]. It is a thymidine analogue and its intratumoral accumulation reflects thymidine kinase-1 activity which participates in DNA synthesis [99]. A pilot study revealed that a $\geq$25% reduction in tracer SUV indicated treatment response and is coupled with higher survival rate compared with patients without metabolic response (median survival, 10.8 v 3.4 months: P= 0.003) [98].

In conclusion the present review describes the role and the future prospects of nuclear medicine in brain malignancies.

SPET using $^{201}TlCl_2$ has been widely accepted as a reliable technique for the diagnosis, therapeutic follow-up and differentiation between recurrence and radiation induced necrosis. However the high cost and limited availability, the radiation dosimetry and the technical problems constitute the main disadvantages of the procedure.

Technetium-99m-MIBI SPET takes the lead in investigating brain neoplasms owing to the combination of encouraging published data and favorable physical characteristics. It is considered as the ideal agent for detecting and grading malignancies, predicting clinical aggressiveness, survival rate and anaplastic transformation of low to high grade gliomas. Moreover it has the primary role in differentiating tumor recurrence from radiation-induced necrosis, evaluating response to therapy, guiding target volume delineation and treatment planning.

The initial data on the role of ^{99m}Tc-TF-SPET in brain tumors are encouraging. It has been proven to be useful in diagnosing and grading brain neoplasms, distinguishing recurrence from radiation necrosis, providing prognostic information in gliomas and meningiomas, predicting possible chemotherapy resistance and differentiating neoplastic from nonneoplastic intracranial hemorrhage. However further investigation is essential in order to endorse the aforementioned and prospective indications of this imaging modality.

The possessive evidences verify the utility of ^{123}I-IMT in determining lesion extent, detecting tumor residue or relapse and distinguishing recurrences from radiation necrosis. On the other hand, it plays a limited role in predicting noninvasive grading of primary brain tumors and thus patient's prognosis.

The recently available hybrid SPET/CT systems improve the diagnostic accuracy and provide precise localization of neoplastic lesions as well as exclusion of false results due to physiological tracer uptake.

Finally PET is particularly attractive for evaluating brain malignancies. Although its application in the evaluation of brain malignancies is problematic, ^{18}F-FDG has a potential role in providing prognostic information and differentiating tumor recurrence from therapy-induced necrosis. Amino acid PET tracers are more sensitive in imaging brain tumor, guiding biopsy and delineating tumor volume for radiotherapy planning. Yet further investigation will confirm the favorable preliminary results of thymidine analogues.

Conflict of interest:None

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