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Although Non-diagnostic Between Necrosis and Recurrence, FDG PET/CT Assists Management of Brain Tumours After Radiosurgery

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Abstract. *Aim: To re-evaluate the role of ^{18}F-fluoro-deoxy-D-glucose (FDG) positron emission tomography/ computer assisted tomography (PET/CT) co-registered with magnetic resonance imaging (MRI) in differentiating adverse radiation effect (ARE) from tumour recurrence after Gamma Knife radiosurgery of brain tumours. Patients and Methods: Twenty-seven PET/CT studies co-registered with MRI were performed on 16 patients after radiosurgery, with 12/16 patients having multiple radiosurgery treatments. Long term follow-up was used for evaluation, with 3/16 patients being histopathologically confirmed. Results: PET/CT was positive in all studies in 6/16 patients, negative in all studies in 6/16 and changed from negative to positive in one. In 2/16 patients, PET/CT was both positive and negative in separate tumour foci. In 9/16 cases with a positive PET/CT, tumour was confirmed. In 6/16 patients with a negative PET/CT, 3/6 had recurrence and 3/6 ARE. In 1/16, equivocal results became negative after retreatment. PET/CT/MRI identified tumour within ARE. Sensitivity of PET/CT/MRI proved to be 64.7%, and specificity 100%. Conclusion: PET/CT/MRI assists management, by revealing metabolism rather than histology.*

A significant proportion of the enlarging, contrast-enhancing lesions, that may be seen on magnetic resonance imaging (MRI) several months after Gamma Knife radiosurgical treatment of brain malignancy, is reported to be due to a form of necrosis or adverse radiation effect (ARE) and not due to regrowth of the tumour (1). Distinguishing between these two entities is very important for correct patient management. Positron emission tomography with ^{18}F-fluoro-deoxy-D-glucose (FDG PET) has been regarded as an extremely useful investigation in this context. However reports show mixed results, with some investigators reporting high accuracy (2-4) and others low sensitivity and specificity (5-7).

The relative frequency of tumour recurrence *versus* ARE after radiosurgery is quoted as 1:3 (8). We have used FDG PET/CT for diagnosis since 2004 in this context, but following a number of equivocal results it was decided to review all cases in order to re-evaluate its role in diagnosis and management of ARE.

Due to the lower spatial resolution of PET compared to MRI and CT, as well as the high background activity of FDG PET, it is often difficult to compare the spatial localization of abnormalities demonstrated by PET in relation to other methods. It was to be expected that combined PET/CT would have largely overcome this problem, but we found that this was not the case. Following the installation of our Siemens Biograph PET/CT scanner it remained difficult to resolve the exact locations of high and low emission in relation to abnormalities on MRI and to the previous Gamma Knife dose plan (Gamma Plan). The preliminary 'side by side' comparison of PET/CT and MRI images by the staff of the Nuclear Medicine, Radiology and Neurosurgery departments failed to provide a satisfactory diagnostic accuracy. For this reason we chose to co-register the PET/CT with MRI when reporting post-radiosurgery cases, since co-registration with MRI has been proposed as a means to increase accuracy (9, 10). We used a technique that matches mutual information.

This article records the results of FDG PET/CT co-registered with MRI on patients that had received Gamma Knife treatment of brain tumours, along with follow-up to the most conclusive point for evaluation.

