Static FET–PET and MR Imaging in Anaplastic Gliomas (WHO III)

Stefanie Bette[1], Patrick Peschke[2], Johannes Kaesmacher[1], Claire Delbridge[3], Thomas Pyka[4], Friederike Schmidt-Graf[5], Claus Zimmer[1], Bernhard Meyer[2], Florian Ringel[2], Jens Gempt[2]

■ OBJECTIVE: **O-(2-[18F]-fluoroethyl)-L-tyrosine—positron emission tomography (FET-PET) imaging is an additional tool for tumor grading and surgery planning. Up to now, not much is known about FET-PET imaging in anaplastic gliomas. Our objective was to assess the FET uptake in anaplastic gliomas, compared with magnetic resonance imaging (MRI), histopathologic markers, and its prognostic value.**

■ PATIENTS AND METHODS: **Forty-six patients (27 males/19 females) with an anaplastic glioma (WHO III) who received MRI and FET-PET imaging before surgery were retrospectively analyzed. Tumor volume was calculated in MRI and FET-PET imaging using a tumor-to-background ratio (TBR), and maximum FET uptake (TBR_{max}) was calculated. Overall survival (OS) and histopathologic markers (isocitrate-dehydrogenase 1/2-mutation, oligodendrial differentiation, and Ki67 proliferation index) were assessed. Univariate and multivariate analysis was performed for OS.**

■ RESULTS: **In univariate analysis a significant correlation of TBR_{max} to OS was observed ($P = 0.031$). Tumor volume in FET-PET imaging (TBR > 2.0) ($P = 0.028$) showed a higher correlation to OS than the volume of the contrast-enhancing tumor part ($P = 0.031$). The highest correlation was observed for intersection of volume TBR > 1.3 and the volume of the contrast-enhancing tumor part ($P = 0.005$); fluid-attenuated inversion recovery volume showed no significant correlation to OS ($P = 0.401$) in the univariate analysis. Anaplastic glioma with oligodendrial differentiation showed significantly higher TBR_{max} values ($P = 0.029$), while no significant difference was observed for isocitrate hydrogenase 1/2-mutation ($P = 0.752$).**

■ CONCLUSION: **Static FET-PET provides significant prognostic information in anaplastic gliomas, which adds to the value of MRI, supporting the use of both modalities preoperatively to assess individual risks and estimate prognosis. Definition of the histopathologic subtype using static FET-PET remains challenging.**

INTRODUCTION

About 30% of all gliomas are anaplastic gliomas (World Health Organization [WHO] grade III). Despite recent advances in treatment and diagnosis, patients show a poor prognosis with a short overall survival (OS) and reduced quality of life. Among the defined WHO grade III tumors, prognosis varies according to the tumor subtype and its molecular features, such as codeletion of 1p19q, isocitrate-dehydrogenase(IDH) 1/2-mutation, p53, and the histopathologic subtype (astrocytoma, oligoastrocytoma, oligodendroglioma).[1-4] As molecular markers become more and more important for diagnosis and treatment planning, knowledge of these markers before histopathologic diagnosis would be helpful.[4,5] Recent studies show that information about histopathologic markers, such as IDH1/2-mutation and

Key words
- Anaplastic gliomas
- Oligodendrial differentiation
- Static FET-PET

Abbreviations and Acronyms
FDG: Fluorine-18 fluorodeoxyglucose
FET: O-(2-[18F]-fluoroethyl)-L-tyrosine
FLAIR: Fluid-attenuated inversion recovery
ID: Initial diagnosis
IDH: Isocitrate hydrogenase
KPS: Karnofsky performance scale
MET: L-methyl-11C-methionine
MRI: Magnetic resonance imaging
OS: Overall survival
PET: Positron emission tomography
TBR: Tumor-to-background ratio
WHO: World Health Organization

From the Departments of [1]Neuroradiology, [2]Neurosurgery, [3]Neuropathology, and [4]Nuclear Medicine, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [5]Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

To whom correspondence should be addressed: Stefanie Bette, M.D. [E-mail: Stefanie.bette@tum.de]

Citation: World Neurosurg. (2016) 91:524-531.
http://dx.doi.org/10.1016/j.wneu.2016.02.094

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

oligodendrial differentiation, could be detected in preoperative magnetic resonance and dynamic O-(2-[18F]-fluoroethyl)-L-tyrosine positron emission tomography (FET-PET) imaging.[6,7]

Multimodal imaging before surgery, including magnetic resonance imaging (MRI) and PET, is important for diagnosis, surgery, treatment planning, and estimation of prognosis for gliomas and brain metastases alike.[8-15] A prognostic value regarding the enhancement of PET-tracers, like L-methyl-11C-methionine (MET) and fluorine-18 fluorodeoxyglucose (FDG), was shown for gliomas in recent studies.[11,16,17] Disadvantages of these tracers are the high physiologic uptake of FDG and the fast metabolism of MET; therefore FET-PET imaging is another promising tool for brain tumor imaging due to higher specificity and high metabolic stability.[8,18] Imaging characteristics of dynamic FET-PET reveal information regarding the OS of high-grade glioma patients,[13,19,20] and further different subgroups could be defined by FET-PET in low-grade gliomas (WHO grade II).[15] To our knowledge, as of yet there is no study about the prognostic value of static FET-PET in combination with MRI in anaplastic astrocytoma (WHO grade III).

