Brain metastases after stereotactic radiosurgery using the Leksell gamma knife: can FDG PET help to differentiate radionecrosis from tumour progression?

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Abstract. Stereotactic radiosurgery (SRS) using the Leksell gamma knife promotes acute and chronic local changes in glucose metabolism. We have been able to find very few papers on Medline on the subject of assessment of metastases by 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) after SRS. The aim of this work was to specify the additional value of FDG PET, in comparison with magnetic resonance imaging (MRI), in differentiating SRS-induced radionecrosis from viable brain metastasis in a clinical setting. Fifty-seven metastases in 25 patients were treated by SRS. An average of 33 weeks later, all the patients underwent FDG PET. At the same time (SD=2 weeks) all the patients underwent MRI. The sensitivity, specificity and accuracy of both FDG PET and MRI examinations were calculated with reference to clinical and radiological follow-up or biopsies. The additional value derived from use of FDG PET after MRI was assessed and progression-free survival rates were compared. The difference in progression-free survival rates between the negative and positive subgroups was significant (P=0.0005) for MRI and even more so (P<0.00001) for FDG PET. Sensitivity, specificity and accuracy were 75% (6/8), 93.9% (46/49) and 91.2% (52/57) for FDG PET, and 100% (8/8), 65.3% (32/49) and 70.2% (40/57) for MRI. In the subgroup of patients with positive or non-diagnostic MRI, the probability of presence of a viable tumour was only 32% (8/25). This probability increased to 100% (5/5) when subsequent FDG PET was positive and decreased to 11.1% (2/18) when FDG PET was negative. The frequency of a viable neoplasm was significantly different (P=0.001) in the FDG PET negative and positive subgroups. MRI and FDG PET both have an important predictive value for persistent viable metastases after treatment by SRS. Neither sensitive but non-specific MRI nor specific but insensitive FDG PET is reliable on its own. While FDG PET significantly improved the diagnostic accuracy in the subgroup of patients with positive and non-diagnostic MRI, it provided no additional value in the MRI-negative subgroup.

Keywords: Metastases – Radiosurgery – Recurrence – Fluorodeoxyglucose – PET

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Introduction

Brain metastases of different malignancies are not rare. Patients with brain metastases usually die within a few weeks without the appropriate treatment. Stereotactic radiosurgery (SRS) with the Leksell gamma knife has been proved to be an efficient therapeutic modality in this situation [1]. SRS controls local tumour growth in the majority of patients. After SRS, radionecrosis and recurrent tumours demonstrate similar image patterns, i.e. a mass effect and contrast enhancement on either magnetic resonance imaging (MRI) or computed tomography (CT). These anatomical imaging modalities can hardly distinguish between them.

Positron emission tomography with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG PET) is a sensitive method of tumour imaging. Many papers have previously addressed the use of FDG PET for imaging of brain tumours, and these have been summarised, for example, in a German position paper [2]. The differentiation of radionecrosis from glioma recurrence, targeting biopsies of glioma, the grading of glioma, the assessment of residual tumours after surgery and the differentiation of lymphoma from

toxoplasmosis were all classified as evidence-based indications for FDG PET. Neither brain metastases nor SRS was mentioned in this paper.

Only a minimal number of papers concerning FDG PET assessment of metastases after SRS were found on Medline. Yamamoto et al. [3] studied the acute effects of SRS on brain tumours using quantitative FDG PET. Acceleration of the phosphorylation process was demonstrated in vivo in metastatic brain tumours as early as 4 h after SRS. Maruyama et al. [4] also found significantly higher glucose influx into brain metastases 4 h after SRS. Influx decreased to below the baseline 2 weeks later. Moreover, the percentage decrease in the volume of the lesion in the 5–6 months following SRS showed a positive correlation with the percentage increase in glucose influx in the 4 h following SRS.

A group from the Karolinska Hospital reported on the prognostic value of FDG PET analysis after SRS of brain metastases first in 11 patients [5], and later in 31 patients [6]. The median survival period for patients with increased FDG accumulation was 12.3 months; on the other hand a significantly longer survival period (19.9 months) was found in the group showing decreased accumulation.