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Patients and Methods

Twenty-seven FDG PET/CT studies were performed on 16 patients (Table I), comprised of 11 men and 5 women (age range: 38-70). Diagnoses were of brain metastases in 13 cases, 4 being from breast carcinoma (BR), 7 from non small cell lung carcinoma (NSCLC), one from small cell lung carcinoma (SCLC) and one from squamous cell pharyngeal carcinoma (SQPH). The other 3 cases were glioblastoma multiforme (GBM). The PET/CT studies were performed 1-65 months after initial Leksell Gamma Knife radiosurgery (Elekta Instrument AB, Stockholm, Sweden). Four of the 16 patients had radiosurgery performed once, 10 patients twice, one patient three times and another one four times, however on two different foci, *i.e.* once on the left focus and three times on the right, respectively. Radiosurgery treatment was performed on a Leksell Gamma Knife Model 4C and dosage was defined by the RTOG protocol 90-05 (11). The co-planar ^{18}F FDG PET/CT images were performed on a Siemens Biograph (Dual Slice) scanner (Siemens Healthcare GmbH, Erlangen, Germany). MRI was performed at another time using a Philips 1.5 Tesla scanner (Philips Healthcare/Philips Medical Systems B.V, Eindhoven, The Netherlands). The images were distributed via the hospital DICOM 3 network. PET/CT was co-registered with MRI using a computer running Oncentra Master Plan 1.4 (Elekta Instrument AB, Stockholm, Sweden), which was connected to the network. This co-registration was performed based on MR-CT registration technique. We have assessed previously the improved accuracy of such co-registration by measuring the deviation between MRI/PET and MRI/PET/CT. This was found to average 3 mm (12). All patients gave written informed consent, according to the Helsinki Declaration. The present study was approved by the Ethical Committee of the Diagnostic and Therapeutic Centre 'Hygeia'.

Any area on PET scan with greater uptake than the adjacent gray/white matter was considered suspicious for tumour recurrence or progression. Lesions showing low uptake of FDG or less than the adjacent gray matter uptake were considered necrosis. To estimate the accuracy of the FDG PET/CT/MRI results, the PET diagnosis was compared to long-term clinical follow-up and MRI follow-up and, if possible, with histopathological results.

ARE has been defined as the presence of an expanding lesion 6-18 months after treatment, which subsequently decreases in size over long-term follow-up (13). In this series we never observed a lesion to decrease in size before follow-up was terminated and therefore our presumption of ARE depends on other clinical and radiological observations.

Results

16 patients underwent in total 27 FDG PET/CT studies co-registered with MRI in association with 31 radiosurgery sessions. The patients were followed-up for 7 to 65 months (mean follow-up time 25.1 months) after the first radiosurgery treatment.

PET/CT was positive in all the studies in 6 patients (8 studies), negative in all the studies in 6 patients (9 studies) and changing from negative to positive in one case (MN) (4 studies). In 2 patients (GK and MI) the PET/CT was both positive and negative in separate tumour foci (2 studies). In one patient (KEM) 4 PET/CT studies were performed. The initial (KEM1) concerned the left focus and PET/CT was negative after radiosurgery. The 3 successive studies (KEM2) concerned the right focus, which appeared three years after the treated left focus. Two of the latter studies were equivocal and the last one was negative, this being effected after three successive Gamma Knife treatments (Table I).

In the present study we used long term clinical and radiographic follow-up to evaluate and interpret our PET/CT/MRI results, except in 3 patients where we had histopathological confirmation (RN, NX, TO). In all the 9 cases where the PET/CT was positive, the evaluation of the clinical features confirmed the presence of tumours in all patients. In cases KE and MP with a positive PET/CT this led to retreatment with Gamma Knife and subsequent control of the tumour. In the cases where the PET/CT was negative in all the studies, 3 patients were diagnosed as ARE and 3 as tumour, thus denoting 3 false negative results. The MN case that changed from PET/CT negative (Figures 1a and 1b) to PET/CT positive (Figure 1c) is also regarded as a false negative. Lastly, patient KEM presented with two lesions. He had a true negative study regarding the left lesion (KEM1). In addition he had successively two equivocal and one true negative PET/CT study regarding the right lesion (KEM2). The latter followed two more gamma knife treatments on the right lesion, the last of which was carried out because the MRI suggested recurrence. Results on these 16 patients are shown in Table I.

Overall, out of 27 studies, 11/27 were true positive (TP), 8/27 true negative (TN), 2/27 equivocal and 6/27 false negative (FN), respectively. There were no false positive (FP) results. This gives values of 100% for specificity (TN/TN+FP) and 64.7% for sensitivity (TP/TP+FN), excluding equivocal studies. Table II shows sensitivity, specificity and accuracy rates, taken from the literature, of various methods currently used to differentiate tumour recurrence from ARE after radiosurgery by gamma knife. Table II also includes the rates of the present study.

