^{18}F-FDG PET/CT usefulness vs Tc99m-Tetrofosmin in the assessment of malignant brain gliomas: Report of two cases

Case Report

Corinna Altini[1], Artor Niccoli Asabella[1], Domenico Rubini[1], Giuseppe Ingravallo[2], Adriano Nicoletti[1], Giuseppe Rubini[1]

[1] Nuclear Medicine Unit, University of Bari "Aldo Moro", Bari, Italy
[2] Pathological Anatomy Unit, University of Bari "Aldo Moro", Bari, Italy

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ABSTRACT

Gliomas account for almost 80% of primary malignant brain tumors in adults. Magnetic Resonance imaging (MRI) is still the gold standard for diagnosis of brain tumors and brain ^{99m}Tc-tetrofosmin Single Photon Emission Computed Tomography (^{99m}Tc-tetrofosmin-SPECT) has been established as a useful tool for their evaluation. Fluorine-18–2-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) provides non-invasive information for staging, clinical assessment and prognosis of glial tumors. We report 2 cases of patients with brain lesions described on MRI suspected for malignancy, however ^{99m}Tc-tetrofosmin-SPECT that didn't show any lesion, ^{18}F-FDG PET/CT revealed radiotracer uptake that supported the hypothesis of malignant gliomas, confirmed later by biopsy. Our cases confirm ^{18}F-FDG PET/CT may be useful for differentiating common enhancing malignant brain tumors and is recommended when differential diagnoses are difficult to narrow using MRI and ^{99m}Tc-tetrofosmin-SPECT. ^{18}F-FDG PET/CT can be used to characterize their aggressiveness and to detect a more feasible site for a stereotaxic biopsy. It yields supplementary non-invasive information to conventional imaging useful in the clinical decision-making.

Key words: Malignant gliomas; Risk stratification; ^{18}F-FDG PET/CT

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Corresponding author: Artor Niccoli Asabella, Piazza G. Cesare 11, 70124 Bari, Italy.
E-mail: artor.niccoliasabella@uniba.it

INTRODUCTION

The term "gliomas" comprehend a group of malignancies heterogeneous for pathogenesis, clinical and biological characteristics as well as for sensitivity to different therapeutic strategies [1].

Malignant gliomas account for almost 80% of primary brain tumors in adults, and they result in more years of life lost than do any other tumor [1]; their frequency increases with age, having a peak between 65-75 years with male/female ratio of 1.6/1. Supratentorial localization is the most frequent[1]. The term 'glioma' encompasses all tumors that origin from glial cells. These include astrocytic tumors (WHO classification: benign astrocytoma grades I, II, III [anaplastic astrocytoma], and IV [glioblastoma]), oligodendrogliomas, ependymomas, and mixed gliomas [1].

The malignant histotypes (grades III, IV) represent only about 1% of adult malignancies, 25% of primary brain tumors and 45-50% of gliomas [1]. Glioblastoma, the most common type of glioma, is associated with very poor survival [2]. Symptoms of gliomas depend on their size, grade and location [1].

Magnetic Resonance Imaging (MRI) is still the gold standard in the primary diagnosis of brain tumors that provides information of size and localization as well as additional insights on secondary phenomena (i.e. oedema and bleeding) [1]. MRI can detect disruption of Brain-Blood Barrier (BBB), which is common of malignant brain tumors; however, even the use of contrast may not indicate much more than the presence of BBB damage and invasive tumor areas remain less defined [2].

Brain ^{99m}Tc-tetrofosmin Single Photon Emission Computed Tomography (^{99m}Tc-tetrofosmin SPECT) has been well established in numerous studies reported in literature, as a useful tool for the evaluation of brain tumors, which is also dependent on BBB integrity [3].

Much interest and effort has been invested into the development and evaluation of brain tumor tracers that do not depend on BBB damage, such as Fluorine-18-2-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), because they are transferred by large-capacity specific transporters across the intact BBB [2]. Other PET radiopharmaceuticals are still investigated, as well as amino acid tracers including ^{11}C-methionine, ^{18}F-fluoroethyltyrosine, and ^{18}F-L-3,4-dihydroxyphenylalanine, that provide high sensitivity in detecting recurrent or residual gliomas. ^{18}F-fluorothymidine is an analog of the nucleoside thymidine useful in tumors with absent or broken BBB and has potential for tumor grading and monitoring of therapy. Tracers to image neovascularization, hypoxia, and phospholipid synthesis are under investigation for potential clinical use [4].

