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Title: How the habitats created by MRI can predict the IDH mutation status and prognosis of the patients with high-grade gliomas

1. Study direction

Prediction of IDH mutation status and prognosis of high-grade glioma patients based on multi-parametric MRI habitat imaging.

The multi-parametric MRI involved in this study scheme generally includes the following types in ideal state: conventional MRI sequences, Dynamic Susceptibility Weighted Contrast Enhanced Magnetic Resonance Imaging (DSC-MRI), Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI), Diffusion Weighted Magnetic Resonance Imaging (DWI), Vessel Size Imaging (VSI), or Magnetic Resonance Spectroscopy (MRS), and multiple combinations of indefinite items are carried out according to different research purposes.

2. Study background and objective

2.1 Background

High-grade glioma (HGG) is the most common primary brain tumor in the central nervous system. It has a highly malignant biological behavior, and is also a disease with complex initial mechanism and in constant dynamic change. Despite the emergence of multi-modal therapy such as immune and molecular targeting in recent years, the overall prognosis of HGG patients has not been significantly improved, and the median survival time has not been significantly improved. The high invasiveness and recurrence rate of HGG can be attributed in part to the significant tumor heterogeneity. Studies have shown that tumors are not homogenous individuals but uneven distribution of tumor cell subsets with different gene mutations or dominant clonal populations formed by tumor stem cells establishing differentiation levels. Genetic

variation among these tumor subclones causes them to compete with each other and change dynamically driven by environmental selection pressures based on local action, in a pattern similar to the occupation of specific habitats by different species in an ecosystem. These tumor cell clusters with the same ability of environmental selection and cell evolution are called habitats.

In terms of imaging, it is not difficult to find significant heterogeneity in the tumor based on differences in signals and enhancement modes. However, there are inevitably subjective differences between observers in the description of medical images such as enhancement, necrosis, edema, and tumor boundaries. Therefore, there is an urgent need for an accurate, objective, quantitative and spatial imaging method to express tumor heterogeneity. Habitat imaging technique is based on this need. Habitat imaging is an image segmentation concept and quantitative analysis technology based on differences in tumor pathology, blood perfusion, molecular characteristics, etc., which can combine various imaging methods to reveal the pathophysiological significance behind tumor imaging heterogeneity and the relationship between regional differences in the microenvironment that drive tumor evolution and adaptive strategies of tumor cells, to evaluate and monitor the temporal and spatial evolution of tumor habitat and predict potential genotypes and phenotypes. In addition, habitat imaging has been proved by many studies that the quantitative parameters obtained from habitat or the radiomics features extracted from habitat can be used as a robust biomarker for the prediction of overall survival, molecular mutation status and clinical treatment effect of patients.

Above all, we have sufficient and firm reasons to deem that habitat imaging based on multiparametric MRI is more conducive to reflect the potential biological information inside the tumor and realize individualized diagnosis and treatment.

2.2 Study objective

The purpose of this study was to construct tumor habitat by combining preoperative or postoperative multi-parametric MRI imaging, so as

(1) to reveal the spatial and/or temporal heterogeneity within tumors;

(2) to explore the value of habitat imaging in the classification and molecular typing of HGG;

(3) to investigate the value of parameters quantitatively obtained from habitat in predicting the overall survival time and risk factors of HGG patients;

(4) to investigate the differential and predictive ability of HGG local recurrence and

intracranial long-distance recurrence;
(5) to verify whether the habitat imaging analysis was more accurate than the traditional holistic tumor analysis in the above studies.

3. Study program

3.1 Study center

The study was a single-center observational retrospective study with data from the hospital information system. The subjects of the study were HGG patients who underwent MRI at the Army Medical Center of PLA (also known as Daping Hospital and the Research Institute of Surgery of the Third Military Medical University) from January 1, 2008 to December 31, 2021 (or at some interval within this period).

3.2 Selection criteria

Inclusion Criteria (if we will predict the molecular status and overall survival):

(1) the patient was over 18 years old;
(2) the lesion was located in the supratentorial space;
(3) a histopathologic diagnosis of HGGs according to the WHO CNS4/5;
(4) all subjects were the first diagnosed cases without any invasive or non-invasive treatment;
(5) access to the complete preoperative MR imaging examinations, at least including four conventional sequences.

