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B**e**- 9 **or**, =

amino acidscbrain tumorcmagnetic resonance imagingcneuroimagingcpositron emission tomography

C<<**re**5**iation**=

BBBZBlooddbrain barrier

CTZComputed tomography

FETZO-(2-e^{1f} Fgfluoroethyl)-L-tyrosine

GFAPZGlial fibrillary acidic protein

HhEZHematoi ylin and eosin stain

METZL-emethyl-^{11}Cg-methionine

MRIZMagnetic resonance imaging

PETZPositron emission tomography

RANOZResponse Assessment in Neuro-Oncology

TACZTime-activity curve

TBRZTumor-to-brain ratio

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PurposeZ Amino acid PET using O-(2-e[f] Fgfluoroethyl)-L-tyrosine (FET) provides important additional information on the ei tent of viable tumor tissue of glioblastoma compared with MRI. Especially after radiochemotherapy, progression of contrast enhancement in MRI is equivocal and may represent either tumor progression or treatment-related changes. Here, the first case comparing post-mortem whole-brain histology of a pretreated glioblastoma patient with dynamic in vivo FET PET and MRI is presented.

MethodsZ A] 1-year-old glioblastoma patient initially underwent partial tumor resection and died eleven weeks after completion of chemoradiation with concurrent temozolomide. Three days before the patient deceased, a follow-up FET PET and MRI scan indicated tumor progression. Autopsy was performed 4f h hours after death. After formalin fii ation, a ^ cm bihemispherical segment of the brain containing the entire tumor mass was cut into 35`` consecutive 2` km coronal sections. Representative sections were stained with HhE, cresyl violet and glial fibrillary acidic protein immunohistochemistry. An ei perienced neuropathologist identified areas of dense and diffuse neoplastic infiltration, astrogliosis and necrosis. In vivo FET PET, MRI datasets and post-mortem histology were co-registered and compared by three ei perienced physicians.

ResultsZIncreased uptake of FET in the area of equivocal contrast enhancement on MRI correlated very well with dense infiltration by vital tumor cells and showed tracer kinetics typical for malignant gliomas. An area of predominantly reactive astrogliosis showed only moderate uptake of FET uptake and tracer kinetics usually observed in benign lesions.

ConclusionsZ This case report impressively documents the correct imaging of a progressive glioblastoma by FET PET.

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- First study to compare modern neuroimaging techniques with post-mortem whole-brain histology
- Amino acid PET using FET delineates vital tumor tissue in progressive glioblastoma
- FET PET tracer uptake kinetics might be helpful to differentiate between areas of necrosis, reactive astrogliosis and vital tumor cells

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In clinical practice, contrast-enhanced MRI is the method of choice for the diagnosis and delineation of brain tumors and usually represents the basis for treatment planning such as resection or radiotherapy.[1,2] The differentiation of glioma tissue with its pronounced regional heterogeneity from surrounding edema is unreliable, however, particularly when the main tumor mass is not sharply demarcated from normal brain tissue, and when no contrast enhancement (CE) is present. A previous study comparing histopathology of whole-brain specimens of several brain tumor patients with MRI data came to the conclusion that conventional MRI does not allow malignant gliomas to be correctly delineated.[3] A number of advanced MRI techniques such as perfusion weighted imaging (PWI) or magnetic resonance spectroscopic imaging are under clinical evaluation to target this diagnostic problem but cannot solve all problems satisfactorily.[4]

In the last decades, there is increasing evidence that PET using radiolabeled amino acids offers a better delineation of cerebral gliomas which helps to guide biopsies and to plan surgical interventions and radiation therapy and is useful in distinguishing tumor recurrence from nonspecific therapeutic scar tissue.[5d1`] Most PET studies in brain tumor patients have been performed with L-e-methyl-$^{11}$Cg-methionine (MET) (half-life, 2` min),[11,12] but for logistic advantages, ^{1f}F-labeled amino acid such as O-(2-^{1f}F-fluoroethyl)-L-tyrosine (FET) (half-life, 1`\.f min) have replaced MET in many neuro-oncological centers in the last decade.[\,13d1] Recently, the Response Assessment in Neuro-Oncology (RANO) working group - an international effort to develop new standardized response criteria for clinical trials in brain tumors - has recommended the additional use of amino acid PET imaging at every stage of brain

tumor management.[f] In 2` 14, Switzerland was the first country to approve [1f]F! FET PET as a medical drug for clinical use.[1^]