Only one paper addressing the sensitivity and specificity of FDG PET after SRS in a selected group of patients with brain metastases was found on Medline. In this recent work by Chao et al. [7], 32 patients with brain metastases were treated by SRS (Leksell gamma knife or linear accelerator). FDG PET showed a sensitivity of 65% and a specificity of 80%. When FDG PET and MRI images were co-registered in a subgroup of 12 patients, FDG PET had a sensitivity of 86% and a specificity of 80%.

Just after the introduction of FDG PET into clinical practice in the PET Centre Prague, the first results to be achieved in the diagnostics of radionecrosis after SRS [8] were enthusiastically received. Because of the lack of existing information on the reliability of FDG PET after SRS of metastases, the present study addressed the sensitivity, specificity and accuracy as well as the prognostic value of FDG PET when compared with MRI in routine clinical settings. The aim was to define the role of FDG PET in the routine follow-up of patients with brain metastases after SRS.

Materials and methods

Patients. The scientific and ethical committees of Na Homolce Hospital approved this project. All patients were referred for examination because of medical, and not research, reasons. Therefore we did not request that the patients gave their informed consent, bearing in mind that the data were to be presented anonymously. Twenty-five patients (14 males, 11 females, 36–76 years old) with brain metastases of histologically proven renal cell cancer (n=8), non-small cell lung cancer (n=7), breast cancer (n=6), melanoma (n=2), colorectal cancer (n=1) and nasopharyngeal (n=1) cancer were examined consecutively by FDG PET during follow-up after SRS. A total of 57 metastases had been previously treated using the Leksell gamma knife (Elekta Instrument AB, Stockholm, Sweden). Twelve patients had only one brain metastasis, five had two metastases and eight had three to six metastases. The median of the minimum dose applied to the lesion periphery was 21 Gy (range 19–23 Gy); the irradiated volume ranged between 0.06 and 25.00 cm^3 (median 1.40 cm^3, interquartile range 0.76–6.10 cm^3). FDG PET followed SRS after 33 weeks on average (interquartile range: 12–62 weeks). While undergoing FDG PET, 12 patients (22 lesions) were under steroids; none of the patients had received chemotherapy within the previous 2 weeks.

FDG PET. Patients were instructed to fast for at least 6 h before imaging. In a dimly lit and quiet room, 210 MBq/70 kg of FDG was administered via a peripheral vein catheter (Nuclear Physics Institute, Academy of Sciences, Czech Republic). Data were acquired using the ECAT EXACT dedicated PET scanner (CTI/Siemens Inc., Knoxville, Tenn.). Thirty minutes later a 2D "hot" transmission scan of the brain was performed, lasting between 5 and 10 min (transmission scanning time was corrected to allow for decay of the transmission sources). It was immediately followed by 3D emission scanning which lasted 15 min. The data acquired were reconstructed by an iterative OS-EM algorithm (matrix: 128^2, brain mode, zoom: 2, subsets: 16, iterations: 6, Hann filter: 5 mm) implemented using ECAT 7.2 software. FDG PET scans were evaluated blindly except for information which was provided as to the approximate location of the irradiated metastases. Lesions were visually assessed as negative when hypo- and/or isoactivity was encountered in grey matter, or when only slightly increased homogeneous activity was seen at the margin around the irradiated lesion in the white matter. Lesions were considered positive when focal accumulation of FDG exceeded any level of activity in the adjacent grey matter. Other lesions were considered as equivocal.

MRI. During the same period as the FDG PET (SD=±2 weeks) all the patients underwent MRI examinations (Magnetom Impact Expert, Siemens). MRI was always evaluated in comparison with previous MRI investigations. Lesions were visually assessed as negative when at least a 50% reduction in pathological volume was found and central necrosis was present. Further growth of lesions with enlargement of the collateral oedema was considered positive. Other lesions were considered to be equivocal.

