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Role of [^{11}C] methionine positron emission tomography in the diagnosis and prediction of survival in brain tumours

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ABSTRACT

Objective: [^{11}C] methionine (MET) positron-emission tomography (PET) is a useful diagnostic and therapeutic tool in neuro-oncology. The aim of this study was to evaluate the relationship between MET uptake and the histopathological grade in both primary brain tumours and brain metastases. A secondary goal was to assess the relationship between MET uptake and patients' survival after surgery.
Methods: We reviewed a consecutive series of 43 PET studies performed at our institution. Out of the 43 patients studied, 35 harboured primary brain tumours (3 grade I, 12 grade II, 7 grade III and 13 grade IV) and 8 patients had brain metastases. We measured the tumour/cortex ratio (T/C ratio) on each PET study and we investigated the correlations among the tracer uptake, tumour grade, tumour type, MRI parameters and outcome.
Results: The mean T/C ratio was 1.8 ± 0.9 for benign lesions and low grade gliomas (grade I and II) and 2.7 ± 1 for high grade gliomas (grade III and IV). In brain metastases it was 2.5 ± 0.7, with a significant difference in MET uptake between low and high grades gliomas ($P = 0.03$). There was no statistically significant difference among all different histologic types.

We found that both contrast enhancement and perfusion studies correlate with MET uptake in brain tumours. Moreover, in Kaplan–Meier curves, the T/C ratio adversely affects long term survival in patients with brain tumours ($P = 0.01$).
Conclusions: MET PET appears to be useful in diagnosis and evaluation of potential malignancy in brain tumours. MET uptake is also related with the overall survival in patients with brain tumours. Nevertheless, further studies are needed in order to define its possible clinical implications in identifying patients at high risk of tumour progression or resistance to therapy.

1. Introduction

Primary brain tumours originate from different type of cells of the central nervous system, such as meningeal cells, neurons or glia. The incidence of these lesions in the adult population has increased in the past fifty years and it is estimated to be 27.4 per 100.000 persons in the United States [1]. Glioma accounts for 45% of all primary brain tumours and approximately 50% of them are highly malignant glioblastomas (WHO grade IV) [2]. Despite most recent advances in neuro-oncology glioblastomas still have a very poor prognosis with a median survival time of 14.2 months after diagnosis [3].

Neuroimaging techniques have improved in the recent years, but it is still difficult to differentiate between histologic tumour grades, which would be extremely important in order to offer the patient the best available treatment with less mortality and morbidity. In the past decade positron emission tomography (PET) with different radiotracers has been used as a complementary diagnostic tool in oncology, especially for evaluating cancer staging. PET is a unique tool that provides metabolic information of brain tumours and it is highly sensitive for diagnosis of malignant primary tumours and metastases.

[^{18}F] fluorodeoxyglucose (FDG) and [^{11}C] methionine (MET) are the most common tracers used in neuro-oncology. [^{18}F]FDG has been proved to be very useful in brain tumour grading [4]. It is

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the most widely used tracer because of the radioisotope's long half life (110 min) that allows transportation to remote hospitals away from the cyclotron where it is synthesized. In contrast, the use of [^{11}C]MET is limited to centres that have their own cyclotron because of the radioisotope's short half life (20 min) [2,5].

MET is an essential amino acid tracer with very low accumulation in the normal brain, which makes it highly sensitive for brain tumour detection [5]. MET has been used for follow up in low-grade gliomas and for differentiating recurrent brain tumour from radionecrosis [6,7]. It has also been found to be useful in selecting the target for optimal brain biopsy, defining the extent of surgical resection [8] and to determine radiation therapy target volume [9,10].

Lately, there is an ongoing controversy in the literature about the efficiency of both [^{11}C]MET-PET and [^{18}F]FDG-PET in differentiating histologic tumour grades. The main goal of our study was to evaluate the relationship between MET uptake and the histopathological grade in both primary brain tumours and brain metastases. A secondary goal was to asses the relationship between MET uptake and patients' survival after surgery.

2. Material and methods

The study design was a retrospective review of a prospectively collected database. It was conducted in compliance with medical ethical guidelines and forcible patient privacy regulations.

2.1. Patients

We examined the metabolic activity of brain lesions in 43 patients who were referred to our PET centre between January 2010 and March 2014 due to a newly diagnosed lesion (8 patients) or due to a suspected brain tumour progression or recurrence after therapy (35 patients).