The accuracy of FDG PET/CT/MRI was assessed both in relation to the final presumed diagnosis (technical accuracy) and also as to whether the PET result led to a correct or an incorrect clinical decision (clinical accuracy). In the 4 false negative patients (MN, TO, KM, IP) the PET was later shown to be in conflict with the presumed diagnosis, but their recurrent tumours appeared from 10 to 31 months after the investigation, making the clinical decision at the time (watch and wait) the correct one. In 4 patients the PET result led to a decision for intervention by craniotomy (RN, NX) or repeat radiosurgery (KE, MP) and in all cases this proved to be correct management. The technical accuracy (TP+TN/TP+FP+TN+FN) was 76% (19/25, excluding equivocal investigation results) but the clinical accuracy was 100%, since every investigation helped in the management of the patient.

Table I. *Imaging and clinical analysis following Gamma Knife radiosurgery in 16 patients.*

ID	ORIGIN	GK date	PET/CT date	PET/CT result	MRI date	MRI result	Diagnosis presumed	Analysis of PET/CT
EA	GBM	06/03	03/05	+			Tumour	Positive
		12/04	03/06	+	10/05	=	Tumour	Positive
PA	GBM	09/04	03/05	+			Tumour	Positive
		06/05	03/06	+	03/06	+	Tumour	Positive
DK	NSCLC	05/04	09/04	–			ARE	Negative
		09/04			12/04	+	ARE	
MN	NSCLC	06/03	09/04	–	07/04	+	ARE	False negative
		04/04	01/05	–	01/05	+	ARE	False negative
			07/05	–	11/05	+	ARE	False negative
			10/05	+	04/06	+	Tumour	Positive
GK	NSCLC	02/04	09/04	+ –	09/04	+	Both	Both
KE	BR	12/04	09/05	+			Tumour	positive
		09/05						
		10/06			02/08	=	? Tumour	
RN	NSCLC	12/04	11/05	+	05/05	+	Tumour#	Positive
MP	BR	04/05	10/05	+	10/05	+	Tumour	Positive
		10/05			01/06	=	? Tumour	
NB	NSCLC	07/04	03/05	–	11/04	+	ARE	Negative
			09/05	–	06/06	+	ARE	Negative
OP	NSCLC	12/04	05/05	–	NA		ARE	Negative
			09/05	–	NA		ARE	Negative
		01/06	02/06	–	NA		ARE	Negative
NX	SCLC	04/09			07/09	–	New lesions	
		07/09	O7/10	+	07/10	+	both#	Both
TO	BR	04/08	12/08	–			ARE#	false negative
		03/10			06/10	perf +	Tumour	
MI	BR	09/03			06/05	=		
		04/05	06/05	+ –	09/05	+	Both	Both
KM	GBM	02/05	11/05	–	05/06	=	ARE	false negative
					09/06	+	Tumour	
KEM1	NSCLC	03/06	10/07	–			ARE	Negative
KEM2		03/09	03/10	+/–	09/10	–	ARE	Equivocal
KEM2		05/10	10/10	+/–	10/10	+	Tumour	Equivocal
KEM2		01/13	08/14	–	07/14	–	ARE	Negative
IP	SQ PH	04/05	02/08	–	02/08	perf -	ARE	False negative
		05/07			06/09	+		
					09/10	=	Both	

GBM: Glioblastoma, NSCLC: non small cell lung cancer, BR: breast cancer, SCLC: small cell lung cancer, SQPH: squamous cell carcinoma of pharynx, ARE: adverse radiation effect. Positron Emission Tomography fused with computerized tomography scan (PET/CT) result: +, positive; –, negative; + –, both results; +/–, equivocal. Magnetic resonance imaging (MRI) result: +, larger; =, unchanged size; –, smaller; perf MRI, perfusion MRI with + or - referring to perfusion result. Diagnosis/Analysis: both means ARE and tumour in the same patient, either in one or separate tumour foci. # indicates confirmed by biopsy. ? tumour indicates control of tumour.

Some patients attracted more focus due to their specific characteristics. In 2 cases, lesions treated twice (MP) or 3 times (KE) by gamma knife, remained stable, but PET/CT-positive and with strong contrast positivity on MRI, and without shrinkage. This required an explanation for the strong contrast positivity – was it due to viable 'stunned' tumour or do ARE sometimes retain contrast?

