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Utility of dynamic contrast-enhanced magnetic resonance imaging for differentiating glioblastoma, primary central nervous system lymphoma and brain metastatic tumor

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ABSTRACT

Purpose: The study aimed to investigate the use of dynamic contrast-enhanced magnetic resonance imaging (MRI)-derived permeability parameters for the differentiation of glioblastoma multiformes (GBMs), primary central nervous system lymphomas (PCNSLs), and brain metastatic tumors (MTs).
Materials and methods: Seventy-five patients with histopathologically confirmed GBMs (n = 38), PCNSLs (n = 16) and MTs (n = 21) underwent dynamic contrast-enhanced MRIs before surgery. The volume transfer constant K^{trans}, the flux rate constant between extravascular extracellular space and plasma K_{ep}, the extravascular extracellular volume V_e and the fractional plasma volume V_p were measured within the entire contrast-enhancing tumor by extended Tofts model. A one-way analysis of variance was used to compare all of the parameters among these three tumors, followed by the post-hoc test. Receiver operating characteristic curves were constructed to evaluate the diagnostic performance of the permeability parameters.
Results: Mean K^{trans} value and V_e value were significantly higher in PCNSLs than in GBMs ($P < 0.001$ and $P = 0.011$) and MTs ($P < 0.001$ and $P < 0.001$). No significant difference was observed in all of the permeability parameters between GBMs and MTs. According to the receiver operating characteristic analyses, both K^{trans} and V_e had good diagnostic performance for discriminating between PCNSLs and GBMs (the area under the curve: 0.847 and 0.785, respectively), as well as between PCNSLs and MTs (the area under the curve: 0.851 and 0.884, respectively).
Conclusions: The K^{trans} and V_e derived from dynamic contrast-enhanced MRI facilitate the differentiation of PCNSLs from GBMs and MTs.

1. Introduction

The discrimination of glioblastoma multiformes (GBMs), brain metastatic tumors (MTs) and primary central nervous system lymphomas (PCNSLs) can be very challenging by conventional magnetic resonance imaging (MRI), especially when there are atypical MRI features in PCNSLs, such as necrosis, hemorrhage or heterogeneous enhancement, which are not uncommon nowadays [1,2]. As the management of these three intra-axial tumors is entirely different, an accurate preoperative differentiation is imperative [3].

Many advanced imaging techniques have been used to distinguishing these three tumors; such as diffusion tensor imaging, proton MR spectroscopy, and dynamic susceptibility contrast-enhanced perfusion-weighted imaging (DSC-PWI) [3–6]. DSC-PWI is the most widely reported technique. Lower cerebral blood volume (CBV) is reported in PCNSLs as compared to GBMs or MTs. GBMs demonstrate an elevated CBV in the peritumoral region in comparison with brain metastases [3,7–9]. However, major disadvantages of DSC-PWI are its low spatial resolution and high sensitivity towards the susceptibility artifacts from hemorrhage, calcification, and metallic surgical implants. Besides, the tumor CBV

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can be underestimated before leakage correction when blood-brain barrier (BBB) breaks down and contrast leakage presents [9,10].

Histologically, the capillary ultrastructures of these three tumors are different. Neovascularization and vascular permeability of GBMs can be variable [3]. PCNSLs usually show little neovascularization but increased vascular permeability due to the architectural distortion of the vessels [11]. MTs have similar vasculatures to that of the original tumors, and are reported to have lower microvascular leakage (K_2) than in GBMs by DSC-PWI processed with leakage correction [8].

Dynamic contrast-enhanced (DCE) T1-weighted MR perfusion imaging is less sensitive to susceptibility artifacts, and enables a noninvasive analysis of the vascular microenvironment by measuring the volume transfer constant (K^{trans}), the flux rate constant (K_{ep}), the fractional blood plasma volume (V_p), and the fractional volume of the extravascular and extracellular space (V_e). It has been increasingly used in clinical trials involving brain tumors, such as glioma grading and predicting the therapeutic response and prognosis [12–14]. However, to the best of our knowledge, few studies have been performed to compare the vascular permeability among GBMs, PCNSLs and MTs by DCE MR imaging [11,15].

The aim of our study was to investigate the utility of DCE MR imaging-derived permeability parameters (K^{trans}, K_{ep}, V_e, V_p) within the entire contrast-enhancing tumor for the discrimination of GBMs, PCNSLs and MTs.

2. Materials and methods

2.1. Patient selection

Our institutional review board approved this retrospective study, and the requirement for informed consent was obtained from all of the patients. From February 2014 to March 2015, 89 patients with histologically confirmed GBMs, PCNSLs and MTs were reviewed. All of the patients underwent conventional MRI and DCE MR imaging preoperatively. For further selection, only patients with no clinical history of previous surgery or treatment were included. Nine patients with poor DCE image quality because of motion, and five patients with tumor therapy before the initial DCE study were excluded. Finally, a total of 75 patients were enrolled, including 38 GBMs (21 men, 17 women, mean age 52 years, range 29–79 years), 16 PCNSLs (7 men, 9 women, mean age 61 years, range 45–75 years) and 21 MTs (12 men, 9 women, mean age 65 years, range 37–81 years). A neuropathologist with four years of experience (Y. Li) performed the histological evaluation. Pathologically, all of the PCNSLs in our study were diffuse large B-cell lymphomas. In the 21 patients with brain metastases, the primary sites of the tumors were lung (n = 16), breast (n = 4) and gastric cancer (n = 1).

