# Cerebral Peritumoral Oedema Study: Does a Single Dynamic MR Sequence Assessing Perfusion and Permeability Can Help to Differentiate Glioblastoma from Metastasis?

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A B S T R A C T

Our purpose was to differentiate glioblastoma from metastasis using a single dynamic MR sequence to assess perfusion and permeability parameters. 24 patients with glioblastoma or cerebral metastasis with peritumoral oedema were recruited and explored with a 3 T MR unit. Post processing used DPTools software. Regions of interest were drawn around contrast enhancement to assess relative cerebral blood volume and permeability parameters. Around the contrast enhancement Glioblastoma present high rCBV with modification of the permeability, metastasis present slight modified rCBV without modification of permeability. In conclusion, peritumoral T2 hypersignal exploration associating morphological MR and functional MR parameters can help to differentiate cerebral metastasis from glioblastoma.

## 1. Introduction

Differentiate single metastatic brain tumour from glioblastoma in a patient with a contrast-enhancing brain mass may be difficult because of their similar morphological aspect on brain imaging [1,2]. It is a challenge because diagnostic and therapeutic decisions depend on tumour type [3,4].

These 2 tumour types present very different vascular properties. Metastasis vessels present the same characteristics as the vessels of the primary lesion without blood brain barrier with capillary fenestration [5]. T2 peritumoral hypersignal non enhanced on T1 reflects vasogenic edema due to increased capillary permeability throughout the tumour vasculature. Glioblastomas, the most malignant gliomas in adults, are among the most angiogenic of all human tumors. Angiogenesis plays an important role in malignant primary tumors [6]. Angiogenesis is a complex process regulated by multiple stimulatory and inhibitory factors that are able to modulate the migration and/or proliferation of microvascular cells with the objective of formation of neovasculature from preexisting vessels. It involves well-coordinated steps including: production and release of angiogenic factors, proteolytic degradation of extracellular matrix components to allow formation of capillary sprout, proliferation and directional migration of microvascular cells, and the final composition of new vessels [7]. According to classification of the World Health Organisation (WHO) [8], the glioblastoma (grade IV) is the histotype of higher grade. It must show endothelial hyperplasia, necrosis, or both.

We tried to approach pathophysiology of peritumoral oedema with perfusion (PWI) and permeability imaging. We speculated that the vascularisation in the peritumoral oedema was raised in glioblastoma (infiltrative lesion) due to angiogenesis; basing on this fact we hypothesized first that perfusion and permeability parameters were much modified on the oedema around glioblastoma than around metastasis. The second hypothesis was these parameters were less modified far from the lesion (glioblastoma or metastasis). These data may reflect a "gradient" of angiogenesis and infiltration and allow a better understanding of the tumor and indirectly a better differentiation. Our goal was to esti-

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mate angiogenesis on peritumoral tissue often present around glioblastoma. We explore simultaneously relative Cerebral Blood Volume (rCBV) and endothelial permeability using a single T2* Echo Gradient echo planar imaging perfusion sequence. Our purpose was to differentiate metastasis from glioblastoma using this sequence.

## 2. Materials and methods

It was a prospective study. The local committee agreed this study, patients were orally informed and consent was obtained, signed consent was not needed because protocol imaging was already accepted for tumoral imaging in our institution. Patients with glioblastoma or cerebral metastasis with peritumoral oedema were recruited. These tumour types were chosen because of their different vascular properties [2]. 24 patients were included (sex ratio M/F: 2; mean age: 64, 8Y, min: 46 max: 83). 13 presented glioblastomas and 11 metastasis (with histological proof, biopsy or tumoral resection). Steroids were not used before imaging.

### 2.1. MR imaging data acquisition

All patients were examined with a 3 T clinical MR imaging unit (HDX, General Electric Medical System, Milwaukee, WI) by using an 8 channels birdcage head coil.