Data analysis. The sensitivity, specificity and accuracy of FDG PET and MRI for the detection of viable neoplasms were calculated and compared with biopsy results or with clinical and radiological follow-up. The incremental value of FDG PET when used after MRI was also defined: using the chi-square test or Yates corrected chi-square test, comparisons were made of the frequency with which viable neoplasms were located after positive and negative MRI results, and also of their appearance in subgroups which were followed up after negative and positive PET analyses. The same tests were also used for the comparison of frequencies of correctly and incorrectly classified foci between different methods or references. Progression-free survival of positive and negative cases was compared separately for PET and MRI by the Kaplan-Meier plot and log-rank test. Statistical analyses were performed with Statistica 5.5 software (StatSoft Inc., Tulsa, Okla., USA).

Results

Three irradiated brain foci were histologically proven (two viable neoplasms, one benign tissue reaction) following stereobiopsy (two cases) or open surgery (one case). Another 54 foci were clinically and radiologically followed up for 26 weeks on average (interquartile range: 18–48 weeks). Viable neoplasms appeared highly suspect in six foci during the follow-up; the remaining 48 foci showed no signs of progression. A total of eight foci were thus considered to be viable neoplasms, and 49 to show normal changes or radionecrosis.

The results observed are summarised in Tables 1 (FDG PET) and 2 (MRI). For the purpose of this analysis, stricter criteria were adopted and equivocal results were considered to be positive. MRI correctly detected all eight viable neoplasms (sensitivity =100%). Five lesions were localised in white matter only, while three were localised partially in white and partially in grey matter. FDG PET was truly positive in five such foci [two breast cancers with volumes of 9.0 and 14.0 cm^3, one colorectal cancer (0.7 cm^3), one non-small cell lung cancer (19.7 cm^3) and one renal cell cancer (13.9 cm^3)]. FDG PET was equivocal in one case (renal cell cancer: 11.0 cm^3) and missed two such foci [one renal cell cancer (2.8 cm^3) and one non-small cell lung cancer (13.2 cm^3)]. The sensitivity of FDG PET was 75%. In this setting MRI was truly negative in only 32/49 foci (specificity =65.3%), while FDG PET was truly negative in 46/49 foci (specificity =93.9%). Fifty-two of 57 foci were correctly assessed by FDG PET (accuracy =91.2%), whereas only 40 were correctly assessed by MRI (accuracy =70.2%). The frequency of correct classification of foci was significantly higher for FDG PET ($P<0.01$). Irradiated volumes did not differ significantly between the recurrent tumour and the radionecrosis group ($P=0.178$). No relationship was found between the results observed and the tumour histology.

The low specificity of MRI, already mentioned above, resulted in a high rate of false positive foci. In the subgroup with positive or non-diagnostic MRI, there was only a 32% (8/25) probability of detecting a viable neoplasm. When FDG PET was applied to this subgroup, the probability of detecting a viable neoplasm increased to 100% (5/5) when FDG PET was positive, and decreased to 11% (2/18) when it was negative. FDG PET was equivocal in two cases and added no information (once in a viable tumour, once in a case without progression). The frequency of a viable neoplasm was significantly different ($P=0.001$) in the FDG PET negative and positive subgroups.

Progression-free survival of positive and negative cases (using the Kaplan-Meier plot) is shown in Fig. 1 for FDG PET and in Fig. 2 for MRI. There are significant differences in progression-free survival between the positive and negative subgroups for FDG PET ($P<0.00001$) and for MRI ($P=0.0005$).

