Substitution of 11C-methionine PET by perfusion MRI during the follow-up of treated high-grade gliomas: Preliminary results in clinical practice

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KEYWORDS
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Methionine;
PET;
Glioma

Summary
Purpose. — Our aim was to compare perfusion magnetic resonance imaging (MRI) and positron emission tomography (PET) using carbon-11 labelled methionine (MET) in gliomas and their value in differentiating tumour recurrence from necrosis.
Materials and methods. — We retrospectively reviewed 28 patients with a high-grade glioma. A total of 33 MR perfusions and MET-PET were ultimately analysable for comparison between the relative cerebral blood volume (rCBV) and MET-PET examinations. Intra- and interobserver reproducibility was assessed and diagnostic value of rCBV compared to MET-PET and histology was assessed by the area under the receiver operating characteristic (ROC) curve.
Results. — ROC curve analysis showed that rCBV had at least equal performances in differentiating tumour recurrence and necrosis than MET-PET. Cut-off value of rCBV for differentiating tumour from necrosis was 182% with a sensitivity of 81.5% and a specificity of 100%.
Conclusion. — In clinical practice, perfusion MRI could replace MET-PET for differentiating necrosis from tumour recurrence.

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Introduction
Magnetic resonance imaging (MRI) is nowadays the technique of choice for accurate brain tumour work-up. It...
is the key modality for characterizing lesion topography and morphology, evaluation of the tumoral extension and plays an important role in the follow-up during treatment. For additional physiological information, morphological MRI can be assisted by complementary MR techniques such as spectroscopy, diffusion weighted imaging and perfusion weighted imaging (PWI); those so called “functional imaging” techniques are a growing necessary step in tumoral work-up [1].

PWI can be used to study the tumour vasculature [2,3] and pinpoint subsection of a given brain tumour where vascularity and endothelial permeability are more altered [4,5], being thus a useful tool for tumour characterization and treatment planning [6]; moreover, there is an increasing interest in the use of PWI as an indicator of the tumoral response to therapy [7,8].

Lately, new treatment protocols, combining fractionated radiotherapy and temozolomide, have increased life expectancy to a survival rate of 26.5% at 2 years [9] against 10% at 6 months when conventional radiotherapy is used alone [10]. As a result, the prevalence and extent of posttreatment necrosis has increased [9,11-13] making it difficult to determine if an enhancing posttreatment lesion should be considered as a local tumoral recurrence or necrosis: indeed they share the same MRI signs such as enhancement, mass effect and vasogenic oedema [2,4,14,15]. This MRI lack of specificity has prompted the development of other techniques such as carbon-11 labelled methionine (MET) positron emission tomography (PET), which is an indirect method for highlighting tumour proliferation and micro vessel density [16,17]. It enables a better tissue characterization and is suited for differentiating residual tumour from necrosis with a specificity and sensibility of 61 and 100%, respectively [9,17,18].

Nowadays, in such situation and in clinical practice, the MET-PET, with its low specificity, is nevertheless the reference examination when one must plan the future therapeutic scheme of a given patient where the differential diagnosis between recurrence and necrosis must be made [19]. The present study was thus undertaken to examine whether PWI could replace MET-PET in such clinical situation.

First pass PWI, has the big advantage of being performed during the “anatomical” conventional MRI, reducing therefore the number of imaging sessions and the global cost, a non-negligible advantage for the patient and nowadays health policy [11,18].

Patients and methods

Patients

Twenty-eight patients (16 males and 12 females), with a mean age of 51-years-old (ranging from 25 to 74-years-old) and with a histological proven intraaxial primitive brain tumour were included in this retrospective study.

The study was carried out in compliance with our institutional ethic committee (CE Accred. No. 2008/29/246).

All tumours were high-grade gliomas and precise diagnostic was obtained by surgery or stereotactic biopsy: according to the World Health Organization (WHO) histologic classification, 23 patients had astrocytic tumours with grades III (n = 9) and IV (n = 14) and the five remaining tumours were grade III oligoastrocytomas.

Of the 28 patients, 18 underwent a combined radiotherapy-chemotherapy treatment consisting of fractioned whole brain radiotherapy (total radiation dose of 60 Gy) associated to temozolomide (Temodal®, Schering-Plough, Kenilworth, N.J., USA). After a rest period of 2 months, three supplementary courses of temozolomide were administered to the patient, repeated every 28 days. In the ten remaining patients, eight underwent external radiotherapy and two received chemotherapy alone.