A number of studies in which imaging has been compared with tissue samples obtained by either biopsy or surgery have shown that amino acid PET reliably detects glioma tissue.[5,1f d2`] More than three decades ago, a comparison of PET and CT data of a patient with anaplastic astrocytoma with whole-brain histopathology has been published.[21] MET PET was able to identify the ei tent of the main tumor mass of an astrocytoma correctly while conventional as well as contrast-enhanced CT and PET using other tracers missed more than 5` l of the tumor tissue. That study was a milestone for the further development of amino acid PET in brain tumor imaging.[21]

Such data, however, are as yet not available for progressive tumors in pretreated patients. A particular problem in the follow-up of glioblastoma is the distinction between early tumor progression and treatment-related changes after radiochemotherapy of malignant gliomas with concurrent temozolomide.[22] Within the first twelve weeks after completion of radiochemotherapy, glioblastoma patients may ei hibit an enlarging area of CE on MRI, followed by subsequent improvement or stabilization without any change in treatment.[22,23] This phenomenon has been termed mpseudoprogressionn and is a consequence of a subacute treatment-related local tissue reaction, which comprises inflammation, edema, and increased permeability of the blooddbrain barrier.[23]

Here, we present the first case study comparing post-mortem whole-brain histology of a glioblastoma patient with in vivo dynamic FET PET and MRI data within three months after completion of radiochemotherapy, i.e., in a critical time window in which

a diagnostic decision must be made between an early tumor progression and a pseudoprogression. We would like to emphasize that the availability of a full record of MRI and PET data of a brain tumor patient in a temporal proi imity to autopsy is a rare coincidence. Furthermore, compared with previous reports this case is ei ceptional because whole-brain histology was generated by the brain mapping group of our center which has outstanding ei pertise regarding large-scale analysis of the human brain, i.e., the analysis of thousands of whole-brain sections for cytoarchitectonic and receptor mapping.[24] Therefore, this case study provides an important set of data that is not available in the literature so far.

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A]1-year-old glioblastoma patient underwent initially partial resection and died eleven weeks after completion of chemoradiation with concurrent temozolomide. The patient participated in a prospective study investigating an integrated-boost-intensity-modulated radiotherapy (IMRT) with FET-PET-adapted local dose escalation in glioblastomas.[25] The university ethics committee and federal authorities approved this study. All patients gave written informed consent before their participation in the study.

The whole dose to the tumor area was ^2 Gray (Gy) using daily single doses of 2.4 Gy for the PET-adapted target volume and]` Gy (single-dose 2 Gy) for the MR-based target volume applied with an integrated-boost technique.[2]

Four weeks after completion of radiochemotherapy, MRI and FET PET were performed for treatment monitoring. The MRI scan showed increasing CE in the irradiated tumor area and FET PET indicated tumor progression. Three days later, the patient suddenly died of circumstances that could not be clarified with certainty by the autopsy.

The FET PET scan was performed in an ECAT E_ACT HR[scanner (CTI, Siemens Medical Systems, Knoi ville, USA). The amino acid FET was produced and applied as described previously.[2^,2f] A dynamic PET scan from ` to 5` min after injection of approi imately 2`` MBq of FET was performed. After correction for random and scattered coincidences as well as dead time and attenuation, the PET data were iteratively reconstructed. The reconstructed dynamic data set consisted of 1] time frames (5 i 1 minc 5 i 3 minc] i 5 min). A routine 1.5 T MRI was acquired at the same day of PET scanning before and after intravenous injection of a gadolinium-based contrast agent using a standard MR head coil.

Two days after the patientps death, the brain was removed during autopsy and additional post-mortem MRI scans of the brain were performed. A T1- (3D MP-RAGE sequence) and a T2-weighted (3D TSE sequence) MR image was acquired in a 3T MR scanner (MAGNETOM Trio, Siemens Medical Systems, Erlangen, Germany) in order to identify the tumor bearing area of the brain that was to be selected for further work-up and to obtain a shape reference for further 3-dimensional reconstruction of the histological sections. Informed consent was obtained from the patientps nei t of kin.

