The Evaluation of D-glucose Weighted Chemical Exchange Saturation Transfer (glucoCEST)-Based Dynamic Glucose Enhanced(DGE) Magnetic Resonance Imaging（MRI） in Brain Tumor

Main research unit: Zhujiang Hospital of Southern Medical University

Principal investigator: Zhibo Wen

Participating units and persons in charge:

Statistical Analysis Unit:

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Confidentiality statement

The ownership of all information contained in this study protocol belong to the investigator of the project. It is provided only for review by the ERC and relevant agencies. It is prohibitive that disclose any information to third parties unrelated to the study without the written consent of the Principal Investigator (PI).

Catalog

Abstract

Subject	**Application of glucose CEST MR imaging in brain tumors**
Sponsor	**Department of Imaging Diagnosis, Zhujiang Hospital, Southern Medical University**
Research Institutes	**Zhujiang Hospital, Southern Medical University**
Principal Investigator	**Zhibo Wen**
Purpose	**Whether glucose CEST MR imaging is superior to gadolinium contrast agents based MR imaging in brain tumors**
Hypothesis	**Glucose CEST MR imaging is more effective than gadolinium contrast imaging in the diagnosis of brain tumors**
Design	**Clinical trial**
Sample Capacity	**100**
Inclusion and Exclusion Criteria	**Minimum Age: 18 Years** **Maximum Age: 75 Years** **Criteria:** **Inclusion Criteria:** **(1) Patient must have a brain mass consistent with a primary brain tumor or metastatic brain tumor(2) able to give consent (3) willingness to participate in this** **Exclusion Criteria:**

	1) presence of any ferromagnetic implant (cardiac pacemakers, aneurysm clip, etc.) (2) pregnancy (3) claustrophobia or anxiety disorder (4) history of vertigo (5) persons with diabetes mellitus (self-report or HbA1C >= 6.5%) (6) Sickle cell disease (7) persons taking prescription medicine for hypertension (8) blood iron deficiency (Hb concentration < 11 g/dL or Hct < 32%) (9) If volunteering for MRI: history of kidney disease and/or eGFR < 60. (10) Middle-ear disorder (11) double vision (12) Seizure disorder (13)Multiple myeloma (14) Solid organ transplant (15) History of severe hepatic disease/liver transplant/pending liver transplant
Interference	**MR Imaging based on DGE**
Measure	**The area of hyperintense and the AUC between 2-5min of DGE**
Patients	**brain tumor patient treated at Zhujiang Hospital of Southern Medical University**
Statistical Method	**Differential test and Consistency analysis were used for statistical analysis**

Background

The priority treatment of brain tumor is surgical resection. Recurrent malignant glioma is the most common and highly malignant primary brain tumor in adults. It mainly includes the pleomorphic glioblastoma (GBM) and anaplastic astrocytoma (AA). The average survival period of GBM is only 14.6 months [1], while the average lifetime of AA is only 2 to 3 years [1, 2]. Residual tumor and highly recurrence rate is the main reason. Besides, the feasibility of reoperation is extremely low. Moreover, progression-free survival (6-month progression-free survival (6M-PFS)) was only 15-21% of patients with recurrent glioma. The response rate of conventional chemotherapy was less than 15% in patients with recurrent glioma [1, 2]. Therefore, accurate clinical assessment of tumor scope is of great significance for GBM expansion surgery to remove the potential tumor immersed area and improve the survival rate of patients.

Recently, natural D-glucose suggested as a potential biodegradable contrast agent. The feasibility of using D-glucose for dynamic perfusion imaging explored to detect malignant brain tumors based on the breakdown of blood brain barrier (BBB)[3]. Our study try to evaluate the feasibility of dynamic glucose enhanced(DGE) magnetic resonance imaging（MRI）in brain tumor, which based on D-glucose weighted chemical exchange saturation transfer (glucoCEST).

In 2015, Xiang Xu et al. first demonstrated the feasibility of DGE MRI in four normal volunteers and three glioma patients [4]. Routinely, D-glucose was used in human biochemical studies. The objective of this study was to evaluate the feasibility of DGE for visualizing BBB permeability in brain tumor models and to compare it with GBCA-based DCE for visualizing BBB permeability.

With glucose CEST MR imaging, we attempt to accurately predict the grade of brain glioma and to evaluate the infiltration range of tumor cells in the edema zone around glioma, so as to provide a more sufficient basis for the formulation of surgical resection plan for patients.

Materials and Methods

Patients:

Brain tumor patient treated at Zhujiang Hospital of Southern Medical University.