Of the 28 patients, 23 patients underwent surgery: 14 partial and nine total resections were obtained. In the case of surgery, 12 patients received radiochemotherapy as a complementary treatment. Table 1 summarizes those observations.

The mean follow-up period was of 13 months ranging from 3 to 40 months.

MR-imaging

All MR examinations were performed on a 1.5 Tesla system (Intera®, Philips Healthcare, Best, the Netherlands) with a standard head coil. For each patient a standardized MR protocol was used consisting of and in the following order:

- T1-weighted “scout” views in the three orthogonal planes;
- diffusion weighted (DW) spin echo—echo-planar imaging in the axial plane with the following parameters: 24 slices, 5 mm slice thickness, 1 mm intersection gap, FOV = 240 × 240 mm, matrix of 128 × 256, TR/TE = 3312 ms/93 ms, acquisition time = 32 s, NSA = 2; the images were acquired using b-values of 0 and 1000 mm²/s. Diffusion gradients were applied in three orthogonal directions and isotropic voxels were obtained as an average of the signal intensities of the three gradients direction. An ADC map was calculated automatically by a dedicated software;
- Fluid Attenuated Inversion Recovery (FLAIR) sequence in the axial plane with the following parameters: 24 slices, 5 mm slice thickness, 1 mm intersection gap, TR/TE/TI = 10000 ms/120 ms/2100 ms, FOV = 240 × 240 mm;
- T1-weighted turbo spin echo (TSE) sequence (24 slices, 5 mm slice thickness, 1 mm intersection gap, matrix of 352 × 512, TR/TE = 530 ms/12 ms, FOV = 240 × 240 mm); Just after, a first bolus of gadolinium chelate (Dotarem, Guerbet Obex, Auckland, New Zealand) at a concentration of 0.5 mmol/kg was injected i.v. to minimize the effect of T1 shortening and the effects of brain blood barrier breakdown.
- T2 weighted TSE sequence (TR/TE: 4390 ms/90 ms, 24 slices, thickness 5 mm, gap of 1 mm, 512 × 512 matrix);
- this sequence is followed by a second bolus injection of gadolinium chelate at a concentration of 0.1 mmol/kg at rate of 10 ml/sec followed by a 30 ml saline flush for the acquisition of the perfusion sequence T2*-weighted dynamic susceptibility contrast (DSC) with the following
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<th>Final diagnostic standard</th>
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<td>+</td>
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<td>resection</td>
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GBM: glioblastoma; AA: anaplastic astrocytoma; AOA: anaplastic oligoastrocytoma; T1 wC+: enhancing evolution in postgadolinium T1 weighted sequence; FLAIR: evolution hypersignal in FLAIR weighted sequence; rCBVmax: maximal relative cerebral blood volume; PET: positron emission tomography; NA: not available.
parameters: TR/TE: 1500 ms/35 ms, 24 slices, thickness 5 mm, gap 1 mm, 128 × 128 matrix;
- lastly, a postgadolinium T1 weighted 3D sequence (TR/TE: 30 ms/3 ms, 130 slices, thickness 1.2 mm, 256 × 256 matrix).

During follow-up period, postgadolinium T1 weighted and FLAIR sequences were analysed searching for, respectively, any enhancing image or hyperintense lesion in order to be measured and compared to earlier and later examinations. If abnormal tissue was suspected, it was correlated to the perfusion maps after coregistration.

Methionine PET protocol

In this series of patients, 33 PWI were performed with a MET-PET with a mean interval between examinations of 12 days (ranging from 3 to 25 days). In all patients, the same MET-PET protocol was used in the positron emission tomography laboratory in Louvain-la-Neuve, Belgium. Following placement of an i.v. line and blindfolding the eyes in order to minimise activation of the cerebral cortex (visual cortex), 20 mCi (740 MBq) of MET was injected. Fifteen minutes later, the patients were positioned on the PET camera (HR 961, CTI-Siemens, Knoxville, TN, USA). A 20 minutes emission scan was performed, followed by 5 minutes transmission scan in order to correct for any attenuation. The data were then reconstructed using filtered retroprojection, after correction for diffusion and attenuation. For the interpretation, the reconstructed images were coregistered on the MR/T1 3D images. The results of the MET-PET used in this study are the clinical protocols for the nuclear physicians.

Histological analysis

Sixteen MR perfusions were correlated with pathological analysis. The mean interval time between the first pass perfusion and the pathological sampling was of 22 days.