Some light may be shed on this by another case (NX), in which a lesion that had responded to radiosurgery but not disappeared, was treated for a second time 3 months later, for extra response, at the time that some new metastases had been discovered and were being treated. One year later this lesion expanded with associated brain oedema and uniform positivity with MRI contrast and strong uptake on PET. Recurrent tumour was assumed and the lesion was removed at craniotomy. However, histology only revealed a small nest of viable tumour. On histological examination the majority of lesions were PET-positive radionecrosis (Figure 2). This could in practice be regarded as a false positive and it is clear that ARE can be strongly positive on FDG

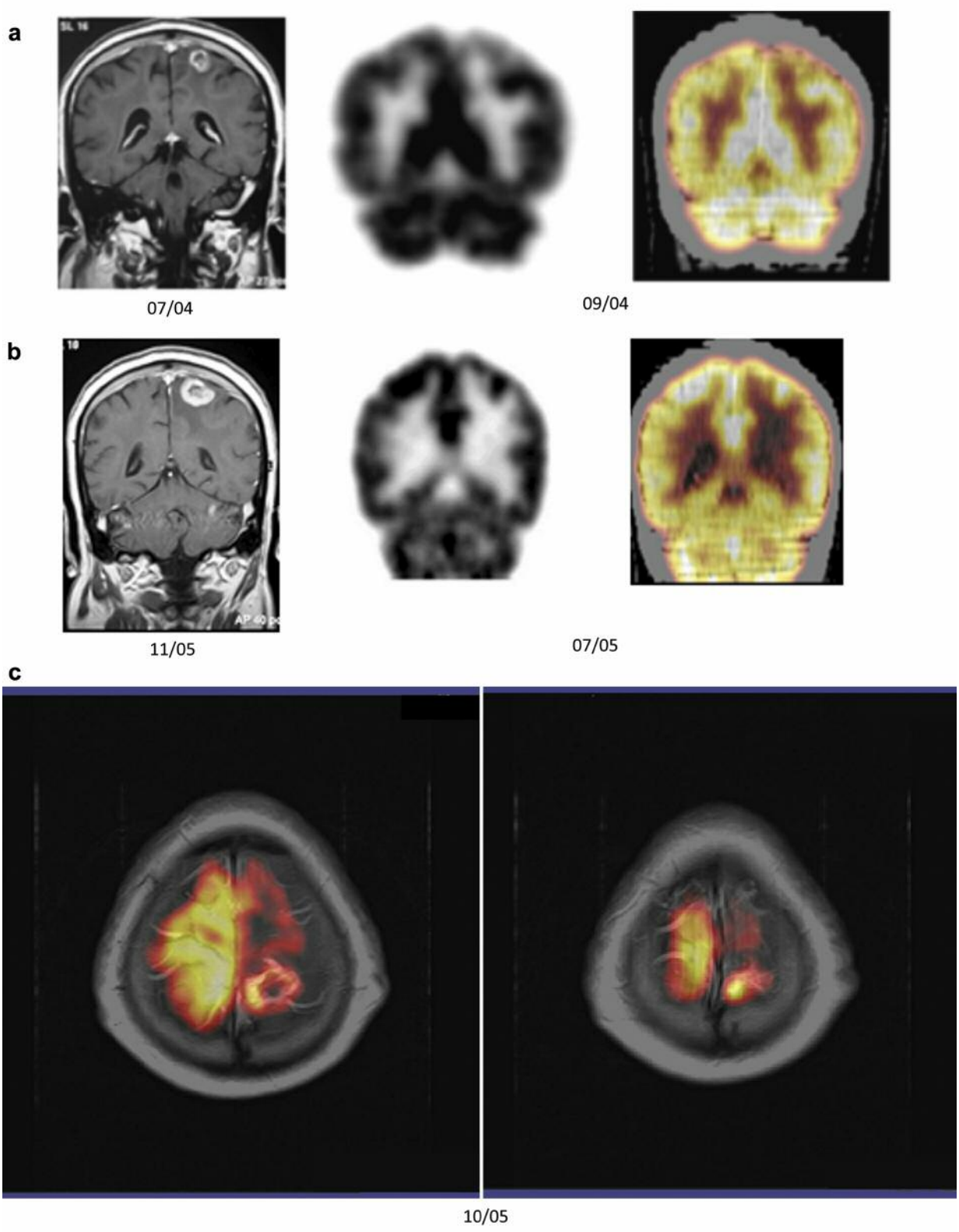