Despite many efforts to develop multimodal approaches for optimizing combinations of radiation, surgery and chemotherapy for malignant gliomas, survival rates remained nearly unchanged [5].

Herein we report two exemplar cases about two patients with undefined brain lesions for whom 18F-FDG PET/CT has been useful for a non invasive assessment of risk stratification and therapeutic strategy.

CASE 1

A 66-year woman referred to the neurosurgery department due to left hemisoma hyposthenia. her brain MRI showed an ovoidal lesion of 15 mm in right thalamus, suspected for a glial primary tumor without excluding the hypothesis of metastasis.

In order to confirm diagnosis and eventually to find a primary tumor, a brain and whole body Contrast Enhancement Computed Tomography (CECT) was requested showing an irregular lesion in right thalamus with a central necrotic area causing asymmetry and mass effect on the right lateral ventricle (Figure 1A, green circle). Whole-body CECT didn't show any primary or secondary tumors and so the hypothesis of a high-grade glial primary tumor was postulated.

In the view to complete the staging and decide a correct treatment she performed a ^{99m}Tc-Tetrofosmin SPECT that didn't show pathological radiopharmaceutical uptake, but dislocation of the right ventricle due to the presence of a space-occupying lesion was evident (Figure 1B, green arrow).

MRI and ^{99m}Tc-Tetrofosmin SPECT findings disagree, so a further investigation was necessary in order to clarify the diagnosis. ^{18}F-FDG PET/CT was performed showing asymmetry between right and left hemispheres and ^{18}F-FDG uptake in the right thalamus with a dishomogeneous pattern, characterized by a peripheral high uptake and a central absence of ^{18}F-FDG uptake due to necrosis (Figure 1C, Figure 1D, green circles). The semiquantitative analysis performed by the Standard Uptake Value (SUV) showed SUVmax of 8.5 in the lesion with ratios tumor/white matter (T/WM) and tumor/gray matter (T/GM) 2.29 and 0.60, respectively. These findings supported the hypothesis of a high malignancy glioma.

Considering surgery's difficulties due to the infiltrating morphology, a stereotaxic biopsy was performed on the basis of ^{18}F-FDG PET/CT findings on the maximum ^{18}F-FDG uptake area. The histologic and immunohisthochemical results showed a glioblastoma grade IV with Ki67 > 18% (Figure 2).

