Looking through the imaging perspective: the importance of imaging necrosis in glioma diagnosis and prognostic prediction

Hui Ma  
First Affiliated Hospital of Sun Yat-sen University

Shanmei Zeng  
First Affiliated Hospital of Sun Yat-sen University

Dingxiang Xie  
First Affiliated Hospital of Sun Yat-sen University

Wenting Zeng  
First Affiliated Hospital of Sun Yat-sen University

Yinqian Huang  
First Affiliated Hospital of Sun Yat-sen University

Liwei Mazu  
First Affiliated Hospital of Sun Yat-sen University

Nengjin Zhu  
First Affiliated Hospital of Sun Yat-sen University

Zhiyun Yang  
First Affiliated Hospital of Sun Yat-sen University

Jianping Chu  
First Affiliated Hospital of Sun Yat-sen University

Jing Zhao  
zhaoj23@mail.sysu.edu.cn  
First Affiliated Hospital of Sun Yat-sen University

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Abstract

Purpose

To investigated the diagnostic value of imaging necrosis (Im\textsubscript{necrosis}) in grading, predicting the genotype and prognosis of gliomas, and further assessed the association of tumor necrosis and hypoxia, which was assessed by dynamic contrast-enhanced MR perfusion imaging (DCE-MRI).

Materials and Methods

We retrospectively included 150 (46 females, mean age: 46 years old) pathologically proved adult diffuse gliomas, and all diagnosis based on the 2021 WHO CNS classification. The pathological necrosis (Pa\textsubscript{necrosis}) and gene mutation information (IDH, 1p19q, EGFR amplification, chr7 gain/10 loss, CDKN2A/B) was collected. All patients underwent conventional (T1WI, T2WI, FLAIR) and DCE-MRI examinations, and has been followed until May 31, 2021. The Im\textsubscript{necrosis} was determined by two expericed neuroradiologists. DCE-MRI derived metric (k\textsubscript{trans}, ve, kep and iauc) maps have been postprocessed and the mean value of each metric in the tumor parenchyma, peritumoral and contralateral area were recorded. Various statistical analyses such as survival analysis were performed.

Results

There was a strong degree of inter-observer agreement in defining Im\textsubscript{necrosis} (Kappa = 0.668, p < 0.001), and a strong degree of agreement between Im\textsubscript{necrosis} and Pa\textsubscript{necrosis} (Kappa = 0.767, p < 0.001). Compared to low-grade gliomas, high-grade gliomas had more Im\textsubscript{necrosis} (85.37%, p < 0.001), and Im\textsubscript{necrosis} significantly increased with the grade of gliomas increasing (p < 0.001). And Im\textsubscript{necrosis} was significantly more identified in IDH-wildtype, 1p19q-non-codeletion, and CDKN2A/B-homozygous-deletion gliomas (all p < 0.01). Using multivariate Cox regression analysis, Im\textsubscript{necrosis} was an independent and unfavorable prognosis factor (Hazard Ratio = 2.113, p = 0.046) in gliomas. Additionally, Im\textsubscript{necrosis} in tumor parenchyma derived from DCE-MRI demonstrated the highest diagnostic efficiency in identifying Pa\textsubscript{necrosis} and Im\textsubscript{necrosis} with high specificity (83.3% and 91.9%, respectively).

Conclusions

Im\textsubscript{necrosis} can provide supplementary evidence beyond Pa\textsubscript{necrosis} in grading, predicting the genotype and prognosis of gliomas, and tumor parenchyma ve can help to predict tumor necrosis with high specificity.

Introduction

Owing to the dramatic proliferation and expansion of tumor cells, necrosis is a common feature of human cancer and is often related to a poor prognosis, especially in glioblastoma multiforme (GBM) [1–3]. The latest 2021 WHO classification of Tumors of the Central Nervous System (CNS) highlighted and underlined the significant value of necrosis in the diagnosis and prognosis of adult diffuse gliomas [4]. Once histological necrosis is identified, a diagnosis of WHO grade 4 astrocytoma or glioblastoma is suggested. However, there is a diagnostic dilemma in grading gliomas by identifying necrosis.