2.2. MR imaging acquisition

An 8-channel head-matrix coil obtained MRI images on a 3.0 T MR System (Magnetom Verio/Trio Tim; Siemens, Erlangen, Germany). Our conventional MRI protocol included the following sequences: axial T1WI (TR, 400 ms; TE, 2.48 ms; section thickness, 5 mm; FOV, 230 mm^2; Matrix, 320 × 256); T2WI (TR, 5090 ms; TE, 91 ms; section thickness, 5 mm; FOV, 230 mm^2; Matrix, 320 × 320); and FLAIR (TR, 8900 ms; TE, 97 ms; section thickness, 5 mm; inversion time, 2300 ms; FOV, 230 mm^2; Matrix, 256 × 256).

Axial DCE MR imaging was performed with volume interpolated gradient echo (VIBE) sequence. Firstly, three non-enhanced datasets were acquired using T1WI VIBE (TR, 3.89 ms, TE, 1.31 ms, slice thickness, 3 mm, FOV, 230 mm^2, matrix, 224 × 161) with flip angles of 5°, 10° and 15° respectively to obtain the T1 map. Secondly, the dynamic sequence started after three baseline acquisitions. An intravenous injection of 0.1 mmol/kg gadodiamide (Omniscan, GE Healthcare, Ireland) was carried out at an injection rate of 4 mL/s via a power injector, followed by a flush of 20 mL of normal saline. The parameters were as follows: TR 3.89 ms, TE 1.31 ms, slice thickness 3 mm, FOV 230 mm^2, Matrix 224 × 161, flip angle 15°. Forty dynamic phases were obtained in total and the temporal resolution was 6 s. Another contrast-enhanced T1WI was acquired after the completion of DCE MR imaging.

2.3. Image processing and analysis

Two neuroradiologists (SS. Lu and J. Yu) with 5 and 6 years of experience, blinded to the diagnosis, analyzed the conventional MR images including lesion number, enhancing pattern, hemorrhage, and necrosis, respectively. The enhancing patterns were classified into two types as follows: (1) homogeneous pattern: well-defined nodular lesions without hemorrhagic components or necrosis and homogeneously enhanced; (2) heterogeneous pattern: lesions with a presence of hemorrhage and/or necrosis and heterogeneous enhancement. The two readers made final decisions by consensus. In cases of disagreement, a senior neuroradiologist with 20 years of experience (XN. Hong) helped to make the final decision.

All of the raw DCE data were transferred from the MRI scanner to an independent personal computer and processed off-line with in-house software (OmniKinetics, GE Healthcare, China). Preprocessing of perfusion data included noise correction and motion rectification. For the purpose of the vascular input function (VIF), a region of interest (ROI) was placed in the superior sagittal sinus according to the previous report [16]. The mean size of ROIs was 6 mm^2 (range, 5–8 mm^2). The VIF curve was approved by a senior neuroradiologist (XN. Hong) to ensure its accuracy. The modified Tofts model was used to calculate pharmacokinetic parameter maps, including K^{trans}, K_{ep}, V_e and V_p maps [17]. Regions of interest encompassing the entire contrast-enhancing tumor were manually drawn on each section from the DCE images of the last dynamic phase, generating a volume of interest (VOI). Necrosis, cystic portion, and large vessels were excluded during the VOI placement. The VOI was then transferred to the matching parametric maps (K^{trans}, K_{ep}, V_e, V_p maps) to obtain the average mean value of the pharmacokinetic parameters. Two experienced neuroradiologists (SS. Lu and J. Yu) performed the delineation of VOIs independently. The results were averaged and used for analysis. The mean VOIs of the enhancing component of GBMs, PCNSLs and MTs were $10.73 \pm 6.78\ cm^3$, $9.13 \pm 7.21\ cm^3$, $9.88 \pm 5.77\ cm^3$, respectively.

2.4. Statistical analysis

The interobserver agreement was measured by intraclass correlation coefficient (ICC). All the data were first assessed for normality by the Kolmogorov-Smirnov test. Then, a one-way analysis of variance (ANOVA) test was used to compare the K^{trans}, K_{ep}, V_e and V_p values and the mean VOIs among GBMs, PCNSLs and MTs. When statistical differences existed, the post-hoc test (least significant difference, LSD) was further performed within each of the two groups. The receiver operating characteristic (ROC) curve was used to determine the optimum thresholds and the diagnostic accuracy of each permeability parameter for discriminating these three tumors. The area under the ROC curve (AUC), sensitivity, and specificity were calculated. Pairwise comparison of ROC curves was further performed to determine the best permeability parameter [18].

The ICC and ANOVA test were performed with the Statistical Package for the Social Sciences software (SPSS, version 13.0, Chicago, Illinois). The ROC curves were analyzed by MedCalc