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Role of PET Imaging in Patients with High-Grade Gliomas Undergoing Anti-Angiogenic Therapy with Bevacizumab – Review of the Literature and Case Report

Irina Götz[1], Anca-Ligia Grosu[1], Timo S Spehl[2]

Abstract: Despite recent advantages in combination therapies, the prognosis of high-grade gliomas remains very poor. A new therapeutic concept in the treatment of brain tumours uses the anti-angiogenic drug bevacizumab to reduce tumour neovascularisation. However, due to a concomitant reduction of contrast agent enhancement in MRI, imaging modalities that do not depend on a disruption of the blood-brain barrier (BBB) would be desirable for therapy monitoring. Positron emission tomography (PET) imaging has emerged as a promising tool for better assessment of treatment response in patients undergoing anti-angiogenic therapy compared to MRI. The most important tracers are amino-acids like ^{11}C-methionin and ^{18}F-FET, but also ^{18}F-FDG and ^{18}F-FLT, a biomarker of cell proliferation. In this review, we provide an overview of current knowledge concerning the value of PET in patients with brain tumours undergoing anti-angiogenic therapy and present a clinical case that illustrates the utility of PET imaging. **Eur Assoc NeuroOncol Mag 2014; 4 (3): 102–8.**

Key words: PET, bevacizumab, therapy monitoring, ^{18}F-FDG, ^{18}F-FLT, ^{18}F-FET

Introduction

High-grade gliomas (HGG) are highly aggressive brain tumours with limited treatment options. The most frequent primary brain tumour, accounting for 20 % of all intracranial tumours, is glioblastoma multiforme (WHO grade IV). Despite recent advances in combination therapy including surgery, radiation therapy, and chemotherapy, the prognosis remains very poor [1]. An important feature of tumour aggressiveness is increased tumour neovascularisation driven by the vascular endothelial growth factor (VEGF) pathway [2]. Tumour vessels are characterised by structural abnormalities that lead to an increase in the permeability of the blood-brain barrier (BBB), thus causing complications like tumour oedema and compression of adjacent structures. Under the premise of arresting tumour progression and local complications by inhibiting pro-angiogenic growth factors [3], the anti-angiogenic drug bevacizumab has been introduced into therapy of recurrent glioblastoma [4, 5] and has been approved by the FDA for this indication.

Under treatment with bevacizumab, high response rates based on morphological imaging using the conventional Macdonald criteria [6] have been reported, ranging from 30–60 % [7]. It must be borne in mind, however, that these response rates are based on a normalisation of the BBB that might not represent true tumour regression, and thus are described as "pseudo-response" [8]. There is growing evidence that bevacizumab may alter the recurrence pattern of malignant gliomas in MRI imaging by suppressing gadolinium-enhancing tumour recurrence more effectively than it suppresses non-enhancing, infiltrative tumour growth [9]. To enable a more precise response assessment, new criteria have been established for response assessment in neuro-oncology (RANO) that include T2-based fluid-attenuated inversion recovery (FLAIR) MRI sequences [10]. However, the morphological changes seen in these imaging sequences also include multiple non-specific changes like radiation-induced gliosis, peritumoural oedema, ischemia, and demyelination [11]. In this context, positron emission tomography (PET) with various tracers has been established to improve diagnostics, response assessment, and therapy planning.

We present an exemplary case of a patient with recurrent glioblastoma multiforme who was treated with bevacizumab. This case highlights the usefulness of PET imaging in response assessment compared to MRI. Furthermore, we give an overview of the current literature regarding PET imaging in patients treated with this promising new therapeutic agent.

Molecular Mechanisms of Bevacizumab

VEGF is a vascular endothelial growth factor correlated with pathological angiogenesis and plays an important role especially in highly vascularised tumours like glioblastoma. The extent of proliferation in this tumour entity has been shown to correlate with an increased recurrence and poor survival [12]. Moreover, a direct relationship between VEGF over-expression and poor prognosis has been reported [13]. Originating from the tumour bulk, glioblastoma cells migrate along normal vascular structures into adjacent brain regions [14], thus making VEGF a promising target for therapeutic agents. Preclinical studies accordingly showed that bevacizumab inhibits tumour growth as a single-agent therapy or in combination with cytotoxic agents [15]. Bevacizumab and other anti-angiogenic agents that bind and inactivate VEGF, including cediranib (AZD2171), aflibercept (VEGF Trap), XL184, and cilengitide (EMD 121974), are thus being evaluated as a possible treatment option for use in recurrent and possibly also newly diagnosed glioblastoma.