Presently, necrosis is primarily determined by pathological examination, in which partial tumor specimens from certain sites of tumors obtained by surgery or biopsy at a single point in time are generally inspected [5]. However, due to tumor heterogeneity and incompleteness of the pathological sample, some instances of pathological necrosis are likely to be missed, which may result in an underestimation of tumor grades, even in this era of molecular diagnosis. As tumor grades influence therapeutic decisions and prognosis, it is imperative to make up the problem of a missed diagnosis of necrosis on pathological evaluation.

As of now, magnetic resonance imaging (MRI) is utilized for routine, noninvasive, preoperative examination in the diagnosis of gliomas. Pathological necrosis usually has corresponding imaging features [6, 7]. Therefore, necrosis in gliomas, when substantially present, can be detected by MRI [8, 9, 10] and plays an important role in diagnosing gliomas and predicting prognosis [6, 9–13]. Moreover, MRI can acquire comprehensive images of entire tumors, which is not possible with pathological examinations.

Taking all of this into account, we speculated whether necrosis diagnosed by MRI (henceforth termed “imaging necrosis”, abbreviated as Im\textsubscript{necrosis}) can be used as a correction or a supplement to necrosis diagnosed by pathological evaluation (henceforth termed “pathological necrosis”, abbreviated as Pa\textsubscript{necrosis}), especially when there is no evidence of Pa\textsubscript{necrosis} owing to limited sampling sites and sampling amounts. Consequently, herein, we retrospectively reviewed MRI findings of adult diffuse gliomas that were diagnosed based on the 2021 WHO CNS classification and assessed the role of Im\textsubscript{necrosis} in grading, predicting the genotype and prognosis of gliomas. We also attempted to analyze the association of tumor necrosis (Im\textsubscript{necrosis} and Pa\textsubscript{necrosis}) and tumor hypoxia, which was assessed by dynamic contrast-enhanced MR perfusion imaging (DCE-MRI).

Materials and Methods

Study Participants

Patients with a primary diagnosis of glioma (June 2013–May 2021) were retrospectively included. Inclusion and exclusion criteria are presented in Online Resource Supplementary Fig. 1. Clinical information of patients was retrieved from the electronic medical records and follow-up information was obtained.
through clinical interviews. Follow-up survival data were available until May 31, 2021. Overall survival (OS) was calculated from the date of the initial surgery to the date of death or the date of the last follow-up visit if the patient was alive or lost to follow-up.

### MRI Parameters

Participants underwent conventional and DCE-MRI imaging using a 3.0T MR system (Magnetom Verio, Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head-neck coil. The parameter details of the conventional MRI and the DCE-MRI were elaborated in Online Resource Supplementary Appendix 1.

### Image Processing

All DCE-MRI data were transferred to the post-processing workstation (detailed in Online Resource Supplementary Appendix 2). Pharmacokinetic parameters, including the transfer constant ($k_{trans}$), rate constant ($kep$), extravascular extracellular volume fraction ($ve = k_{trans}/kep$), and initial area under the curve in the first 60 s ($iauc$), were automatically generated. Regions of interest (ROIs) were selected across three consecutive maximum tumor parenchyma slices. At each slice, three ROIs were put in tumor parenchyma, according to 3D transverse T1-weighted images (T1WI) and T2-weighted fluid-attenuated inversion recovery (T2WI-FLAIR), avoiding necrosis, cystic, and vessel areas, tumor peripheral zones (edema: within a 1-cm distance from the outer enhancing tumor margin; approximately 2 mm diameter), and contralateral normal brain tissues (control), respectively (Fig. 1). The mean (Mean) values of each metric was recorded.

