Prediction of radiosensitivity in primary central nervous system germ cell tumors using dynamic contrast-enhanced magnetic resonance imaging

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Objective: To evaluate the feasibility of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for predicting tumor response to radiotherapy in patients with suspected primary central nervous system (CNS) germ cell tumors (GCTs).

Methods: DCE-MRI parameters of 35 patients with suspected primary CNS GCTs were obtained prior to diagnostic radiation, using the Tofts and Kermode model. Radiosensitivity was determined in tumors diagnosed 2 weeks after radiation by observing changes in tumor size and markers as a response to MRI. Taking radiosensitivity as the gold standard, the cut-off value of DCE-MRI parameters was measured by receiver operating characteristic (ROC) curve. Diagnostic accuracy of DCE-MRI parameters for predicting radiosensitivity was evaluated by ROC curve.

Results: A significant elevation in transfer constant ($K_{\text{trans}}$) and extravascular extracellular space ($V_e$) ($P=0.000$), as well as a significant reduction in rate constant ($K_{\text{ep}}$) ($P=0.000$) was observed in tumors. $K_{\text{trans}}$, relative $K_{\text{trans}}$, and relative $K_{\text{ep}}$ of the responsive group were significantly higher than non-responsive groups. No significant difference was found in $K_{\text{ep}}, V_e$, and relative $V_e$ between the two groups. Relative $K_{\text{trans}}$ showed the best diagnostic value in predicting radiosensitivity with a sensitivity of 100%, specificity of 91.7%, positive predictive value (PPV) of 95.8%, and negative predictive value (NPV) of 100%.

Conclusions: Relative $K_{\text{trans}}$ appeared promising in predicting tumor response to radiation therapy (RT). It is implied that DCE-MRI pre-treatment is a requisite step in diagnostic procedures and a novel and reliable approach to guide clinical choice of RT.

Keywords: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI); extravascular extracellular space; germ cell tumors (GCTs); radiosensitivity; rate constant; transfer constant

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Introduction

Primary central nervous system (CNS) germ cell tumors (GCTs) are rare and account for 0.5% of all primary CNS tumors in the West (1), while they are more common in China and other Asian countries and constitute approximately 2.0-7.9% of primary CNS tumors in adults or children (2,3). GCTs encompass a wide pathologic spectrum, and each specific subtype has different treatment options and prognosis. However, there are some overlaps in clinical presentation and tumor markers among GCTs subtypes, and conventional neuroimaging characteristics are of little diagnostic value for differentiating GCT subtypes. Furthermore biopsy is not widely practiced recently, because anatomically GCTs are located deep and adjacent
to some important structures and vessels. In addition, the sample is often insufficient to confirm the diagnosis (4). Thus, diagnostic radiation serves as an alternative method to determine the histological type of GCTs (5,6). But side effects and late sequelae induced by radiation therapy (RT) have led to questions on the reliability of diagnostic radiation. Hence, we tried to find a non-invasive imaging method to replace the diagnostic radiation for predicting tumor response to RT, so that the treatment strategy could be determined or modified according to radiosensitivity of tumors, rather than just based on histological assessment.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a non-invasive quantitative technique in assessing microvascular permeability, and in distinguishing benign from malignant tumors of the brain, breast, kidney, and sino-nasal (7-9). Recently, several studies demonstrated that DCE-MRI data could monitor the early changes in tumor response to therapy, so that it can be used to evaluate tumor response to various treatments before the tumor size appears to change (10-13). Furthermore, kinetic parameters derived from DCE-MRI can reflect tumor microenvironment variables, which play an important role in the assessment of tumor response to RT (14). Certain studies evaluated the predictive role of DCE-MRI in assessing tumor response to radiotherapy carried out for the cervix, colorectal, and brain tumors (15-17). However, to date, clinical research regarding GCTs’ response to RT is hardly seen. Therefore, our study aims to investigate the changes in pharmacokinetic DCE-MRI parameters in tumor tissue before RT and evaluate the feasibility of DCE-MRI in predicting radiosensitivity of GCTs.