All patients had protocol as followed: Axial Fast SpinEcho (SE) T2, Axial SE T1, Axial FLAIR, during automatic injector bolus gadolinium (volume: 0.1 mmol/kg; injection rate: 10 $cm^3$/s), Axial Echo-Planar Echo Gradient PERFUSION [9]: echo time: 30 ms, repetition time: 1500 ms, matrix: 128 × 128, field of view: 24 × 24 $cm^2$, slice thickness: 5 mm, intersection gap: 1 mm, NEX: 1, 20 slices, 65 scans, Axial SE T1-weighted post gadolinium with fat saturation. Delta R2* (ΔR2*) was assessed from perfusion sequence; ΔR2* was described to reflect contrast leakage [10].

To optimize signal to noise ratio and baseline, we used fat saturation on perfusion sequence.

To determined injection parameter we performed in vitro test to define the good contrast quantity needed. 0.1 ml/kg allow good signal to noise ratio without "aliasing" when calculating ΔR2*. The injection rate was determines basing on our clinical experience.

### 2.2. Signal analysis

Image processing was performed using DPTools (http://www.fmritools.org). No registration was performed. Basing on FLAIR images to delineate peritumoral hypersignal and T1-weighted post gadolinium images to delineate the edges of the tumour, we drew around the tumour in each patient several circular regions of interest (ROI), every ROI contained 172 $mm^2$. We drew 2 ROIs in the T2-hypersignal around the lesion in the first centimeter without including contrast enhancement and 2 ROI in the distant T2-hypersignal (more than 1 cm from contrast enhancement) on axial plane. We also drew a ROI on contralateral brain white matter to normalize our measures (Fig. 1). Color maps were created (Figs. 2 and 3).

### 2.3. Parameters studied

For perfusion parameters, we analysed rCBV, using the indicator dilution theory (central volume theorem of Stewart–Hamilton [11,12] and the relationship between endovascular gadolinium concentration and the variation in MR imaging signal intensity (Fig. 4).

For permeability parameters, we studied: ΔR2* that was described to reflect contrast leakage: dynamic contrast-enhanced MRI methods have been established to characterize changes in tumor vasculature by elaborate PWI analyses [13–20]. It has been shown, that fractional blood volume (fBV) values (that can be calculated by T1 dynamic gadolinium enhancement permeability sequences), correspond to contrast leakage inside tissues, which reflects angiogenetic activity in tumors [21,22]. However, permeability can be also estimated by T2* weighted scans [23,24]. It has been shown that in gliomas, relative cerebral blood volume (rCBV) obtained with T2* weighted PWI can be underestimated due to extravasation of contrast [10] with concomitant signal intensity loss in the extravascular space on T2* weighted sequences [10,25]. In T2* weighted sequences, rCBV values are assessed by integrating the resulting transverse relaxivity changes that occur over a dynamic first pass injection [10,25]. However, because contrast agent also has a T1 relaxation effect, the susceptibility contrast signal intensity loss can be masked by signal intensity increase in