According to the literature, imaging necrosis is defined as a region within the tumor that does not enhance or that shows markedly diminished enhancement, high signal intensity on T2WI, low signal intensity on T1WI, and an irregular border [6]. Examples are shown in Fig. 2 and Online Resource Supplementary Fig. 2. Two experienced radiologists have reviewed all conventional MRI and then to determine jointly whether there was Im necrosis. To assess the interobserver agreement, one of these two experienced radiologists and a third radiologist repeatedly assessed 68 cases after the initial assessment. The assessed images were randomized within each type of pathology, and the observers were blinded to the clinical and pathological information and thoroughly acquainted with the criteria.

### Pathological and Molecular analysis

Pa necrosis was defined according to pathological reports provided by the Pathology Department of our hospital, if available. The status of 1p19q codeletion, EGFR amplification, chr7 gain/10 loss (+ 7/-10), and CDKN2A/B homozygous deletion were determined by fluorescence in situ hybridization with a specific probe. IDH mutation was determined by high-throughput sequencing including IDH1 and IDH2 mutations. The pathological diagnosis and grading of gliomas were reassigned according to the 2021 WHO classification of Tumors of the Central Nervous System (the fifth edition) [4, 14, 15] (Online Resource Supplementary Fig. 3).

### Statistical Analysis

Statistical Analysis Data were analyzed using IBM SPSS Statistics 26 software, the SPSSAU data scientific analysis platform (https://spssau.com/), and the R programming language (version 4.1.2, The R Foundation for Statistical Computing). Normally distributed continuous variables were compared using unpaired $t$-tests, whereas nonparametric tests were used for non-normally distributed variables. Descriptive data are expressed as mean ± SD, except where otherwise stated. Unpaired $t$-tests, nonparametric tests, and different chi-squared tests were used to compare differences between parameters. Receiver Operating Characteristics (ROC) curves were used to evaluate diagnostic efficacy. Simple kappa was calculated to assess the consistency of different diagnoses and interobserver agreement. Kaplan–Meier survival analysis was used to analyze survival data. Hazard ratios (HR) were estimated according to the Cox proportional hazard method. A two-sided $p$ value < 0.05 was considered significant. Detailed statistical methods are shown in Online Resource Supplementary Appendix 3.

### Results

#### Patients’ Demographic and Clinical Findings

We initially identified 150 eligible patients (median age = 46 years, range 21–79 years), and 104 (69.33%) were male (Table 1). All the diagnoses assigned to the patients according to the latest integrated histo-molecular classification criterion were presented in Online Resource Supplementary Fig. 3 and Table 1 in detail. Pa necrosis was identified in 70/74 of high-grade gliomas (HGGs) and 3/24 of low-grade gliomas (LGGs) which were IDH-mutant and 1p/19q-deleted oligodendrogliomas, while Im necrosis was identified in 70/76 of HGGs and 12/43 of LGGs. All the clinical information were presented in Table 1 and Online Resource Supplementary Appendix 4.
### Table 1: Participant Demographic Findings

