Perfusion-Weighted Imaging of Peritumoral Edema can Aid in the Differential Diagnosis of Glioblastoma Mulltiforme Versus Brain Metastasis

Osnat Halshtok Neiman MD[1], Siegal Sadetzki MD[2], Angela Chetrit MSc MPH[2], Stephen Raskin MD[1], Gal Yaniv MD PhD[1] and Chen Hoffmann MD[1]

[1]Department of Diagnostic Imaging, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[2]Cancer & Radiation Epidemiology Unit, Gertner Institute, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** MRI differentiation between metastases and high grade gliomas is a challenging task. Contrast enhancement and size of edema do not provide clear-cut differentiators. The differences in the properties of the peritumoral edema between these tumor types may be exploited to distinguish between them, using MRI perfusion sequences, which are capable of imaging edema in the clinical setting and may be a reliable method to make this differentiation.

Objectives: To assess the ability of perfusion-weighted imaging to differentiate between high grade gliomas and brain metastases.

Methods: During 5 months, 21 patients (age 40–85, median age 61, 16 males and 5 females) with either glioblastoma multiforme (GBM) or metastasis (pathology proven), underwent MRI for assessment of the tumor prior to surgery. Most of the scans were done at 3 Tesla. The scans included perfusion-weighted imaging sequences. Perfusion in the tumor, in the peritumoral edema and in normal tissue were assessed using Functool® software. The ratios of tumor perfusion and peritumoral edema perfusion to normal tissue perfusion were calculated and compared.

Results: Bleeding artifact precluded perfusion assessment in four patients. There was no statistically significant difference between the tumor perfusion ratios of high grade gliomas and those of metastases. The edema perfusion ratios were higher in GBM than in metastases ($P = 0.007$).

Conclusions: Perfusion-weighted imaging of peritumoral edema can help to differentiate between GBM and metastases.

IMAJ 2013; 15: 103–105

KEY WORDS: peritumoral edema, tumor, perfusion-weighted MRI, metastasis, glioblastoma multiforme (GBM)

Magnetic resonance imaging is an indispensable tool in the evaluation of brain tumors, but, even with the aid of MRI, the differential diagnosis of an intracranial mass remains difficult. Particularly challenging is the differentiation between a solitary metastasis and a high grade glioma, two of the most common brain tumors in adults. Contrast enhancement has limited specificity, and although the edema of metastases is usually more extensive than that of high grade gliomas, the difference is variable.

A possible differentiator between metastasis and glioma is the composition of the peritumoral edema. The peritumoral edema of metastases is caused by capillary leakage due to compressive effects of the mass and the fact that tumor capillaries resemble extra-axial tumor vessels and have no blood brain barrier [1]. Metastatic peritumoral edema is purely vasogenic, and infiltrating tumor cells are not present outside the perivascular spaces [1]. The peritumoral edema of high grade gliomas, on the other hand, is a mixture of vasogenic edema and infiltration of neoplastic cells along the perivascular spaces [2,3].

A cell-containing area, such as in the peritumoral edema of high grade gliomas, is associated with feeding blood vessels [4] and, as such, is expected to have increased blood perfusion [5]. An area that contains mainly fluid, as in perimetastatic edema, requires fewer feeding blood vessels and is expected to have lower blood perfusion.

MRI enables the investigation of perfusion in the peritumoral edema by using a perfusion-weighted sequence [1,6], which can measure relative blood flow volume within small regions of the tissues. The aim of our study was to assess the ability of perfusion-weighted imaging to differentiate between high grade gliomas and brain metastases.

PATIENTS AND METHODS

The study population included consecutive patients with intracranial mass lesions who underwent MRI prior to surgery as part of a regular workup during a 5 month period in a tertiary hospital in central Israel. The inclusion criterion for this study was the presence of one or more lesions manifesting peritumoral edema, which were proven in post-resection pathology to be either glioblastoma multiforme or metastatic cancer. If there were multiple lesions, only lesions undergoing resection were included in the analysis.

The study group comprised 21 patients, 14 with high grade gliomas and 7 with metastases (age 40–85 years, median age

Table 1. Clinical data of patients with metastatic brain tumors

Gender	Age (yrs)	Prior known malignancy	Pathology results
Female	52	No	Metastatic squamous cell carcinoma, involving dura and brain parenchyma
Male	58	NSCLC	Residual metastatic carcinoma is seen within reactive brain tissue and necrosis
Male	67	Lung ca	Metastastic undifferentiated carcinoma, non-small cell type (lung origin is favored)
Male	64	NSCLC	Metastatic adenocarcinoma with papillary and mucinous features
Female	85	No	Malignant melanoma
Female	69	NSCLC	Metastatic adenocarcinoma compatible with lung
Female	40	Esophgeal adenocarcinoma	Metastatic papillary adenocarcinoma

61, 15 males and 6 females). One patient from the GBM group had a known prostate carcinoma. Five patients from the metastasis group had a prior known malignancy. Their malignancies and the biopsies pathology result are detailed in Table 1.