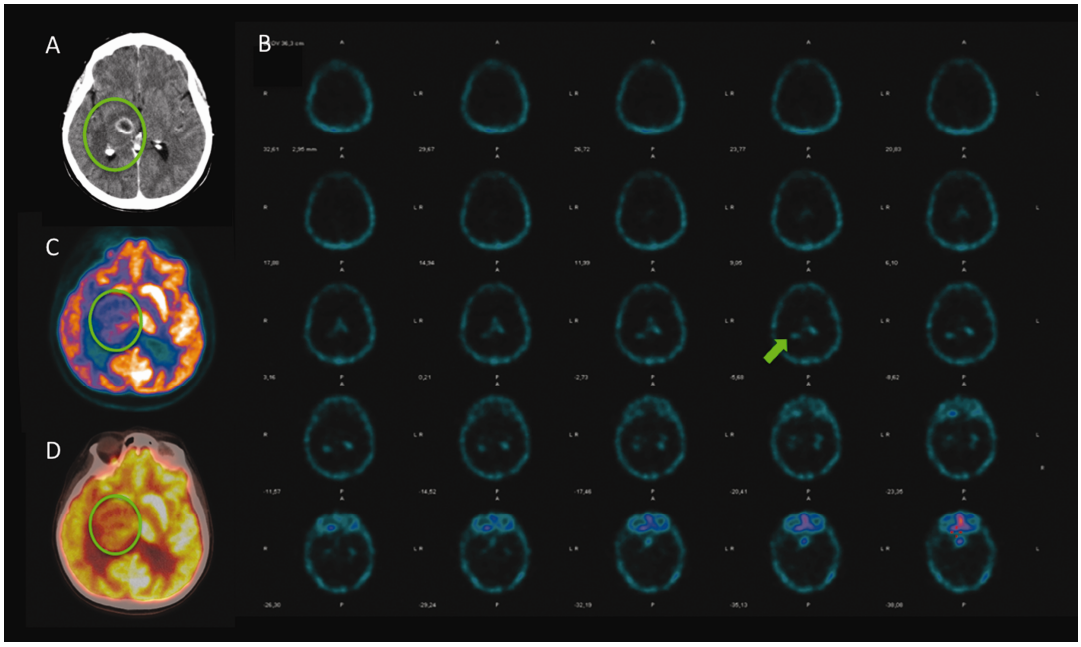

Fig 1. Brain CECT transaxial image showed an irregular lesion in right thalamus with a central necrotic area causing mass effect on the right lateral ventricle (A). Brain ^{99m}Tc-tetrofosmin-SPECT transaxial images (B) don't show any area of pathological uptake. ^{99m}Tc-tetrofosmin uptake in scalp, choroid plexus and pituitary gland is physiologic. ^{18}F-FDG PET/CT transaxial PET (C) and fused images (D) show ^{18}F-FDG uptake in the right thalamus with dishomogeneous pattern, characterized by peripheral high uptake and central absence of ^{18}F-FDG uptake due to necrosis (SUVmax 8.5, T/WM 2.29, T/GM 0.60).

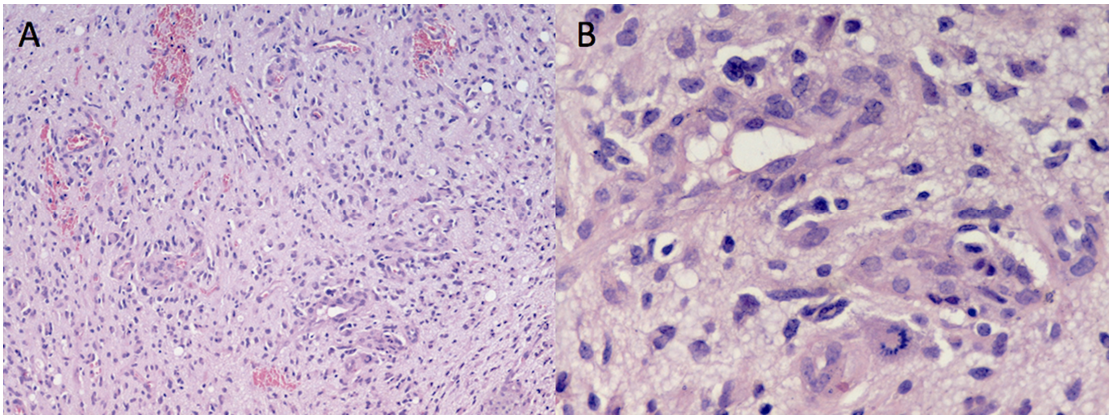

Fig 2. Histological section hematoxylin and eosin original magnification 100x (A) and 400x (B) shows pleomorphic neoplastic astrocytes with marked nuclear atypia, associated to microvascular proliferation characterized by hyperplastic endothelial cell; note also the atypical mitotic figure.

CASE 2

A 65-year woman came to neurologist attention for pressure cephalea with temporospatial disorientation.

A brain MRI was performed showing a solid lesion of about 3 cm in the left thalamus compressing the third ventricle causing subocclusion and supratentorial hydrocephalus; morphological signs suggested the hypothesis of middle-high grade glial primary tumor. For endocranial hypertension a ventricular-peritoneal drain catheter was positioned.

The ^{99m}Tc-Tetrofosmin-SPECT performed 1 week later, didn't show any pathological uptake (Figure 3A), disagreeing with the MRI hypothesis.