<table>
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<th>Parameter</th>
<th>NA</th>
<th>type</th>
<th>numbers</th>
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<th>sum1</th>
<th>(\chi^2)a</th>
<th>(p)1</th>
<th>Phi1</th>
<th>imaging necrosis (%, n = 150)</th>
<th>sum2</th>
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</thead>
<tbody>
<tr>
<td>age (n = 150)</td>
<td>0</td>
<td></td>
<td>104</td>
<td>40.09 ± 12.72 (n = 35)</td>
<td>-</td>
<td>-4.877#</td>
<td>0.000***</td>
<td>0.992$</td>
<td>40.54 ± 11.08 (n = 54)</td>
<td>-</td>
</tr>
<tr>
<td>sex (n = 150)</td>
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<td>male</td>
<td>104</td>
<td>40.09 ± 12.72 (n = 35)</td>
<td>-</td>
<td>-4.877#</td>
<td>0.000***</td>
<td>0.992$</td>
<td>40.54 ± 11.08 (n = 54)</td>
<td>-</td>
</tr>
<tr>
<td>idh (n = 144)</td>
<td>6</td>
<td></td>
<td>86</td>
<td>0.01</td>
<td>0.921</td>
<td>0.009</td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.921</td>
</tr>
<tr>
<td>1p19q (n = 109)</td>
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<td>78</td>
<td>17.132\b</td>
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<td>0.466</td>
<td></td>
<td></td>
<td>17.132\b</td>
<td>0.000***</td>
</tr>
<tr>
<td>cdkn2a/b homozygous</td>
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<td></td>
<td>58</td>
<td>5.99c</td>
<td>0.014*</td>
<td>0.443</td>
<td></td>
<td></td>
<td>5.99c</td>
<td>0.014*</td>
</tr>
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<td>egfr amplification</td>
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<td></td>
<td>58</td>
<td>0.013b</td>
<td>0.909</td>
<td>0.05</td>
<td></td>
<td></td>
<td>0.013b</td>
<td>0.909</td>
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<tr>
<td>chr7 gain/10 loss</td>
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<td>23</td>
<td>0.158c</td>
<td>0.691</td>
<td>0.094</td>
<td></td>
<td></td>
<td>0.158c</td>
<td>0.691</td>
</tr>
<tr>
<td>group (n = 119)</td>
<td>28</td>
<td></td>
<td>76</td>
<td>64.274b</td>
<td>0.000***</td>
<td>0.81</td>
<td></td>
<td></td>
<td>64.274b</td>
<td>0.000***</td>
</tr>
</tbody>
</table>

Note: Sum1, \(\chi^2\)a, \(p\)1, and Phi1 represent the statistical results for pathological necrosis, while sum2, \(\chi^2\)b, \(p\)2, and Phi2 represent the statistical results for imaging necrosis. \# and \$ represent chi-square tests with continuity correction and Fisher’s exact tests, respectively.
Interobserver Agreement of Imaging Necrosis and Correlation between Imaging and Pathological necrosis

With \( \text{Im}_{\text{necrosis}} \), there was a strong degree of inter-observer agreement (Kappa = 0.668, \( p < 0.001 \), 95\%CI: 0.489–0.846). And the spot-like, dotted, long-stripe, long tubular, and fissural enhancements (shown in Online Resource Supplementary Figs. 4 and 5), which made the presence of Im \(_{\text{necrosis}} \) difficult to determine, should not support the presence of Im \(_{\text{necrosis}} \).

In this study, the following four groups were determined: Im \(_{\text{necrosis}} \) + Pa \(_{\text{necrosis}} \) group (representing patients with both Im \(_{\text{necrosis}} \) and Pa \(_{\text{necrosis}} \), \( n = 74 \)), no Im \(_{\text{necrosis}} \) group (representing patients without Im \(_{\text{necrosis}} \) and Pa \(_{\text{necrosis}} \), \( n = 28 \)), Only Im \(_{\text{necrosis}} \) group (representing patients with Im \(_{\text{necrosis}} \) but without Pa \(_{\text{necrosis}} \), \( n = 7 \)), and Only Pa \(_{\text{necrosis}} \) group (representing patients with Pa \(_{\text{necrosis}} \) but without Im \(_{\text{necrosis}} \), \( n = 4 \) groups). We found a strong degree of agreement between Im \(_{\text{necrosis}} \) and Pa \(_{\text{necrosis}} \) (Kappa = 0.767, \( p < 0.001 \), 95\%CI: 0.637–0.897). However, using the chi-square test with continuity correction, differences between cases that demonstrated Im \(_{\text{necrosis}} \) or Pa \(_{\text{necrosis}} \) were significant (\( p < 0.001 \), Online Resource Supplementary Table 2).

