Imaging Primary Brain Tumors by Single-Photon Emission Computerized Tomography (SPECT) with Technetium-99m Sestamibi (MIBI) and Tetrofosmin

Luca Filippi, Riccardo Santoni, Carlo Manni, Roberta Danieli, Roberto Floris and Orazio Schillaci*

Department of Biopathology and Diagnostic Imaging, University "Tor Vergata", Rome, Italy

Abstract: In spite of many advances in diagnosis and therapy, primary brain tumors remain a serious challenge for clinicians. In particular, high-grade gliomas are characteristically radioresistant and their localization and invasive growth pattern often reduce the effectiveness of surgery. MRI and CT scan proved powerful tool to diagnose primary brain tumors. Nevertheless, these methods have some limitations, especially after surgery and radiochemotherapy, in discriminating between residual neoplasia versus radionecrosis / scar tissue. Scintigraphy by MIBI and Tetrofosmin, successfully used as imaging agents in oncology (i.e. breast and lung cancer), was also applied in diagnosis and follow-up of brain tumors. These two radiotracers are synthetic lipophilic cationic complexes and their uptake and retention depend on perfusion and cellular metabolism so that the level of radiotracer uptake corresponds to the cellular activity of the tumor. Although these two radiopharmaceuticals present similar imaging properties, very few studies in brain tumors imaging were performed with Tetrofosmin. On the contrary, MIBI was widely proved useful in diagnosis of brain tumors, showing high specificity and sensitivity. A trend between MIBI uptake and gliomas grade was observed, while this relationship is not present in glioblastomas, which exhibit a variable uptake. Most important, MIBI was demonstrated effective in patients' follow-up after treatments, well differentiating tumoral viable tissue versus radionecrosis. Since MIBI and Tetrofosmin are physiologically taken by intracranial structures like choroid plexus, the detection of small tumoral lesion in para-ventricular areas, especially in case of recurrence, may be problematic. In such cases, the dual integrated modality imaging system SPECT/CT might be considered of value to obtain a precise anatomical localization and to exclude the presence of disease in sites of physiologic tracer accumulation.

Keywords: Brain tumors, technetium labeled compounds, single photon emission computerized tomography, recurrence.

INTRODUCTION

In spite of many advances in diagnosis and therapy, brain tumors still represent a serious challenge for clinicians. Today, contrast-enhanced CT or MRI is the first examination performed in a patient with symptoms typical of brain tumor (i.e. nausea, headache, seizure or focal neurological signs). Both MRI and CT allow exactly localizing brain neoplasia and defining the extension of the tumoral mass to the surrounding normal tissue. Nevertheless, these techniques present some limitations, especially regarding patients' follow-up after treatments when discrimination between tumor recurrence/ persistence versus scar tissue is required [1]. In such cases, nuclear functional imaging by SPECT and PET was successfully proposed to obtain a metabolic characterization of the morphological lesions detected by MRI or CT scan. The routinely used PET radiotracer fluorine-18 fluoro-deoxyglucose (FDG) proved useful to diagnose primary brain tumors and their recurrences; moreover, the entity of FDG uptake was found to correlate with brain tumor histology [2, 3]. Nevertheless, FDG is physiologically taken by normal brain tissue, so this radiotracer is less accurate in detecting very low grade gliomas due to their relatively low target to background uptake ratio [4]. To overcome the drawbacks of FDG, ^{11}C methionine was applied in brain tumors imaging. Its uptake is related to the increased amino acid transport and protein synthesis and it is accumulated in the neoplastic lesion and not in the normal parenchyma. Actually, ^{11}C methionine proved useful to visualize low grade gliomas not detected by FDG [5, 6]. Although PET technology is becoming more and more available in many institutions, its diffusion is still limited and it presents very high cost. Moreover, in the case of ^{11}C methionine an *in situ* cyclotron should be available due to the short ^{11}C physical half-life.