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

FDG PET result	Histology/follow-up		
	Progression	No progression	Total
Negative	2	46	48
Equivocal	1	2	3
Positive	5	1	6
Total	8	49	57

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

MRI result	Histology/follow-up		
	Progression	No progression	Total
Negative	0	32	32
Equivocal	3	3	6
Positive	5	14	19
Total	8	49	57

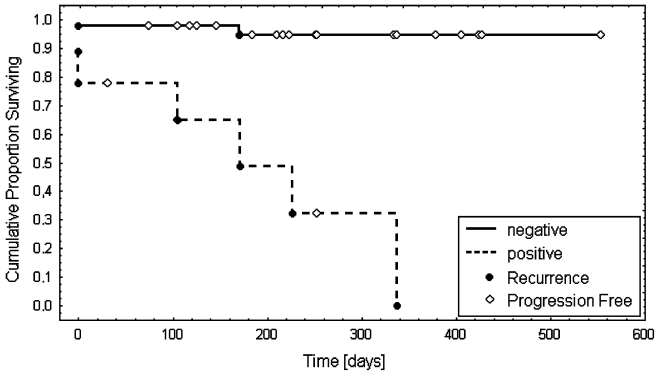


Fig. 1. Progression-free survival for patients with FDG PET positive (including equivocal) and negative results (Kaplan-Meier plot)

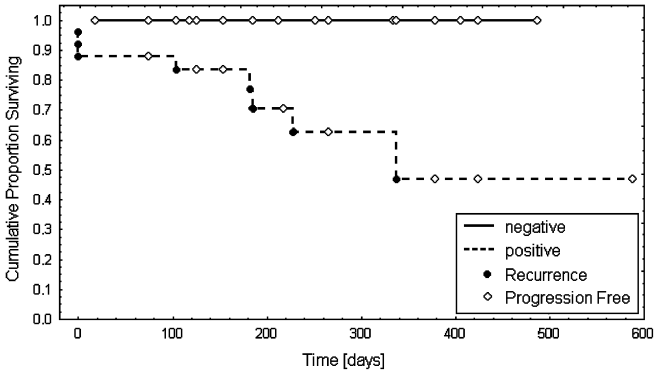


Fig. 2. Progression-free survival for patients with MRI positive (including equivocal) and negative results (Kaplan-Meier plot)

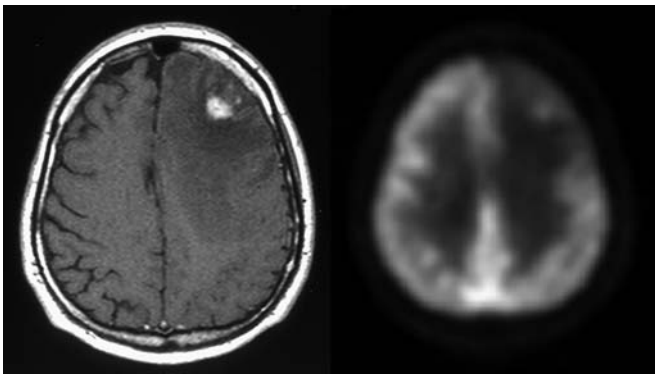


Fig. 3. Case no. 17: In the left frontal lobe there was evident progression of metastasis of renal cell carcinoma on T1-weighted post-contrast MRI, 28 months after SRS (*left*). FDG PET (*right*) was considered positive because FDG accumulation in the corresponding focus was slightly higher than in the adjacent grey matter. Open surgery took place within 1 month and a local recurrence of metastasis was confirmed by histology

