Dynamic susceptibility contrast-enhanced perfusion MR Imaging of Brain Tumors.

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Learning objectives

To show that multiparametric MR, including perfusion-weighted imaging (PWI), is the method of choice for the diagnostic work-up and follow-up of patients with brain tumors.

Background

Conventional MRI sequences, before and after contrast administration, are excellent to show tumor morphology and signal intensity, but provide little information on tumor vascularity. Enhancement after injection of a gadolinium-chelate often does not correlate with tumor grade. We report our experience with dynamic susceptibility contrast-enhanced (DSC) perfusion MRI in a prospective series of 42 patients with brain tumors. Time-enhancement curves and parametric maps, especially relative Cerebral Blood Volume (rCBV), were correlated with tumor histology, clinical evolution and post-operative follow-up. We address the technical issues involved with performing DSC perfusion and discuss the advantages and shortcomings of the technique.

Imaging findings OR Procedure details

Time-enhancement curves reflect tumor histology, capillary density and fenestration of blood vessel walls, and are of use to differentiate brain tumors. Increased vascularity in brain tumors is generally quantified in MR perfusion techniques in terms of rCBV. rCBV is equal to the total volume of blood within a certain volume of brain or tumor and can be estimated from the area above the curve (integral) of the signal intensity versus time curve.

Primary gliomas

Several studies have demonstrated that rCBV correlates with glioma grading. Low grade gliomas (WHO I and II) have rCBV values between 1.11 and 2.14 and high grade gliomas have rCBV values between 3.54 and 7.32 [9,35]. High-grade gliomas, such as anaplastic astrocytoma (WHO III) or glioblastoma multiforme (WHO IV) have a high mitotic activity. When the tumor outgrows its metabolic demands, this results in hypoglycemia and hypoxia, which cause the expression of angiogenic cytokines, in particular vascular endothelial growth factor (VEGF). VEGF stimulates the growth of tortuous blood vessels, with abnormally permeable vessel walls, due to basement membrane degradation and absence of the smooth muscle layer. When performing DSC PWI, contrast "leaks" through the blood vessel walls into the extracellular spaces, which results in an increased
blood volume and high rCBV values (Fig 1). Low-grade gliomas have less mitotic activity, less hypercellularity and pleiomorphism than high grade-gliomas, and less angiogenetic activity, which results in lower rCBV [12]. Exception to this rule is oligodendroglioma, a tumor which may display foci of high rCBV without enhancement, irrespective of tumor grading.

(Solitary) cerebral metastases

Glioblastoma multiforme (GBM) and solitary brain metastasis can present with a similar appearance on anatomic imaging, but require a different management. Theoretically, PWI can help because of the different architecture of the capillaries within GBM and metastasis. GBM can present with variable capillary density and blood-brain-barrier (BBB) disruption, causing permeability changes that vary from nearly normal to very leaky. The tumor and capillary proliferation diffusely infiltrate into the surrounding brain tissue, which explains why the borders of the tumor are ill-defined.

Conversely, in brain metastasis, the structure of the tumor and the capillaries closely resembles the parent tumor, invariably with complete absence of the BBB. This is due to prominent capillary fenestrations, which cause vast amounts of peritumoral vasogenic edema. Most authors state that solitary metastasis and GBM show a tendency towards high intra-tumoral rCBV values, but the difference has never been shown to be statistically significant. According to some groups, there may be a statistically significant difference in rCBV in the peri-tumoral region of GBM (0.89 ± 0.51) compared to metastasis (0.31 ± 0.12) [12].

Primary central nervous system lymphoma

Lymphoma can mimic many other intra-cerebral tumors. It is important to establish a correct diagnosis, because lymphoma can be treated with chemo- and radiotherapy and seldom necessitates surgery, whereas in primary glial tumors, surgical removal of the mass is usually the first line of treatment. Lymphoma is a tumor with very high cellularity, without angiogenesis; this results in lower rCBV values (1.10 ± 0.32) compared to high-grade glioma [11] (Fig 2). The intense enhancement observed in CNS lymphomas is due to BBB destruction.

Meningioma

Meningiomas are highly vascular extra-axial tumors with very high rCBV values. Several studies have reported higher rCBV in meningiomas than in high-grade gliomas. This is due to increased density of blood vessels, which lack a BBB [7]. In “typical” meningiomas, rCBV values up to 8.02 ± 4.74 have been reported, whereas in "atypical" meningiomas, rCBV values as high as 10.50 ± 2.1 have been described [37]. Meningiomas present with a typical rCBV curve, with an early downward slope and incomplete recovery of T2*
signal intensity, which stays below baseline, due to the high capillary density of the tumor (Fig 3).

**Hemangioblastoma**

Hemangioblastoma is a benign hypervascular tumor, primarily found in the cerebellum and the spinal cord, and sometimes related to von Hippel-Lindau syndrome. The typical solid-cystic hemangioblastoma consists of a hypervascular nidus associated with a tumor cyst. Morphologic differentiation from pilocytic astrocytoma may be difficult; increased rCBV values in hemangioblastoma may be helpful in differentiating these tumors (Fig 4).

**Pre-operative set up and biopsy guidance**

Contrast enhancement does not always correspond to the most aggressive cell population, nor does it always demarcate the tumor boundaries. Perfusion imaging demonstrates regions of higher angiogenesis, which most likely correspond to areas of high tumor cell turn-over. In GBM, regions of increased angiogenesis may extend beyond the enhancing parts of the tumor, which may be helpful for stereotactic guidance or pre-operative planning (Fig 5).

