Microvascular permeability parameters (Ktrans, Ve) in glioma grading and correlation analysis with intratumoral susceptibility signal intensity on HR-SWI

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Aims and objectives

Introduction

Glioma is the most common intracranial primary tumor of central nervous system. The optimum therapeutic treatment and prognosis evaluation largely depend on the tumor pathological grades. As we know, the continued growth of the tumor needs neovascular proliferation. Pathological angiogenesis has been demonstrated to be associated with tumoral differentiation and aggressiveness[1]. Previous study[2] indicates that neoangiogenesis as well as vascular permeability and the appearence of VEGF (vascular endothelial growth factors) are important mediators of brain tumor growth.

Currently, dynamic contrast-enhanced MRI (DCE-MRI) can provide very important information about neovascularity and angiogenesis in gliomas. The volume transfer constant (Ktrans) has been reported as a reliable biological indicator in glioma grading on several studies [3,4]. However, contrary to Ktrans, the Ve value are rarely reported in literatures, and has been considered to be related with the volume of EES (extravascular extracellular space) and the permeability of the vessels; and the Ve value will increase in tumor necrosis or cystic area and decrease in high cellularity area[5]. The diagnostic performance of this quantitative parameter remains to be confirmed.

High resolution susceptibility weighted imaging (HR-SWI) is a new MR imaging method that can enhance sensitivity to susceptibility effects associated with microvessels structures and blood products[6]. Due to the unique advantage, HR-SWI has been used widely in the assessment of vascularity and micro- or macro-hemorrhage within brain tumors. The basic foundation for evaluation of intracranial neoplasms on HR-SWI are those low signal intensity structures termed "intratumoral susceptibility signals" (ITSS) that cannot all be detected by conventional MR imaging[7].

Thus theoretically, there may be certain relationship between Ktrans as well as Ve and ITSS signal due to the identical tumor vascular tissue. The purpose of this study was firstly to assess the ability of using Ktrans (volume transfer constant), Ve(extravascular extracellular space) and ITSS (intratumoral susceptibility signal intensity) in grading of gliomas, and secondly to determine whether Ktrans (max) and Ve(max) values correlates with the degree of ITSS in the same segment of glioma on High Resolution Susceptibility Weighted Imaging at 3.0 Tesla.
Methods and materials

Eighteen patients with different types of gliomas (12 men, 6 women; aged 12-63 years, with mean of 42±13 years) were enrolled in this study. MR imaging protocol included dynamic contrast enhanced T1-weighted MR perfusion and non-contrast enhanced HR-SWI. We respectively correlated the Ktrans(max) as well as Ve(max) with the degree of ITSS in the same tumor segments. Analysis of variance (ANOVA) was used to compare Ktrans and Ve values and Kruskal-Wallis test was used to compare ITSS degrees among different grades of gliomas. Spearman correlation analysis was used to determine relationship between Ktrans(max), Ve(max) and the degree of ITSS, and tumor grade. Receiver operating characteristic (ROC) curve analyses was conducted to decide the diagnostic performance of Ktrans and Ve for glioma grading.
Results

Ktrans\(_{(\text{max})}\) and Ve\(_{(\text{max})}\) were significantly lower in LGG (low grade glioma, grade II) (0.017 and 0.076 respectively) than in HGG (high grade glioma, grade III and grade IV) (0.014 and 0.663 respectively).

Moreover, the ROC curve analyses demonstrated that the cut-off values of Ktrans\(_{\text{(max)}}\) and Ve\(_{\text{(max)}}\) were 0.045/min and 0.449 for differentiation significantly between LGG and HGG with the same sensitivity (90.0%) and specificity (100%) (p<0.01 and p<0.01 respectively). The areas under the curve (AUC) of Ktrans\(_{\text{(max)}}\) and Ve\(_{\text{(max)}}\) were 0.944 and 0.950, respectively; there was no statistical difference between Ktrans\(_{\text{(max)}}\) and Ve\(_{\text{(max)}}\). The cut-off values of ktrans\(_{\text{(max)}}\) (0.045 min\(^{-1}\)) and Ve\(_{\text{(max)}}\) (0.449) also generated a best combination of the same sensitivity (85.7%) and specificity (100%) for differentiating grade II from grade III (p<0.01 and p<0.01 respectively), and the AUC was 0.920 and 0.929, respectively; and no statistical difference were found between Ktrans and Ve. The degree of ITSS signals in the LGG was significantly lower than that in the HGG (p<0.01).