The brain was dissected as followsZ A rostral cut was carried out through the mammillary bodies and a dorsal cut was placed through the occipital lobes. The brain region between the two cuts consisted of large parts of both parietal lobes, parts of the temporal lobes and infratentorial parts of the brain. It contained the tumor mass and adbacent brain regions. The entire specimen was embedded in paraffin and further processed for histology. The remaining brain tissue consisting mainly of large parts of the frontal and occipital lobes was returned to the mortician. A large-scale microtome was used to cut the specimen into 35`` successive coronal sections with a thickness of 2` km.

Representative coronal sections through the brain covering the entire tumor region were stained with hematoi ylin-eosin and cresyl violet and immunohistochemically using an antibody against glial fibrillary acidic protein (GFAP), an astrocyte marker protein (dilution 1Z5``, DAKO). Each section was microscopically ei amined by an ei perienced neuropathologist (B.S.) who manually marked areas of solid tumor and pronounced tumor infiltration of adbacent brain tissue vs. minor neoplastic infiltration

mii ed with reactive astrogliosis as well as necrotic regions on photographic copies of the brain slices.

To match the reconstructed histological volume with the ei -vivo MR volume, linear and non-linear correction procedures were used.[2\] Most artefacts (e.g. ms wiss cheesen artefacts due to focal post mortal bacterial proliferation, shrinkage of the brain due to fii ation and embedding in paraffin, and distortion of the sections due to cutting) could be eliminated, but the tumor-bearing area showed distortions that could not be corrected by the algorithms usually applied for data fusion in non-tumor bearing human brains. Therefore, histological sections were visually co-registered with the FET PET and MRI images using anatomical markers and the software PMOD (j ersion 3.5` 5, PMOD Technologies Ltd.). After fusion of the in vivo FET PET and MRI datasets with post-mortem histology, the FET uptake and the contrast-enhancing regions in MRI were correlated to regions of presumed predominant neoplastic infiltration vs. astrogliosis and necrosis.

PET data analysis was performed on summed PET images (2`-4` min p.i.). For reference, a spherical background volume-of-interest (j OI) was positioned in the hemisphere contralateral to the lesion in healthy brain parenchyma (diameter of the background j OI, 3` mm). The ei tent of neoplastic infiltration apparent in the FET PET was determined using a 2D auto-contouring process with a tumor-to-brain ratio (TBR) of 1.] or more. This cut-off is based on a biopsy-controlled study in untreated gliomas.[5] The mean FET uptake ratio was calculated in selected regions of the tumor mass and adjacent gliotic tissue with sparse neoplastic infiltration. The spatial overlap between FET uptake above the threshold of 1.] and ei tent of viable tumor tissue in histology were visually evaluated by three ei perienced physicians (M.P., K-J.L., N.G.) in consensus and compared with the area of CE in MRI. The time-activity

curves (TAC) of tracer uptake were evaluated using the dynamic PET data. The TACs for tumor tissue were evaluated by spherical j OIs (volume of the background j OI, ` .1 mlcdiameter, 5 mmcnumber of voi els, 41) in five different positions (across 25 sections) in areas showing viable tumor tissue.

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The co-registration and fusion of the data sets yielded a satisfactory alignment in the space ai es but the evaluation of the tumor area was hampered by deformations of the brain after removal from the cranial cavity, formalin fii ation and paraffin embedding.[3`] Therefore, a direct overlay analysis of the different tissue compartments in the tumor area in the histological specimen with PET and MRI data was not meaningful and the further analysis was based on a visual comparison which took into account deformations based on anatomical landmarks.

The glioblastoma mainly consisted of densely packed anaplastic tumor cells showing astrocytic differentiation. The tumor contained a large central necrosis with finger-like ei tensions into the adlacent tumor tissue which were surrounded by pseudopalisading tumor cells. The solid tumor merged into the adlacent densely infiltrated brain tissue without sharp bordersc the latter showed a focal transition into gliotic brain tissue containing only few neoplastic cells. There were numerous foci of vascular proliferations within the tumor itself and in the adlacent tumor-infiltrated brain tissue. Many blood vessel walls were thickened and hyalinised as a consequence of irradiation.

An overview of the results of the imaging modalities in the solid brain regions densely infiltrated by neoplastic cells is presented in Figure 1.