Magnetic resonance imaging (MRI) was performed in all patients on a 3 T Trio Tim Syngo MR B15 (Siemens, Erlangen, Germany) using our routine clinical protocol. All MRI included at least T1, T2, fluid-attenuated inversion recovery (FLAIR)-weighted images, diffusion-weighted images, perfusion-weighted images and postcontrast T1-weighted sequences. We registered tumour contrast enhancement, which was classified as a dichotomous variable (none or contrast enhancement). All perfusion studies from each patient and maps of cerebral blood volume (CBV) and flow (CBF) were analyzed. The patients were categorized as having normal CBV or high CBV in the brain tumour.

An experienced neuropathologist classified each tumour as primary brain tumour or metastases. In the glioma group, every tumour was graded according to the WHO classification in four grades (I–IV) [5,11].

The mitotic activity of the tumours was evaluated by the Ki-67 proliferation index obtained by immunohistochemical staining with anti-Ki-67/MIB-1 (Monoclonal Mouse Anti-Human ki-67 Antigen Clon MIB-1 Ready-to-use, Dako). The Ki-67 index was quantified visually in all cases at high power magnification (40×). The results were expressed as the percentage of Ki67 positive cells measured in the area containing the largest number of positive tumour cells.

2.2. [^{11}C] MET-PET acquisition

All patients underwent a [^{11}C] methionine-PET after fasting during 4 h and after receiving adequate hydration for rapid tracer excretion. [^{11}C] methionine, 296 ± 30 MBq was injected intravenously and the images were acquired 20 min postinjection. The patient was positioned supine and the head was immobilized in a head rest. The images were acquired on a Gemini GXL PET/CT scanner. After an initial scout of the head for localizer positioning, the low-dose CT (120 kV/110 mA) for attenuation correction was performed. Single-bed emission scan was then obtained in 3D mode.

2.3. Data analysis

Image analysis was performed using the PMOD software (PMOD Technologies Ltd, Zurich, Switzerland) running on a workstation. For the semiquantitative analysis, the tumour/cortex ratio (T/C) was computed by using a target to background technique [12,13]. The tumour target was defined with a volume of interest (VOI). First a VOI was set manually by using a sphere containing the brain tumour. Then the system established automatically the target by using a region growing algorithm which selects these voxels above a preselected threshold (TVOI). The maximum uptake and volume of the tumour was computed for each TVOI and expressed in cubic centimetres (Fig. 3).

The background was measured by a volume of interest (VOI) containing the non specific uptake. This was drawn manually selecting a 10 mm diameter circle on the contralateral cortex (CVOI) at the same level than the maximum tumour uptake. Mean uptake was computed for each CVOI. The T/C ratio was calculated by dividing the maximum tumour tracer uptake (TVOI) by the mean value of tracer uptake of the contralateral normal cortex.

2.4. Statistical analysis

All interval, non-normally distributed continuous variables were summarized as the median and the minimum and maximum. For normally distributed data the mean and standard deviation (SD) were used. The paired samples *t*-test for continuous variables was used to investigate a possible relation between T/C ratio, contrast enhancement and perfusion parameters in MRI. Non-parametric correlation (Spearman Rho) was used for determining the relationship between the MET uptake and proliferation activity (Ki67). Analysis of variance (ANOVA) and post hoc comparisons with Bonferroni correction were used to compare histopathological tumour grade and T/C ratio. Survival intervals were defined as the time from PET until death or until the date of the last clinic visit. Survival curves were calculated using the Kaplan–Meier technique. A proportional hazard regression model (Cox model) was used to investigate the predictive value of MET uptake on survival.

Statistical analyses were performed using SPSS software (IBM SPSS Statistics v20.0.0). *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Patients characteristics

We included a total of 43 PET studies, in 35 patients with primary brain tumours and 8 patients with brain metastases. There were 19 females and 24 males and the mean age of the patients was 47 years (±15 years, min: 16, max: 74). According to the WHO classification the primary brain tumours were divided into grade I (3 patients), grade II (12 patients), grade III (7 patients) and grade IV (13 patients) (Table 1). The results of the neuropathological exam are summarized in Table 1.

A total of 8 lesions from 43 patients were newly diagnosed brain lesions (4 low grade gliomas, 2 glioblastomas and 2 metastases) and therefore the PET scans were performed before treatment. In the remaining 35 patients the PET studies were done to exclude tumour progression or recurrence. Follow up was conducted until the last clinical visit [*n* = 19, median 18 months (min: 2, max: 42) after PET]