Figure 1. *Patient MN 1a initial magnetic resonance imaging (MRI) scans (07/04), positron emission tomography scan (PET) and PET fused with computerized tomography scan (PET/CT) (09/04) showing adverse radiation effect (ARE) in the left parietal region of the cortex. 1b, PET/CT (07/05) shows slightly higher uptake in the same area than the previous studies, however the lesion was still considered ARE. 1c, Positron emission tomography fused with MRI scan (PET/MRI) (10/05) with definitely increased fluoro-deoxy-D-glucose FDG uptake in the treated area is suggestive of recurrence.*

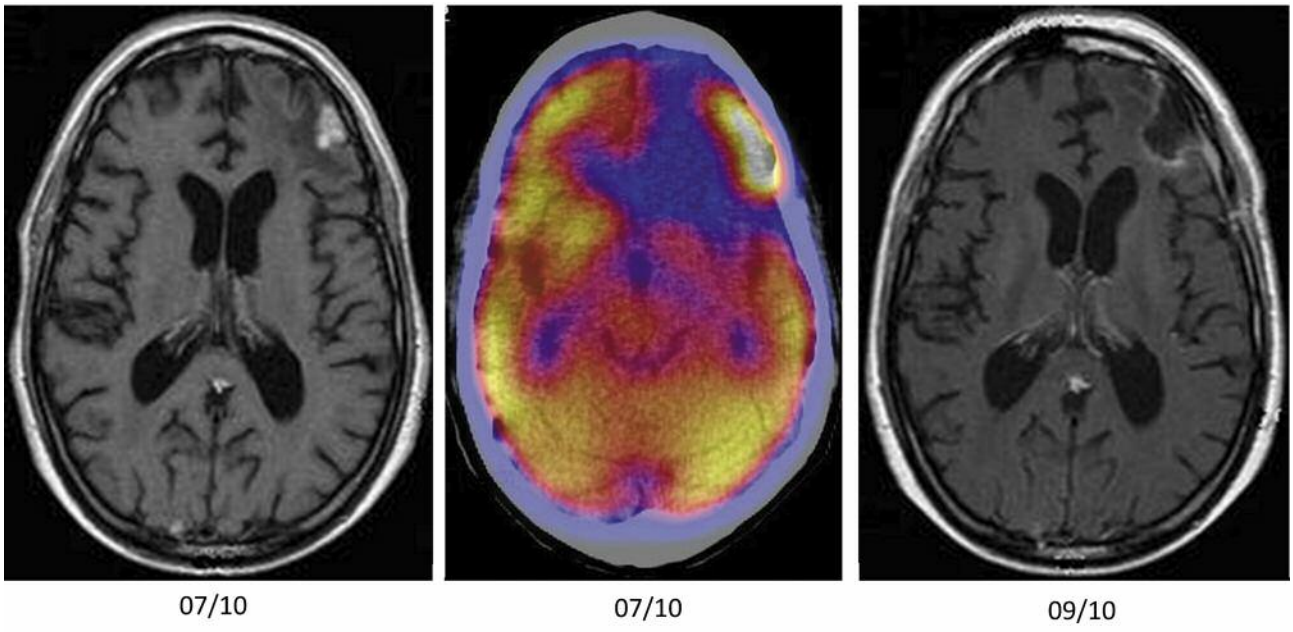

Figure 2. *Patient NX left: Magnetic resonance imaging (MRI) scan shows contrast enhancement in the left parietal area, middle positron emission tomography scan fused with computerized tomography scan (PET/CT) is intensely positive and right MRI after excision biopsy which showed mainly radiation necrosis and only a small nest of viable tumor.*