**Association of Imaging Necrosis with Integrated Glioma grading**

Most patients with HGGs (85.37\%) were found to have \( \text{Im}_{\text{necrosis}} \), while most with LGGs (83.78\%) or WHO grade 2 (70.27\%) tumors were found to have no \( \text{Im}_{\text{necrosis}} \). There were 4/30 WHO grade 2 patients with \( \text{Im}_{\text{necrosis}} \). Of those, two were diagnosed as IDH-mutant and 1p/19q-deleted oligodendrogliom, two as IDH-mutant astrocytoma with very small extent of \( \text{Im}_{\text{necrosis}} \) and negative status of Pa \(_{\text{necrosis}} \) and CDKN2A/B.

Significant differences in the presence of \( \text{Im}_{\text{necrosis}} \) with a large effect size were found between HGGs and LGGs, and among different grades of gliomas (Table 1, \( p < 0.001 \)). Cochran–Armitage tests showed an upward trend in \( \text{Im}_{\text{necrosis}} \) from lower to higher grades of gliomas (\( p < 0.001 \)). Multiple comparisons with Bonferroni correction showed that the difference between WHO grades (any two grades) and \( \text{Im}_{\text{necrosis}} \) was significant (all \( p < 0.01 \)).

**Association of Imaging Necrosis and Molecular profiles of gliomas**

No significant correlation was found between \( \text{Im}_{\text{necrosis}} \) and EGFR amplification or +7/-10 cytogenetic signature (\( p > 0.05 \)) (Table 1). However, there were significant correlations between the expression of other molecular markers such as IDH, 1p19q, and CDKN2A/B and the presence of \( \text{Im}_{\text{necrosis}} \). According to Table 1, the proportion of IDH-wildtype, 1p19q-non-codeletion, or CDKN2A/B-positive cases with \( \text{Im}_{\text{necrosis}} \) was significantly higher than that of cases without \( \text{Im}_{\text{necrosis}} \) with a medium effect size, respectively (75.82\% vs. 32.08\%, 85.94\% vs. 51.11\%, 20\% vs. 0, respectively).

**Association of Imaging Necrosis with Patient Prognosis**

One-hundred and thirty patients were included in the final survival analysis, compared with gliomas with \( \text{Im}_{\text{necrosis}} \) patients without \( \text{Im}_{\text{necrosis}} \) had a significantly longer survival time (\( p < 0.001 \), Fig. 3A). By reference with the gliomas with Pa \(_{\text{necrosis}} \) patients without Pa \(_{\text{necrosis}} \) had a significantly longer survival time as well (\( p < 0.001 \), Fig. 3B).

The differences among the OS of Im \(_{\text{necrosis}} \), Pa \(_{\text{necrosis}} \), and No \(_{\text{necrosis}} \) groups were statistically significant (\( p < 0.01 \), Fig. 3C). Further, after Bonferroni correction (Bonferroni-corrected significance level: \( p = 0.008 \) (0.05/6)), there were significant differences between Im \(_{\text{necrosis}} \) and Pa \(_{\text{necrosis}} \) groups (\( p < 0.001 \)). According to Fig. 3C, the OS of Only Pa \(_{\text{necrosis}} \) group (\( n = 2 \)) was shorter than the OS of No \(_{\text{necrosis}} \) group (\( n = 28 \)) and Only Im \(_{\text{necrosis}} \) group (\( n = 7 \)). Between the two survival curves of No \(_{\text{necrosis}} \) and Only Im \(_{\text{necrosis}} \) groups there were marked crossovers, but within a certain time period (time spanning about from 5-month to 40-month postoperatively), the OS of Only Im \(_{\text{necrosis}} \) group was shorter than the OS of No \(_{\text{necrosis}} \) group.
Further, when added significant variables such as age, IDH, 1p19q, and Im\textsubscript{necrosis} into the multivariate Cox proportional hazards regression analyses, only Im\textsubscript{necrosis} (HR = 2.113, 95\% CI: 1.015–4.402, \(p = 0.046\)) was significant and independently related to the patients outcome, indicating that Im\textsubscript{necrosis} is an independent and unfavorable prognostic factor.