Although conventional scintigraphy (i.e. single photon emission tomography [SPECT] and planar images) presents lower spatial resolution when compared to PET, the high diffusion of Anger camera, the device used to perform conventional scintigraphy, has accounted for the search of − emitting radiotracers as brain tumors imaging agents. ^{201}Tallium was firstly used to detect cerebral neoplasia [7] showing high sensitivity but relatively low specificity mainly due to its physical characteristics suboptimal for imaging with Anger camera. Sestamibi (MIBI) and Tetrofosmin are two technetium labeled radiotracers with similar functional properties widely used in myocardial perfusion scintigraphy as well as imaging agents in many tumors (i.e. in breast, lung and parathyroid cancer). As both these radiotracers label technetium, a satisfying imaging quality is obtained due to the gamma rays energy (140 KeV) optimal for Anger camera and the relatively high photons flux.

*Address correspondence to this author at the Viale Mazzini 121, 00195 Rome, Italy; Tel: +39-06-20902419; Fax: +39-06-37359664; E-mail: oschil@tiscali.it

1573-4056/05 $50.00+.00 ©2005 Bentham Science Publishers Ltd.

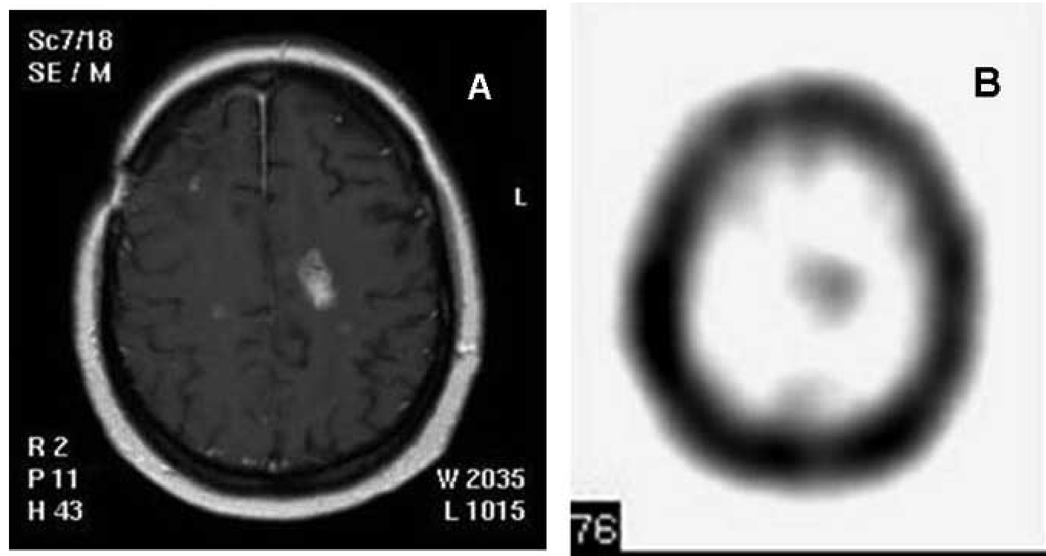

Fig. (1). Suspicion of glioblastoma recurrence in the left para-ventricular space at MRI (A). In the same region, SPECT (B) was positive for tumoral viable tissue then confirmed by patient's clinical evolution.

In the following we will discuss the epidemiology and clinical features of the brain tumours typically characterized with clinical brain imaging. We then briefly describe the radiopharmaceuticals covered in this review. Thirdly, we deal with their respective clinical applications, relating these to their molecular and biophysical properties.

BRAIN TUMOURS: EPIDEMIOLOGY AND CLINICAL FEATURES

The incidence of primary brain tumors in Europe and United States is age-related and is just about 1-10 cases/ 100.000 persons per year with poor discrepancy in the different regions. There are two main peaks of incidence: the former in childhood between 0 and 4 years, the latter in the elderly between 65 and 79 years [8, 9, 10].

According to 1993 World Health Organization (WHO) classification, primary brain tumors are classified in relation to their cellular origin, so five different groups are identified: tumors arising from neuro-epithelial cells, from cranial or spinal nerves, from meninges, form lymphatic and heamatopoietic tissue and from germ cells [11]. In the year 2000 the previous cited classification was revised, so that some variations were included, considering also the immunophenotypic features.