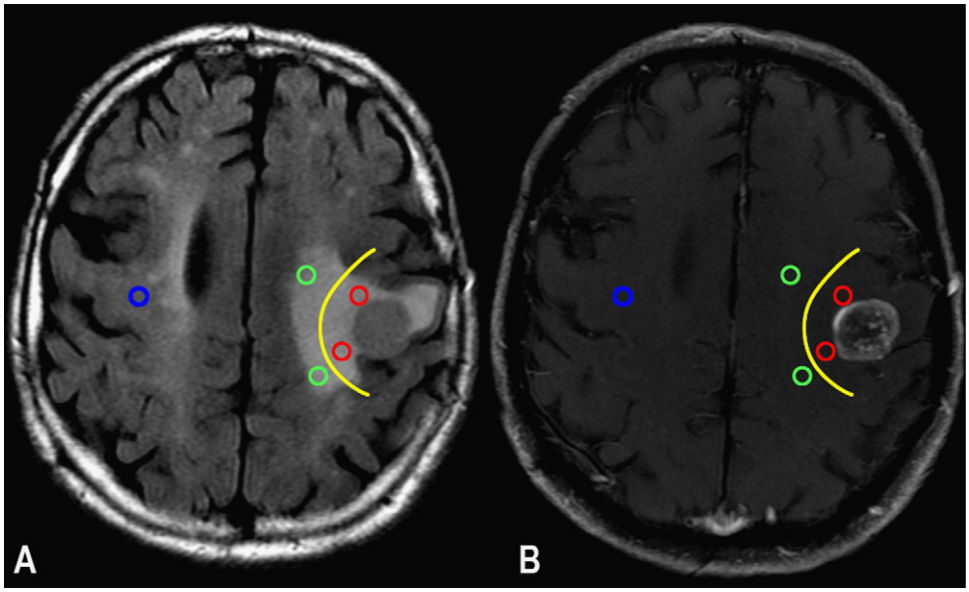


**Fig. 1.** ROI positioning. (A) Flair, and (B) T1 gadolinium enhanced with fat saturation (axial plane). 2 ROIs (red) are placed in the T2-hypersignal around the lesion in the first centimeter without including contrast enhancement, 2 ROI (green) are placed in the distant T2-hypersignal (more than one centimeter from contrast enhancement) and 1 ROI (blue) is placed in the contralateral white matter. Yellow line delineates the first centimeter around the tumor.