The study was approved by our institutional review board and conducted according to the Declaration of Helsinki.

MAGNETIC RESONANCE IMAGING

The MR scans were mostly performed with the 3T MR system (HDX GE Medical Systems Milwaukee, WI, USA) and partly with the 1.5T system (HDX GE Medical Systems) using an eight channel head coil in a standard tumor protocol. The protocol included a T1 sagittal scan as a surview (TE=7.892-17, TR=340-680), true axial T2 (TE=102.72-130.256, TR=3200-7500), FLAIR (TE=122.326-137.52, TR=8000-9500), DTI (TE=6.868-106.8, TR=2047.85-8500), T2 GRE (TE=15, TR=300-800), DWI, and contrast-enhanced FSPGR (TE=2.892-12.376, TR=7.824-70.76) in three orthogonal planes, all sequences in FOV (field of view) 240 mm.

Perfusion-weighted MRI was performed with a first-pass, contrast-enhanced, T2-weighted, single-shot, gradient-echo, echo-planar sequence using a rapid bolus (5 ml/s) of 0.2 mmol/kg of contrast material (DOTAREM 0.5 mmol/ml) through an 18 or 20 G intravenous line. The parameters of the sequence were: TR/TE 2000 ms/54 ms, flip angle 40°, bandwidth 62.5 kHz, FOV 28 x 21 cm, matrix 96 x 128, section thickness 6 mm and section gap 1.5 mm. The precise algorithm for calculating relative cerebral blood volume was previously described [1,2].

In brief, rCBV maps were generated using an AD.HD workstation (GE Medical Systems), available in the Functool® software program (GE Medical Systems). Analysis was performed by drawing ROIs (region of interest) on tumor, peritumoral edema and normal brain tissue, in a single axial image in which the tumor and peritumoral edema were most significant [Figure 1]. The peritumoral edema was defined in T2 and FLAIR sequences as a hyperintense signal in the white matter surrounding the tumor.

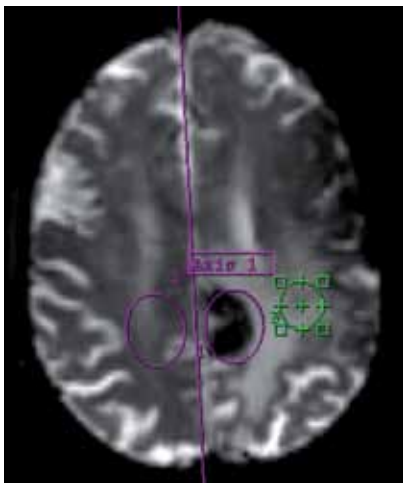

Figure 1. Measurement of perfusion using Functool® software in a 58 year old man with metastatic carcinoma of lung. ROI 1 measures tumor perfusion, ROI 2 measures normal brain tissue perfusion and ROI 3 measures peritumoral edema perfusion

The software automatically generated a round ROI with fixed size. The tumor ROI was changed to contain enhancing tumor only. An identical ROI was generated in the contralateral normal brain tissue in a symmetrical position. The peritumoral edema's ROI was localized in the center of the peritumoral edema and adjusted to contain only white matter peritumoral edema.

STATISTICAL ANALYSIS

Differences in the study parameters between the GBM and the metastasis groups were assessed using the Wilcoxon non-parametric test. We calculated ratios of peritumoral edema to normal brain and tumor to normal brain ratios for both tumor types.

RESULTS

One patient in the glioma group and one in the metastases group were excluded from the calculation of the rCBV value of the peritumoral perfusion and two patients from the metastases group were excluded from the different rCBV evaluations of the tumor perfusion due to blood artifacts in the tumor [Table 2].

For tumor perfusion, no significant differences between the groups were noticed for the rCBV (median 289 and 252 in the glioma and the metastasis groups respectively, $P = 0.8$). The rCBV values of peritumoral perfusion ranged between 25 and 266 and were significantly higher in the glioma group compared to the metastasis group (median 100 and 44 respectively,

GMB = glioblastoma multiforme
FOV = field of view
rCBV = relative cerebral blood volume

ROI = region of interest

Table 2. Perfusion data (rCBV values) and calculated ratios

	GBM	Metastasis	*P* value
Tumor perfusion			
No. of cases	14	5*	
Median	289	252	
Range	115–646	185–594	0.8
Peritumoral perfusion			
No. of cases	13*	6*	
Median	100	44	
Range	25–266	28–156	0.05
Normal tissue perfusion			
No. of cases	14	7	
Median	178.5	226	
Range	81–321	144–367	0.16
Tumor perfusion / Normal tumor perfusion			
No. of cases	14	5*	
Median	1.49	1.26	
Range	0.89–3.96	0.82–1.75	0.2
Peritumoral perfusion / Normal tumor perfusion			
No. of cases	13*	6*	
Median	0.66	0.22	
Range	0.14–1.21	0.13–0.56	0.007

*Patients excluded from group due to blood artifact

P = 0.05). The rCBV values of normal tissue perfusion ranged between 81 and 367 with a non-significant lower median in the glioma group compared to the metastasis group (*P* = 0.16). The ratios of peritumoral edema perfusion to normal tissue perfusion were threefold higher in the glioma group compared with the metastasis group. The values ranged from 0.14 to 1.21 (median 0.66) in the glioma group and from 0.13 to 0.56 (median 0.22) in the metastasis group (*P* = 0.007).