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Therapeutic Studies with Bevacizumab in Glioblastoma

The first phase-II study on bevacizumab and irinotecan (BEV/IR) in recurrent glioblastoma by Vredenburgh et al proved the feasibility of this regime and revealed an improvement in 6-months progression-free survival (PFS) of 46 % compared with historical data [4]. The response rate was 57 %, toxicity was moderate. Regarding side-effects, the authors reported thromboembolic complications in 4 patients and one CNS haemorrhage [4]. The response rate in the trial of Kreisl et al examining 56 patients was 35 % based on the Macdonald criteria, 6-months PFS was 29 % [16]. In addition to an increase in PFS, a clinical benefit was evident in terms of decreased cerebral oedema in 24 patients (50 %). 15 patients were able to decrease corticosteroids and 25 patients (52 %) had improved neurologic symptoms. Based on these 2 trials, the FDA granted accelerated approval of bevacizumab for the treatment of recurrent glioblastoma multiforme in May 2009.

The BRAIN study [5] confirmed that bevacizumab, alone or in combination with irinotecan, was well-tolerated and effective in recurrent glioblastoma. This was a non-comparative trial. The randomised design was intended only to prevent bias in treatment assignment. Additionally, data of the BRAIN study were analysed by Vredenburgh et al to evaluate whether bevacizumab may have corticosteroid-sparing effects [17]. The results showed sustained reduction of corticosteroids in 30 % of the bevacizumab-alone group and 20 % of the bevacizumab-plus-irinotecan group, respectively. However, the data has to be interpreted cautiously due to the exploratory nature of the analysis.

Other studies reported bevacizumab as an effective treatment option in radionecrosis. In a series of 6 patients with biopsy-proven cerebral radiation necrosis treated with bevacizumab, MRI follow-up demonstrated radiographic response in all patients with an average reduction of 79 % for the post-gadolinium studies and 49 % for the FLAIR images and was noted for a mean follow-up time of up to 5.9 months [18].

First results of 2 phase-III trials were reported at the ASCO meeting in June 2013 and were published in the *New England Journal of Medicine* in February 2014 [19, 20]. The RTOG study 0825 [19] reported that addition of bevacizumab to the standard treatment regime with temozolomide for newly diagnosed GBM did not improve overall survival. A small effect was seen regarding prolonged PFS, but this did not reach the significance criterion. The patient group receiving bevacizumab even showed a decline of neurocognitive status. These results discourage the use of bevacizumab for patients with the best prognosis at the outset. The analysis did not identify a group of patients who experienced benefit from first-line bevacizumab.

AVAglio, a phase-III registration trial including > 920 patients worldwide, revealed similar findings for OS. The double-blind, randomised trial evaluates the benefit of an addition of bevacizumab to the standard of care in the first-line treatment of patients with glioblastoma. Median overall survival in each arm was 17 months. Median PFS was 10.6 months in the interventional arm with bevacizumab vs 6.2 months in the control arm ($p < 0.001$). In contrast to the RTOG trial, this difference was statistically significant. Even more, health-related quality of life was improved for patients receiving bevacizumab in the AVAglio trial [20] in contrast to the RTOG trial.

More encouraging results were reported for the GLARIUS study involving 182 MGMT unmethylated glioblastoma patients. Patients in the experimental arm received 4 cycles of bevacizumab over 6 weeks of radiation, then bevacizumab plus irinotecan were administered every 2 weeks until progression. At 6 months, PFS was significantly higher with BEV/IR: 9.74 vs 5.99 months ($p < 0.0001$). Overall survival was also significantly longer: 16.6 vs 14.8 months ($p = 0.031$). The experimental arm also required less corticosteroids [21].

Taken together, there is growing evidence for the usefulness of bevacizumab in the treatment of glioblastoma with regard to PFS. However, the expectations of the community regarding overall survival were not fulfilled by the 2 phase-III trials. Additionally, it is even not clear whether bevacizumab improves or impairs the neurological condition of the patients.

Due to high costs, severe side effects, and complicated image interpretation, reliable biomarkers for therapy monitoring are required. PET has emerged as a very promising tool in this field.

