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ORIGINAL ARTICLE

# Dynamic contrast-enhanced T2\*-weighted MR imaging: A peritumoral brain oedema study

## Étude de l'œdème cérébral péritumoral par IRM en contraste dynamique T2\*

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### KEYWORDS

Glioblastoma;  
Meningioma;  
Edema;  
Angiogenesis;  
MRI;  
Perfusion

### Summary

**Background and Purpose.**—Glioma and meningioma are the two most common types of primary brain tumor. The aim of the present study was to analyze, using dynamic susceptibility contrast MR perfusion imaging, the effect of angiogenesis on peritumoral tissue.

**Methods.**—In this prospective study, conducted from December 2003 to March 2005, out of 18 patients recruited, 12 were included (six with meningioma, six with glioblastoma). Using rates of maximum signal drop (MSD), we drew regions of interest (ROI) starting near the lesion, and gradually moving outwards to areas of distant edema in axial and sagittal planes at 10, 20 and 30 mm from the tumor. We also drew ROI on the contralateral brain white matter to obtain a normal baseline for comparison (relative MSD; rMSD).

**Results.**—In regions of peritumoral T2 hypersignals, we observed a decrease in rMSD with distance from glioblastoma due to reduced angiogenesis, and an increase in rMSD with distance from meningioma, probably due to a reduced mass effect.

**Conclusion.**—In our study, dynamic susceptibility contrast MR perfusion imaging, using MSD as a parameter, revealed differences between meningioma and glioblastoma peritumoral tissue due to changes in angiogenesis.

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**MOTS CLÉS**

Glioblastome ;  
Méningiome ;  
Œdème ;  
Angiogenèse ;  
IRM ;  
Perfusion

**Résumé**

*Objectif.* – Les gliomes et les méningiomes sont les deux principaux types de tumeurs cérébrales. Le but de cette étude était d'analyser en IRM de perfusion par susceptibilité magnétique avec injection de contraste, l'influence de l'angiogenèse sur le tissu péri-tumoral.

*Méthode.* – Une étude prospective menée de décembre 2003 à mars 2005 nous a permis de recruter 18 patients. Douze ont été inclus (6 méningiomes, six glioblastomes). Nous avons mesuré la chute maximale de signal (MSD) en dessinant des régions d'intérêt dans l'œdème proche, puis à distance de la lésion, à 10, 20 et 30 mm dans le plan axial et sagittal. Nous avons également placé une région d'intérêt dans la substance blanche controlatérale pour normaliser nos mesures (rMSD).

*Résultats.* – Nous avons observé une diminution de la valeur rMSD avec la distance dans les glioblastomes en rapport avec la diminution de l'angiogenèse et une augmentation de la valeur rMSD avec la distance dans les méningiomes, probablement liée à la diminution de l'effet de masse.

*Conclusion.* – Dans notre étude, l'analyse de l'œdème périlésionnel en IRM de perfusion par susceptibilité magnétique avec injection de contraste, avec le paramètre de chute de signal (MSD), a montré une différence entre les méningiomes et les glioblastomes en rapport avec l'angiogenèse.

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**Introduction**

Neoplasms require a rich vascular network to supply the blood necessary for proliferation. Glioma and meningioma are the two most common types of primary brain tumor. They present very different vascular properties [1]. Meningiomas are the most common extra-axial brain tumors, with a vascular supply that is usually derived from dural vessels [2]. Gliomas, the most common intra-axial primary brain tumor, have variable degrees of neovascularity and blood–brain barrier (BBB) alterations, depending on the grade and histological subtype. Approaching the pathophysiology of peritumoral edema through perfusion imaging with the use of maximum signal drop (MSD) rates as a parameter, we speculated that vascularization within peritumoral edema would be raised in glioblastoma and that the vascular contribution, as revealed by the MSD, would be higher in glioblastoma than its potential mass effect. Although meningioma and glioblastoma both have mass effects, glioblastoma presents with higher rates of angiogenesis. For this reason and because the mass effect may be a confounding co-variable, we chose meningioma as our model of mass effect. The objective of our study was to assess the angiogenesis, using dynamic susceptibility contrast magnetic resonance (MR) perfusion imaging, in the peritumoral tissue, often seen with meningioma and glioblastoma.