Spearman correlation coefficients between ITSS degree and glioma grade was 0.73 (p<0.01). Ktrans\(_{\text{(max)}}\) and Ve\(_{\text{(max)}}\) values were positively correlated with the degree of ITSS (both p<0.01). Ktrans\(_{\text{(max)}}\) values were positively correlated with the Ve\(_{\text{(max)}}\) values (p<0.01).

Through comparative analysis of DCE and SWI images, we found that irrespective of tumor grade, the visual Ktrans\(_{\text{(max)}}\) and Ve\(_{\text{(max)}}\) maps showed a significant correlation with the degree of ITSS within the same tumor segments. For low-grade gliomas, there was no or sporadic dotlike ITSS within the tumor, which displayed relatively low Ktrans\(_{\text{(max)}}\) values on corresponding Ktrans map. By contrast, conglomerated mixed dotlike and fine linear ITSS signals were seen frequently in high-grade gliomas that always showed higher values of Ktrans\(_{\text{(max)}}\), and a portion of those ITSS signals corresponded with the area of visual Ktrans\(_{\text{(max)}}\). On the other hand, the areas of visual Ktrans\(_{\text{(max)}}\) and Ve\(_{\text{(max)}}\) did not always accurately correspond to places with the densest ITSS signals, especially glioblastomas.

Interestingly, there was one glioblastoma multiforme with 2 month of process that showed no signs of ITSS signal on HR-SWI, however, this unique tumor inconsistently exhibited significantly high microvascular permeability (high ktrans and Ve) on DCE-MRI.
**Table 1:** The mean $K_{\text{trans(max)}}$ and $V_e(\text{max})$ values of different grades of gliomas. $K_{\text{trans(max)}}$/min$^{-1}$: the maximal value of volume transfer constant, $V_e(\text{max})$: the maximal value of volume of extravascular extracellular space. LGG: grade II glioma, HGG: grade III and grade IV glioma.

<table>
<thead>
<tr>
<th>Tumor grade</th>
<th>$K_{\text{trans(max)}}$/min$^{-1}$</th>
<th>$V_e(\text{max})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade II</td>
<td>0.017±0.009</td>
<td>0.076±0.139</td>
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<tr>
<td>Grade III</td>
<td>0.094±0.067</td>
<td>0.629±0.310</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0.161±0.024</td>
<td>0.764±0.165</td>
</tr>
<tr>
<td>LGG</td>
<td>0.017±0.009</td>
<td>0.076±0.139</td>
</tr>
<tr>
<td>HGG</td>
<td>0.114±0.065</td>
<td>0.663±0.274</td>
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</table>

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Fig. 1: A-B.Box plot of transfer constant (Ktrans(max)), extravascular extracellular space (Ve(max)) between low and high-grade gliomas. The mean values of Ktrans(max) and Ve(max) were significantly lower in LGG (low grade glioma, grade II) (0.017 and 0.076 respectively) than in HGG (high grade glioma, grade III and grade IV) (0.014 and 0.663 respectively). C-D.Box plot of transfer constant (Ktrans(max)), extravascular extracellular space (Ve(max)) between grade II and grade III gliomas. The mean values of Ktrans(max) and Ve(max) were significantly lower in grade II (0.017 and 0.076 respectively) than in grade III (0.094 and 0.629 respectively).