Inclusion Criteria (if we will differentiate recurrence from distant intracranial recurrence):

(1) the patient was over 18 years old;
(2) the lesion was located in the supratentorial space;
(3) a histopathologic diagnosis of HGGs according to the WHO CNS4/5;
(4) underwent concurrent chemoradiotherapy with temozolomide after surgical resection or biopsy;
(5) underwent preoperative and postoperative MRI, at least including four conventional sequences;
(6) had newly appeared or enlarging, measurable, contrast-enhancing mass which raises clinical suspicion of tumor recurrence and distant intracranial recurrence;
(7) adequate follow-up examinations to determine treatment response on clinic-radiological consensus or pathologic confirmation.

Exclusion Criteria:

(1) patient with other brain tumors or other grade gliomas at the same time;
(2) patient with severe basic diseases at the same time;
(3) patient with a survival time of less than 30 days, which can be caused by severe surgical trauma stress;
(4) poor image quality and heavy artifact affect the subsequent image processing.

4. Study data and variable collection

(1) Basic clinical information:

age, sex, height, weight and previous underlying diseases of the patient;

(2) Image and date collection:

the original MR image and the date of each MRI from preoperative to postoperative to recurrent to follow-up to the last examination, and records tumor location, volume, boundaries, and enhancement patterns;

(3) Pathological and immunohistochemical data collection:

the specific diagnosis of high-grade glioma and specific molecular characteristics, including IDH, MGMT, TERT, 1p/19q, etc.

(4) Methods of operation and postoperative treatment:

the extent of resection includes gross total resection, subtotal resection and partial resection, and the adjuvant therapy includes radiation, chemotherapy, chemoradiotherapy, untreated and unknow.

(5) Prognostic data collection:

specific overall survival time, recurrence time after treatment, whether there is an endpoint time.

(6) Quantitative parameter collection:

the corresponding characteristic quantitative parameters were extracted according to different magnetic resonance sequences.

* The data will be collected from the Hospital Information System (HIS), Picture Archiving and Communication System (PACS) and telephone follow-up.

5. Advanced image processing and habitat construction

The multi-parametric MRI images of all patients will be exported from the PACS

system in DICOM format. First of all, all DICOM data will be converted to Nifti format. Subsequently, skull stripping will be performed. Next, the image will be resampled and registered. A deep learning model of nnU-Net will be employed to segment preliminary subregions of enhancing tumor, edema and necrosis on the four conventional structure sequences. Finally, the habitat construction will be carried out using a K-means clustering. Parameter values can be extracted quantitatively from habitats and radiomics features can be extracted quantitatively too.

6. Statistical analysis

Independent-samples T-test or Mann-Whiney U-test will be used to analyze the differences in quantitative parameter values between IDH-mutant HGGs and their wild-type counterpart in each habitat, using Benjamini-Hochberg's procedure for controlling the false discovery rate in multiple comparisons. The Chi-square testing will be used to analyze the constituent ratio of variables. ROC will be applied to evaluate the value of differentiating IDH mutation status and verify the differential efficacy of precise tumor habitats constructed by multi-parametric MRI and traditional tumor habitats. The cutoff values for each habitat were determined by using Youden index. The OS of HGG patients were analyzed using Kaplan-Meier survival analysis and Log-rank test. Specific statistical methods shall be formulated according to specific circumstances

7. Outcomes

Primary outcomes: multi-model habitats constructed by multiparametric MRI predict IDH mutation status and the prognosis in high-grade gliomas (in progress);

Secondary outcomes: multi-model habitats constructed by multiparametric MRI differentiate recurrence from distant intracranial recurrence (in the stage of preparation);

Exploratory outcomes: validate the advantages of habitat imaging and potential links to pathophysiology.

8. Ethical issues

(1) Documents and procedures to apply for and obtain approval from the Ethics committee in accordance with the Declaration of Helsinki and the code of ethics of the country in which the research is conducted;

(2) Before each patient is enrolled in the study, the study physician is responsible for

providing a complete and comprehensive written description of the purpose, procedures, and possible risks of the study to him or her or her designated representative. Patients should be made aware of their right to withdraw from the study at any time. A written patient informed consent should be given to each patient before enrollment. The research physician is responsible for obtaining informed consent before each patient is enrolled in the study, and informed consent should be kept as a clinical research document for future reference;

(3) Follow-up of subjects during and after the study;

(4) Confidentiality regulations for subjects' privacy.

9. Reference

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