**Materials and Methods****Patients**

This prospective study was conducted from December 2003 to March 2005, and was approved by the local ethics committee. Patients were informed of their participation in the study, but their signed consent was not necessary as the imaging protocol was already in place for tumor imaging at our institution. Only patients with meningioma or

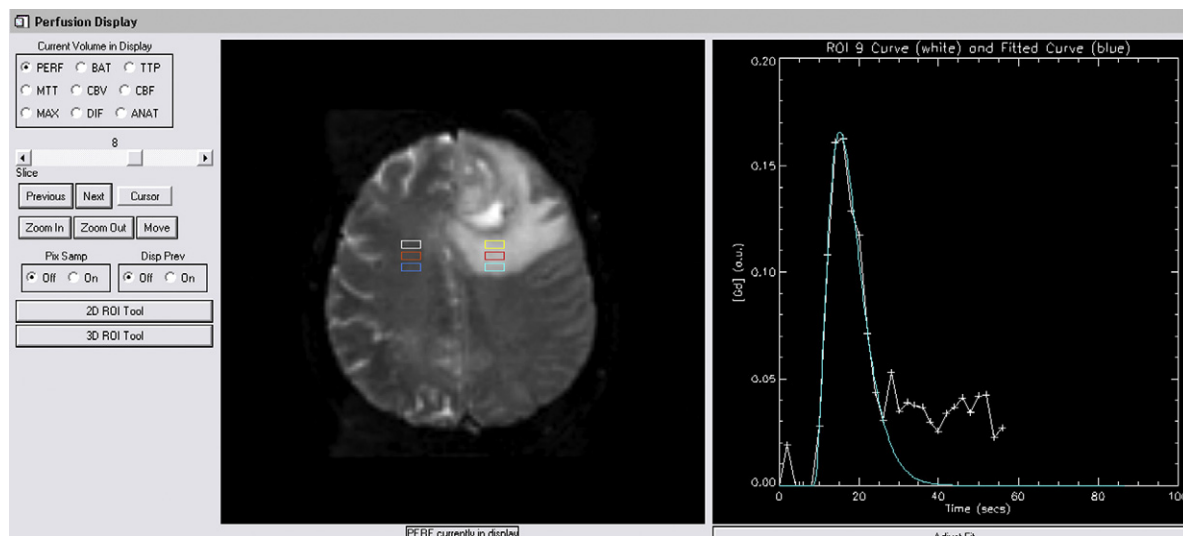
glioblastoma were recruited, and these two tumor types were selected because of their different vascular properties [1]. Also, only patients with more than 30 mm of peritumoral edema were included. All lesions were histologically confirmed. Of 18 patients recruited, six were dropped from the study: three because of considerable head movement; two because of minimal spread of edema (< 30 mm); and one because of very poor-quality images (geometric distortions). Of the 12 included patients (gender ratio M/F: 0.33; mean age: 59.5 years [min: 50, max: 75 years]), six presented with glioblastoma and six with meningioma.

**MRI data acquisition**

All patients were examined with a 1.5-T clinical MR imaging (MRI) unit (Signa 9, gradient strength 23 mT/m; General Electric Medical Systems, Milwaukee, WI), using the standard head coil, and all underwent the following imaging protocol: axial fast spin-echo (SE) T2-weighted; axial SE T1-weighted; axial FLAIR with automatic injection of gadolinium bolus (0.2 mmol/kg); axial echo-planar perfusion [3] (echo time: 60 mins; repetition time: 2300 mins; matrix: 128 × 96; field of view: 24 × 24 cm<sup>2</sup>; slice thickness: 5 mm; intersection gap: 1 mm; NEX: 1; 12-slice; 30-scan); and axial SE T1-weighted post-gadolinium.

**Perfusion parameter**

To avoid the effects of arterial input function, we used the MSD rate, which corresponds to the decrease in signal intensity induced by a susceptibility magnetic effect when the contrast agent bolus passes through the capillary vessels. The MSD parameter is an useful indicator of the status of brain microcirculation, as it is sensitive to weak signal–noise ratios and faithfully reflects the cerebral blood volume of the brain [4]. This allows the use of this parameter to explore alterations in blood volume related to



**Figure 1** PERFTOOL software. To obtain a perfusion curve, we drew 3 ROI near the lesion and gradually extended outwards to distant edema in a sagittal plane at 10, 20 and 30 mm from the tumor. We also drew ROI on contralateral brain white matter to obtain a normal baseline for our measures.

*Interface du logiciel «Perftool». Exemple de courbe de perfusion tissulaire obtenue pour une des régions d'intérêt (ROI). Ces ROIs 3D sont dessinées dans l'œdème péritumoral (l'hémisphère droit) et dans la partie saine controlatérale (l'hémisphère gauche).*

either a mass effect (meningioma) or angiogenesis extending into the parenchyma (glioblastoma). All signal intensities within the areas of peritumoral brain edema were measured. The MSD rates were then compared with those of the contralateral normal white matter (relative MSD, rMSD) in all patients. FLAIR sequencing was used to ensure that all measures were taken in the surrounding edema present with all tumors.