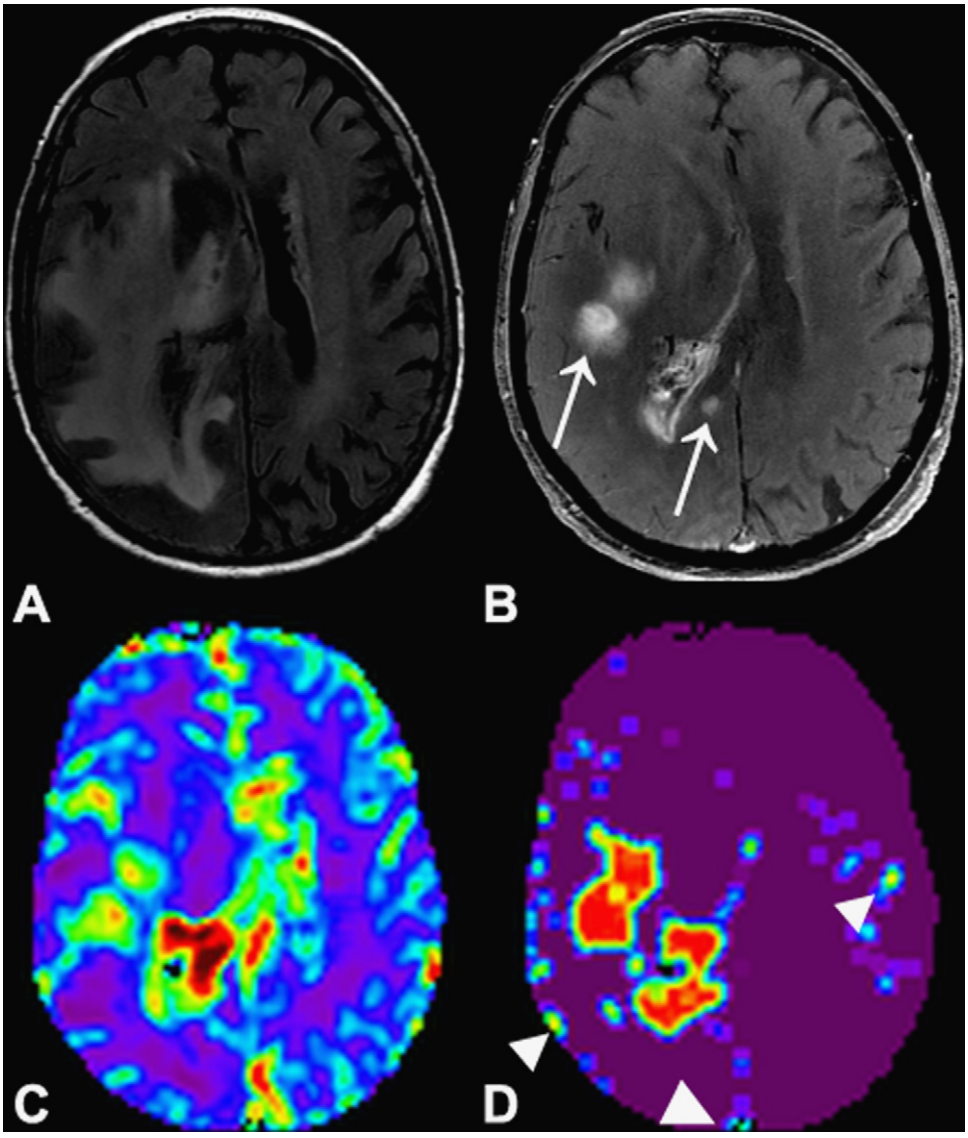


**Fig. 2.** glioblastoma study (superior part of the tumor). (A) Axial FLAIR: mass effect and important oedema on the right, (B) axial SE T1 fat sat after contrast injection: mass effect with contrast enhancement (arrow), (C) CBV map: moderate increased perfusion in the oedema around the contrast enhancement and (D) Permeability map: increased permeability (red) in the oedema around the contrast enhancement, note the vascular artefacts (arrow head).

regions where these T1 effect are significant [10]. In these instances and regions, rCBV will be underestimated, and may affect grade prediction in brain tumor. Therefore "corrected" rCBV (rCBVc) has been proved to be significantly correlated with glioma tumor grade [10]. To do this correction, the value called $\Delta R2^*$ (that is similar to the above described fBV values) is calculated from the T2* weighted sequence to estimate contrast extravasation. $\Delta R2^*$ is described as a robust and time-efficient strategy for approximately removing the T1 effect that diminishes estimated rCBV [10]. Employing T2* weighted sequences with this technique, will therefore allow for estimation of rCBV and permeability (as a marker for angiogenesis) by a single imaging sequence [26].

### 2.4. Statistical analysis

Means and *T* test were performed.

## 3. Results (Table 1)

### 3.1. Perfusion

rCBVmean values were $0.77 \pm 0.51$ for metastasis and $2.07 \pm 3.59$ for glioblastoma in proximal oedema. In distal oedema rCBVmean values were: $2.72 \pm 1.58$ for metastasis and $3.21 \pm 2.24$ for glioblastoma. There was statistical difference between glioblas-

**Table 1**
Perfusion and permeability mean value.

| | CBV | | Permeability (fBV) | |
|---|---|---|---|---|
| | Proximal | Distal | Proximal | Distal |
| Metastasis | 0.77 | 2.72 | 1.86 | 0.54 |
| Glioblastoma | 2.07 | 3.21 | 8.96 | 0.15 |
| *p* | Significant | No significant | Significant | No significant |

