Volumetric Analysis of F-18-FET-PET Imaging for Brain Metastases

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BACKGROUND: **The knowledge of exact tumor margins is of importance for the treating neurosurgeon, radiotherapist, and oncologist alike. The aim of this study was to investigate whether tumor volume and tumor margins acquired by magnetic resonance imaging (MRI) are congruent with the findings acquired by O-(2-(18F)-fluoroethyl)-L-tyrosine–positron emission tomography (FET-PET).**

METHODS: **Patients received FET-PET and MRI before surgery for brain metastases. Metastases were quantified by calculating tumor-to-background uptake ratios using FET uptake. PET and MRI-based tumor volumes, as well as areas of intersection, were assessed.**

RESULTS: **Forty-one patients were enrolled in the study. The maximum tumor-to-background uptake ratio measured in all of our patients harboring histologically proven viable tumor tissue was >1.6. Absolute tumor volumes acquired by FET-PET and MRI were not congruent in our patient cohort, and tumors identified in FET-PET and MRI only partially overlapped. The ratio of intersection (intersection of tumor defined by MRI and tumor defined by FET-PET at the ratio of tumor defined by FET-PET) was within a range of 0.27–0.68 when applying the different thresholds.**

CONCLUSIONS: **Our study therefore indicates that treatment planning based on MRI or PET only might have a substantial risk of undertreatment at the tumor margins. These findings could have important implications for the planning of surgery as well as radiotherapy, although they have to be validated in further studies.**

INTRODUCTION

In recent years, patients with brain metastases experienced a significant improvement in overall survival due to advances in systemic therapy.[1,2] To improve local control in cases of brain metastases, treatment has been changed toward a more aggressive regimen with surgical tumor resection and stereotactic irradiation in addition to systemic therapies.[1,3–5] Regular follow-up examinations with MRI are conducted to identify tumor progression and to initiate further local therapy in case of disease relapse.[6]

Surgery of metastatic brain tumors and evaluation of tumor response to radiation therapy and/or chemotherapy requires proper identification and localization of viable tumor tissue.[6,7] For gliomas, a substantial discrepancy between tumor extension visualized by MRI and real tumor extension is well known and an accepted fact.[8,9] This tumor extension can reach far beyond the areas found by conventional imaging modalities. In case of metastatic brain disease, its infiltrative growth pattern and extension beyond MRI margins is the object of recent research.[10]

Amino acid positron emission tomography[11] imaging, especially with the fluorine-18-labeled compound O-(2-(18F)-fluoroethyl)-L-tyrosine (FET),[12] is a promising functional imaging modality that is increasingly used in the clinical work-up of patients with glioma, yet not established in brain metastases. Other tracers, like

Key words
- Brain irradiation
- Brain metastasis
- Brain metastasis resection
- FET-PET
- MRI

Abbreviations and Acronyms
CT: Computed tomography
FET: O-(2-(18F)-fluoroethyl)-L-tyrosine
MET: L-methyl-11C-methionine
MRI: Magnetic resonance imaging
MRI_{Gd}: Volume of contrast-enhancing tumor tissue
MRI_{Gdn}: Volume of contrast-enhancing tumor tissue and noncontrast-enhancing tumor tissue (necrotic tissue)
PET: Positron emission tomography
TBR: Tumor-to-background standardized uptake value ratio
TBR_{max}: Maximal standardized uptake ratio
VOI: Volume of interest

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L-methyl-11C-methionine (MET), fluorine-18 fluorodeoxyglucose, and (18)F-fluorodihydroxyphenylalanine, have been evaluated to some extent for the use of brain tumor imaging.[13–16] However, compared with the fluorine-18-labeled compound FET, the distinct inferior signal-to-noise ratio in case of fluorine-18fluorodeoxyglucose and the short half-life and quick metabolism in case of MET are major disadvantages.[11]

With regard to brain metastases, little is known about FET imaging characteristics.[17] Valid uptake values and imaging characteristics in terms of tumor volume and tumor extension compared with MRI have yet to be established. A systematic interindividual approach comparing FET-positron emission tomography (PET) and MET-PET for patients with brain metastases was realized by Grosu et al.[18] Only pretreated patients were included and the resulting total number of patients with active brain disease was low ($n = 5$). A published study by Galldiks et al.[17] evaluated the use of FET-PET to differentiate tumor progression from treatment-related tissue changes in metastatic brain disease by dynamic imaging in pretreated patients. They pointed out an accuracy of 93% to diagnose local recurrent metastasis by dynamic analysis of the FET-PET data. An evaluation of tumor extension or volumetric assessment by MRI compared with PET was not conducted.