The primary brain tumors originating from neuro-ectoderm (PNETs) are the most common tumors.

In particular, gliomas, arising from glial cells, account for approximately the 45% of all brain tumors. Gliomas are further subdivided in astrocytic (astrocytomas), oligodendro-glial, ependimal and mixed tumors. Astrocytomas are then classified into four grades of malignancy according to their histopathological characteristics: low-grade (grade I), high grade (grade II), anaplastic astrocytomas (grade III) and glioblastoma multiforme (grade IV).

Most clinical manifestations of brain tumors are due to the "mass effect" which is characterized by increase of intracranial pressure and destruction of the surrounding brain tissue. As a consequence, these events produce clinical non specific manifestations like alterations of personality, focal neurological symptoms, headache and seizures.

Surgery often represents the treatment of choice. In the locally advanced disease, surgery is performed mainly to reduce tumor bulk and brain compression. Especially when tumors present an infiltrative pattern of growth, surgical exeresis is incomplete and further treatments are needed. In particular, patients with higher gliomas have a survival benefit when both radiation therapy and chemotherapy are performed. Because chemotherapy alone presents a limited efficacy in high grade gliomas, many innovative clinical trials have been undertaken for instance gene therapy and anti-angiogenesis agents [12].

RADIOPHARMACEUTICALS

Hexakis (2-methoxyisobutylisonitrile) technetium-99m (MIBI) is a lipophilic and cationic radiotracer proposed as Thallium 201 (^{201}Tl) alternative imaging agent for myocardial perfusion. Subsequently, several applications of MIBI in the scintigraphic visualization of several tumors were reported [13, 14]. MIBI is provided in a kit vial containing a lyophilized mixture. Labeling is achieved by adding a sufficient amount of $^{99m}TcO_4^-$ to the vial and warming the mixture in a bath of boiling water for 10 minutes (min). The final ph is 5.5 and the labeling efficiency is greater than 90%. After its constitution, MIBI is good for 6 hours. MIBI presents a net charge of 1+ with a coordination number of 6 and six isonitrile ligand [15].

Several studies have demonstrated that the mechanism of MIBI uptake depends on mitochondrial and plasma membrane potentials [16]. In fact, MIBI is physiologically taken by tissues with a relatively high mitochondrial content

Table 1. MIBI Scintigraphy Results Reported in Some Papers

AUTHORS	AIM	RESULTS
O' Tuama *et al.* (1993)	to investigate MIBI utility in children brain tumors (n= 19)	Sensitivity: 67%; specificity: 100%
Bagni *et al.* (1995)	Pre-surgical evaluation in 27 patients	Trend between MIBI uptake and gliomas grade of malignancy
Maffioli *et al.* (1996)	MIBI utility in case of post-treatment CT scan not conclusive between recurrence versus scar	Sensitivity, specificity and accuracy: 85%. Positive and negative predictive value: 97% and 53%, respectively.
Naddaf *et al.* (1998)	MIBI usefulness to diagnose lymphomas in AIDS patients	Sensitivity: 100%; specificity: 69%.
Soler *at al.* (1998)	Retrospective study with MIBI SPECT in 35 patients with clinical deterioration (recurrence vs scar)	Specificity and sensitivity: 100 %.
Nagamachi *et al.* (2001)	Relation between MIBI uptake and proliferative activity (antigen MIB-1)	Significant correlation between MIBI uptake and MIB-1 index
Minutoli *et al.* (2003)	MIBI in differential diagnosis between neoplastic from non neoplastic intracranial hematoma (n = 29)	MIBI sensitivity and specificity: 100%
Beauchesne *et al.* (2004)	To investigate whether the metabolic tumor volume (MTV) calculated by MIBI SPECT after therapy is correlated with patients survival	MTV < 32 cm^3 : median survival of 358 days. MTV $\geq$ 32 cm^3: median survival of 238 days.