Seven MET-PET were studied and compared to pathological sampling with a mean delay of 26 days. Cerebral biopsies were obtained in order to plan the best therapeutic scheme.

Postprocessing

After MR acquisition, PWI and anatomical (postcontrast T1 weighted and FLAIR) images were sent to a workstation (Sun Advantage Windows 2.0®) using a dedicated software for combined coregistration and perfusion maps analysis (FuncTool® software, GE Healthcare, Chalfont Saint-Giles, United Kingdom). This program studies the enhancement of a given region, which is a measure of the degree of the blood brain barrier (BBB) breakdown. From those data, perfusion parameters are obtained by postprocessing the time-signal intensity curves. Parametric images are then obtained that enables a relative and comparative study of cerebral blood volumes (CBV).

Practically, a region of interest (ROI) is defined in a grey matter vascularized region (in our study, the putamen was chosen without including the globus pallidus, a known source of artefact). From the obtained perfusion curve, two points are then highlighted: when the contrast bolus is detected and when it disappears, excluding thus the recirculation phenomenon. The software can then provide a comparative colorimetric map of the rCBV. Highly vascularized region such as vessels can then be depicted and excluded from the analysis.

In parallel, the native perfusion curve is displayed and enables a clear depiction of the contrast arrival dynamics. At the time to peak, comparative loss of signal between healthy grey and white matter regions as well as vascularized and pathological regions are then obtained.

For further analysis, a ROI (sized 4 to 6 pixels) is placed in an area displaying both a hot colour on the CBV colorimetric map and high signal intensity on postgadolinium T1 weighted images. Because of some image distortion, inherent to gradient echo EPI technique, coregistration between anatomical T1 weighted and perfusion images can be somewhat imprecise: therefore, in a second time, the ROI is correctly replaced, helped by the perfusion parametric maps. Then, a ROI of the same size is positioned in the contralateral normal appearing white matter, confirmed by FLAIR sequences. The CBV, expressed as a percentage, is then calculated by dividing the CBV measured in the pathological area by the one obtained in the contralateral normal appearing white matter.

Intra- and interobserver reproducibility

In seven patients, the rCBV was measured twice (i.e. 14 measurements) in order to study the intraobserver reproducibility. The interobserver reproducibility was studied in the same way using the measurements of 14 rCBV by three different radiologists.

Statistical analysis

The possible existence of a systematic bias, the correlation between the measurements and their concordance was studied using the Student test, the Pearson correlation coefficient and the limits of agreement of Bland-Altman, respectively. The diagnostic value of rCBV compared to the MET-PET and histology was assessed by the area under the receiver operating characteristic (ROC) curve. Values are expressed as the mean ± SD. All tests are two-tailed. A p value less than 0.05 was considered as significant. The statistical analysis was performed by the software SPSS (SPSS INC., Chicago, IL) and MedCalc (Mariakerke, Belgique).

Results

Number of perfusion included into analysis

Out of the 28 patients, a total a 47 PWI were obtained and analysable. Of those 47 PWI, 14 examinations had to be excluded because not performed with a MET-PET. Finally, 33 combined MR and PET examinations were included for further analysis.
MR and PET combined examination analysis

Of the 33 combined MR and PET studies, 31 matched perfectly: 25 studies were positive in both modalities and six were negative. No false positive (type I error) was observed. Nevertheless, two negative MR perfusion corresponded to two positive MET-PET, resulting in two false negative examinations (type II error).

For these 33 perfusions performed with a MET-PET, a mean value of $489\% \pm 426$ for rCBV is obtained for a positive MET-PET ($n=27$) and a mean value of $125\% \pm 43$ for rCBV for a negative MET-PET ($n=6$) ($p<0.001$). The surface under the ROC curve is $0.944 \pm 0.034$ with a sensitivity of 81.5% and a specificity of 100% for an optimal cut-off of 182% (Fig. 1).

MR and histology data analysis

In the sample of 16 PWI for which a pathological sampling was obtained, a match was obtained in 14 cases (12 true positives and two true negatives). No false negatives were observed. Therefore, the proportion of patients with a negative MR perfusion who were correctly diagnosed (i.e. nontumoral histology) was 1. There were two cases of false positives and, therefore, a positive predictive value of 0.85 (12/[12 + 2]).

For those 16 PWI, a mean value of rCBV of $684\% \pm 458$ is observed for a positive histology ($n=12$) and a mean value of rCBV of $258\% \pm 107$ is obtained for a negative histology ($n=4$) ($p=0.010$). The surface under the ROC curve is $0.833 \pm 0.107$ with a sensitivity of 67% and a specificity of 100% for an optimal cut-off of 378% (Fig. 2).