The aims of this study were to characterize FET uptake of brain metastases from different primary tumors and to evaluate whether tumor volume and tumor margins acquired by MRI are congruent with findings acquired by FET-PET.

METHODS

Between January 2010 and July 2012, patients with newly diagnosed brain metastases or progression/recurrence of previously diagnosed/treated brain metastases who underwent resection or biopsy of these lesions and had a preoperative FET-PET and MRI were included. Patient age, tumor histology, initial tumor diagnosis, and first diagnosis of brain metastases, as well as previous therapies were assessed. FET-PET and MRI images were obtained as part of the clinical care; analysis was conducted retrospectively.

MRI

MRI scans were conducted on a 3T MR scanner (8-channel phased array head coil, Achieva 3T; Philips Medical Systems Netherland B.V., Best, the Netherlands). The scans provided T_2-weighted FLAIR images (TR/TE of 12,000/140 milliseconds, inversion time 2850 milliseconds), T_2 gradient echo (TR/TE of 813/16 milliseconds), and precontrast and postcontrast T_1-weighted 3-dimensional MPRAGE (TR, 9 milliseconds; TE, 4 milliseconds; field-of-view 240 (anterior-posterior) × 240 (right-left) × 160 (feet-head) mm; voxel size, 1 mm^3; acquisition time, 5.56 minutes). For contrast-enhanced imaging, Magnograf (MaRoTrast, Jena, Germany) was administered intravenously (0.2 mL/kg, 0.1 mmol/kg, and 4 mL/sec), using an MRI-compatible contrast medium injection system (Spectris Solaris EP, Siemens Medical, Erlangen, Germany).

FET-PET

For this study, FET-PET scans were acquired on a SIEMENS Biograph 64 PET/CT scanner (München, Germany). For standardized metabolic conditions, patients were asked to fast for a minimum of 4 hours before the PET scan. The target dose of 185 MBq 18F-FET was injected. Before the PET emission scan was performed, 30 minutes after injection (10-minute acquisition time; 1 bed position, 3-dimensional mode, 128 × 128 matrix), a short low-dose computed tomography (CT) scan (eff. mAs, 12) was obtained for attenuation correction purposes. The PET/CT scanner acquired 63 contiguous transaxial planes covering 15.5 cm of axial field of view. PET data were reconstructed by filtered backprojection using a Hann filter (Hann 4.9) with corrections for attenuation, scatter, and radioactive decay.

Tumor volumetry

Imaging-based tumor volumetry was done after image fusion of the MRI on FET-PET data using the BrainLab iPlan 3.0 cranial planning software (BrainLAB AG, Feldkirchen, Germany).[19,20] PET tumor volumes were obtained using a standard "volume of interest" (VOI) method by applying a VOI around the tumor voxel with the highest FET uptake. Tumor-to-background standardized uptake value ratios (TBRs) relating maximal counts in the tumor VOI to the mean counts in a background VOI, which were derived from a cortical region in the contralateral (nontumor) hemisphere, were calculated by the method described by Popperl et al.[21] previously and used by us[22] in other studies. PET tumor volumes for TBRs of >1.3, >1.6, and >2.0 were calculated through a threshold-based semiautomatic segmentation (**Figure 1A**), as described by Arbizu et al.[19] To exclude physiologic FET uptake in other tissues a 3-dimensional box was adjusted to the tumor area and the respective thresholds to define tumor areas were applied.

Volumetric analysis of MRI images was performed on a 3-dimensional basis using the BrainLab (BrainLAB AG, Feldkirchen, Germany) iPlan 3.0 cranial planning software. Tumor volumes defined by MRI were manually segmented for each slice.

Volumes of contrast-enhancing lesions on MRI T_1 sequences with gadolinium were measured and defined as MRI_{Gd}.

Total tumor volumes, which means the volume contrast-enhancing tissue and noncontrast-enhancing tumor tissue (necrotic tissue), were assessed as well and defined as MRI_{Gdn}.

Besides the measurement of tumor volumes on MRIs and FET-PET, we assessed the volumes of intersection (**Figure 1B**) for the different FET-PET uptake threshold ratios and tumor visualized by MRI (with [$=MRI_{Gdn}$] and without [$=MRI_{Gd}$] necrosis/noncontrast-enhancing) tumor areas. In cases of multiple metastases, only the volumes of resected/biopsied lesions were assessed.

Statistical data analysis

Statistical analyses, including descriptive data analyses, were performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, Illinois, USA). Unpaired t-tests and Pearson's correlations were conducted. For all analyses, a difference with an error probability of less than 0.05 was considered to be statistically significant.

Ethics

The present study has been approved by the ethics committee (Klinikum rechts der Isar) and has therefore been performed in accordance with the ethical standards laid down in the 1964