Glioma grading using an optimized T1-weighted dynamic contrast-enhanced magnetic resonance imaging paradigm

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Abstract

Background

Glioma grading is a critical procedure for selecting the most effective treatment policy. Biopsy result is the gold standard method for glioma grading, but inherent sampling errors in the biopsy procedure could lead to tumor misclassification.

Aim

This study evaluated grading performances of a more comprehensive collection of the physiological indices quantified using an optimized dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) paradigm for glioma grading.

Methods

Thirty-five patients with glioma underwent DCE-MR imaging to evaluate the grading performances of DCE-MRI-derived physiological indices. The statistical differences in the physiological indices between the different grades of gliomas were studied, and the grading performances of these parameters were evaluated using the leave-one-out cross-validation method.

Results

There were significant statistical differences in DCE-MRI-derived physiological indices between the different grades of gliomas. The mean rCBVs for grade II (low-grade glioma, LGG), grade III, grade IV, and high-grade (HGG) gliomas were 2.03 ± 0.78, 3.61 ± 1.64, 7.14 ± 3.19, and 5.28 ± 3.02, respectively. The mean rCBFs of 1.94 ± 0.97, 2.67 ± 0.96, 4.57 ± 1.77, and 3.57 ± 1.68 were, respectively, quantified for grade II (LGG), grade III, grade IV, and high-grade gliomas. The leave-one-out cross-validation method indicates that the grades of glioma tumors could be determined based on a specific threshold for each physiological index; for example, the optimal cutoff values for rCBF, rCBV, Ktrans, Kep, and Vp indices to distinguish between HGGs and LGGs were 2.11, 2.80, 0.025 mL/g min, 0.29 min^{-1}, and 0.065 mL/g, respectively.

Conclusions

From the results, it could be concluded that glioma grades could be determined using DCE-MRI-derived physiological indices with an acceptable agreement with histopathological results.

Background

Gliomas are the most common primary cerebral neoplasms which are categorized as highly vascularized malignant tumors [1,2,3,4]. More than half of all brain tumors in patients are gliomas, approximately 53% [5]. Brain tumors are classified according to their morphological, immunochemical, and molecular characteristics. In the World Health Organization (WHO) classification criteria, tumors are assigned a grade based on the histopathological features and immunohistochemical evaluations [6, 7].

Glioma grading is a critical procedure in selecting the most effective therapy policy. High-grade gliomas are usually treated by adjuvant radiation therapy and chemotherapy (after surgery) with a more aggressive treatment plan, whereas low-grade glioma would be differently treated [8]. Biopsy results are the gold standard method for glioma grading, but inherent sampling errors in the biopsy procedure could lead to tumor misclassification [9,10,11]. Gliomas are typically heterogeneous. If the biopsy sites are not properly selected or the biopsy samples have been too small, a lower grade might be assigned to the tumor. These erroneously assignments lead to selecting a non-optimal therapeutic strategy [12, 13]. There is an increasing interest in other complementary techniques such as imaging approaches. The magnetic resonance imaging (MRI) method is the most common imaging modality in the evaluation of brain tumors. Conventional MRI techniques have inherent limitations in evaluating the proliferation potential of the tumors [14, 15]. Advanced MRI methods are required to investigate the microvascular, angiogenesis, metabolism, micronecrosis, and cellularity characteristics of tumors. The bio-imaging markers can provide valuable supplementary information for glioma grading [13]. Recently, several sophisticated MRI techniques have been introduced that allow assessing the metabolic and physiological characteristics of the brain tissues [14, 16].

The perfusion weighted-magnetic resonance imaging (PW-MRI) method is one of the clinically most relevant procedures of functional MRI, which is used to assess microvasculatures, neovascularization, and capillary permeability of tumors. The assessment of tumor hemodynamics (including blood flow, blood volume, and vessel permeability) could give considerable insight into the angiogenic process of the tumor and provide additional pathological information for preoperative glioma grading [3, 17].

Tumor neo-angiogenesis results in tortuous and leaky vessels due to the lack of muscularis propria, widened interendothelial junctions, and a discontinuous or absent basement membrane. Therefore, the permeability of tumor microvasculature would significantly increase. The permeability indices describe the predominant characteristics of tumor vessels [18]. Physiological characteristics of the tumors including microvascular proliferation, aggressive cellular characteristics, and tumor-induced angiogenesis could be indirectly evaluated using perfusion indices [19].

The cerebral hemodynamic and permeability parameters are currently quantified using dynamic susceptibility contrast MRI (DSC-MRI) and dynamic contrast-enhanced MRI (DCE-MRI) approaches, respectively. Pioneer studies have shown that cerebral hemodynamic indices could be accurately quantified using an optimized DCE-MRI paradigm [20,21,22]. Quantification of tumor hemodynamics (including cerebral hemodynamic and permeability indices) based on single-dose imaging would be a useful alternative approach for tumor assessments, taking into

account the cost of double-dose acquisitions and patient safety issues. This study employs an optimized DCE-MRI-based paradigm to quantify cerebral hemodynamic and permeability indices in gliomas and evaluates the performance of the extracted parameters for glioma grading.