(i.e. heart, liver, kidney, and skeletal muscle tissue). Increased membrane potential and mitochondria content may explain for MIBI accumulation in human carcinoma cells. MIBI uptake seems to occur passively as showed by the poor correlation between cellular MIBI uptake and ATP depletion.

Moreover, MIBI also presents an active transport out of the tumor cells, against the potential gradient. This mechanism also accounts for the tumor resistance to several groups of citotoxic agents (i.e. vinca alkaloids, anthracyclins, actinomycin D). The resistance phenotype is due to a 170 kDa plasma-membrane glycoprotein (Pgp) codified by MDR1 gene, located on chromosome 7.

Pgp seems to be able to transport toxic agents (i.e. antineoplastic agents) out of tumoral cells through an energy dependent efflux pump.

Since MIBI is recognized as substrate by Pgp, this radiotracer has been also proposed as possible agent for the scintigraphic assessment of mutidrug resistance in tumors [17].

Tetrofosmin (1, 2- bis [bis (2-ethoxyethyl) phosphino] ethane) has been recently synthesized and represents a lipophilic complex which is routinely used for myocardial perfusional scintigraphy. From technical point of view, the advantage of tetrofosmin is its easy labeling with technetium since it is not necessary to heat the radiopharmaceutical.

The mechanism of accumulation within the mitochondria is similar to MIBI, so it was successfully suggested as potential tool for the imaging of various tumors, including cerebral neoplasia.

CLINCAL APPLICATIONS

MIBI was firstly applied in brain tumors imaging by O'Tuama *et al.* [18] who successfully used this radiotracer to detect a pediatric atrocytoma in the posterior cranial fossa. As previously described for ^{201}Tl, MIBI was found to be minimally taken by the normal brain due to its almost total exclusion by the blood brain barrier (BBB). Unfortunately, MIBI is strongly accumulated in the choroid plexus and this may reduce the ability of MIBI scintigraphy in detecting tumors in the deep para-ventricular space. While potassium perchlorate is known to inhibit choroid plexus uptake in ^{201}Tl scintigraphy, it has no effects to prevent this phenomenon when MIBI is used.

In a successive work [19], by comparing MIBI and ^{201}Tl in 19 children with brain tumors of different origin the same Author found that sensitivity was exactly the same for MIBI and ^{201}Tl (67%) while the specificity was higher for MIBI (100%) than for ^{201}Tl (91%). Moreover, semiquantitative analysis showed that tumor to background ratio was significantly greater for MIBI. Lesion boundaries were better defined with MIBI. The better definition of the lesion edge obtained with MIBI is most probably due to the physical characteristics of ^{99m}Tc (higher signal to noise ratio than ^{201}Tl).

Bagni et colleagues [20] performed MIBI SPECT in 27 patients for pre-surgical evaluation of primary brain tumors.

MIBI uptake was assessed visually, using a 4-point scale to compare the intensity of tumor MIBI uptake to background activity. Moreover, the vascular supply was also assessed by DSA (digital subtraction angiography). Among astrocytomas, a trend between MIBI uptake and the grade of the gliomas was found; on the contrary glioblastomas present a variable uptake also in relation to the solid to cystic ratio in the tumors. In this paper, the Authors suggested that MIBI accumulation in brain tumors may depend by neoplasia vascular supply, by BBB integrity and by the density of the viable tumoral cells.

As MIBI uptake depends on cells perfusion and proliferation, Nagamachi *et al.* [21] investigated the relation between MIBI and proliferative activity in gliomas by using the monoclonal antibody to Ki-67 antigen (MIB-1). A significant correlation between MIBI uptake and MIB-1 index percentage (i.e. positive nuclear area for MIB-1) was found.

Although relatively rare in healthy people, intracranial lymphomas are quite common tumors in AIDS patients. In such cases, MIBI SPECT was found to have 100% sensitivity and 69% specificity in discriminating lymphomas versus other intracranial lesions characterized by contrast-enhancement at MRI or CT scan (i.e. toxoplasmosis) [22].

