

The diagnostics of recurrent gliomas using FDG–PET: still questionable?

¹Otakar Bělohávek, ²Jan Klener, ³Josef Vymazal,

²Vladimír Dbalý, ²František Tovaryš

¹Department of Nuclear Medicine — PET Centre, Na Homolce Hospital, Prague, Czech Republic

²Department of Neurosurgery, Na Homolce Hospital, Prague, Czech Republic

³Department of Radiology, Na Homolce Hospital, Prague, Czech Republic

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Abstract

BACKGROUND: For a number of years, FDG–PET was considered as a gold standard for the differential diagnosis of recurrent glioma and radionecrosis. Recently published papers have introduced a wealth of scepticism into this area. The aim of this work is to specify the added value of FDG PET, as compared to MRI, in terms of diagnostics of recurrent gliomas in the clinical setting of the PET Centre Prague.

MATERIAL AND METHODS: MRI and FDG–PET were used to examine 29 patients for suspicious glioma recurrence, after 30 open neurosurgical operations or re-operations combined with chemo- and/or radiotherapy. The sensitivity, specificity and accuracy of both examinations were calculated with respect to their micromorphological findings ($n = 28$) or the clinical and radiological follow-up ($n = 2$).

RESULTS: MRI detected 23/24 tumour recurrences (sensitivity = 95.8%) and FDG PET only 15 of these (sensitivity = 62.5%). MRI specified only 3/6 radionecrotic lesions (specificity = 50.0%), while FDG PET identified 5/6 (specificity = 83.3%). Overall accuracy was 26/30 (86.7%) for MRI and 20/30 (66.7%) for FDG PET. In the subgroup of MRI positive or equivocal findings ($n = 29$) FDG PET was clearly positive in 15 cases. High-grade glioma recurrence was subsequently confirmed in all of them. On the other hand negative or equivocal FDG PET was associated in 5/14 cases (35.7%) with radionecrosis, in 3/14 (21.4%) with low-grade glioma and in 6/14 (42.9%) with high-grade glioma.

Correspondence to: MUDr. Otakar Bělohávek, CSc.
Department of Nuclear Medicine — PET Centre
Na Homolce Hospital, Roentgenova 2
150 30 Prague 5, Czech Republic
Tel: (+420) 257 272 463 or 165, fax: (+420) 257 272 163
e-mail: otakar.belohlavek@homolka.cz; www.homolka.cz/nm

CONCLUSIONS: MRI is the method of choice for the detection of glioma recurrence but it is associated with a high rate of false positive results. FDG PET has significantly lower sensitivity; nevertheless it does help to specify MRI positive lesions. FDG PET positive lesions give a very high probability of high-grade glioma, but its equivocal and negative findings are of no clinical value.

Key words: glioma, recurrence, radionecrosis, FDG, PET

Introduction

The combined incidence of primary intracranial and spinal axis tumours is between 2 and 19 in 100,000 persons per year, depending on age, arriving at a plateau (17.9 to 18.7 in 100,000) at between 65 and 79 years of age [1]. The most common primary brain tumours are those derived from glial precursors (astrocytes, ependymocytes, and oligodendrocytes). They are well known as gliomas. Tumour grading systems commonly divide gliomas into 4 grades according to their micromorphology and proliferative activity. A level of simplification is sometimes adopted and grade I–II gliomas are known as low-grade, while grade III–IV gliomas are called high-grade.

The treatment of gliomas is based on open surgery. The growth of gliomas is commonly infiltrative and surgery tends to be more cytoreducing than total. Because of this, surgery is usually followed by radiotherapy and cytotoxic chemotherapy to control further tumour growth. Corticotherapy is often necessary to reduce collateral oedema. Both tumour recurrence and complex therapy can induce similar local tissue changes that result in impairment of the blood-brain barrier.

Morphological imaging modalities with high spatial resolution, such as contrast-enhanced MRI or CT, are very sensitive means of diagnosing pathological brain foci. However, these methods are almost incapable of distinguishing between tumour recurrence and benign post-therapeutic tissue changes. Sequential scanning during the follow-up period, when the regression of changes is apparent, is helpful. On the other hand, progression of changes can represent either tumour recurrence or acute or delayed post-therapeutic changes. Therefore, other diagnostic approaches are needed to enable reliable differentiation.