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Fig. 2: The ROC curve analyses demonstrated that the cut-off values of Ktrans(max) and Ve(max) were 0.045/min and 0.449 for differentiation significantly between LGG and HGG with the same sensitivity (90.0%) and specificity (100%)(AUC 0.944 for Ktrans and 0.950 for Ve respectively)(both p<0.01)
Fig. 3: The ROC curve analyses also demonstrated that the cut-off values of $K_{\text{trans}}(\text{max})$ and $V_e(\text{max})$ were 0.045/min and 0.449 for differentiation significantly between grade II and grade III gliomas with the same sensitivity (90.0%) and specificity (100%)(AUC 0.920 for $K_{\text{trans}}$ and 0.929 for $V_e$ respectively)(both $p<0.01$)

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Table 2: The relationships between Ktrans(max), Ve(max), the degree of ITSS and tumor grades. NOTE-**Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed). N= 18 represents all of the gliomas. N=17 represents the rest of gliomas in which one case of glioblastoma with no ITSS signal on HR-SWI was excluded.

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<table>
<thead>
<tr>
<th></th>
<th>Ktrans</th>
<th>Ve</th>
<th>ITSS</th>
<th>Grade</th>
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<tr>
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<td>.707**</td>
<td>.792**</td>
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<td><strong>P value</strong></td>
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<td>.000</td>
<td>.001</td>
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<td><strong>N</strong></td>
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<td>18</td>
<td>17</td>
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<tr>
<td><strong>Correlation coefficient</strong></td>
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**Fig. 4:** MR images of a 44-year-old woman with right frontal low-grade astrocytoma (WHO grade II). A, The axial T2-weighted image shows an ill-defined mass with high signal intensity in the right frontal lobe. B-C, Corresponding Ktrans and Ve map shows relatively low Ktrans(max) and Ve(max) values (0.008 and 0.013, respectively). D, HR-SWI demonstrates no evidence of the ITSS signals. E, Corresponding histopathologic specimen (CD34 immunostaining, original magnification ×200) shows slender microvessels within the tumor.

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**Fig. 5:** MR images of a 44-year-old woman with a anaplastic oligodendrogliomas. A, The contrast-enhanced axial T1-weighted image shows a mass with irregular peripheral rim enhancement in the right temporal lobe. B, Signal concentration curve showed a quick wash-in pattern of time-intensity curve due to blood-brain barrier breakdown. C, HR-SWI reveals conglomerated dotlike or fine linear ITSS signal in the inner portion of the enhancing rim on the contrast-enhanced T1-weighted image. D-E, Corresponding Ktrans and Ve map shows high Ktrans(max) and Ve(max) values (0.057 and 0.812, respectively) in the tumor segment, including a maximum degree of ITSS. But those areas of visual Ktrans(max) and Ve(max) do not completely correspond with the areas of attenuated prominent ITSS signals (white arrows). F, Corresponding histopathologic specimen (CD34 immunostaining, original magnification ×200) shows the microvessels with increased MVD and enlarged diameter.
Fig. 6: MR images of a 13-year-old boy with a glioblastoma multiforme with 2 month of process. A, The contrast-enhanced axial T1-weighted image shows a mass with regular peripheral rim enhancement in the right frontal lobe. B, Signal concentration curve shows a quick wash-in pattern of time-intensity curve due to blood-brain barrier breakdown. C-D, Corresponding Ktrans and Ve map shows high Ktrans(max) and Ve(max) values (0.183 and 0.649, respectively) in the whole tumor. E, Strangely, HR-SWI reveals no evidence of the ITSS signals. F, Corresponding histopathologic specimen (CD34 immunostaining, original magnification ×200) shows the microvessels with increased MVD and enlarged diameter.

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Conclusion

Ktrans and Ve values are well correlated with glioma grade, both of them can be used not only to distinguish the low from the high grade gliomas, but also grade II from grade III via testing microvascular permeability. This is the first time that we reported a close relationship between DCE-MRI parameters (Ktrans(max), Ve(max)) and ITSS signals derived from HR-SWI. The Ktrans (max) and Ve(max) showed a significant correlation with the degree of ITSS. However, the direct correspondence relationship between the regions of ITSS and Ktrans(max) or Ve(max) was not changeless, especially high grade glioma, regions with highest permeability do not always represent the richest microvessel area.

In addition, we highly doubt that HR-SWI may have some certain defects in displaying microvessels on early stage of HGG. However, DCE-MRI is superior to HR-SWI at showing those growing microvessels with high permeability. Further studies with larger populations are needed to test our deduction.
Personal information

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