### Signal analysis

Image processing was performed using PERFTOOL software. The algorithm is based on the intravascular indicator dilution theory [5]. Instead of deconvolving the signal, we determined the maximum signal decrease from an average baseline of six scans. Using FLAIR images to delineate peritumoral hypersignals, and T1-weighted post-gadolinium images to delineate the edges of the tumor, we drew several rectangular regions of interest (ROI) around each patient's lesion; each ROI contained 20 voxels ( $468 \text{ mm}^3$ ). The ROI extended from close to the lesion, and moved gradually outwards towards areas of distant edema in axial and sagittal planes at intervals of 10, 20 and 30 mm. We also drew ROI on the contralateral brain white matter to determine a normal baseline of comparison for our measures (Fig. 1).

### Statistical analyses

The Mann–Whitney test was used to determine whether or not the calculated MSDs were significantly different between glioblastoma and meningioma in peritumoral tissue. Values were calculated as means and standard deviations, and  $p < 0.05$  was considered significant.

## Results

The mean rMSDs found in the surrounding edema of glioblastoma and meningioma were  $0.58 \pm 0.37$  and  $0.82 \pm 0.43$  respectively, and the difference was significant ( $p < 0.001$ ). The rMSDs in the surrounding edema of glioblastoma were, on average,  $0.76 \pm 0.13$  at 10 mm,  $0.64 \pm 0.21$  at 20 mm and  $0.51 \pm 0.15$  at 30 mm from the tumor. The rMSDs in the surrounding edema of meningioma were, on average,  $0.48 \pm 0.08$  at 10 mm,  $0.69 \pm 0.08$  at 20 mm and  $0.81 \pm 0.08$  at 30 mm from the tumor.

### Glioblastoma

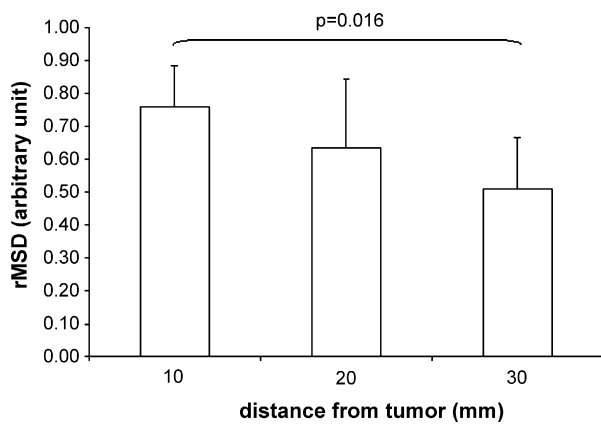
We observed a decrease in rMSD with distance from the tumor. The rMSD parameter was significantly different ( $p = 0.01$ ) between the ROI at 10 mm and 30 mm from the tumor. However, there were no significant differences in rMSD between ROI at 10 mm and 20 mm, and at 20 mm and 30 mm (Fig. 2).

### Meningioma

In contrast, the value of the rMSD increased with distance from the tumor. In addition, the rMSDs were significantly different between ROI at 10 mm and 20 mm ( $p = 0.006$ ), at 20 mm and 30 mm ( $p = 0.025$ ) and at 10 mm and 30 mm ( $p = 0.004$ ) (Fig. 3).

## Discussion

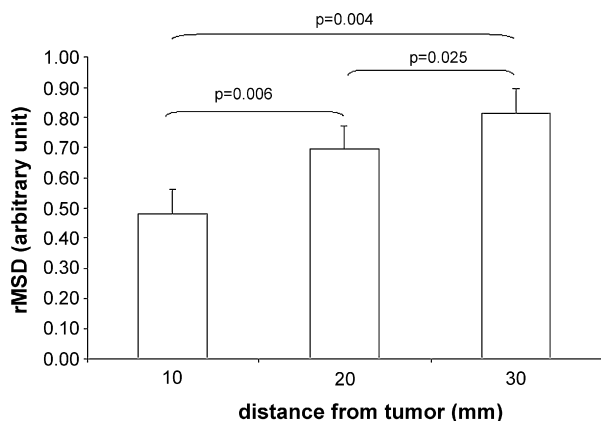
Tumor neoplasms need a rich vascular network to supply the blood necessary for proliferation. Angiogenesis is a complex process regulated by multiple stimulatory and inhibitory



**Figure 2** Histogram showing the decrease in relative maximum signal drop (rMSD) rates in the peritumoral edema of glioblastoma with distance from the lesion.