The aim of this study was to assess MRI and static FET-PET imaging in anaplastic gliomas, its correlation to histopathologic markers such as IDH1/2-mutation and oligodendrial differentiation, and its impact on OS.

PATIENTS AND METHODS

This retrospective, noninterventional, single-center study was approved by the local institutional review board (5625-12). The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.[21]

Forty-six consecutive patients who received MRI and FET-PET imaging (obtained within clinical routine) before neurosurgical intervention (surgery or biopsy) and who were diagnosed with solid anaplastic glioma (WHO grade III, relapse or newly diagnosed, gliomatosis was excluded) between August 2007 and October 2013 were included.

Date of the tumor's initial diagnosis (ID), relapse disease, death or last contact, and preoperative and postoperative Karnofsky performance scale (KPS) score were assessed. OS was calculated from the date of the FET-PET scan, as well as the date of initial tumor diagnosis. Surgery was performed in an attempt to remove the whole tumor, sparing motor and language function. At our department intraoperative neuronavigation, intraoperative brain-mapping, and in selected cases of anaplastic glioma, 5-aminolevulinic acid (5-ALA) fluorescence is used. Extent of resection was assessed in the postoperative MRI and classified as biopsy/subtotal or total tumor resection. Total tumor resection was defined as the resection of the whole fluid-attenuated inversion recovery (FLAIR) hyperintense and contrast-enhancing tumor part. Subtotal resection was defined as residual tumor in the early postoperative MRI (either FLAIR-hyperintense and/or contrast-enhancing tumor). Adjuvant treatment including chemotherapy, radiotherapy, or combined radiochemotherapy was assessed. For patients with recurrent disease during follow-up, the performed adjuvant therapy for recurrent disease was recorded.

Magnetic Resonance Imaging

MRI scans were done as described earlier[22] on a 1.5 or 3T MRI scanner (Philips Achieva 3T, Philips Medical Systems, Amsterdam, The Netherlands; B.V. or Siemens Verio/Avanto, Siemens Healthcare, Erlangen, Germany). Axial T2-weighted (w) FLAIR images (Achieva: acquisition time 3:00 minutes, TR/TE of 12000/140 milliseconds (ms), 0.45 x 0.45 x 4 mm^3 spatial resolution; Verio: acquisition time 3:44 minutes, TR/TE 8560/136 ms, 0.8 × 0.7 × 4 mm^3 spatial resolution), and precontrast and postcontrast T1w images (Achieva: acquisition time: 2:53 minutes, TR/TE 530/10 ms, 0 x 45 x 0.45 x 4 mm^3 spatial resolution; Verio: T1 inversion recovery, time of inversion 860 ms, acquisition time 4:02 minutes, TR/TE 2000/9 ms, 0.9 x 0.7 x 4 mm^3 spatial resolution) or magnetization prepared rapid gradient echo (Achieva: acquisition time 5:55 minutes, TR/TE 9/4 ms, 1 mm isotropic spatial resolution; Verio: acquisition time 4:18 minutes, TR/TE 1900/2.45 ms, 1.1 x 1.1 x 1 mm^3 spatial resolution) were acquired. For contrast, Magnograf (MaRo-Trast, Jena, Germany) was administered intravenously (0.2 mL/kg, 1 mL/sec) using an MRI-compatible contrast medium injection system (Spectris Solaris EP, Siemens Medical, Erlangen, Germany).

FET PET Imaging

Also, FET-PET was performed as described previously.[22] After a fasting period of 4 hours before FET-PET, scans were conducted on a Biograph 64 PET/CT scanner (Siemens). The PET-Scanner acquires 63 contiguous transaxial planes, simultaneously covering 15.5 cm of axial field of view. An intravenous injection of the target dose of 185 MBq 18F-FET was conducted after a 15-minute transmission scan. The PET emission acquisition was performed 30 to 40 minutes after injection (128 x 128 matrix). Data reconstruction was conducted by filtered back-projection using a Hann filter (Hann 4.9) after correction for scatter and attenuation.

Data Analysis

Imaging analysis was done analogous to previous studies[8,9,22] by fusion of MRI and FET-PET using a 3-dimensional planning software (BrainLab IPlannet 3.0 cranial planning software; BrainLab AG, Feldkirchen, Germany). Tumor volume on FET-PET was acquired using a threshold-based method. The background Region of Interest, derived from a cortical region in the contralateral (nontumor) hemisphere, was calculated. Then the tumor volumes were calculated in comparison to the background volume of interest, using a tumor-to-background ratio (TBR) (**Figure 1**). Tumor volumes for TBR of >1.3, >1.6, and >2.0 and the maximum FET uptake (TBR_{max}) were measured. In MRI, the volume of the whole T2w FLAIR hyperintensity and in postcontrast T1w images the volume of only the contrast-enhancing tumor part were measured, and the intersection, as well as the union of T2w FLAIR volume/postcontrast T1w volume and FET-PET volume, were calculated as it was described and established before using the IPlannet 3.0 cranial planning software.[8] Apart from the absolute intersection volumes, the ratio of the intersection volume to the corresponding TBR volume was calculated as it was described in a previous study.[8] Tumor volumes were measured in each patient separately as described earlier and then the median volume of all patients (and the interquartile range) was calculated.

Histopathology

Histopathologic analysis was done in the Department of Neuropathology according to the WHO criteria of 2007.[2] Analysis of