Positron emission tomography with 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG PET) is a sensitive method of tumour imaging. Several papers have previously dealt with FDG PET for brain tumours [2–13]. Some of them were summarised in a German position-paper [14], which concluded that differentiation between glioma

ma recurrence and radionecrosis by FDG-PET is evidence-based (category 1a). In 2000, Langleben and Segall [15] published another review. They pointed out the heterogeneity of previously published studies and concluded that it was not possible to derive a single numerical value for the accuracy of PET in differentiating a recurrent tumour from a late-delayed radiation injury. In published studies, the sensitivity of FDG-PET varies between 80 and 100% and its specificity between 40 and 100%.

Our hospital works extensively with the diagnostics and treatment of brain tumours. In our previous series [16] FDG-PET appeared to be a powerful method for the confirmation of the recurrence of brain metastases after stereotactic radiosurgery but its lower sensitivity disallows any reliable exclusion of tumour recurrence. Because of the existing controversies in the literature and a strong clinical demand for a method of differentiation between recurrent gliomas and benign post-therapeutic changes, we decided to evaluate the sensitivity, specificity and accuracy of FDG PET when compared to MRI in routine clinical settings. The aim of this work is to specify the added value of FDG PET in comparison to MRI in the diagnostics of recurrent gliomas in the clinical setting of the PET Centre Prague.

Material and methods

Patients

The scientific and ethical committees of Na Homolce Hospital have approved this project. All patients were referred for examination for medical, and not research, reasons. Therefore we did not request that the patients give their informed consent, because the data were to be presented anonymously. Twenty-nine patients (21 males, 8 females, 17–65 years old) underwent 30 FDG-PET examinations for suspected recurrence of glioma. FDG-PET followed 4–64 months after appropriate complex therapy, including surgery (median = 13 months). In 28 cases stereobiopsy or open surgery followed an average of 3.8 weeks after FDG-PET (interquartile range: 1.2–9.5 weeks). Two other cases were clinically and radiologically followed-up for 12 and 28 months respectively.

FDG PET

Patients were instructed to fast for at least 6 hours before imaging. In a dimly lit and quiet room, 210 MBq/70 kg of FDG was administered via a peripheral vein catheter. Data were acquired using the ECAT EXACT dedicated PET scanner (CTI/Siemens Inc., Knoxville, TN). Thirty minutes later a 2D "hot" transmission scan of the brain was performed, lasting between 5 and 10 minutes (transmission scanning time was corrected to allow for decay of the transmission sources). It was immediately followed by 3D emission scanning, which lasted 15 minutes. The data acquired were reconstructed with segmentation by iterative OS-EM algorithm (matrix: 128², brain mode, zoom: 2, subsets: 16, iterations: 6, Hann filter: 5 mm) implemented using ECAT 7.2 software (apart from a few studies made when the PET Centre Prague began operations, which were acquired in 2D mode after the administration of 370 MBq of FDG, and reconstructed using ECAT 7.1 software with 8 subsets and 2 iterations). FDG PET scans were blindly evaluated retrospectively. Lesions were visually assessed as negative when no focally enhanced activity was encountered in the brain. Lesions were considered positive when focal accumulation

of FDG was clearly apparent. Other lesions were considered as equivocal (such as slightly enhanced activity within the margins of metabolic defect, indistinguishable from an activated gyrus).

MRI

Out of the series of MRI examinations, the ones closest to FDG-PET were selected for the purpose of this analysis. On average MRI was completed 1.0 weeks before FDG-PET (interquartile range: 3.4 weeks before – 1.0 weeks after FDG-PET) using the Magnetom Impact Expert, Siemens and Magnetom Symphony, Siemens. MRI was typically evaluated in comparison with previous MRI investigations. Lesions were visually assessed as negative when there was no considerable change to previous post-operative examinations. The presence of a post-contrast enhancement in the form of a thin ring was considered as a usual blood-brain-barrier disruption. However, the nodular enhancing lesions, not present in previous examinations, were considered as tumour recurrence. Other lesions were considered to be equivocal. The above described analysis is however valid predominantly for gliomas of higher grades. The detection of a recurrence of low-grade gliomas is usually based on the presence of a post-contrast enhancement but rather on the presence of iso- or hyperintense nodular lesion on PD- and T2-weighted images.

Data analysis

The sensitivity, specificity and accuracy of FDG PET and MRI in the detection of glioma recurrence were calculated and compared with the micromorphology or clinical and radiological follow-up. The incremental value of FDG PET when used after MRI was also defined. The Yates corrected Chi-square test was used to compare the frequency of correctly and incorrectly classified foci between the different methods or references. Statistical analyses were performed using Statistica 5.5 software (StatSoft Inc., Tulsa, OK., USA).

Results

High-grade glioma recurrence ($n = 21$), low-grade glioma recurrence ($n = 3$) and radionecrosis ($n = 4$) were found by micromorphological analysis. The other two patients under clinical and radiological follow-up were considered as radionecrosis.