Role of PET Imaging in Response Assessment to Bevacizumab Therapy

PET imaging is increasingly used in HGG. It relies on the fact that it can visualise functional changes in tumour tissue rather than morphological details. Multiple different features of brain tumours can be addressed, eg, glucose metabolism, amino-acid uptake, or proliferation activity. These can serve as valuable biomarkers for diagnostics and response assessment.

Glucose Metabolism

The most widely used PET tracer in oncology is ^{18}F-fluorodeoxyglucose (^{18}FDG). The use of ^{18}FDG-PET in brain tumours was reviewed by a National Comprehensive Cancer (NCCN) panel in 2009. Based on current evidence and consensus, a role for ^{18}FDG-PET in the management of brain tumours was proposed for diagnosis, staging/restaging, prognosis, and possibly for treatment planning and response monitoring [22]. ^{18}FDG-PET relies on an increased glycolytic metabolism of glial tumour cells mediated by increased hexokinase activity [23] and over-expression of glucose transporters [24] (Table 1). Furthermore, ^{18}F-FDG uptake is strongly correlated with angiogenesis markers in gliomas [25]. Thus, it could serve as a biomarker for tumour neovascularisation. There is a study that investigates ^{18}FDG-PET for treatment monitoring of high-grade gliomas under treatment with bevacizumab and irinotecan [26]. In this study, Colavolpe et al report that ^{18}FDG-PET was the most powerful predictor of OS and PFS in a group of 25 patients in both uni- and multivariate analysis ($p < 0.001$). Interestingly, in multivariate analysis, ^{18}FDG-PET performed better in predicting survival than histological grading, steroid

Table 1. Various tracers used for imaging of HGG undergoing bevacizumab therapy and their respective molecular properties

Tracer	Radiopharmaceutical name	Isotope	Half-life	Molecular target (localisation)	Intracellular processing	Molecular weight	Penetration through intact blood-brain barrier
^{18}F-FDG	2-deoxy-2-[^{18}F]-fluoro-D-glucose	^{18}F	109 min	Mainly GLUT-1 (transporter), substrate for hexokinase (HK-2, enzyme)	Intracellular storage, "trapping"	181.15 g/mol	Yes
^{11}C-MET	[^{11}C]-methionine	^{11}C	20 min	L-type amino-acid carriers (membrane)	Incorporated into proteins	149.21 g/mol	Yes
^{18}F-FET	O-(2-[^{18}F] fluoroethyl)-L-tyrosine	^{18}F	109 min	L-type amino-acid carriers (membrane)	Not incorporated into proteins	227.23 g/mol	Yes
^{18}F-FLT	3'-deoxy-3'-[^{18}F]-fluorothymidine	^{18}F	109 min	Thymidin-kinase (TK-1, enzyme)	DNA synthesis, proportional to proliferation	244.22 g/mol	Unclear (see text)
^{18}F-DOPA	3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine	^{18}F	109 min	DOPA-decarboxylase (enzyme)	Intraneuronal storage in vesicles	215.18 g/mol	Yes

Min: minutes. For details, see text.

intake, Karnofsky Performance Status, and number of previous treatments [26]. In another study, mean ^{18}FDG uptake in anaplastic gliomas treated with bevacizumab turned out to be a significant prognostic factor at 4 weeks post-treatment [27]. These examples underline the clinical usefulness of glucose metabolism as an independent biomarker for therapy monitoring.

Amino-Acid Uptake

Despite the usefulness of ^{18}FDG-PET in general oncology, it is limited as a tracer in brain neoplasms due to its high physiological uptake of grey matter, where small tumours can be masked and low-grade tumours may not be discernible from white matter due to lower uptake. Therefore, multiple other biomarkers have been tested that have low uptake in normal brain tissue and thus allow for better contrast in PET imaging. Among the most promising PET tracers are radio-labelled amino-acids (AA), such as ^{18}F-fluoroethyl-L-tyrosine (FET), whose half-life of 109 minutes makes it more readily available than the previously widely used ^{11}C-methionine (MET). Uptake of radio-labelled AA is fairly low in normal brain tissue [28, 29]. Increased AA uptake in gliomas is related to an over-expression of L-type amino-acid transporters in the cell membrane [30, 31] (Table 1). These carriers are particularly up-regulated in HGG and it has been suggested in a rat model that tumours can stimulate transporter expression, especially in their vasculature [32]. ^{18}F-FET-PET is increasingly used as a diagnostic agent for detection of tumour recurrence and to exclude radiation necrosis, where MRI is of low specificity [28, 29, 33]. Moreover, it facilitates radiation therapy planning and thus could lead to better overall survival. In the first study on this issue with 44 patients with recurrent high-grade gliomas, fractioned stereotactic radiotherapy was performed after definition of the tumour volume using MET-PET/MRI/CT or merely MRI/CT. Patients from the first group had, in an univariate analysis, a significantly longer survival compared to those patients whose treatment was based on MRI/CT only [34]. Ongoing studies like the multicentre, randomised, phase-II German GLIAA study (clinicaltrials.gov: NCT01252459) will examine if ^{18}F-FET-PET-based radiotherapy planning can truly increase overall survival.

