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Original Research

2-Hydroxyglutarate magnetic resonance spectroscopy for preoperative IDH molecular profiling – A review of the literature and real-world clinical translation in a busy neurosurgical neuro-oncology unit

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Highlights

- 2 hydroxyglutarate is a highly specific tool for identifying IDH mutant gliomas.
- Challenges remain in standardisation of technique and post processing.
- Ratio of 2 hydroxyglutarate to creatinine shows promise as diagnostic tool.

Abstract

2-hydroxyglutarate (2HG), a metabolic by-product that accumulates in IDH-mutated (IDHmut) glioma cells, can be quantified through magnetic resonance spectroscopy (MRS) offering a non-

invasive method to determine molecular subtype. Incorporation of 2HG MRS into standard pre-operative MR protocol offers an adjunct to surgical decision making but limitations in post-processing and barriers exist to its integration into routine clinical practice. Our study explored the real-world translation of 2HG MRS into a busy neuro-oncology surgical unit at the Royal North Shore Hospital campus.

69 Spectra were acquired and reported prospectively between March 2018 and March 2024 in patients with suspected glioma using a 3T Siemens Vida MRI, in addition to standard clinical magnetic resonance imaging and assessment. SV PRESS MRS was acquired with optimised parameters and the spectroscopic waveform analysed externally by a single center. The MRS voxel was localised on 3D FLAIR sequencing. Immunohistochemistry and genomic analysis were available for 30 patients to validate 2HG outcomes against standard ex vivo methods.

Utilising 1.2 mM as threshold calculated sensitivity was 80.9%, specificity 77.8%. Positive predictive value was 89.5% and negative predictive value was 63.6%.Utilising 3 mM as threshold calculated specificity 100% given the absence of false negatives but sensitivity was significantly reduced<10%.

2HG/Cr ratio with a cutoff of 0.085 for positivity yielded sensitivity 94.7%, specificity 66.67% and accuracy 85.7%

Our experience re-demonstrates the potential of 2HG MRS in preoperative imaging in suspected IDHmut gliomas in a busy neuro-oncology unit but highlights the limitations of real-world clinical translation, technical complexities and difficulty in standardization.

Introduction

Advances in molecular subtyping have heralded a paradigm shift in the way histological subtypes of gliomas are differentiated, with particular focus on isocitrate dehydrogenase 1/2 [IDH1/2] gene mutation and chromosome 1p and 19q codeletion [1], [2], [3], [4].

It has been demonstrated that incorporation of molecular markers outperforms the prognostic value of the previous histopathological classification of gliomas [5], [6]. This increased importance has been reflected in the integration of molecular markers into the WHO 2021 classification guidelines [7].

Numerous studies have demonstrated the importance of IDH mutations in stratifying biologically distinct subgroups of gliomas [8], [9].

Traditionally, molecular subtyping comes from tissue samples obtained at time of biopsy or resection. As a result, surgery has been a cornerstone in the management of lower grade gliomas. In addition to confirming histologic diagnosis, maximal tumour resection has been shown to improve overall survival. However, extent of resection must be balanced with preservation of neurologic function, impairment of which is a negative prognostic indicator [10] Gross total resection can be challenging to achieve in many cases due to glioma infiltration into eloquent

cortical and subcortical regions. In certain circumstances, surgery may not be feasible due to patient co-morbidities, tumour location or patient preference. This would leave the treating team without important information that determines response to chemotherapy and prognosis.

Radiogenomics is an evolving field of study that utilises advances in image acquisition and analysis to correlate imaging features with molecular markers of diseases [11].

2-hydroxyglutarate (2HG) is a metabolic product of the mutant IDH enzyme and accumulates in the cytoplasm of glioma cells with IDH1 mutation and in the mitochondria of cells with IDH2 mutation [12], [13], [14].

In 2016 Choi et al published a prospective longitudinal imaging study demonstrating that a quantitative assessment of 2HG by MRS could serve as a non-invasive clinical imaging biomarker for IDH-mutated gliomas. These advances have resulted in an improved correlation between MR signs and IDH mutation status, which complement the prediction of the IDH phenotype and may have potential in evaluating the efficacy of individualized molecular targeted therapy.

2HG MRS is a specialised imaging technique that is currently not in widespread use in Australia.

There is debate regarding its reliability in a real-world setting and the appropriate threshold for 2HG interpretation to determine IDH mutation. Incorporation of 2HG MRS into a standard pre-operative MR protocol offers an adjunct to surgical decision making but limitations in post-processing and barriers exist to its integration into routine clinical practice.

Our study explored the real-world clinical translation of 2HG MRS into a busy neuro-oncology surgical unit on the Royal North Shore Hospital campus.

Section snippets

Methods

Spectra were acquired from 71 patients who were underwent imaging at North Shore Radiology (NSR). Scans were undertaken prospectively between March 2018 and March 2024 in patients with suspected or known glioma. Patients were referred directly from primary neurosurgical referrers or through the North Shore local Health District (NSLHD) MDT neuro-oncology tumour board

Patients were separated into three subgroups

1. Relapse detection group; this included patients with previously resected low grade …

…

Results

69 spectra were acquired of which 30 patients had immunohistochemistry and genomic data available for inclusion in the final analysis

Two attempts at MR spectroscopy failed to obtain sufficient data; one was degraded by movement artefact and the other lesion was too small to place a voxel accurately. 2HG peak was measured at 2.25 ppm – levels in this cohort ranged from 0.13 to 5.4 mM. An example patient with voxel placement and post processed 2HG MRI is shown in Image 1 – this patient reflects …

Discussion

IDH mutation initiates a cellular cascade through the effects of the oncometabolite 2HG, which appears to modulate cellular programs including hypoxia sensing, histone demethylation, and induction of a globally hypermethylated state of DNA with increased angiogenesis. [16], [17] 2HG is highly specific to IDH-mutant gliomas, making it an ideal non-invasive diagnostic marker for these tumours.

In 2012, Choi et al. reported a novel non-invasive detection of 2HG by proton MRS. They used a method of …

Conclusion

Our experience re-demonstrates the potential of 2HG MRS in preoperative imaging in suspected IDHmut gliomas. However, the integration of this technique into routine clinical practice faces several technical and operational challenges inherent to high-volume medical environments.

Overcoming these obstacles and maintaining the performance of 2HG MRS in clinical settings necessitates a multifaceted approach, encompassing technical optimisation, standardisation of protocols, and specialised training …

CRediT authorship contribution statement

Frances Anne McHugh: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **James Jiang:** . **Heidi Luton:** . **Jonathan Parkinson:** . **Raymond Cook:** . **Allison Newey:** . **Chungo Choi:** . **Marina Kastelan:** . **Patrick Horsley:** . **Michael Back:** . **James Drummond:** . …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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