Discussion

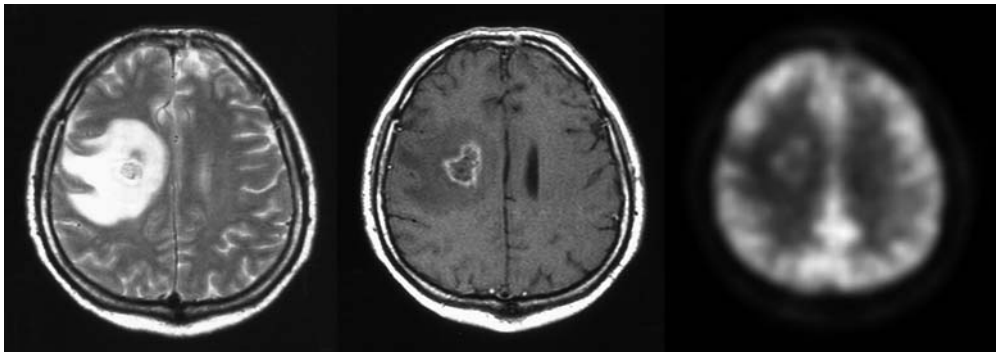
There is no reason to use FDG PET as a first-line diagnostic tool in the case of brain metastases. Modern MRI scanners achieve higher spatial resolution and FDG trapped in surrounding grey matter compromises the sensitivity of FDG PET; for example, Griffeth et al. [9] detected only 68% of metastases using FDG PET, while Thompson et al. [10] identified 80% of primary glial neoplasms with a volume enhancement greater than 10 cm^3 and only 25% when volume enhancement was smaller than 6 cm^3. Therefore it could be hypothesised that after SRS, MRI will again have a higher sensitivity than FDG. This is supported by the results of the study by Chao et al. [7] (post-irradiation FDG PET sensitivity of 65% for brain metastasis without MRI co-registration and 86% for brain metastasis with MRI co-registration). The sensitivity of 75% found for FDG PET in the present study confirms their findings. All the sensitivities mentioned here have been calculated from small series, and the differences were not significant. In our series, all tumour recurrences appeared totally or partially in white matter. Even lower sensitivity could be hypothesised when lesions are localised only in grey matter. Due to the small size of the series we could not define FDG PET performance in subgroups with different tumour types and/or volumes. It might be of interest to investigate the recurrence of metastases of both renal cell and non-small cell lung cancer which exhibited either increased or normal FDG uptake. There was no false negative MRI result in our series. In such a setting the less sensitive FDG PET would not be able to add any new information.

It is generally accepted that it is difficult to distinguish radionecrosis from recurrence of neoplasm on MRI or CT. Our data are in agreement with this: MRI had a specificity of only 65.3%, and the probability of detecting a viable neoplasm was only 32% in the subgroup with positive or non-diagnostic MRI. FDG PET, by contrast, has high specificity and can help to identify viable neoplasms in this subgroup when it is positive (Fig. 3). When it is negative, it also lowers the probability of the presence of a viable neoplasm (Fig. 4). However, owing to its lower sensitivity FDG PET cannot reliably exclude the presence of a viable neoplasm.

MRI, and to an even greater extent FDG PET, is a strong predictor of a progression-free period. The results of the project undertaken by the Karolinska Hospital group [5, 6] were reproduced in our series.

It is apparent that FDG is a suboptimal tracer for brain tumour diagnostics owing to the physiologically high uptake in grey matter. On the other hand, FDG is easily available for the majority of PET centres, and in daily clinical routine it will probably remain the only available tracer for many sites in the near future. Among a number of other potentially suitable tracers, most experience has been obtained with labelled amino acids [11]. The majority of papers have focussed on use of L-[methyl-^{11}C]methionine (MET) in glioma patients [12, 13].

Fig. 4. Case no. 14: In the right frontal lobe there was evident enlargement of metastasis of renal cell carcinoma with collateral oedema on MRI, 15 weeks after SRS (*left:* T2-weighted; *middle:* T1-weighted post-contrast). It was considered to be a probable local recurrence. FDG PET (*right*) was considered negative because only slightly increased FDG accumulation was seen in the margin around the irradiated lesion in the white matter (this pattern is common after SRS). The patient was followed up for a further 26 weeks and showed clinical and radiological signs of regression



Another amino acid, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) could have better prospects from a logistical point of view [14]. No paper dealing with the use of labelled amino acids to detect brain metastases after SRS was found in the literature. It might be interesting to study MET or FET in the settings used in this study. These tracers were not available for the purposes of this study.

In conclusion, despite its significantly higher accuracy, our data suggest that FDG PET is not sensitive enough to detect viable metastases after SRS. We can recommend FDG PET only when MRI results are positive or equivocal in white matter during follow-up after SRS. Positive FDG PET confirms the presence of a viable neoplasm. Negative FDG PET significantly increases the probability of radionecrosis, but owing to its lower sensitivity it cannot reliably exclude the presence of a viable neoplasm. Our results require confirmation by a multicentre study on larger series of patients.

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