The results observed are summarised in Tables 1 (FDG PET) and 2 (MRI). Because of the two times higher frequency of radionecrosis in comparison to tumour recurrence in the equivocal findings subgroup for both MRI and FDG PET, equivocal results were deemed to be negative for the purpose of assessing sensitivity, specificity and accuracy.

Table 1. Distribution of FDG PET results according to histology/follow-up

		Histology/follow-up		
		Glioma recurrence	Radionecrosis	Total
FDG PET	Negative	7	1	8
	Equivocal	2	4	6
	Positive	15	1	16
	Total	24	6	30

Table 2. Distribution of MRI results according to histology or follow-up

		Histology/follow-up		
		Glioma recurrence	Radionecrosis	Total
MRI	Negative	0	1	1
	Equivocal	1	2	3
	Positive	23	3	26
	Total	24	6	30

Regardless of tumour grade, MRI detected 23/24 tumour recurrences (sensitivity = 95.8%) and FDG PET only 15 of them (sensitivity = 62.5%). The sensitivity of MRI was significantly higher in comparison to FDG PET ($p = 0.0129$). MRI specified only 3/6 of radionecrotic lesions (specificity = 50.0%), while FDG PET located 5/6 (specificity = 83.3%). Overall accuracy was 26/30 (86.7%) for MRI and 20/30 (66.7%) for FDG PET (non-significant difference, $p = 0.127$).

It is well known that low-grade gliomas often do not accumulate FDG. Therefore another evaluation was carried out excluding 3 cases of low-grade glioma: FDG PET detected 15/21 tumour recurrences (sensitivity = 71.4%), and specified 5/6 radionecroses (specificity = 83.3%) with an overall accuracy of 20/27 (74.1%).

The higher specificity of FDG PET as compared to MRI opens up the question of whether it could further specify MRI positive lesions. In the subgroup of MRI positive or equivocal findings ($n = 29$), FDG PET was clearly positive in 15 cases (Fig. 1). High-grade glioma recurrence has been confirmed in all of them. On the other hand negative or equivocal FDG PET was associated in 5/14 cases (35.7%) with radionecrosis, in 3/14 (21.4%) with low-grade glioma and in 6/14 (42.9%) with high-grade glioma (Fig. 2). The frequency of occurrence of a recurrent glioma was significantly different ($p < 0.05$) between the FDG PET negative and positive subgroups.

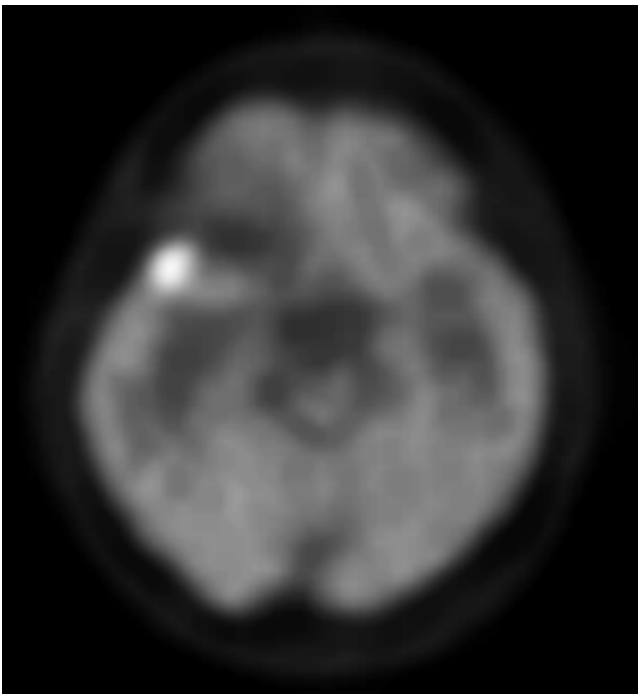


Figure 1. An example of true positive FDG PET 13 months after surgery for glioblastoma. At the transverse slice there is focally increased uptake of FDG in the right temporal lobe. This focus corresponds to contrast enhancement of $12 \times 12 \times 12$ mm at MRI 2 weeks later. Following surgery recurrence of glioblastoma was revealed.