In all areas that were identified as tumor mass or as brain tissue densely infiltrated by anaplastic tumor cells on the histological sections, increased FET uptake was noted which demonstrates that FET PET identified progressive tumor tissue. Tumor tissue showed also CE on MRI, which, however, has little specificity with respect to the differentiation of tumor and treatment-related changes (Figures 2 and 3).

In most sections, the solid tumor and the adjacent densely infiltrated brain regions were surrounded by a smaller rim of astrogliosis containing scattered neoplastic cells. In those areas, FET uptake in tumor tissue and astrogliosis could not be differentiated due to the limited spatial resolution of PET. In one section, however, there was a larger area of astrogliosis with only few intermingled neoplastic cells which extended beyond the tumor mass. This area could be evaluated separately for FET uptake (Figure 3). In this area, FET uptake was slightly increased with a tumor-to-brain ratio of 1.5, which is lower than the threshold value of 1.] that is used to differentiate neoplastic from non-neoplastic tissue in FET PET of cerebral gliomas.[5] The FET uptake in the tumor mass and in the densely infiltrated brain tissue was 2.3. Thus, the area of astrogliosis with only scattered neoplastic infiltration could be clearly distinguished from the solid malignant tumor tissue. The area of central necrosis in this large glioblastoma showed neither FET uptake nor contrast-enhancement on MRI. Additionally, the FET uptake kinetics of the area of viable solid tumor showed a curve pattern characteristic for high-grade gliomas,[31,32] i.e., a steep increase in the early phase after injection followed by a constant descent (Figure 3 C). The evaluation of regional time-activity curves of FET uptake across 25 sections of histologically identified tumor tissue showed uniformly a curve pattern characteristic for high-grade gliomas. In contrast, the TAC of FET uptake in the gliotic area without dense neoplastic infiltration showed a steadily increasing tracer uptake (Figure 3 C), similar to the curve pattern typically observed in benign lesions and low-grade gliomas.[31,32]

E**i**=/ A==**ion**

To the best of our knowledge, this is the first post-mortem study that compares whole-brain histology with in vivo dynamic FET PET and MRI of a patient with a glioblastoma within three months after completion of radiochemotherapy. At the time of investigation, the patient showed an enlarging area with CE on MRI indicating either tumor progression or pseudoprogression, a phenomenon that occurs at this stage in up to 3`l of the patients.[23,33] The present case study demonstrates that FET PET reliably identified viable tumor tissue in all parts of this large progressive glioblastoma and allowed the differentiation of areas with pronounced astrogliosis and only minor, scattered neoplastic cells. Furthermore, all parts of this progressive glioblastoma showed FET kinetics typical for malignant gliomas while astrogliosis showed a curve pattern typical for benign brain lesions or low-grade gliomas.

The differentiation of early tumor progression and pseudoprogression in patients with malignant gliomas after radiochemotherapy is a major diagnostic challenge. A previous study has shown that FET PET allows differentiating pseudoprogression and early progression in glioblastoma patients within the first twelve weeks after radiotherapy with concomitant temozolomide with an accuracy of \]l , which could not be achieved with conventional MRI based on the RANO criteria.[22,34] Further studies demonstrated that FET PET is also useful to differentiate between radiation injury and tumor recurrence in cerebral gliomas or brain metastases with an accuracy of about \`l .[34d3f] A limitation of those studies is the fact that in many of the patients, the diagnosis is based on clinicoradiological follow-up and not on histological assessment. Furthermore, there is no study in the literature comparing regional histology with FET uptake in progressive and recurrent gliomas. It is frequently discussed whether the increased FET accumulation in brain tumors is due to a

disruption of the blooddbrain barrier (BBB) as indicated by CE in MRI. Since FET is transported via the system L amino acid transporter it enters also the normal brain tissue and a disruption of the BBB is not a prerequisite for intratumoral accumulation.[13] Even though this phenomenon is not obvious in the present case study, increased FET uptake has frequently been observed beyond the area of CE in malignant gliomas and also in low-grade gliomas without BBB leakage.[3,4]

Despite the ei tensive methodological approach a perfect fusion of the histological slices and the in vivo imaging data in the tumor area was not possible. This was due to the fact that after removal of the brain from the skull the tumor area showed a protuberance that could not be corrected by the morphing algorithms that are applied for data fusion in non-tumor bearing human brains. Nevertheless, the 3-dimensional alignment of the data set allowed for a reasonable comparison of the presence of tumor tissue in the coronal histological slices and in the corresponding FET PET studies as demonstrated in Figure 1 and 2.