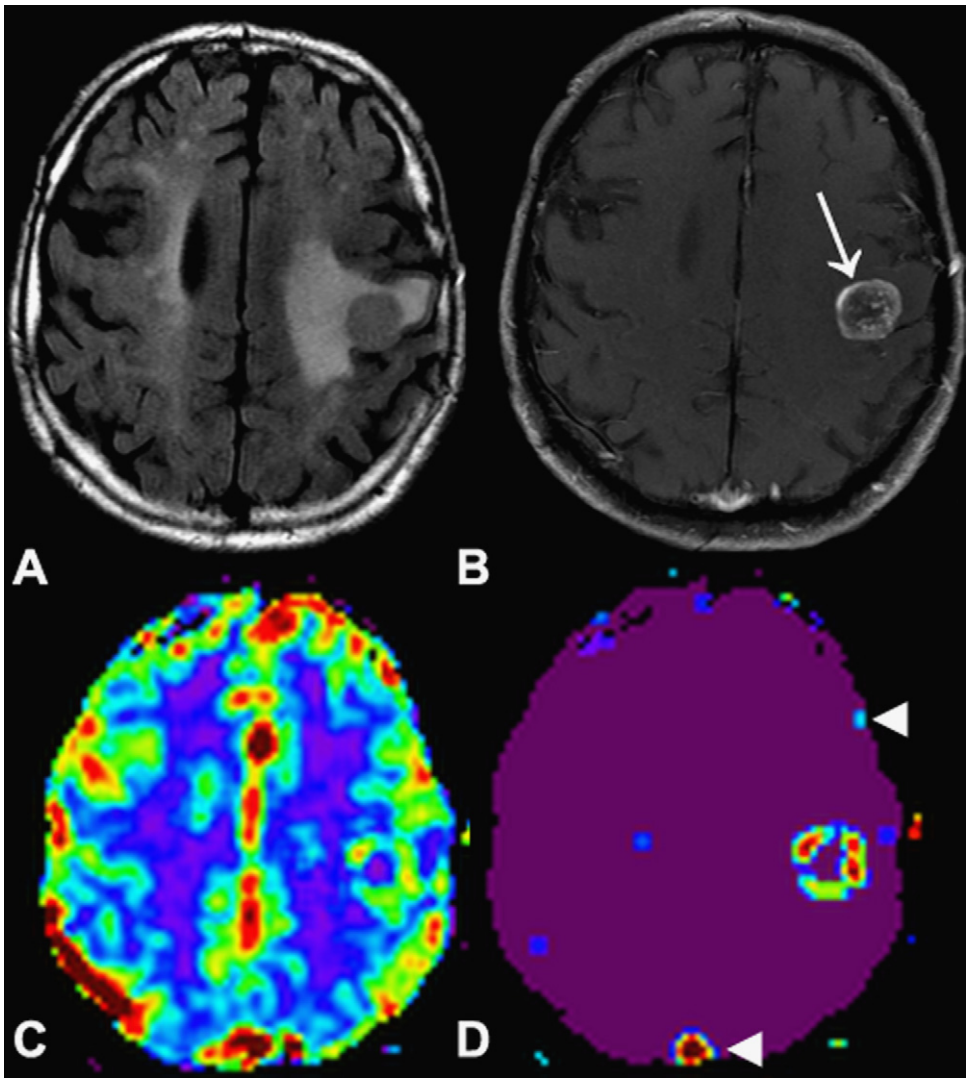


**Fig. 3.** Metastasis study. (A) axial FLAIR: mass effect and oedema on the left frontal lobe, (B) axial SE T1 fat sat after contrast injection: metastasis with contrast enhancement and central necrosis (arrow), (C) CBV map: no increased perfusion in the oedema around the contrast enhancement, and (D) Permeability map: permeability raised in the tumor, no increased permeability in the oedema around the contrast enhancement, note the vascular artefacts (arrow head).