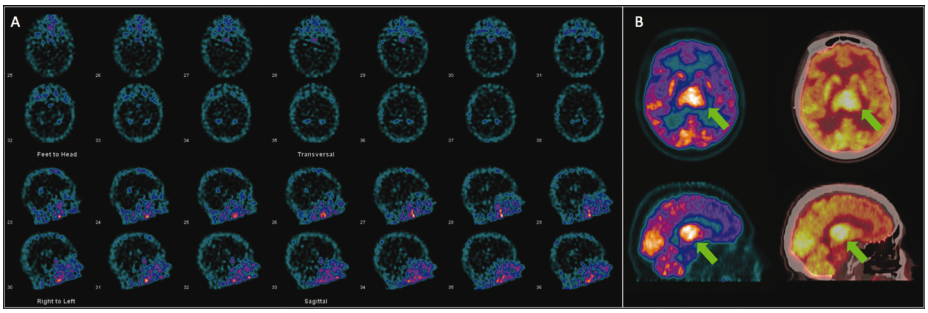

Fig 3. Brain ^{99m}Tc-tetrofosmin-SPECT transaxial and sagittal images (A) don't show evidence of pathological uptake. ^{18}F-FDG PET/CT transaxial and sagittal PET and fused images (B) show homogeneous pathological ^{18}F-FDG uptake in the left thalamus (SUVmax 15, T/WM 2.77, T/GM 1.36).

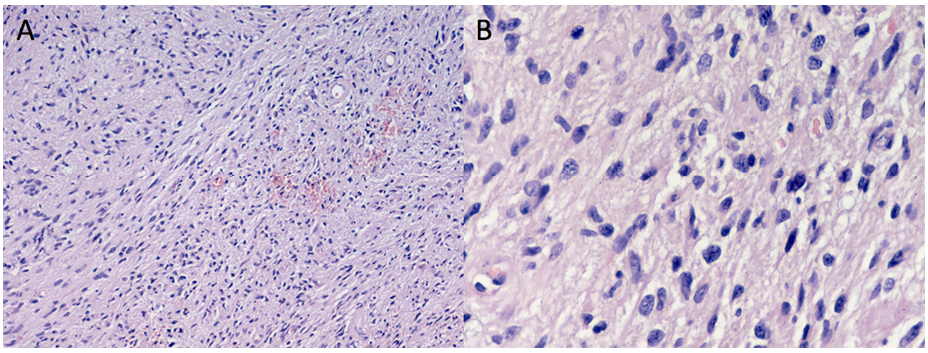

Fig 4. Histological section hematoxylin and eosin original magnification 100x (A) and 400x (B) shows numerous neoplastic astrocytes with moderate pleomorphism and nuclear atypia; note the absence of vascular proliferation and necrosis.

In order to clarify the possible diagnosis, brain ^{18}F-FDG PET/CT was performed (Figure 3B, green arrows) that showed focal pathological ^{18}F-FDG uptake in the left thalamus, as described at MRI. Lesion's SUVmax resulted 15, T/WM and T/GM 2.77 and 1.36, respectively. These findings supported the hypothesis of poorly differentiated gliomas with high malignancy. Apparently the ^{18}F-FDG uptake seems asymmetric in the two occipital lobes, but the control of MIP image and the similarity of SUV of 11 in both sides confident with position related differences.

The patient was then operated and the histologic and immunohistochemical results showed an anaplastic astrocytoma grade III with Ki67 > 13% (Figure 4).

DISCUSSION

Tumor grade is highly significant in determining clinical outcome of patients with malignant gliomas. Stratification of tumors into risk-groups based on prognostic parameters is the major component of treatment, because it may modify strategies in order to improve disease outcome [6].

Thallium-201 (^{201}Tl) SPECT has been used for the assessment of the biologic activity of primary and recurrent intracranial neoplasms. However, ^{201}Tl is not an ideal radiopharmaceutical for SPECT imaging due to its low-energy gamma emission and the poor photon flux associated with the limited amount of administrable dose [7].

Technetium-99m-labeled compounds, such as Technetium-99m-hexakis-2-methoxyisobutyl isonitrile (^{99m}Tc-MIBI) and ^{99m}Tc-tetrofosmin are lipophilic cationic tracers. Disruption of BBB combination with their cationic charge and liphophilic properties, negative transmembrane potential, higher metabolic activity and mitochondrial density of the tumors are involved in uptake these tracers. Futhermore they are more suitable for SPECT imaging because they have the 140 keV gamma-ray energy and high photon flux and offer

practical advantages of a kit-based continuous availability [7].