Another aspect of the study was the regional allocation of FET kinetics in different parts of this progressive glioblastoma. Different tracer kinetics in malignant and benign tissues appears to be a special property of FET since it has not been observed for other amino acid tracers such as MET or FDOPA.[41,42] A comparison of regional histology with FET kinetics has been reported in untreated low-grade gliomas using stereotactic biopsies which demonstrated that areas with malignant transformation ei hibited a malignant curve pattern characteristic for high-grade gliomas, i.e. a steep increase in the early phase after inlection followed by a constant descent.[43] Such studies, however, are as yet not available for the evaluation of progressive tumors. In the present study, the regional evaluation of FET kinetics of

this pretreated and progressive glioblastoma revealed a malignant curve pattern in all parts of histologically identified tumor mass. In contrast, an area of reactive gliosis with only scattered neoplastic cells showed moderate FET uptake and a benign curve pattern similar to that observed in non-neoplastic lesions (Figure 3). Thus, dynamic FET PET may be helpful in the differentiation between progressive gliomas and treatment-related changes.

Although these results are promising, the accuracy of FET PET in differentiating tumor progression and treatment related changes is limited to \`l and cannot replace a biopsy in case of doubt.[44,45] Moreover, it has to be considered that FET uptake is not specific for neoplastic tissue and pitfalls have been reported for brain abscesses, demyelinating processes, in the proi imity of cerebral ischemic lesions, and hematomas.[4] ,4^ Furthermore, in rare cases increased FET uptake has been reported several years after high dose brachytherapy in areas of reactive astrogliosis.[4f] Unspecific FET uptake, however, is apparently a rare finding in routine diagnostics of brain tumors. In our study, no sign of unspecific FET uptake beyond the histological confirmed tumor tissue could be observed. Especially, there was only moderate uptake in an area of reactive astrogliosis adlacent to the tumor, which is in line with an ei perimental study in rats showing only low FET uptake in peritumoral astrogliosis up to a radiation dose of 1`` Gy.[4\]

It should be noted that also advanved MR methods, particular PWI, can contribute significantly to the differentiation of tumor progression and therapy-related changes,[4] a recent comparative study of both methods using hybrid PETdMRI, however, suggests that FET PET has a superiority over PWI in this diagnostic issue.[5`]

Con/ lA=ion=

FET PET identified viable tumor tissue in all parts of the tumor mass of this large progressive glioblastoma and allowed the differentiation of adjacent gliotic areas with only minor infiltration by scattered neoplastic cells. The tumor mass showed a malignant curve pattern, which confirms that dynamic FET PET contributes to differential diagnosis in recurrent gliomas.

E**e/ laration of intere**=**t**Fnone

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0**i**?A**re Ca**>**tion**=

0**i**?HI Representative coronal sections of whole-brain histology stained with cresyl violet (A). An ei perienced neuropathologist indicated areas of astrogliosis (green), neoplastic tissue (red) and necrosis (blue) (B). Corresponding co-registered in vivo contrast-enhanced MR (C) and FET PET (D) images

0**i**?H J Representative post-mortem whole-brain histological sections (coronal) stained with cresyl violet (A, Bc E, F) in comparison with in vivo contrast enhanced MRI (Cc G) and FET PET (Dc H). An ei perienced pathologist indicated areas of astrogliosis with only few, scattered neoplastic cells (green), tumor mass and densely infiltrated brain tissue (red) and necrosis (blue) on the histological sections. The FET uptake and the area of contrast enhancement were in good agreement with viable tumor tissue

0**i**?H K Whole-brain histology (A) and corresponding FET PET image (B) for evaluation of FET uptake kinetics (C). Areas of astrogliosis (A, greenc B white arrow) and viable tumor tissue (A, redc B white arrowheads) showed clear differences in FET uptake kinetics (C). The histologically identified areas of cell-dense tumor tissue showed a curve pattern characteristic for high-grade gliomas (C, red) and could be clearly distinguished from the reactive astrogliosis with only few, scattered tumor cells (C, green). The TAC of unaffected brain parenchyma is included for comparison (C, black)