Discussion

There is no reason to use FDG PET as a first line diagnostic tool in the case of brain glioma. Modern MRI scanners achieve higher spatial resolution and FDG trapped in surrounding grey matter compromises the sensitivity of FDG PET. Valk et al. [10]

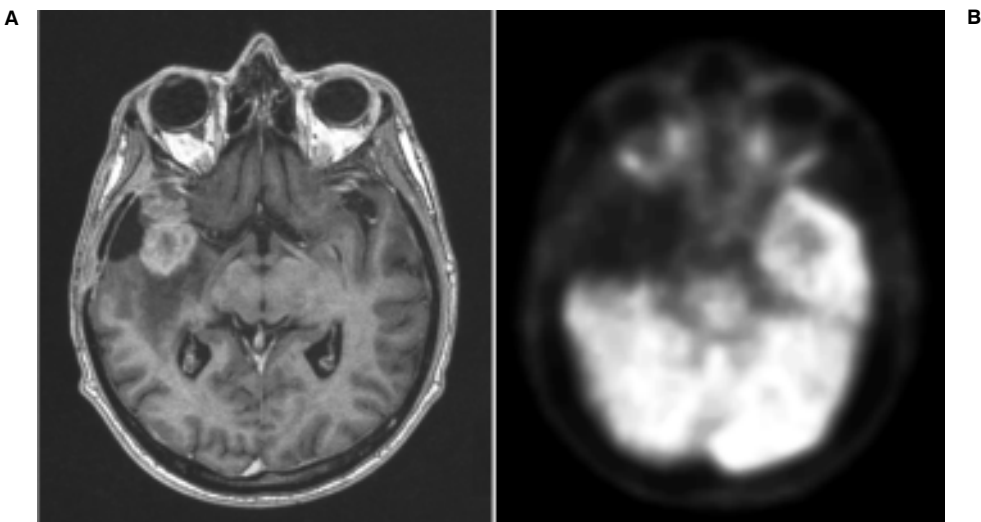


Figure 2. An example of false negative FDG PET 13 months after surgery for glioblastoma. **A.** T1-weighted gradient echo sequence after administration of contrast agent: a nodular lesion $39 \times 21 \times 21$ mm with a positive post-contrast enhancement is located medially to the post-resection pseudocyst in the right temporal lobe. This finding is highly suspicious of recurrent glioma; **B.** Focal defect in FDG uptake due to the post-resection pseudocyst in the right temporal lobe. Within 3 weeks recurrence of glioblastoma was histologically confirmed. FDG PET was false negative despite large lesion size.

concluded that some cells from the irradiated volume might appear morphologically intact, but have little or no metabolic or clinical activity. This fact could explain the lower sensitivity of FDG PET. Following on from this, it could be hypothesised that low FDG accumulation might reflect the fact that the residual tumour is under control by therapy. Thompson et al. [17] identified 80% of primary glial neoplasms larger than 10 cm³ and only 25% when the volume enhancement was smaller than 6 cm³. Ricci et al. [9] reported sensitivity of 73% and specificity of 56%. Also, our overall sensitivity of 62.5% (71.4% for high-grade gliomas) concurs with the results of these and other published papers, because all the calculations of sensitivity are taken from small series and the differences are not significant. The only discrepancy found is when our work and the others are compared with the paper by Di Chiro et al. [4] — where 100% sensitivity and sensitivity was achieved on the basis of 95 patients. Due to the small series we were unable further to define FDG PET performance in subgroups with different tumour types and/or volumes.

It is generally accepted that it is difficult to distinguish radionecrosis from glioma recurrence using MRI or CT. Our data are in agreement with this (MRI specificity of 50%). The more specific FDG PET could help to specify positive or equivocal MRI findings. All clearly positive FDG PET identified the recurrence of high-grade glioma in this series. This is the same result we achieved in our previous work [16] when positive FDG PET reflected the recurrence of brain metastases after radiosurgery. Despite significant differences in tumour occurrence between the FDG PET negative and positive subgroups in our previous work, as well as in this one, the insufficient sensitivity of FDG PET means that it is not capable of reliably excluding tumour recurrence.

It is apparent that FDG is a sub-optimal tracer for brain tumour diagnostics due to its physiologically high uptake in the grey matter. This disadvantage could be overcome by the use of labelled amino-acids. Of these, the one with the most perspective seems to be O-(2-[¹⁸F]fluoroethyl)-L-tyrosine (FET) [18]. But, at this point, labelled amino-acids are not as readily available to the majority of centres, including the PET Centre Prague, as FDG.

Conclusions

Sensitive MRI is the method of choice for the detection of glioma recurrence, but it is associated with a high rate of false positive results. In our series, FDG PET shows a significantly lower sensitivity and non-significantly worse accuracy; nevertheless it does help to specify MRI positive lesions; FDG PET positive lesions indicate a very high probability of high-grade glioma recurrence, but its equivocal and negative findings are of no clinical value because they can indicate radionecrosis as well as low-grade and even high-grade glioma recurrence.

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