*Histogramme montrant la diminution de rMSD dans l'œdème péritumoral des glioblastomes avec l'augmentation de la distance.*

factors that are able to modulate the migration and/or proliferation of microvascular cells to form new vascular networks from the preexisting vessels. It involves well-coordinated steps, including: the production and release of angiogenic factors; proteolytic degradation of extracellular matrix components to allow formation of capillary branches; proliferation and directional migration of microvascular cells; and the final appearance of new vessels [6]. Angiogenesis also depends on tumor type: in benign neoplasms such as meningioma, vascular proliferation occurs by recruiting existing capillaries whereas, in high-grade glioma, the existing capillaries are inadequate to maintain a sufficient blood supply and thus, neoangiogenesis is triggered. Although both meningioma and glioblastoma have mass effects, this was not assessed in our present study as it was not deemed relevant. However, as the mass effect can be considered a confounding co-variable, we chose to use meningioma as a model of mass effect.



**Figure 3** Histogram showing the increase in relative maximum signal drop (rMSD) rates in the peritumoral edema of meningioma with distance from the lesion.

*Histogramme montrant l'augmentation du rMSD dans l'œdème péritumoral des méningiomes avec l'augmentation de la distance.*

Regions of the highest MSD are those that histologically show the greatest hypervascularity [3]. However, MSD does not measure vascularity directly—it's a complex function of contrast dose, rate of injection, blood volume, blood flow, cardiac output and MRI parameters. The MSD of the perfusion signal is a clinically useful indicator of brain microcirculation status, and can explore any alterations of cerebral blood volume related to angiogenesis in brain tumors.

Angiogenesis plays an important role in malignant primary tumors [7]. According to the World Health Organization (WHO) classification system [8], glioblastoma grade IV is the higher-grade histotype that includes endothelial hyperplasia, necrosis or both. Glioblastoma, the most malignant type of glioma in adults, is also among the most angiogenic of all human tumors. Moreover, glioblastoma is an infiltrative lesion that, to spread through edema, needs a vascular supply. The reduced rMSD parameter in the peritumoral edema of glioma with distance from the tumor corresponds to angiogenesis that is greatest nearer the tumor and decreases with distance from the tumor. This corresponds to the angiogenesis front. The lack of a statistically significant difference between the ROI at 10 mm and 20 mm, and at 20 mm and 30 mm, is probably related to angiogenesis heterogeneity. Glioblastoma development is not linear, so tumor infiltration and angiogenesis may well vary between two different 'intermediate' (20 mm) ROI.

In contrast, meningioma is an extra-axial benign tumor that is often associated with cerebral edema. Its vascular supply is most commonly derived from dural vessels [2]. Our patients did not have angiograms in their records but, based on surgical findings and the literature [9,10], meningioma with a blood supply of exclusively dural origin are typically free of edema. Our patients presented major edema (> 30 mm), so their vascularization was considered to be both meningeal and pial.

Various hypotheses have been proposed for edema pathogenesis, including: ischemia, mechanically caused by tumor compression [11], which becomes more likely as the size of the tumor increases [12,13]; stasis, induced by tumor in venous drainage areas, followed by venous congestion [14]; excretory–secretory phenomena, in which substances produced by the tumor appear in adjacent brain tissue [15], such as prostaglandins [16], expression of hormone receptors [17] and secretion of vascular endothelial growth factor (VEGF) [18]; and hydrodynamic processes, whereby agents extravasated from the tumor appear in the immediate surrounding brain tissue [19,20]. We assumed there was no angiogenesis in areas of T2-weighted peritumoral hypersignals because the patients presented with no infiltrative or atypical meningioma. The MSD of the perfusion signal reveals alterations in cerebral blood volume. In our opinion, given the lack of angiogenesis in the T2 peritumoral hypersignals, part of the increased rMSD in the peritumoral edema of meningioma with distance from the tumor suggests compression phenomena. Normal vessels are compressed by the mass effect, which is greater nearer to the lesion. This mass effect probably depends on several associated mechanisms, such as tumor compression, excretory–secretory phenomena or hydrodynamic processes, which probably lead to vasogenic edema.

## Conclusion

Dynamic susceptibility contrast MR perfusion imaging, using the MSD as a parameter, demonstrates the difference in peritumoral tissue between meningioma and glioblastoma. According to our results, the differences observed were related to the angiogenesis process. Indeed, in meningioma, we have found peritumoral edema due to a mass effect, and tumor edema due to an infiltrative malignant lesion, mass effect and the development of tumor angiogenesis.

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