Recently, Minutoli *et al.* [23] reported a new interesting application of MIBI in discriminating neoplastic from nonneoplastic intracranial hematoma. Twenty-nine patients with clinical symptoms due to intraparenchymal cerebral hemorrhage were studied by MIBI SPECT to detect early brain hemorrhagic tumors. SPECT was performed 10 min (early images) and 3 h (delayed images) after MIBI intravenous administration. Images were visually assessed; moreover, MIBI index was calculated by comparing the counts in the lesion area to the counts in the contralateral homologous mirror image. MIBI index was calculated in the early images (ER) and in the delayed ones (DR); in addition the retention index (RI) was calculated. In 19 patients (65, 5%) a nonneoplastic hemorrhage was found, while in 10 patients a neoplastic hematoma was diagnosed. MIBI was true positive in all neoplastic lesions and true negative in all nonneoplastic patients. Furthermore, a significant statistical difference in DR ($p< 0.01$) and in RI ($p < 0.05$) was found between the two groups.

Regarding MIBI usefulness in brain tumors follow-up, Maffioli *et al.* [24] firstly evaluated the ability of MIBI SPECT in cases of pre-treated patients whose CT scan was not conclusive between radiation necrosis and tumor relapse. In this paper, the Authors reported that SPECT showed an overall sensitivity, specificity and accuracy of 85% and the positive and negative predictive values were 97% and 53%, respectively. Among the different histotologies, SPECT sensitivity and specificity were much higher in low and high grade gliomas (88% and 92%, respectively) when compared to intracranial lymphomas (70% and 50%, respectively). Therefore, the Authors concluded that the best results in follow-up of patients with suspicion of brain tumors relapse are obtained when SPECT and CT are used in association.

Soler *et al.* [25] analyzed in a retrospective study the usefulness of MIBI SPECT in diagnosis of supratentorial malignant gliomas recurrence versus radionecrosis. Actually, after conventional radiotherapy clinical deterioration may occur due to either tumor recurrence or radiation induced changes. In this work, 35 patients with clinical deterioration were studied; MIBI SPECT was performed contextually with CT scan. MIBI uptake was visually assessed by two blinded nuclear physicians. Semiquantitative analysis was applied by drawing regions of interest (ROI) and comparing tumor uptake to background and to the pituitary gland uptake. Pituitary gland is located outside the BBB and represents a site of MIBI physiological uptake. Since MIBI uptake in pituitary gland seems to be constant, tumor to pituitary gland ratio was though to be a good functional index to assess tumor viability. Moreover, a mathematical algorithm was used to calculate tumor volume. The functional indices and tumor evolution were statistically correlated to tumor recurrence proved by biopsy or by rapid clinical evolution. MIBI SPECT was true positive in 31 patients and true negative in 4 patients, without false positive or negative results. Nevertheless, in all but eight patients with recurrence CT scan was enabling to identify tumor viability. So, MIBI SPECT was proved to be more accurate than CT scan in detecting supratentorial gliomas recurrences.

Regarding the statistical analysis, no significant correlation was found between tumor volume calculated by MIBI SPECT and patients' survival. On the contrary, statistical analysis of quantitative data showed that patients could be divided in two groups according to the survival duration and the tumor to pituitary gland uptake ratios: the former group characterized by long mean survival and the latter by short mean survival.

A recent paper by Beauchesne *et al.* [26] investigated whether ^{99m}Tc-MIBI uptake in malignant gliomas after radiochemotherapy may be prognostic of patients' survival at the end of cranial irradiation. Fifty-seven patients with supratentorial malignant gliomas were studied. SPECT was performed within 10 days after radiation treatments. Metabolic tumor volume (MTV) based on an ellipsoid model was calculated from the three tomographic slices. The Authors reported that patients with a MTV < 32 cm^3 had a median survival of 358 days; on the contrary, patients with a MTV ≥ 32 cm^3 have a median survival of 238 days ($p< 0.05$). In addition, SPECT results were always compared with contextually performed CT scan: the latter imaging modality gave non conclusive results in 26 patients, in whom MIBI allowed to confirm tumor presence in 25 cases while it was negative in 1 patient free from disease. So, the authors concluded that SPECT MIBI may be used as an useful tool in establishing prognosis of glioma patients at the end of radiation therapy.