In addition to radiation therapy planning, ^{18}F-FET PET could play a major role in the assessment of response in patients undergoing therapy with bevacizumab. Case reports hint that ^{18}F-FET-PET may indicate therapy failure earlier than MRI [35, 36]. There are 2 studies that suggest that ^{18}F-FET-PET could serve as a reliable biomarker to predict treatment failure and is superior to MRI based on RANO criteria for the detection of tumour progression [37, 38]. In the study of Galldiks et al [37], FET-PET predicted a significantly longer PFS and OS than RANO criteria-based MRI reading. Furthermore, in 40 % of the patients, FET-PET was discordant with MRI and revealed treatment failure earlier than MRI (median time benefit 10.5 weeks). Similar results have been reported by Hutterer et al [38], where in 36.4 % of all cases, FET-PET and MRI were discordant and PET was able to detect treatment failure earlier than MRI. FET-PET was also a very good predictor of therapy response (for details see Table 2). Both authors used identical criteria for therapy response (45-% reduction of tumour volume, as defined by Hutterer et al [38]) and similarly conclude that ^{18}F-FET-PET could serve as a valuable biomarker to detect treatment failure earlier than conventional imaging methods. In addition, a recent study by Heinzel et al [39] has demonstrated that using ^{18}F-FET-PET to detect therapy failure in HGG treated with bevacizumab is actually cost-effective, reducing both costs and therapy-associated side effects where there is no benefit to be expected. In this study, the number needed to diagnose was as low as 2.4 [39]. As a footnote, ^{18}F-FET-PET has also been reported to be of good value in therapy monitoring of patients with rare indications like progressive brain-stem gliomas [40].

Table 2. Overview of studies examining PET as a biomarker for response assessment in HGG treated with bevacizumab

Author, year	Therapy	Tracer	PET response criteria	n	PD in MRI based on RANO criteria	Non-responders in PET	PFS responders vs non-responders (PET)	OS responders vs non-responders (PET)	Time benefit (PET vs MRI)
Hutterer et al, 2011	BEV/IR	^{18}F-FET	Reduction > 45 % of tumour volume	11	18 %	54 %	10.24 vs 4.1 mo p = 0.025	11.0 vs 5.85 mo (compared to MRI responders) p = 0.12	9 wk (range: 4–14 wk)
Galldiks et al, 2012	BEV/IR	^{18}F-FET	Reduction > 45 % of tumour volume	10	0 %	40 %	9 vs 3 mo p = 0.001	23.0 vs 3.5 mo p = 0.001	10.5 wk (range: 6–12 wk)
Chen et al, 2007	BEV/IR	^{18}F-FLT	> 25 % reduction of FLT uptake	21 (19 eligible)	33 %	53 %	"Tendency for prolonged PFS" p = 0.061	10.8 vs 3.4 mo p = 0.003	na
Schwarzenberg et al, 2012	BEV/IR or BEV alone (n = 3)	^{18}F-FLT	> 25 % reduction of FLT uptake	30	24 %	47 %	"PET predictive for PFS" p < 0.001	12.5 vs 3.8 mo p < 0.001 (12.9 vs 9.0 using MRI)	"PET earlier" (not specified)
Harris et al, 2012	BEV/IR or BEV alone (n = 2)	^{18}F-FLT and/or ^{18}F-DOPA	Voxel-wise changes in predefined regions	24	na	na	"^{18}F-DOPA PET stratified short- and long-term PFS"	"^{18}F-DOPA PET stratified short- and long-term OS"	na
Colavolpe et al, 2012	BEV/IR	^{18}F-FDG	SUVmax and T:CL ratio	25	40 %	Not specified	"FDG-PET most significant predictor of PFS" p < 0.001	"FDG-PET most significant predictor of PFS" p < 0.001	"FDG uptake may predict MRI response"

BEV: bevacizumab; IR: irinotecan; PD: progressive disease; PFS: progression-free survival; OS: overall survival; mo: months; wk: weeks; na: not available; RANO: response assessment in neuro-oncology; T:CL: SUV ratio of tumour-to-contralateral hemisphere reference. Time benefit is time interval between diagnosis of progressive disease in PET vs MRI, when PET was able to detect progressive disease earlier. For details, see text.