**Materials and methods**

**Patients**

The study was approved by the institutional review board of Beijing Tiantan Hospital and informed consent was obtained from all patients. Thirty-five patients clinically diagnosed with primary CNS GCTs from Jun 2013 to Nov 2014 were recruited in this study. Patients were included if they fulfilled the following inclusion criteria: patients with untreated mass in pineal, basal ganglia, and/or suprasellar region, which were suspiciously diagnosed as GCTs by clinical symptoms, tumor markers, and neuroimaging manifestations; normal or slightly elevated levels of \( \beta \)-human chorionic gonadotropin (\( \beta \)-HCG) in serum and cerebrospinal fluid, and normal levels of \( \alpha \)-fetoprotein (AFP). Exclusion criteria were elevated levels of \( \beta \)-HCG, i.e., >1,000 mIU/mL, children younger than 5 years, stereotactic radiotherapy, chemoradiotherapy, or any other MR contraindications.

DCE-MRI was conducted prior to diagnostic radiation. All patients received 10 Gy diagnostic radiation after baseline MRI examination. Two weeks after diagnostic radiation, patients were evaluated on radiosensitivity and divided into two groups: responsive group and non-responsive group. Criteria for responsive groups were reduction in tumor size \( \geq 50\% \) compared with baseline tumor size in MRI (18), and levels of \( \beta \)-HCG, AFP in serum and cerebrospinal fluid within normal limits.

**MRI protocol**

MRI was performed on a 3.0 T MR system (Trio Tim, Siemens healthcare, Germany) with an eight-channel head coil. The MRI protocol included sagittal T1WI [repetition time (TR)/echo time (TE), 1,200/11 ms; field of view (FOV) 220 mm × 220 mm] and axial T1WI (TR/TE, 2,000/9.8 ms; FOV 220 mm × 186 mm), axial T2WI (TR/TE, 4,500/84 ms; FOV 220 mm × 186 mm), slice thickness/gap, 5.0/0 mm, matrix 256×256, T1-magnetization prepared rapid gradient echo (T1-MPRAGE) (TR/TE, 2,300/3.01 ms; slice thickness/gap, 1.0/0 mm, matrix 256×256, FOV 240 mm × 240 mm).

**DCE-MRI processing**

DCE-MRI was performed using a T1-weighted 3D radial gradient-recalled echo sequence (Volumetric Interpolated Breath-hold Examination, VIBE). The parameters are as follows: TR/TE: 3.86/1.39 ms, flip angle: 12°, slice thickness/gap: 3.0/0 mm, matrix 256×256, T1-magnetization prepared rapid gradient echo (T1-MPRAGE) (TR/TE, 2,300/3.01 ms; slice thickness/gap, 1.0/0 mm, matrix 256×256, FOV 240 mm × 240 mm).
and registration were performed before pharmacokinetic evaluation. The artery input function was measured automatically by gadolinium dose in an intermediate mode. The transfer constant ($K_{\text{trans}}$), extravascular extracellular space ($V_e$), and rate constant ($K_{ep}$) were calculated using the Tofts and Kermode pharmacokinetic model (19). Meanwhile, maps for pharmacokinetic parameters were generated automatically. The region of interest (ROI) was selected by an experienced neuroradiologist inside the tumor as well as in normal brain tissue to obtain the pharmacokinetic DCE-MRI parameters. Normal brain tissue was defined as right or contralateral frontal subcortical white matter which showed no enhancement. During the drawing of ROI, cystic, necrotic, hemorrhagic regions, and normal vessels within the ROIs were avoided. Relative pharmacokinetic DCE-MRI parameters were defined as the ratio of DCE-MRI parameters between tumors and normal brain tissue.

### Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Differences in DCE-MRI parameters between groups were compared by Wilcoxon signed-rank test and Mann-Whitney U-test. The correlation between DCE-MRI parameters and changes in tumor volume was analyzed using Spearman’s correlation analysis. Taking radiosensitivity as a gold standard for reference, the cut-off value of DCE-MRI parameters was calculated by receiver operating characteristic (ROC) curve. The area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to evaluate diagnostic value of DCE-MRI parameters. P<0.05 was considered statistically significant.