**Correlation of tumor necrosis and tumor hypoxia derived from DCE-MRI**

Since the pathology is the golden standard for necrosis diagnosis. Thus we analyzed the associations with Pa\textsubscript{necrosis} and DCE-MRI parameters. Most DCE-MRI metrics demonstrated a significant difference in identifying gliomas with Pa\textsubscript{necrosis} with a very large effect size (Table 2). ROCs analysis showed that the Tumor-veMean displayed the best diagnostic performance with the largest AUC of 0.891 (95\%CI: 0.788–0.995, \(p < 0.0001\)), and the optimal cutoff point was 0.17 with a sensitivity of 96\% and specificity of 83.3\%.

Similarly, we performed the analysis regarding to Im\textsubscript{necrosis} (Table 2), and the Tumor-veMean displayed the best diagnostic performance as well, with the largest AUC of 0.929 (95\%CI: 0.872–0.986, \(p < 0.0001\)), and the optimal cutoff point was 0.17 with a sensitivity of 89.2\% and specificity of 91.9\%.
Table 2
Non-parametric tests between DCE-related data of different groups with or without pathological necrosis/imaging necrosis and ROC analyses

<table>
<thead>
<tr>
<th>parameter</th>
<th>type</th>
<th>Medium</th>
<th>standard deviation</th>
<th>p of Non-parametric tests</th>
<th>Cohen's d</th>
<th>AUC</th>
<th>p of ROC</th>
<th>95% CI</th>
<th>optimal Youden index</th>
<th>sensitivity</th>
<th>specificity</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>tumor-kep-Mean</td>
<td>no Pa necrosis</td>
<td>0.06</td>
<td>0.089</td>
<td>0.000***</td>
<td>0.758</td>
<td>0.824</td>
<td>0.000***</td>
<td>0.711 ~ 0.936</td>
<td>0.565</td>
<td>0.94</td>
<td>0.625</td>
<td>0.07</td>
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<td>Pa necrosis</td>
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<td></td>
</tr>
<tr>
<td>tumor-kep-Mean</td>
<td>no Im necrosis</td>
<td>5.45</td>
<td>9.183</td>
<td>0.000***</td>
<td>1.046</td>
<td>0.872</td>
<td>0.000***</td>
<td>0.761 ~ 0.983</td>
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<td>0.833</td>
<td>0.86</td>
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<tr>
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<td>Im necrosis</td>
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<td>2.381</td>
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<tr>
<td>tumor-kep-Mean</td>
<td>no control-iauc</td>
<td>0.03</td>
<td>0.124</td>
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<td>1.535</td>
<td>0.899</td>
<td>0.000***</td>
<td>0.803 ~ 0.996</td>
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<td>1</td>
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<td>control-iauc</td>
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<td>0.116</td>
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<tr>
<td>tumor-kep-Mean</td>
<td>no tumor-ktrans</td>
<td>0.06</td>
<td>0.081</td>
<td>0.000***</td>
<td>0.846</td>
<td>0.856</td>
<td>0.000***</td>
<td>0.772 ~ 0.939</td>
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<tr>
<td>tumor-kep-Mean</td>
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<tr>
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<td>0.005**</td>
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<td>0.003**</td>
<td>0.558 ~ 0.776</td>
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<td>8.562</td>
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<td>1.063</td>
<td>0.914</td>
<td>0.000***</td>
<td>0.857 ~ 0.971</td>
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<td>0.946</td>
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<td>0.909</td>
<td>0.000***</td>
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<td>0.372</td>
<td>0.62</td>
<td>0.034*</td>
<td>0.509 ~ 0.731</td>
<td>0.226</td>
<td>0.415</td>
<td>0.811</td>
<td>0.01</td>
</tr>
<tr>
<td>tumor-kep-Mean</td>
<td>control-iauc</td>
<td>0.01</td>
<td>0.021</td>
<td></td>
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* represents p < 0.05, ** represents p < 0.01, and *** represents p < 0.001