Minimum Age: 18 Years

Maximum Age: 75 Years

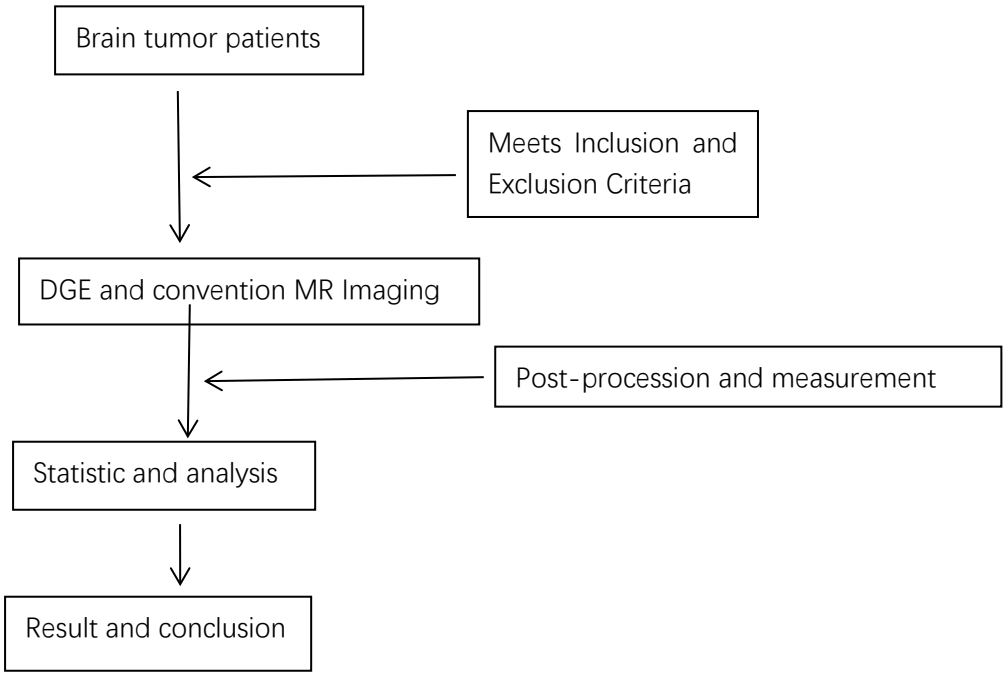
Inclusion Criteria:

(1) Patient must have a brain mass consistent with a primary brain tumor or metastatic brain tumor(2) able to give consent (3) willingness to participate in this

Exclusion Criteria:

(1)Presence of any ferromagnetic implant (cardiac pacemakers, aneurysm clip, etc.) (2) Pregnancy (3) Claustrophobia or anxiety disorder (4) History of vertigo (5) Persons with diabetes mellitus (self-report or HbA1C >= 6.5%) (6) Sickle cell disease (7) Persons taking prescription medicine for hypertension (8) Blood iron deficiency (Hb concentration < 11 g/dL or Hct < 32%) (9) If volunteering for MRI: history of kidney disease and/or eGFR < 60. (10) Middle-ear disorder (11) double vision (12) Seizure disorder (13) Multiple myeloma (14) Solid organ transplant (15) History of severe hepatic disease/liver transplant/pending liver transplant.

Methods



Methods of DGE

Time-resolved glucose signal changes were detected using chemical exchange saturation transfer (glucoCEST) MRI. Dynamic glucose enhanced (DGE) MRI was used to measure tissue response to an intravenous bolus of D-glucose. Starting the dynamic glucose scan, 3mimutes later, a brief hyperglycemic state was established by intravenous infusion of hospital-grade D50 glucose (D50, 25 g of dextrose in 50 mL of water sterile solution), followed by 20 mL of saline solution in 1 arm. The glucose infusion was performed using a power injector at an infusion rate of 0.2 mL/s, corresponding to total infusion times of 250 seconds. Performing dynamic contrast enhancement based on Gd-DTPA in 30 minutes later, which was used for comparison as golden standard. Dose of agent is ccording to the proportion of 0.2ml/kg body weight. The Gd-DTPA infusion was performed using a power injector at an infusion rate of 3 mL/s, followed by 20 mL of saline solution in 1 arm.

Statistic Analysis

Statistic tools: SPSS 23.0

Basic principles:

All statistical inferences were tested by bilateral tests, the test level of statistical significance was set at 0.05, and the confidence interval of parameters was estimated by 95% confidence interval. The parametric method is used as far as possible. When the data does not meet the parametric method conditions, the data transformation method can be used to make it meet the conditions. If the data still does not meet the parameter method conditions, the non-parametric method can be considered.

Missing data:

The case data that did not meet the statistical requirements were excluded.

Description statistics:

The mean, standard deviation and confidence interval are given for measurement data. The minimum, maximum, P25, median and P75 are given if necessary. The mean and standard deviation of the trip value were calculated from paired measurement data. Median and mean rank are given when nonparametric methods are used. The enumeration data give the frequency distribution and the corresponding percentages. Rank data give frequency distributions and corresponding percentages, as well as median and mean rank. The positive rate, positive number and the number of cases in the denominator were given in qualitative data.

Baseline data analysis:

Descriptive analysis of baseline data, including baseline levels of endogenous glucose CEST in brain tissue.

Analysis of influencing factors:

Motion artifacts have a certain image for CEST value measurement, which may lead to measurement error.

Ethical considerations

This clinical study must under the Helsinki Declaration and the relevant Chinese regulations on clinical research. The clinical study plan, informed consent and other data should be submitted to the ethics committee for approval before the starting. During the clinical study, the modification of clinical study plan and the informed documents can’t be performed before approved by the ethics committee. The investigator take care of the rights and safety of the subject and ensures the subject's privacy.

References:

[1]. Stupp, R., et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 2005. 352(10): p. 987-96.
[2]. Curran, W.J., et al., Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst, 1993. 85(9): p. 704-10.
[3]. Xu, X., et al., Dynamic glucose enhanced (DGE) MRI for combined imaging of blood-brain barrier break down and increased blood volume in brain cancer. Magn Reson Med, 2015. 74(6): p. 1556-63.
[4]. Xu, X., et al., Dynamic Glucose-Enhanced (DGE) MRI: Translation to Human Scanning and First Results in Glioma Patients. Tomography, 2015. 1(2): p. 105-114.