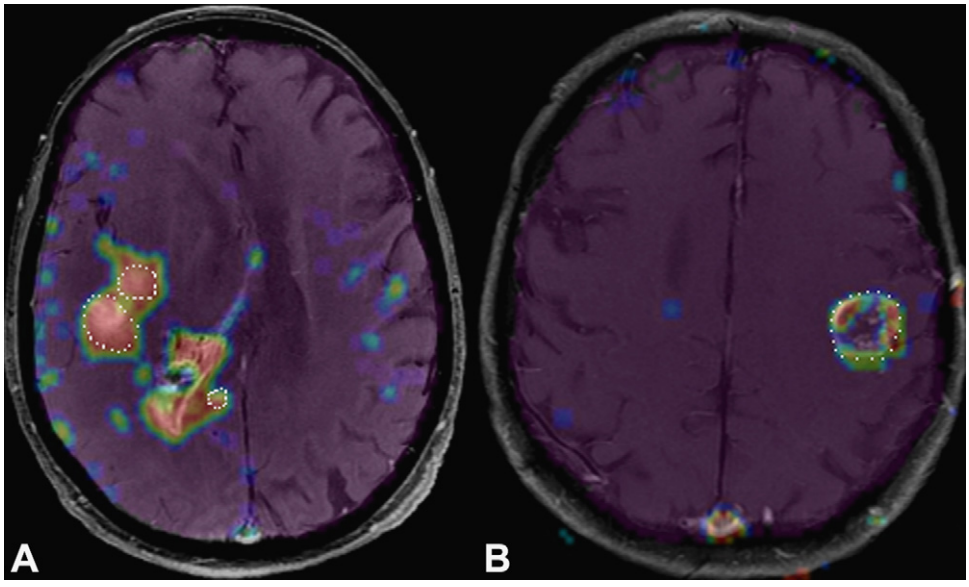


**Fig. 4.** Visual comparison of the permeability change extends. Mixed images of axial SE T1 fat sat after contrast injection and permeability map (white plots delineate contrast enhancement). (A) Glioblastoma study and (B) metastasis study. Permeability change extends is higher around glioblastoma than metastasis.

toma and metastasis in proximal oedema ($p = 0.0003$) but not in distal oedema ($p = 0.05$).

### 3.2. Permeability

In proximal oedema: 156 ROI were drawn around glioblastoma, 45% were positive (meaning there was permeability modification) and fBV mean value was 8.96. 118 ROI were drawn around metastasis, 11% were positive and fBV mean value was 1.86. Difference was statistically significant.

In distal oedema: 112 ROI were drawn around glioblastoma, 4% were positive and fBV mean value was 0.54.128 ROI were drawn around metastasis, 1% was positive and fBV mean value was 0.15. Difference was not statistically different.

## 4. Discussion

### 4.1. Sequence

Permeability and rCBV estimation needs acquisitions without contrast agent to obtain a good baseline and dynamic acquisitions during and after the injection to estimate contrast leakage and volume. We explore simultaneously relative Cerebral Blood Volume (rCBV) and endothelial permeability using a single T2* Echo Gradient echo planar imaging perfusion sequence. Perfusion and permeability parameters obtained simultaneously avoid two contrast injections, is less time consuming and is easier to calculate with this kind of software.

### 4.2. Perfusion (rCBV)

Our results are similar to literature values [27–30] and reflect physiopathology of this tumour type. In proximal oedema, glioblastoma (infiltrative tumours) present the higher rCBV. T2 hypersignal around metastasis seems to be linked to vasogenic phenomena's.

In distal oedema, the 2 tumour types present the similar rCBV values which reflect the lack of tumoral infiltration and angiogenesis. T2 hypersignal is induced by the tumour (vasogenic oedema, mass effect or venous drainage default) [31].

### 4.3. Permeability

Permeability reflects interstitial microvascular contrast leakage due to abnormal vessels.

The data obtained on glioblastomas study show permeability modification around glioblastoma with multiple positive ROI (45%) in proximal oedema. In distal oedema only 4% of ROI were positive corresponding to less tumoral infiltration.

On metastasis study, less than 11% of the ROI were positive around the tumors which correspond to the lack of tumoral infiltration and angiogenesis. We attribute the positivity of these ROI to partial volume effect due to a vessel or a tumoral part. Distal ROI are similar to distal ROI around gliobastoma that correspond to the absence of tumoral infiltration or angiogenesis.

## 5. Conclusion

In our study, the association of morphological MR and functional MR parameters to explore peritumoral T2 hypersignal can help to differentiate brain masses. A single sequence is needed to obtain perfusion and permeability (functional data's). Glioblastoma present high rCBV with modification of the permeability around the contrast enhancement. Metastasis present slight modified rCBV without modification of permeability around the contrast enhancement. These results correspond to a perilesional oedema around metastasis and infiltrative lesional oedema around glioblastoma.

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