MIBI AND MULTIDRUG RESISTANCE

As previously described in this paper, MIBI is recognized as substrate by the Pgp, a membrane-bound protein which is able to transport several molecules out of the cell through an energy dependent efflux pump. So, scintigraphy with MIBI was proposed to evaluate the multidrug resistance phenotype in several tumors (i.e. in breast and lung cancers). Few experiences were performed to investigate the capacity of MIBI scintigraphy in detecting brain tumors chemoresista-

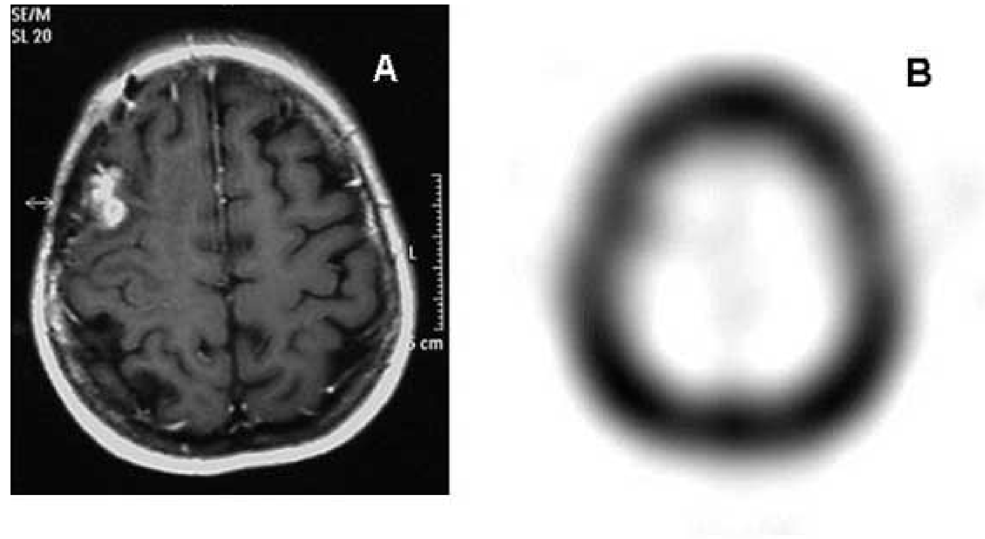

Fig. (2). Suspicion of glioblastoma recurrence in the right parietal lobe at MRI (A). In the same region, 99mTc-SESTAMIBI SPECT (B) shows no focal radiotracer uptake so excluding tumor recurrence as then confirmed by patient's follow-up.

nce. On our opinion, one of the most interesting work in this field was performed by Yokogami et al [17]. The Authors studied 16 pre-treatment patients (of whom two with metastatic brain tumors) and 4 post-treatment patients. ^{201}Tl SPECT was performed at 20 min (early images) and 3 h (delay images) post injection; three days later, MIBI SPECT was performed in a similar way. A semiquantitative calculation of uptake was obtained for both the radiotracers by comparing the radioactivity in the tumor region to the contralateral uninvolved region of the brain. Three parameters were calculated: uptake index on the early image (early UI), uptake index on the delayed images (delayed UI) and the retention index (RI). Contextually, the expression of MDR-1 gene and its product (the Pgp) were analyzed in all patients and compared with SPECT results. Both MIBI and ^{201}Tl were highly accumulated in the tumor area. Moreover, MIBI gave more defined imaging than ^{201}Tl. MIBI SPECT in post-therapy patients showed radiotracer uptake in a patient with malignant transformation; on the contrary, no MIBI uptake was found in patients free from disease at follow-up. The RI of MIBI was significant ($p < 0.05$) lower than that of ^{201}Tl in metastatic brain tumors but not in malignant gliomas. Biological analysis showed that MDR-1 gene and Pgp were present in normal endothelial cells and not in tumoral tissue, moreover, Pgp expression was found to be inversely related to gliomas grade of malignancy. So, the authors concluded that Pgp is most probably not the main cause of chemoresistance in gliomas.