Combined MR, PET and histology data analysis

Lastly, there are seven cases of PWI carried out with a MET-PET and a histological sampling ($n=7$), all of them showing concordant results.

Intra- and interobserver reproducibility

The intraobserver reproducibility revealed no systematic bias and a significant correlation was found for the series of measures ($r=0.888$; $p=0.008$). The Bland-Altman limits of agreement for the concordance are between $-356$ and $+328$.

The interobserver reproducibility also revealed no systematic bias and a significant correlation was also found for the series of absolute measures ($0.575 \leq r \leq 0.875$ according to the 2 to 2 comparisons; $p \leq 0.032$). If the evolution of the measures of rCBV in the course of time is taken into account, the observed interobserver correlation of the differences is also satisfactory ($0.766 \leq r \leq 0.904$; $p \leq 0.076$; $n=6$).

Discussion

In clinical neuro-oncologic imaging, conventional MRI is the cornerstone technique for the follow-up of treated high-grade glioma. The main goal of repeated MR acquisition is to detect, precociously, new abnormal modification in the vicinity of the treated tumour site. Most of high-grade tumoral lesions are characterized by a proliferation of immature blood vessels with breakages in the BBB [4,5,14,20] whereas radiotherapy induces an acute transient vasodilatation and increased vascular permeability (Fig. 4) resulting in both situation in an enhancing lesion surrounded by variable quantity of oedema [11,13,14,18].

It is important to note that this enhancement is related to the rupture of the BBB with no relation nor quantitative information about the underlying vascularization [2,4,7,15,20] because it is observed invariably when the endothelial cells are damaged by chemo- and/or radiotherapy [3,11,13,18,21]. Therefore, the main differential diagnosis of those de novo contrast-enhancing lesions are tumour recurrence and posttreatment brain injury. It is hazardous to make a clear distinction between those two
entities with morphological MRI [2,22] because of the low MR specificity in such situation [9]. They share, indeed, the same MR signs: enhancement in the tumour resection site, mass effect, vasogenic oedema [2,4,14,15] and T2/FLAIR hyperintensities (Fig. 5) [13]. Moreover, posttreatment brain injury and tumour recurrence usually appear during the same time frame, especially with the introduction of new combined chemo- and radiotherapy [23,24]. Therefore, in order to optimize patient care and thus to avoid unnecessary further work-up and treatment (chemotherapy or radiotherapy), a precise diagnosis is mandatory [11,15].

To overcome MR low specificity and to increase clinicians ability to differentiate residual tumour from brain tissue necrosis, other imaging modalities can be used. MET-PET is one of them and has featured, respectively, a sensitivity and specificity of 100 and 61%, for differentiating both entities [9,17,18]. Indeed, MET cellular uptake has been closely related to cellular proliferation and microvessel density and thus it can be employed to assess tumour grade [17].

PWI is another imaging modality used to estimate rCBV and thus reflects the vascularity and angiogenesis of the studied brain tumour. Sadeghi et al. have shown the existence of a positive correlation (r = 0.65 and p < 0.001) between CBV ratio and MET uptake ratios in a glial tumour group [17], suggesting that the degree of vascularization is a major factor in the transfer of MET within gliomas. Although MET-PET is a promising and accurate imaging technique, it does have some limitations that narrow its field of action. The main ones are the limited number of available equipment, the high cost, its low spatial resolution [13] and its non-negligible false positive rate such as haematomas, inflammatory processes and necrosis [12,18]. As a result, in routine clinical practice, PWI has clear advantages compared to MET-PET. Relative CBV has been described as a good indicator for assessing tumoral microvascularization and angiogenesis [2,3]. Briefly, the reduction of the observed signal in an elementary volume depends not only on the blood vessel tracer concentration and diameter but also on the number of vessels per volume unit (vascular density); the summation gives a quantification of tumoral angiogenesis [7,20].
In clinical practice, because of those limitations and as a result of our study, there are some arguments for substitution of MET-PET by perfusion MRI. Indeed, in the 33 PWI performed with the MET-PET, our study showed a perfect correlation in 31 cases (25 true positives and six true negatives). No false positives were observed, indicating an optimal positive predictive value of the PWI. Nevertheless, two discordant cases were found with low rCBV (171 and 191%) associated to a positive MET-PET. These two PWI were carried out in the same patient, with a MET-PET but without any pathological examination. Since stereotactic biopsy had been performed in this patient just before MRI and PET studies, and since he did not die of his disease after 2 years, a probable false positive result of the MET-PET, due to an inflammatory reaction secondary to the stereotactic biopsy, could be proposed. The diagnostic performance of PWI was thus at least equal or even better than the MET-PET, in our patient cohort.