Table II. *Sensitivity, specificity and accuracy values of various methods concerning differentiation between brain tumour recurrence and necrosis, patient numbers and authors of the studies are stated.*

Investigation	Patient No.	% Sensitivity	% Specificity	% Accuracy	Ref.
FDG PET/MRI	12(M)	86	80		(13)
	16	64.7	100	76	Present st
	50(Gl)	76.5	75		(31)
FDG PET-MRI	117	80.3		86.8	(27)
	25(M)	75	93.9	91.2	(32)
	119	38	86		(30)
MET PET-MRI	77(51M)	79(M)	75(M)		(33)
	(26Gl)	75(Gl)	75(Gl)		
	80	87.8	80	85.9	(34)
MET PET/MRI	50(Gl)	91.2	87.5		(31)
FET PET/MRI	31(M)	95	91	93	(35)
FET PET	119	94	88		(30)
FDOPA-PET/MRI	81	98	86	95	(36)
FLT PET/MRI for recurrence	18(Hggl)	100	100		(37)
CHO PET/MRI	55	92.3	87.5		(38)
CHO PET/MRI	50(Gl)	73.5	87.5		(31)
MRS	455(Gl)	83(Cho/Cr)	83 (Cho/Cr)		(39)
		88 (Cho/NAA)	86(Cho/NAA)		
T1/T2 matching identifying ARE	68	83.3	91.1		(26)

PET/MRI, co-registration of PET and MRI. PET-MRI, side by side reading of PET and MRI. MET PET, Methionine PET. FET PET, Fluoroethyl-L-tyrosine PET. FDOPA PET, Fluoro-l-phenylalanine PET. FLT PET, Fluoro-L-thymidine PET. CHO PET, Choline PET. MRS, Magnetic resonance spectroscopy. Hggl, High-grade glioma. M, Metastases. Gl, Glioma. Cho/Cr, Ratio of choline to creatinine. Cho/NAA, Ratio of choline to N aspartic acid. Ref., References. St., study.

PET/CT. One false negative diagnosis (TO) was initially supported by needle biopsy showing only evidence of necrosis. At the time of the first PET/CT assessment, 8/16 cases were regarded as having tumour and 8/16 as ARE. At the last clinical assessment, 12/16 patients were regarded as having tumour.

Discussion

Despite the emergence of new radiopharmaceuticals ^{18}F-FDG remains the widest used radiopharmaceutical worldwide for the evaluation of brain tumours with PET, and over the last years an increasing number of publications show the significant potential of FDG in that field (14, 15). FDG PET has been used to distinguish necrosis of all types from active tumour for many years and is to date the commonest method in cases requiring such investigation in centers where PET is available (14, 16). However FDG PET has the disadvantage that it is taken up by normal brain tissue. Therefore, on an FDG PET study, areas of increased uptake cannot always be distinguished easily against an already high level background (17). It became clear with our first PET/CT images that a side-by-side comparison with MRI was inadequate. It was decided to find a way to improve the resolution of our investigations.

The gold standard for distinguishing tumour recurrence from ARE is excision biopsy. Needle biopsy may not be an adequate technique for histological confirmation in lesions with mixed tumour and necrosis as it was the case with patient TO. In most studies in the literature histological confirmation is not frequently used, because it is invasive and can have complications such as infection and hematoma (18, 19). On the other hand radiographic confirmation based on clinical and long-term radiographic follow-up is used as the alternative standard to check on the accuracy of FDG PET studies (13). In the present work we used clinical and radiographic follow-up except in 3 patients where we had histopathological confirmation.

^{11}C-MET and ^{18}F-FET PET studies, indicative of amino acid transport and ^{18}F-FLT PET studies showing tumor cell proliferation, have proved to be superior (20, 21), because they show uptake against a low-level background. These radiopharmaceuticals were not available to us then. Diffusion-weighted MRI, MR spectroscopy (MRS) and perfusion MRI have been recommended recently (16, 22-25) as investigations of comparable accuracy but are not widely practiced. The description of T1/T2 matching to differentiate radiation effects from tumour growth (26) is a simple and relatively accurate method. Table II shows the sensitivity, specificity and accuracy in various studies (13, 26, 27, 30-39). From this table, it is concluded that there is no supreme investigation available to differentiate between tumour and ARE.