**Post-treatment evaluation of gliomas**

Differentiating tumor recurrence from radiation necrosis is a formidable clinical challenge. On conventional MRI both conditions may present as heterogeneously enhancing lesions. Histologically both entities are very different. Delayed radiation necrosis is an occlusive vasculopathy. Irradiating the endothelium leads to fibrinoid necrosis of the vessels, endothelial thickening and vascular trombosis. This process is entirely different from the vascular proliferation without luminal obliteration in a recurrent tumor. This difference also explains why rCBV values in radionecrosis are lower than in recurrent tumor (Fig 6), as demonstrated by Hu and colleagues in a recent paper [14]. They concluded that rCBV>0.71 predicted tumor growth, whereas rCBV<0.71 predicted radionecrosis with an accuracy of ± 95%.

**Limitations and pitfalls of DSC perfusion**

**Susceptibility**

Metals, brain-bone-air intervals, calcium, blood degradation products and melanin cause magnetic field inhomogeneity and degrade the T2* sequence.

**Leakage effects**
rCBV may be underestimated due to gadolinium leaking into the interstitial space and masking the susceptibility-contrast signal loss. T2*-weighted acquisitions have some T1-sensitivity, such that contrast leakage may cause artifactual increase of the T2*-signal intensity versus time curve. This is particularly problematic in tumors with severe blood-brain-barrier leakage, such as glioblastoma. This problem may be corrected using software methods, such as gamma variate fitting and baseline correction [32] or by pre-loading with a small dose of gadolinium [30].

Images for this section:

![Images](image_url)

**Fig. 1.** PWI helps to differentiate low-grade from high grade glioma.

Top row: diffuse astrocytoma (WHO I). Axial T1-weighted images before (A) and after contrast injection (B) demonstrate an inhomogeneously enhancing right frontal tumor. rCBV color map (C) and time enhancement curve (D: red=tumor, yellow=normal white matter) both show decreased rCBV values in the tumor. Bottom row: high grade glioma (WHO IV). This left frontal tumor invades the corpus callosum, crosses the midline, and presents as a mass with central necrosis and irregular peripheral enhancement. rCBV color map (G) demonstrates that the enhancing regions are correlated with increased rCBV values. The signal intensity versus time curve (H: red=tumor, yellow=normal white matter) shows the increased CBV as a large area above the tumor curve.

**Fig. 1:** PWI helps to differentiate low-grade from high grade glioma.
Fig. 2: Primary non-Hodgkin B-cell lymphoma.

(A) Axial post contrast T1-weighted image demonstrates an enhancing mass in the left cerebellar hemisphere. (B) Axial diffusion-weighted trace image shows diffusion restriction, due to the high tumor cellularity. (C) rCBV color map and time enhancement curve (D) (yellow=normal parenchyma, red=lymphoma) demonstrate slightly elevated rCBV in the lymphoma, reflecting the leakiness of the BBB.
Fig. 3. Meningioma.
Sharply interhemispheric frontal tumor with intermediate signal intensity on precontrast T1-weighted images (A) and prominent contrast enhancement (B). The color map (C) demonstrates very high rCBV values in the tumor. The time enhancement curve shows incomplete recovery of the T2* signal, which stays below baseline. This is due to the hypervascular nature of the tumor, with increased capillary density.
**Fig. 4:** Perfusion imaging helps to differentiate posterior fossa tumors.

**Top row:** Pilocytic astrocytoma. Axial turbo FLAIR (A) and post-contrast T1-weighted images (B) demonstrate a cystic tumor in the pons and mesencephalon, with an enhancing nodule. The rCBV color map (C) demonstrates no increase of rCBV.

**Bottom row:** Hemangioblastoma. Axial turbo FLAIR (D) and post-contrast T1-weighted images (E) reveal a large inhomogeneous tumor, with a solid enhancing nodule and an accompanying cyst, surrounded by edema. The rCBV color map (F) shows marked increase of rCBV in the enhancing nodule. The high rCBV in the hypervascular nodule allows differentiation between hemangioblastoma and pilocytic astrocytoma.
Fig. 5: Perfusion imaging is helpful in pre-operative planning.

Axial pre-contrast (A) and post-contrast (B) T1-weighted images show an irregularly enhancing tumor in the left occipital lobe, surrounded by vasogenic edema. Axial color map (C) shows high rCBV values in the enhancing tumor. Furthermore, increased rCBV values are also observed in the splenium; this was shown to be an infiltrating component of the anaplastic astrocytoma. This part of the tumor is, even in retrospect, not seen on the anatomical MR images. The information provided by PWI is important in the preoperative planning, prognosis prediction, and management of the patient.
Fig. 6: Perfusion imaging is helpful in differentiating radiation necrosis from recurrent tumor.

**Top row:** Post-operative follow-up after resection, chemo- and radiotherapy of an anaplastic astrocytoma (WHO III). Axial pre-contrast (A) and post-contrast (B) T1-weighted images show an irregularly enhancing region within the surgical resection site. The rCBV color map (C) and time-enhancement curve (D) demonstrate no increase of rCBV. The area over the curve is not significantly different for the lesion (red) and normal parenchyma (yellow). This was interpreted as radiation-induced change. During a 2-year follow-up no tumor recurrence was seen.

**Bottom row:** Post-operative follow-up after resection, chemo- and radiotherapy of a GBM (WHO IV). Axial pre-contrast (E) and post-contrast (F) T1-weighted images show an region of ring enhancement in the left frontal lobe. The rCBV color map (G) and time-enhancement curve (H) demonstrate an elevated rCBV. The lesion was a histologically proven recurrent tumor.
Conclusion

MR perfusion is a useful adjunct to conventional MR in the diagnosis, grading and post-operative follow-up of brain tumors. The routine implementation of this technique improves diagnostic accuracy and can have important clinical consequences.

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