Proliferation Activity

In addition to radio-labelled amino-acids, 3'-deoxy-3'-^{18}F-fluorothymidine PET (^{18}F-FLT) is increasingly used for therapy monitoring in brain tumours. ^{18}F-FLT is a thymidine analogue that visualises tumour cell proliferation [41]. Uptake of FLT correlates with the activity of thymidine-1-kinase which is expressed during the DNA synthesis phase of tumour cells [42]. After phosphorylation, FLT is trapped inside the cell [43]. FLT uptake correlates with the Ki-67 proliferation index and FLT uptake has been shown to correlate with tumour grading and cell proliferation [44] (Table 1). It has been successfully investigated in brain malignancies [45, 46] and has been demonstrated to predict overall survival in HGG patients [47].

^{18}F-FLT has also been investigated for its utility in treatment response assessment in HGG undergoing therapy with bevacizumab: in preclinical studies, ^{18}F-FLT has been shown to be a sensitive marker of treatment efficacy in a rat model [48]. In this study, it was superior to ^{18}FDG regarding evaluation of treatment efficacy. First clinical data were reported as early as 2007: in a pilot study with 21 HGG patients, Chen et al were able to demonstrate that ^{18}F-FLT-PET is highly predictive of overall survival as early as 6 weeks after treatment initiation [49]. Response was defined as a > 25-% reduction of FLT uptake in the tumour mass compared to pre-treatment scans. In 2011, another study confirmed these results [50]. Using the same criteria, Schwarzenberg et al reported that changes in tumour ^{18}F-FLT uptake were highly predictive of PFS and OS in patients with recurrent malignant glioma undergoing bevacizumab therapy and FLT-PET was more predictive than MRI for early treatment response [50]. In another study, ^{18}F-FLT kinetics were analysed in recurrent HGG in 15 patients, and it reported that a persistently decreased ^{18}F-FLT uptake (by means of measurements after 2 and 6 weeks) in the tumour was a predictor for longer survival [51].

There is one study that combines the amino-acid 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (^{18}F-DOPA) with ^{18}F-FLT-PET [52]. Here, voxel-wise changes in tracer uptake were analysed in 24 patients with HGG. Harris et al reported that voxel-wise increase in PET uptake in areas of pre-treatment contrast enhancement defined by MRI stratified 3-month progression-free survival and 6-month overall survival (OS)

[52]. Log rank analyses, however, revealed that only the volume fraction of increased ^{18}F-DOPA uptake between 2 post-treatment time points stratified long- and short-term OS, while ^{18}F-FLT uptake did not. The authors state that ^{18}F-DOPA might be slightly superior to ^{18}F-FLT.

However, there is growing uncertainty about the mechanisms of transport of ^{18}F-FLT into brain tumours. There is data suggesting that the uptake of ^{18}F-FLT is highly dependent on BBB breakdown and much less on phosphorylation itself [53]. This hypothesis was confirmed in another study where uptake of ^{18}F-FLT was largely related to leakage into extracellular space via a disrupted BBB, whereas the effect of nucleoside transporters was regarded to be much lower in comparison [54]. Taken together, these facts might limit the general use of ^{18}F-FLT in patients undergoing therapy with bevacizumab. In addition, the presence of benign lesions showing BBB disruption cannot be distinguished from malignant tumours [55] in ^{18}F-FLT-PET. Thus, ^{18}F-FLT-PET needs to be carefully evaluated. Further investigations in this field will be necessary before ^{18}F-FLT can be recommended for general use in brain tumours.

Outlook: Imaging of Angiogenesis and Hypoxia in Brain Tumours

In malignant gliomas, $a_v\beta_3$ integrin plays a key role in tumour angiogenesis and invasion [56]. To date, there is a single study reporting the use of ^{18}F-labelled glycosylated Arg-Gly-Asp peptide (^{18}F-Galacto-RGD) to successfully visualise $a_v\beta_3$ expression in patients with glioblastoma [57]. This tracer might be a promising tool not only for planning and monitoring integrin-targeted therapies but possibly also for bevacizumab therapy planning.