Methods

Imaging protocols

MRI scans were performed on a 1.5-Tesla clinical MRI scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). The MRI protocols included axial pre- and post-contrast T1-weighted spin-echo (TR/TE = 370/8.7 ms; flip angle = 90; slice thickness = 5 mm; NEX = 1; matrix = 512 × 464) and transverse T2-weighted spin-echo (TR/TE = 3300/99 ms; echo train length = 11; flip angle = 120; slice thickness = 5 mm; NEX = 2; matrix = 384 × 288) sequences. Variable flip angle technique(VFA) was used for T1 mapping, which employs a gradient echo sequence with different flip angles (α = 2°,10°,20°, and 25°; TR = 12 ms; TE = 3.5 ms; matrix size = 256 × 224; NEX = 1; slice thickness = 5 mm).
The gradient-recalled echo sequence (GR) was used for T1W DCE-MR imaging. The scanning parameters applied for perfusion imaging were: TR = 4.13 ms, TE = 1.54 ms, field of view = 200 × 200 mm2, matrix size = 256 × 224, flip angle = 15°, NEX = 1, slice thickness = 5 mm, number of measurements = 70, and gap = 5 mm.
DCE-MR images were obtained following the administration of gadoteric acid (Dotarem; Guerbet, Paris, France) in a dose of 0.1 mL/kg body weight. The injection was performed using an automatic injector at a rate of 2mL/ second followed by a 15 mL saline flush at the same rate.

DCE-MRI analysis

Motion correction of DCE-MR images was performed using the MCFLIRT function in the FMRIB Software Library (FSL; University of Oxford: http://www.fmrip.ox.ac.uk/fsl/). A 3 × 3 mean filter was used for data smoothing, and brain extraction was performed using a semi-automatic MATLAB-based program (ver. 2008a, The MathWorks TM, Natick, Massachusetts, United States).
T1W DCE-MRI data were analyzed using in-house-developed perfusion software (based on MATLAB software). The permeability indices were quantified based on the modified Kety-Tofts model. The ROIs were determined by a mouse pointer-aided method. For each physiological index, the mean values of the ROIs were registered.

Semi-quantitative analysis

Semi-quantitative indices including the initial area under the curve (IAUC60(mmol/L*Sec)), the peak contrast enhancement (Peak (mmol/L)), and the slope of the time-contrast enhancement curve (Wash-in rate (mmol/L/Sec)) are quantified using the time-contrast concentration curve. IAUC index is a robust estimation for tissue vascularization [23,24,25].
The area under the time-contrast enhancement curve from the time point of the contrast uptake to 60 s after the onset time was considered as the IAUC60. The trapezoidal method was used for the IAUC60 calculation. The peak is the absolute maximum contrast enhancement for the time-contrast concentration curve. The wash-in rate is the slope of the best-fitted line from the contrast uptake to 10 s after the onset time. The wash-in rate was determined by the sum-of-least-squares method.

Quantification of CBV and CBF indices based on the DCE-MRI data

Cerebral blood volume (CBV) and cerebral blood flow (CBF) indices could be determined based on the T1W DCE-MRI data with good agreement with the DSC-MRI-derived cerebral hemodynamic indices [22]. In this study, cerebral hemodynamic indices were quantified based on the DCE-MRI using a validated method [20, 22, 26]. Cerebral blood volume (CBV) was measured using Eq. 1:

$$\mathrm{CBVUncorrected}=H\rho\int C(t)dt\int Ca(t)dt \quad (1)$$

where $C(t)$ and $C_a(t)$ are the arterial and tissue time–concentration curves, ρ is the brain tissue density (1.04 g/mL), and $H = (1 - \mathrm{Hart})/(1 - \mathrm{Hcap})$ was applied to differentiate capillary hematocrits (Hcap = 25%) from large vessel hematocrits (Har = 45%).

CBV is the blood volume of the intravascular space. The blood volume of the leakage space has been reported as a part of the CBVuncorrected. Therefore, CBVuncorrected was corrected by the removal of volume contribution of fractional leakage space (Ve) as:

$$\mathrm{CBVcorrected} = \mathrm{CBVuncorrected} - \mathrm{veCBVuncorrected} \quad (2)$$

CBF index (in mL/100gr.min) was quantified using the following equation:

$$\mathrm{CBF}.R = 1\rho.HF - 1\{F\{C(t)\}F\{\mathrm{Ca}(t)\}\} \quad (3)$$

where R is the residual function, and $\mathrm{F}-1\{\}$ denotes the inverse Fourier transformation.

Patients

Thirty-five patients diagnosed with glioma underwent DCE-MR imaging to assess the performance of DCE-MRI-derived physiological indices for glioma grading. Patients were selected from individuals seeking medical oncologist consultations at Erbil Teaching Hospital. Prior to their participation in the study, informed consent was obtained from all patients. The patients were scanned before any medical interventions, and their glioma grades were determined based on the biopsy results. The demographic information of the patients is summarized in Table 1. The study was approved by the local committee for medical research ethics.