Discussion
In this study, we assessed the importance of the identification of imaging necrosis in the preoperative evaluation of glioma. We found strong agreement between observations of Im necrosis and Pa necrosis. Moreover, Im necrosis was found to be significantly related with glioma-related key gene mutations, such as
1p19q non-codeletion and CDKN2A/B homozygous deletion. And it is an independent imaging marker for predicting tumor prognosis.

Our study indicated that there was strong agreement between the inter-observer agreement of Im\textsubscript{tumor necrosis} and Pa\textsubscript{tumor necrosis}. And during the analysis, we found that the regions with an absence or marked decrease of enhancement inside the intensified areas was easily mistook as Im\textsubscript{tumor necrosis}. To be mentioned that there was one WHO grade 2 IDH-mutant astrocytomas with an very short OS (5 months) who died from glioma-related causes. When we reviewed the raw data and identified that this patient had a small extent of Im\textsubscript{tumor necrosis}, which indicated a high grade gliomas. And we deduced that Pa\textsubscript{tumor necrosis} was unluckily missed due to the limited tumor specimen. Considering that pathological samples were partial while imaging observation can capture full tumors, above mentioned situation can be avoided if to made a judgement of Im\textsubscript{tumor necrosis}, which was exactly one unique advantage for radiographic examination. In comparison, we also found seven patients with Im\textsubscript{tumor necrosis} were diagnosed as WHO grade 2 or 3 oligodendrogliomas, indicated that necrosis plays a limited prognostic value in oligodendrogliomas. Hence, if there is evidence of oligodendroglioma, such as calcification and filiform or localized internal homogeneous enhancement, presence of Im\textsubscript{tumor necrosis} did not indicated a high-grade tumor.

Previous studies have highlighted that Im\textsubscript{tumor necrosis} shown by pre-operative MRI is an independent unfavorable prognosis factor [5, 6, 10, 19–21]. Our results are in accordance, and they showed that patients with Im\textsubscript{tumor necrosis} had a poorer prognosis than those without Im\textsubscript{tumor necrosis}. Besides, the latest WHO CNS classification emphasizes the role of molecular markers in the diagnosis and prognosis of gliomas, such as IDH, 1p19q, CDKN2A/B, 7+/10-, and EGFR [4]. Consistent with previous findings [16–18] and our results demonstrated that Im\textsubscript{tumor necrosis} is less likely to occur in gliomas with IDH-mutation, 1p19q codeletion, or CDKN2A/B homozygous deletion; thus, Im\textsubscript{tumor necrosis} can be an imaging marker helpful for gene prediction. From this prospect, Im\textsubscript{tumor necrosis} might be more important than Pa\textsubscript{tumor necrosis}, since it can be non-invasively obtained before operation. However, there was no significant difference between the expressions of 7+/10- cytogenetic signature or EGFR amplification and the presence of Im\textsubscript{tumor necrosis}. This negative result might also due to the small sample size and insufficient number of events.

In this study, we also sought for a quantitative metrics for indicating tumor necrosis. Our results revealed that, compared with tumor without Im\textsubscript{tumor necrosis}/Pa\textsubscript{tumor necrosis}, DCE-rerived parameters in tumor parenchyma were significantly higher in gliomas with Im\textsubscript{tumor necrosis}/Pa\textsubscript{tumor necrosis}. And vein tumor parenchyma demonstrated the highest diagnostic efficiency in identifying tumor necrosis with high sensitivity and specificity. This may be attributed to the fact that gliomas grow uncontrollably fast, resulting in severe hypoxia and necrosis, and thus an extensively hyperpermeable vasculature is generated resulting in inadequate oxygen and supplements. The greater the levels of perfusion and permeability in the tumor tissue, the higher the k\textsubscript{trans} and v\textsubscript{e} values, and the higher the degree of tumor malignancy [22–24]. Hence, DCE-MRI metrics, especially v\textsubscript{e} in tumor parenchyma (cut-off value: 0.17), might be used as a supplementary metric to the morphological observation for delinating of tumor necrosis.