Another interesting biomarker in HGG undergoing therapy with bevacizumab might be hypoxia. ^{18}F-misonidazole (^{18}F-MISO) is the most intensively studied PET tracer for hypoxia detection, and baseline ^{18}F-MISO uptake has been shown to correlate with tumour aggressiveness in glioblastoma [58]. Furthermore, regional hypoxia measured by ^{18}F-MISO correlated with time to progression and survival [59]. In solid tumours, it has been proposed that drugs that induce vascular normalisation could alleviate hypoxia and increase the efficacy of conventional therapies if both are carefully scheduled. Thus, ^{18}F-MISO was proposed as a potential tool for tracking the normalisation window in patients undergoing anti-angiogenic therapy, which is considered as the period of radiation and chemotherapy response enhancement due to improvement of oxygenation [60], but this has not been researched so far. In how far ^{18}F-MISO is useful to evaluate anti-angiogenic therapy in glioblastoma is not clear, but currently under investigation, eg, in the HYPONCO study (clinicaltrials.gov: NCT01200134).

To draw a reliable conclusion regarding the best imaging method under anti-angiogenic therapy we need more validation trials comparing MRI and PET, ideally performed on the same day. Contrast enhancement on MRI might not be accurate enough after anti-angiogenic-agent therapy like bevacizumab and leads to pseudo-response. Amino-acid PET has a high sensitivity and specificity in detecting tumour tissue and it is not influenced by the blood-brain barrier. These are good arguments for PET in such situations.

It is worthwhile to correlate both imaging techniques with histology. However, it is often hardly possible. So we have to decide about pseudo-progression or tumour progression from the clinical course and repeated imaging scans.

Conclusion

PET imaging is increasingly used in brain tumour imaging. Many different functional aspects of tumour growth and metabolism can be investigated and used for diagnosis, treatment planning, and response assessment. Use of novel therapeutic agents like bevacizumab that severely alter tumour appearance in conventional imaging requires reliable biomarkers for therapy monitoring, as demonstrated by the case presented in this paper. PET is a promising, possibly cost-efficient method to reliably assess tumour response to bevacizumab therapy and may thus be included in the clinical management of recurrent high-grade gliomas treated with anti-angiogenic drugs.

Conflict of Interest

The authors have no conflict of interest to disclose.

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Appendix: Case Report

In December 2009, a 51-year-old woman was diagnosed with glioblastoma multiforme in the left thalamus, putamen, and insular cortex. Histology was acquired by stereotactic biopsy. MGMT promotor methylation was not determined. She was treated with radio-chemotherapy up to 60 Gy in 30 fractions of 2 Gy and daily temozolomide (TMZ) 75 mg/m^2. After radiation therapy, adjuvant chemotherapy with temozolomide 150–180 mg/m^2 (according to the 5/28 scheme [1]) was continued. During further therapy, continuous daily medication with 16 mg dexamethasone and 533 mg *Boswellia serrata* was administered due to a perifocal oedema with a midline shift. In July 2010, the gadolinium-enhanced MRI and ^{18}F-FET-PET scans both showed tumour progression (Figure 1A) with new lesions in the mesencephalon. The patient experienced an episode of aphasia, suffered from Cushing's syndrome and a pathological elevation of liver enzymes. Corticosteroids were stopped and instead a therapy with bevacizumab 400 mg every 4 weeks was started. Chemotherapy with TMZ was continued.

After the start of bevacizumab in September 2010, MRI and PET showed tumour regression. However, imaging results were clearly discordant: decrease of contrast enhancement in the T1-weighted MRI was much greater than the decrease of FET uptake in ^{18}F-FET-PET (Figure 1B). In the next follow-up 2 months later, a discrepancy of tumour localisation between ^{18}F-FET-PET and MRI was seen. PET revealed progressive infiltration in the caudate nucleus and thalamus, barely visible on MRI (Figure 1C). Based on the results of the FET-PET study, stereotactic fractioned re-irradiation with 20 Gy was performed in the region of the left thalamus and further chemotherapy was switched from TMZ and bevacizumab to irinotecan and bevacizumab. The irradiation dose was equivalent to 30 Gy in 2-Gy fractions assuming an α/β of 2 for brain tissue, and correlates to a biologically effective dose of 60 Gy. The hypofractionated regime was chosen so as not to limit the patient's quality of life due to a long radiation therapy.