Table 1 Demographic and clinical characteristics of the studied patients

Full size table

Patients' data were analyzed using the mentioned algorithms and methods in the previous section. For each patient, the region of interest (ROI) was selected on the high perfusion area of the CBV map [27]. The relative cerebral hemodynamic changes (rCBV and rCBF) were measured as the mean cerebral hemodynamic magnitude of tumor ROI divided by the mean value in the mirror ROI on the contralateral normal lobe.

Statistical analysis

The normality of the distribution of DCE-MRI-derived physiological indices was checked using the Shapiro–Wilk test. The *Mann–Whitney* U *test* and independent student T test analyses were used to evaluate the difference in the parameters between the different grades of gliomas.

Evaluation of DCE-MRI-derived physiological indices for glioma grading

In classification studies, cross-validation methods are used to achieve an optimal classifier. In this method, different classification structures are examined and the classification performances of these structures would be determined. Finally, the classification structure with the best classification performance is chosen. The results of these methods are not reliable when the study sample size is small. The leave-one-out cross-validation method could yield reliable results in such cases. In this study, the leave-one-out cross-validation method is used to evaluate the grading performances of DCE-MRI-derived physiological parameters for glioma grading.
The grading performances of the physiological indices were evaluated for the patients with different glioma grades including grade II (LGG), grade III, grade IV, and high-grade gliomas (HGG, including grade III and grade IV gliomas).
The accuracy, sensitivity, specificity, positive prediction value (PPV), and negative prediction value (NPV) of the physiological indices for glioma grading were determined according to the biopsy results as the gold standard method.
In this study, tumor grade was determined based on the biopsy results and PW-MR imaging data. Kappa index was used to determine the agreement between these grading approaches. The magnitude of the kappa index is ranged from zero to 1. There is a better agreement between the two grading methods when the Kappa coefficient is closer to 1. The kappa coefficient is calculated using Eq. 4.

$$k=p(a)-p(e)1-p(e) \tag{4}$$

where $P(a)$ and $P(e)$ are, respectively, the observed and expected agreements between the tumor grades determined using the imaging indices and biopsy results. $P(a)$ and $P(e)$ were calculated using the following equations:

$$P(a)=\mathrm{TH}+\mathrm{TLTH}+\mathrm{TL}+\mathrm{FH}+\mathrm{FL} \tag{5}$$

$$P(e)=\mathrm{TH}+\mathrm{FLTH}+\mathrm{TL}+\mathrm{FH}+\mathrm{FLTH}+\mathrm{FHTH}+\mathrm{TL}+\mathrm{FH}+\mathrm{FLTL}+\mathrm{FHTH}+\mathrm{TL}+\mathrm{FH}+\mathrm{FLTL}+\mathrm{FLTH}+\mathrm{TL}+\mathrm{FH}+\mathrm{FL} \tag{6}$$

where TH is the number of patients that were correctly classified using the proposed method as higher-grade glioma (compared with the pathological results), TL is the number of patients that were correctly classified using the proposed method as lower-grade glioma, FH is the number of patients that were wrongly classified using the proposed method as higher-grade glioma, and FL is the number of patients that were wrongly classified using the proposed method as lower-grade glioma.
The grading performances of DCE-MRI-derived physiological indices for glioma grading were also investigated based on a unique classification score including cerebral hemodynamic (rCBV and rCBF), permeability (Ktrans, Kep, etc.), and semi-quantitative (IAUC60 and Peak) indices. In the unique classification score, the weights of the physiological indices were assumed to be the same and equal to 1.

The grading performance of the unique classification score for glioma grading was determined using the method described in Seeger et al. and Matsusue et al. studies [28, 29]. In this method, a grade is assigned to the tumor of each patient. If the patient is classified as a subject with a higher grade glioma, the value of 1 assigned and the value of zero would be assigned to the patient with a lower grade glioma. For each patient, the assigned values are summed. If the achieved value is greater than 3, the patient is classified as a subject with a higher grade of glioma. Otherwise, the patient's tumor would be considered a lower-grade glioma. The classification metrics of this grading system (including kappa coefficient, accuracy, sensitivity, etc.) were also determined using the biopsy results as the gold standard method.
The statistical analyses were performed using SPSS (ver.16.0, SPSS Inc., Chicago, IL) and MATLAB (ver. 2008a, The MathWorks TM, Natick, Massachusetts, United States) softwares.

Results

DCE-MRI data were analyzed using a valid method and the perfusion maps including cerebral hemodynamic (CBV and CBF), permeability (Ktrans, Kep, etc.), and semi-quantitative (IAUC60, Peak, etc.) indices were extracted. The exemplary maps achieved for a 57-year-old woman with glioblastoma multiforme (GBM) are shown in Fig. 1.