DISCUSSION

High grade gliomas are the most common primary malignant brain tumor in adults, while intracranial metastases are the most common brain tumor in general [7]. Together, these two entities comprise most of the brain tumors in adults. Both high grade gliomas and metastatic lesions may be treated with resection and radiation. While metastatic brain tumors have a variable clinical course and may be indolent, gliomas have a high rate of local recurrence and have a more dismal outcome [8]. As the treatments available are not without costs and side effects, the differential diagnosis and expected prognosis are highly important [8].

Unfortunately, the differential diagnosis between solitary brain metastases and high grade gliomas is challenging. Contrast enhancement, size and shape of the tumor and its peritumoral edema may be helpful, but all characteristics are non-specific and subject to individual interpretation, resulting in a high level of inter-observer variability. Despite this variability, objective differences are known to exist in the peritumoral areas of each type of tumor: pure vasogenic edema surrounding metastases versus vasogenic edema with cell infiltration around high grade gliomas.

The present retrospective study compared perfusion ratios in both tumor and peritumoral areas in 14 patients with glioma and 7 with metastatic brain lesions, with all lesions unaffected by blood artifacts.

Despite the small number of patients and some overlap between the ranges of the results, the median values of peritumoral area perfusion ratios were significantly higher in high grade gliomas as compared to solitary brain metastases.

In our study, no significant difference was noted in tumoral calculated perfusion ratios (tumor/normal tissue) between GBMs and metastases, as described by Hakyemez et al. [2]. Perfusion in both GBMs and metastases was high due to the high vascularity of these tumors, and thus the calculated perfusion ratios values are not statistically different between these two entities.

Despite the small number of patients and some overlap between the ranges of the results, the median values of peritumoral area perfusion ratios were significantly higher in high grade gliomas as compared to solitary brain metastases. The mean value was 100 for GBMs compared to 44 for metastases.

Findings from the present study indicate that the cellular content of peritumoral edema may be assessed by an MRI perfusion sequence; therefore, MRI-determined rCBV may aid in differentiating high grade gliomas from metastases. This may be of clinical relevance in the population of patients presenting with a solitary brain tumor and unknown underlying malignancy.

Our group was small but showed a clear trend, and the cumulative data of this research and that of others suggest a possible future role of this investigation as a tool to aid in the preoperative differential diagnosis between high grade gliomas and intracranial metastases.

Corresponding author:
Dr. O. Halshtok Neiman
Dept. of Diagnostic Imaging, Sheba Medical Center, Tel Hashomer 52621, Israel
Phone: (972-3) 530-2530, **Fax:** (972-3) 535-7315
email: osnatx@gmail.com

References

1. Senturk S, Oguz KK, Cila A. Dynamic contrast-enhanced susceptibility-weighted perfusion imaging of intracranial tumors: a study using a 3T MR scanner. *Diagn Interv Radiol* (Ankara, Turkey) 2009; 15 (1): 3-12.
2. Hakyemez B, Erdogan C, Gokalp G, et al. Solitary metastases and high-grade gliomas: radiological differentiation by morphometric analysis and perfusion-weighted MRI. *Clin Radiol* 2010; 65 (1): 15-20.
3. Kelly PJ, Daumas-Duport C, Kispert DB, et al. Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. *J Neurosurg* 1987; 66 (6): 865-74.
4. Fischer I, Gagner JP, Law M, et al. Angiogenesis in gliomas: biology and molecular pathophysiology. *Brain Pathol* (Zurich, Switzerland) 2005; 15 (4): 297-310.
5. Server A, Orheim TE, Graff BA, et al. Diagnostic examination performance by using microvascular leakage, cerebral blood volume, and blood flow derived from 3-T dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in the differentiation of glioblastoma multiforme and brain metastasis. *Neuroradiology* 2011; 53: 319-30
6. Chiang IC, Kuo YT, Lu CY, et al. Distinction between high-grade gliomas and solitary metastases using peritumoral 3-T magnetic resonance spectroscopy, diffusion, and perfusion imagings. *Neuroradiology* 2004; 46 (8): 619-27.
7. Nguyen TD, DeAngelis LM. Brain metastases. *Neurol Clin* 2007; 25 (4): 1173-92.
8. Giese A, Westphal M. Treatment of malignant glioma: a problem beyond the margins of resection. *J Cancer Res Clin Oncol* 2001; 127 (4): 217-25.