### Results

#### Patient characteristics

Of 35 patients suspected for primary CNS GCTs recruited

<table>
<thead>
<tr>
<th>Table 1 DCE parameters of normal brain tissue and tumor tissue [median (min, max)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DCE parameters</strong></td>
</tr>
<tr>
<td>$K_{\text{trans}}$ (/min)</td>
</tr>
<tr>
<td>$K_{ep}$ (/min)</td>
</tr>
<tr>
<td>$V_e$</td>
</tr>
</tbody>
</table>

DCE, dynamic contrast-enhanced.
Table 2 DCE parameters of responsive group and non-responsive group [median (min, max)]

<table>
<thead>
<tr>
<th>DCE parameters</th>
<th>Responsive group</th>
<th>Non-responsive group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(K_{\text{trans}}) (1/min)</td>
<td>0.035 (0.020, 0.056)</td>
<td>0.026 (0.010, 0.080)</td>
<td>0.037</td>
</tr>
<tr>
<td>(K_{\text{ep}}) (1/min)</td>
<td>0.513 (0.152, 1.120)</td>
<td>0.486 (0.350, 2.460)</td>
<td>0.351</td>
</tr>
<tr>
<td>(V_{c})</td>
<td>0.116 (0.020, 0.260)</td>
<td>0.117 (0.010, 0.220)</td>
<td>0.431</td>
</tr>
<tr>
<td>Relative (K_{\text{trans}})</td>
<td>4.000 (2.222, 15.000)</td>
<td>1.513 (0.340, 6.500)</td>
<td>0.000</td>
</tr>
<tr>
<td>Relative (K_{\text{ep}})</td>
<td>0.647 (0.340, 4.505)</td>
<td>0.133 (0.034, 1.490)</td>
<td>0.002</td>
</tr>
<tr>
<td>Relative (V_{c})</td>
<td>10.636 (3.550, 65.000)</td>
<td>14.000 (2.167, 49.300)</td>
<td>0.157</td>
</tr>
</tbody>
</table>

DCE, dynamic contrast-enhanced.

Figure 1 MR images in an 11-year-old female patient with pineal region mass sensitive to RT. The mass shows marked hyperintensities in \(K_{\text{trans}}\) map (A) and \(V_{c}\) map (B); and marked hypointensities in \(K_{\text{ep}}\) map (C). Enhanced T1-weighted MRI (D) demonstrates that the mass has obvious homogeneous enhancement. RT, radiation therapy; MRI, magnetic resonance imaging.
between the two groups by ROC curve analysis (Figure 3). ROC curve analysis showed that the cut-off value of $K_{\text{trans}}$, relative $K_{\text{trans}}$, and relative $K_{ep}$ was 0.022, 2.066 and 0.188, respectively, and indicated a good level of diagnostic accuracy for the prediction of radiosensitivity. The AUC, sensitivity, specificity, PPV, NPV parameters for predicting radiosensitivity are presented in Table 3. As shown in Table 3, relative $K_{\text{trans}}$ showed best diagnostic value in predicting radiosensitivity with a sensitivity of 100%, specificity of 91.7%, PPV of 95.8%, and NPV of 100%.

**Discussion**

The present study investigates the differences in pharmacokinetic DCE-MRI parameters of normal brain tissue and tumors in patients with CNS GCTs, and demonstrates the efficacy of DCE-MRI in predicting radiosensitivity of CNS GCTs.

Characterized by angiogenesis, solid tumors often have abnormal blood vessel structure, function, and enhanced microvascular permeability. Currently both animal studies (20,21) and clinical studies (7-9) revealed that DCE-MRI is widely used to assess microvascular permeability, which may further contribute to distinguish benign from various solid malignant tumors. However, very little is currently known concerning tumor vasculature of CNS GCTs. In our study, we found that, similar to most solid tumors, tumor tissue of GCTs has a mildly increased $K_{\text{trans}}$. It indicates that the

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**Figure 2** MR images in a 10-year-old male patient with multilocular pineal region mass after ventriculo-peritoneal shunt operation. Marked hypointensities were shown in $K_{\text{trans}}$ map (A); in $K_{ep}$ map (B); and in $V_e$ map (C) except for slightly patchy hyperintensities in the wall of cyst. Enhanced T1-weighted MRI (D) appeared as honeycomb-like enhancement in the mass. MRI, magnetic resonance imaging.
increased microvascular permeability of GCTs might be due to the disruption of the blood-brain barrier (BBB). This finding is consistent with previous studies, which proposed that BBB is relevant in patients with metastatic GCTs (22). Furthermore, an elevation of \( V_e \) in GCTs corresponds to a relative increase in extravascular extracellular spaces, which implied that GCTs changed in a tumor microenvironment.