^{99m}Tc-tetrofosmin SPECT is a low cost and wide availability technique and can be a suitable radiotracer for the differentiation of glioma recurrence from radiation necrosis, neoplastic from non-neoplastic intracerebral hemorrhage, benign from malignant brain space-occupying lesions and for the assessment of the proliferation potential of gliomas and meningiomas [6].

Malignant gliomas have heterogeneous clinical and biological behaviors that correspond to a wide variability in the BBB invasion and blood flow. ^{99m}Tc-tetrofosmin uptake depends on these 2 factors. High malignant gliomas with intact BBB might present as false negative by brain ^{99m}Tc-tetrofosmin-SPECT, as in our two patients [3].

^{18}F-FDG PET/CT allows the lesions evaluation on the basis of their metabolic activity, independently to BBB integrity and is successfully applied for brain tumor imaging as far as diagnosis, prognosis and response to therapy assessment [5]. ^{18}F-FDG PET/CT yields both qualitative and quantitative information regarding glucose uptake and metabolism, and provides non-invasive means for the clinical assessment of glial tumor metabolic activity. The usefulness of ^{18}F-FDG PET/CT in the assessment of grading and prognosis may represent an important area of challenge [8].

The interpretation of qualitative and semiquantitative information provided by ^{18}F-FDG PET/CT is still under-debate. Pardo et al. assigned at ^{18}F-FDG PET/CT images a score from 0 to 4, in order to determine clinical utility and applicability to patient management. The images were ranked on a qualitative scale from hypometabolic areas as compared to normal white matter (score 0) to uniform hypermetabolism throughout all tumor regions (score 4). Glial tumors with high ^{18}F-FDG PET/CT scores (3-4) corresponded to patients with statistically significant shortened progression-free survival times. Patients with low ^{18}F-FDG PET/CT scores (0-2) revealed statistically significant increases in progression-free survival. Hypermetabolic ^{18}F-FDG PET/CT regions (scores 3-4) may portend high-grade tumor recurrence; yet, this by no means establishes the diagnosis. Similarly, hypometabolic or eumetabolic ^{18}F-FDG PET/CT areas (scores 0 to 2) can correspond to histologically benign or intermediate grade glial tumors [5].

Glucose metabolism can be used to characterize the aggressiveness of brain tumors and may supplement pathological grading. However, a differentiation between WHO grade 3 and 4 tumors is not possible owning to the comparable high uptake [8].

In the two cases we reported ^{18}F-FDG uptake was higher in grade III anaplastic astrocytoma than in the grade IV glioblastoma (SUVmax 15 vs 8.5).

Hustinx et al. evaluated SUVs and activity ratios in primary brain tumors on ^{18}F-FDG PET/CT and concluded that SUV measurements of brain tumor were influenced by a wide variety of factors, such as plasma glucose level, steroid treatment, tumor size and heterogeneity, time after injection and previous irradiation [9]. SUVmax, T/WM and T/GM ratios could be useful in characterizing brain tumors but their importance is limited due to the absence of validated cut-off values [10].

Di Chiro reported that the regional cerebral metabolic glucose rate, determined by ^{18}F-FDG PET/CT, was a better predictor of survival in patients with malignant glioma than was histologic classification [11].

In general, functional measures related to tumor proliferation are expected to deliver more reliable information on prognosis than morphologic imaging methods [2].

Often, brain tumors exhibit different degrees of anaplasia in different tumor locations. Thus, surgical biopsies, especially when taken stereotactically, may miss the most malignant tumor part and therefore underestimate the tumor grade. To overcome this problem, targeting of biopsies toward the most malignant tumor part is an important clinical utility of ^{18}F-FDG PET/CT [2].

Furthermore ^{18}F-FDG PET/CT can help in the detection of sites for biopsy, corresponding to the lesions with highest ^{18}F-FDG uptake [12].

CONCLUSION

^{18}F-FDG PET/CT may be useful for differentiating common enhancing malignant brain tumors and is recommended when differential diagnoses are difficult to narrow using MRI and ^{99m}Tc-tetrofosmin-SPECT. ^{18}F-FDG PET/CT yields supplementary non-invasive information to conventional imaging useful in the clinical decision-making.

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