Several studies have demonstrated a statistically significant correlation between tumor rCBV and glioma staging [2,4,15,17]. Regions with a high endothelial permeability (reflecting the degree of enhancement following administration of a gadolinium chelate) and high rCBV values (relative density of blood vessels) probably represent regions with high degree of angiogenesis and thus with a higher tumour grade [4]. Conversely, a low rCBV within necrosis is probably the result of occlusion of blood vessels leading to coagulation necrosis and necrotic leucoencephalopathy, a process similar to ischemia caused by endothelial damages [11,25,26].

On a PWI standpoint, there is no clear cut-off value for differentiating tumour from necrotic tissue. Sugahara et al. found that any lesion with a normalized rCBV above 260% represented, in all cases, recurrent tumour and when it was less than 60%, only non-neoplastic contrast – enhancing tissue was found [14]. Our results showed a cut-off rCBV value of 182% with a sensitivity and specificity of 81.5 and 100%, respectively. Those results are close to the values proposed by Jain et al. where their cut-off value was set at 165% for a sensitivity and specificity of 83 and 100%, respectively [11].

Several reasons have been advanced to explain this overlapping between tumour and nontumoral necrotic tissue rCBV value. In a glioma treated by external radiotherapy, hypoperfused necrotic tissue may coexist with areas of vascularized recurrent tumour resulting in a increase in the rCBV [2,11,14]; moreover, after irradiation, occluded vessels are found within the treated area but modifications in their morphology have also been described such as aneurysms, telangiectasia, vascular elongation and proliferation of the endothelial lining [11,14] resulting also in an increase of the rCBV [11]. On the other hand, a decrease in the rCBV may been seen in recurrent tumoral tissue: first, when petechial haemorrhages induced by irradiation may produce susceptibility artefacts and thus reduce the rCBV [14] or, secondly, when increased vascular permeability provoke interstitial oedema, compression of small blood vessels, hypoperfusion and thus lowering of rCBV [11].

In our study, when analyzing the 16 perfusions performed with a pathological sampling (by stereotactic biopsy or surgery), we reported two false positive cases (high rCBV with a negative pathological analysis) supporting the fact that high rCBV does not always indicate tumour activity but may also represent phenomena of posttherapeutic vascular hyperplasia and change in the vessels morphology.

There are some limitations to our study. First, the use of MRI to evaluate tumour perfusion; the value of CBV is affected by the arterial input function and the type of sequence which variation are lessened by the concept of relative value measured with respect to a normal reference zone [20]. Rupture of the blood brain barrier can modify the first pass curve and result in underestimation of the area under the curve. An initial injection of a half dose of gadolinium chelate prior to perfusion sequence may reduce this artefact [20].

Secondly, with identical acquisition parameters, variations of 20 to 30% within observers and between observers are found in the literature. These variations are especially important when the lesions are heterogeneous and angiogenic [20]. In our study, the interobserver variations indicated good correlation for rCBV variation in time (for the same patient) but a poor concordance for absolute rCBV values probably due to inadequate measurements for the reference ROI because of a zone of artefacts or the promiscuity of a blood vessel.

Thirdly, the perfusion images in computerized tomography (perfusion CT) could have given better performances than those of the MRI [27] because of the linear relationship between the attenuation of X-ray beam and the concentration of the contrast medium. This is not the case for MRI where the relationship is logarithmic [7,11,21]. Also contrary to MRI, the measurements are not affected by haemorrhages, calcifications or surgical materials [18]. The MRI is, however, able to cover a larger volume [21] and particularly to obtain a morphological and functional image in one examination.

In conclusion, PWI is a promising technique as a follow-up technique and especially in differentiating necrosis from tumour extension or recurrence compared to MET-PET. Moreover, in a single examination, functional and anatomical information can be gathered with clear economical issues. In clinical routine, it could therefore limit unnecessary invasive or non-invasive treatment when necrosis is suspected. Caution should be brought to high rCBV as it does not always indicate a tumour recurrence but can also represent phenomena of post-therapeutic vascular hyperplasia. More studies are needed to validate the technique and for its use in routine follow-up of treated high-grade glioma.

Conflicts of interests
None.

References