Radiosensitivity is an important characteristic of CNS GCTs concerning tumor response to RT. Although optimal management for GCTs remains controversial, RT is well known as a critical component in multi-modal treatment of GCTs and provides favorable outcomes and long-term survival (1,23-25). Thus, prediction of tumor response to RT is a prerequisite for optimal selection of the timing and the field of RT. Kinetic data obtained by DCE-MRI regarding the changes in microvascular permeability and microenvironment can enhance understanding of the underlying mechanism of tumor response to RT (15-17). Although our attempt to analyze the relationship between pharmacokinetic DCE-MRI parameters and changes in tumor volume failed to show any significant correlation, the differences in \( K_{\text{trans}} \), relative \( K_{\text{trans}} \), and relative \( K_{\text{ep}} \) between the responsive and non-responsive groups were significant, which was consistent with the result of Hans's study (17). They performed DCE-MRI in 31 patients with rectal cancers before chemoradiotherapy, and demonstrated that responsive tumors had higher values of DCE-MRI parameters than non-responsive tumors. This finding indicated that different response of GCTs was caused by pharmacokinetic parameters concerning tumor microvascular permeability.

In addition, we used the cut-off value of \( K_{\text{trans}} \), relative \( K_{\text{trans}} \) and relative \( K_{\text{ep}} \) to stratify GCTs for predicting radiosensitivity. Relative \( K_{\text{trans}} \) showed the best diagnostic value in predicting response with a sensitivity of 100% and specificity of 91.7% by ROC curve analysis. Unlike absolute value, relative pharmacokinetic parameters are more objective and accurate, and can overcome the impact of environment and individual differences. Our study showed that relative \( K_{\text{trans}} \) may be more applicable than absolute value with high sensitivity and specificity. Given methodologic simplicity, noninvasiveness, and wider applicability, we propose that relative \( K_{\text{trans}} \) derived from DCE-MRI should replace diagnostic radiation as a useful and requisite step in the diagnostic procedures.

Our study has some limitations. The response evaluation criteria for diagnostic radiation were inconsistent with the requirement of the Response Evaluation Criteria in Solid Tumors Standard (26). However, previous studies tested the precision and repetition of this diagnostic means using the same criteria (18,23). Moreover, these criteria of diagnostic radiation have been applied in clinical practice for several decades (27). Additionally, owing to low prevalence of

### Table 3 ROC curve analysis of DCE-MRI parameters for assessment of radiosensitivity in GCTs

<table>
<thead>
<tr>
<th>DCE parameters</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative ( K_{\text{trans}} )</td>
<td>0.933</td>
<td>100</td>
<td>91.7</td>
<td>95.8</td>
<td>100</td>
</tr>
<tr>
<td>Relative ( K_{\text{ep}} )</td>
<td>0.812</td>
<td>100</td>
<td>66.7</td>
<td>85.2</td>
<td>100</td>
</tr>
<tr>
<td>( K_{\text{trans}} )</td>
<td>0.701</td>
<td>87.0</td>
<td>50.0</td>
<td>76.9</td>
<td>66.7</td>
</tr>
</tbody>
</table>

ROC, receiver operating characteristic; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; GCTs, germ cell tumors; DCE, dynamic contrast-enhanced; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.
GCTs, the sample size of this study is relatively small and the interpretation of the results will be limited.

Conclusions

This study demonstrates that relative $K_{trans}$ derived from DCE-MRI is helpful in predicting radiosensitivity of GCTs. It can be used to guide clinical choice of RT and assist in finding new clinical perspective and insight for clinical diagnosis of GCTs. Our results imply that DCE-MRI may replace diagnostic radiation and serve as a novel and reliable approach to assess radiosensitivity of GCTs before treatment and represent a requisite step in the diagnostic procedures.

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References