We chose to combine the greater sensitivity of MRI with the superior specificity of FDG PET/CT by co-registering the two studies. Normally a PET image, alone, does not contain enough topographical information to allow accurate co-registration with other tomographic studies. However, the performance of co-planar CT provides topographical accuracy equivalent to MRI. This allows an accurate, automated co-registration by ONCENTRA of CT to MRI, which is greatly superior to methods using subjective visual comparison. We had, in fact, previously attempted visually controlled fusion, using the Siemens LEONARDO system, without success.

Co-registration of MRI and PET has been described previously (10, 13, 27). It improves the performance of FDG PET, since MRI delineates the area of the tumour, so that increased FDG uptake in that area, higher than the expected, may be considered recurrent tumour. Using this principle we found that the evaluation of metabolism in exactly matching slices and areas was extremely valuable in the follow up of radiosurgical treatment. In retrospect, the correct clinical decision was facilitated in all cases. The ratio of true positive results to the sum of true positive plus false negative results, giving a sensitivity of 64.7%, suggests however that this may not always be the case. Since lesion metabolism seems to be more important in relation to prognosis than histological diagnosis (28), the false negatives may not be an important factor.

The proportion of patients suffering from ARE as opposed to recurrence after radiosurgery, defined by FDG PET, is quoted as 3:1 (8) but in our study the ratio was changed to 1:1 after the first PET/CT and even reversed to 1:3 when the clinical and radiological assessment was included in the diagnostic process. Other cases might have become positive for tumour, if they had survived longer or tumour cells might have been found if post-mortem examinations had been performed.

This much higher incidence (or detection) of tumour raises the question as to whether ARE should be regarded as a clinical entity separate from tumour recurrence or a reaction that may occur parallel with the evolution of malignant brain disease. Valk *et al.* (29) have reported apparently viable tumour coexisting with necrosis in all their cases examined histologically. Langleben and Segall (28) noted that all the patients in their series showed tumour cells regardless of PET or MRI findings.

The present study had a limitation apart from the small number of cases. The evaluation of the lesions was carried out only visually, without any quantitation of the lesion uptake, which might have clarified some equivocal cases. Hatzoglou *et al.* compared FDG PET/CT with MRI perfusion in differentiating radiation injury from viable tumour and have concluded that SUV ratio ($SUV_{lesion\ max}/SUV_{normal\ brain}$) by using a cutoff value greater or equal to 1.4 increases the sensitivity and specificity of the method rather than SUV_{lesion}

$_{max}$ alone (16). Lastly on a meta-analysis by Dunet *et al*. on five studies, 119 patients were submitted to FET and FDG PET for the evaluation of isolated brain lesions and consequent histology. FET PET showed a pooled sensitivity of 94% (95% CI: 0.79-0.98) and a pooled specificity of 88% (95% CI: 0.37-0.99). The area under the curve was 0.96 (95% CI: 0.94-0.97). On the contrary FDG-PET showed a sensitivity of 38% (95% CI: 0.27-0.50) and a specificity of 86% (95% CI: 0.31-0.99), with an area under the curve of 0.40 (95% CI: 0.36-0.44), thus, rendering FET preferable to FDG for brain diagnosis (30).

The strong point of the present work was the long-term follow-up of our patients with multiple gamma knife treatments on the same lesion and multiple PET/CT examinations as well as pathological confirmation when that was possible. It was proven that in practice the importance of FDG PET/CT is not to make a tissue diagnosis, but to assist clinical management at a specific time point.

In conclusion our study has proven that co-registration of FDG PET with MRI improves the accuracy of interpretation. Despite a significant false negative rate, FDG PET is effective as a clinical tool in the management of post-radiosurgery lesions. This is because the prognosis is related more to metabolic activity than to a pathological diagnosis. A compound diagnostic approach using several different assessments over time improves the accuracy of identification of ARE *versus* tumour. ARE and tumour recurrence are not alternatives and usually exist together. Since ARE may be PET-positive, PET/CT/MRI can help improve tumour management.

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