^{99M}TC-TETROFOSMIN

Tetrofosmin is a technetium labeled compound characterized by similar mechanism of uptake as compared to MIBI. As a matter of fact, tetrofosmin is routinely used as imaging agent in myocardial scintigraphy as well as in oncologic diagnosis. Nevertheless, few studies on tetrofosmin application in brain tumor imaging were performed.

Soricelli and coworkers [27] investigated the capacity of Tetrofosmin to diagnose primary intracranial tumors. Twenty-six patients were studied by Tetrofosmin SPECT: in a first group (A) of seven patients the timing for optimal acquisition was evaluated by acquiring SPECT at 20 and 40 and 120 min after radiotracer injection, in a second group (B) two sequential ^{201}Tl and Tetrofosmin studies were performed 20 min after injection and compared. In group A no significant difference in tumor to background ratio among the scans at several interval of time was observed. In group B, imaging with Tetrofosmin presented higher quality than that with ^{201}Tl. So, Authors suggest that Tetrofosmin may be a suitable radiotracer for brain tumor imaging.

As Tetrofosmin presents a similar biodistribution as compared to MIBI, it is almost totally excluded from brain parenchyma by BBB but it is strongly accumulated by choroid plexus. So, the detection of small lesions in the deep para-ventricular space may be problematic. In fact, Barai S. *et al.* [28] demonstrated the poor sensitivity in case of posterior fossa tumors mainly due to the presence of high non specific uptake.

When discrimination between disease and physiological uptake is difficult, the dual integrated imaging modality SPECT/CT may be very helpful. Using the hydrid camera, the anatomical information provided by CT scan is combined with SPECT functional findings so that a precise anatomical localization of the sites of focal uptake can be obtained. Schillaci *et al.* [29] compared the results of SPECT/CT to SPECT alone in a large series of patients (n = 81). They found a significant impact of SPECT/CT in 33 of 81 patients, suggesting that SPECT/CT may be a powerful tool to improve SPECT diagnostic accuracy. Further studies specifically performed in patients with brain tumors are needed to evaluate the utility of hybrid camera in this clinical field.

CONCLUSIONS

MIBI and Tetrofosmin are technetium labeled compounds which were firstly introduced as imaging agent for myocardial scintigraphy. These two radiopharmaceuticals are passively accumulated in cells characterized by high metabolic activity so they have been successfully used also in oncology (i.e. lung, parathyroid, breast cancer). Regarding brain tumors imaging, MIBI was widely applied in diagnosis and follow-up, while few experiences were performed using Tetrofosmin.

MIBI was proved useful to detect intracranial tumors before therapy with higher sensitivity and specificity for gliomas than for the other histologies (i.e. lymphomas). Moreover, the entity of MIBI uptake was found to be related to the grade of malignancy of gliomas.

In patients' follow-up, MIBI scintigraphy showed great diagnostic accuracy to discriminate tumor recurrence versus scar tissue also when compared to CT scan.

As MIBI is a substrate of Pgp, it was proposed to diagnose chemoresistance in brain tumors patients. Nevertheless, the preliminary experiences suggest that Pgp expression is inversely related to the grade of malignancy of gliomas so that Pgp seems not to be the main cause of chemoresistance in these tumors.

Tetrofosmin scintigraphy presents similar characterisitics in sensitivity and specificity as MIBI, so it may represent a suitable tool to image brain tumors.

Unfortunately, both these radiopharmaceuticals are physiologically undertaken by choroid plexus so that the detection of small lesions in the deep para-ventricular space may be problematic. To overcome this drawback, we think that the dual integrated imaging modality SPECT/CT might be of value to obtain a more precise anatomical localization, so improving the diagnostic accuracy of SPECT findings.

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Received: August 30, 2004 Accepted: September 15, 2004