The current study has some limitations. First, since evidence of pathological necrosis was obtained from pathology reports of our hospital, there may be a detection bias. However, this study based on clinical, real-world evidence can exactly address the current clinical deficits. Second, this is a single-center study, subgroups analysis (such as the +7/–10 cytogenetic signature subgroup) had a small sample, which might resulting in insufficient power to reach definite conclusions. Further multicenter studies with large sample sizes will help improve the efficacy of Im\textsubscript{tumor necrosis} in predicting the expression of molecular markers and prognosis.

Conclusion

Based on the latest WHO CNS guidelines, the present study depicted the importance of imaging necrosis in diagnosing gliomas. Detection of imaging necrosis in gliomas probably suggests an HGG unless there is imaging evidence for oligodendrogliomas. Imaging necrosis was significantly associated with glioma-related key gene mutations, such as 1p19q non-codeletion and CDKN2A/B homozygous deletion. And it is an independent imaging marker for predicting tumor prognosis. Additionally, the Tumor-veMean derived from DCE-MRI can help to predict necrosis with high sensitivity and specificity. Overall, in this study, we reevaluated the imaging necrosis in the assessment of gliomas and provided a feasible solution to solve the frequent diagnostic dilemma of gliomas.

Declarations

Funding

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Hui Ma: Conceptualization, Methodology, Writing-Original Draft, Funding acquisition; Shanmei Zeng: Validation, Visualization, Investigation, Project administration; Dingxiang Xie: Validation, Visualization, Investigation, Project administration; Wenting Zeng: Formal analysis, Data collection; Liwei Mazu: Data collection; Nengjin Zhu: Data collection; Yingqian Huang: Data collection; Zhiyun Yang: Writing-Review & Editing; Jianping Chu: Writing - Review & Editing, Funding acquisition; Jing Zhao*: Conceptualization, Supervision, Writing - Review & Editing, Funding acquisition.

All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
References


Figures

Figure 1

Representative ROI delineations. A 53-year-old man diagnosed with IDH-wildtype glioblastoma. (A) contrast-enhanced T1-weighted image(T1WI-CE); (B) the time-signal intensity curve; (C) the transfer constant (ktrans) image; (D) rate constant (kep) image; (E) extravascular extracellular volume fraction (ve) image; (F) initial area under the curve in the first 60 s (iauc) image. On images B-F, ROI 1 marked green represented tumor parenchyma tissues, ROI 2 marked yellow represented the peripheral zones, and ROI 3 marked blue-turquoise represented contralateral normal brain tissues.
Figure 2

Representative MR images with (A, B) or without (C) imaging necrosis. (A) A 43-year-old man with a WHO grade 4 IDH-wildtype glioblastoma; (B) a 53-year-old woman with a WHO grade 4 IDH-wildtype glioblastoma; (C) a 67-year-old man with a WHO grade 4 IDH-wildtype glioblastoma. Red arrows represent necrosis, and red asterisks represent cysts which are defined as rounded regions that exhibit low-intensity T1-W signals and extremely high-intensity T2-W signals matching the cerebrospinal fluid signal, with a thin, smooth, regular, slightly enhancing or non-enhancing wall.
Figure 3

Survival curves for cases of imaging necrosis (A), cases of pathological necrosis (B), and cases of both pathological and imaging necrosis (C).

Supplementary Files

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- SupplementaryMaterials20230623.docx