Without ^{18}FET-PET imaging at this time point re-irradiation would probably not have been performed because there was barely contrast enhancement on MRI.

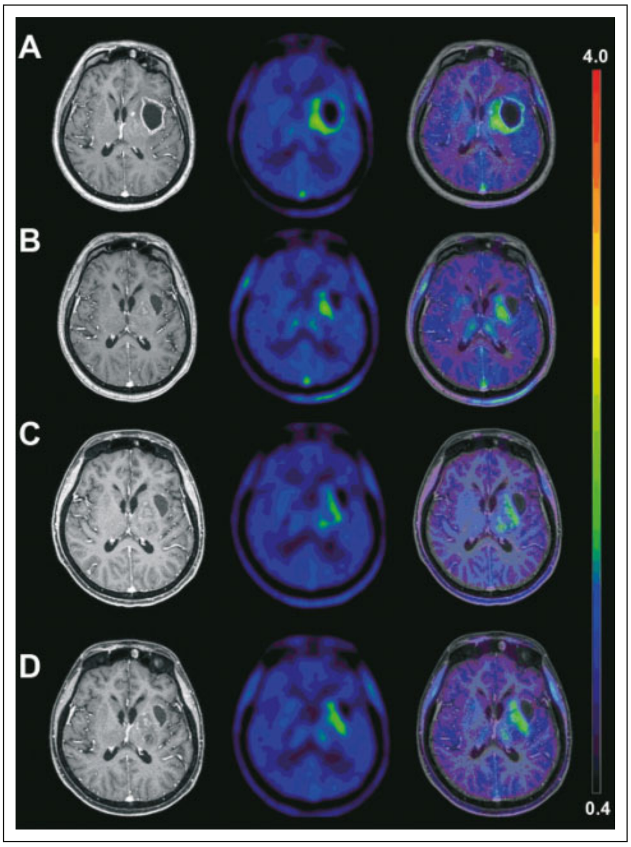

Figure 1. Imaging results of a patient with glioblastoma undergoing bevacizumab therapy. First column: MRI (MP-RAGE with contrast enhancement); second column: [18]F-FET-PET (parametric images scaled to mean uptake in a right temporal reference region); third column: image fusion. **(A)** scan prior to therapy 07/2010; **(B)** scan after 8 weeks of bevacizumab 09/2010; **(C)** scan after 16 weeks of bevacizumab 11/2010; **(D)** scan after re-irradiation with 20 Gy, 01/2011. Bevacizumab therapy was continued. For details, see text.

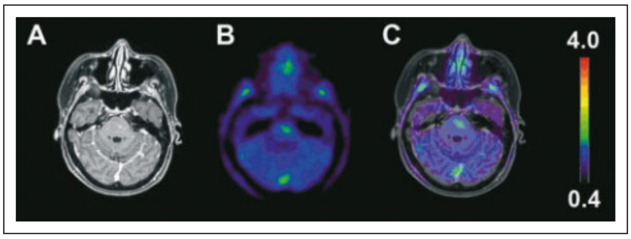

Figure 2. (A) T1-weighted MRI, **(B)** parametric [18]F-FET-PET, and **(C)** fused images of a distant tumour manifestation in the mesencephalon. Note that the Gd-enhancing lesion on the T1-weighted MRI is rather small and only visible on the left side, whereas the extent of [18]F-FET uptake is much larger and extends to the right side.

After radiation (Figure 1D), [18]F-FET-PET presented a small decrease of uptake but still a visible tumour mass. In addition, progressive infiltration of the mesencephalon was seen, as compared to a small, focal enhancing lesion on MRI (Figure 2). In contrast, MRI showed only minimal contrast enhancement without relevant changes to the MRI prior to reirradiation. The patient died 16 months after primary diagnosis. This case illustrates the often discordant results between contrast enhancement in MRI and amino-acid uptake in PET and demonstrates the clinical utility of PET for response assessment and therapy management.

We assume that the decrease of contrast enhancement was due to a reduction of the brain-blood barrier damage by bevacizumab and not due to a real tumour reduction. However, it was not possible to decide whether the MRI or the PET scan showed the real tumour dimension. An autopsy was not performed.