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Incorporation of Edited MRS into Clinical Practice May Improve Care of Patients with *IDH*-Mutant Glioma

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ABSTRACT

BACKGROUND AND PURPOSE: Isocitrate dehydrogenase (*IDH*) mutation and 1p/19q codeletion classify adult-type diffuse gliomas into 3 tumor subtypes with distinct prognoses. We aimed to evaluate the performance of edited MR spectroscopy for glioma subtyping in a clinical setting, via the quantification of D-2-hydroxyglutarate (2HG) and cystathionine. The delay between this noninvasive classification and the integrated histomolecular analysis was also quantified.

MATERIALS AND METHODS: Subjects with presumed low-grade gliomas eligible for surgery (cohort 1) and subjects with *IDH*-mutant gliomas previously treated and with progressive disease (cohort 2) were prospectively examined with a single-voxel Mescher-Garwood point-resolved spectroscopy sequence at 3T. Spectra were quantified using LCModel. The Cramér-Rao lower bounds threshold was set to 20%. Integrated histomolecular analysis according to the 2021 WHO classification was considered as ground truth.

RESULTS: Thirty-four consecutive subjects were enrolled. Due to poor spectra quality and lack of histologic specimens, data from 26 subjects were analyzed. Twenty-one belonged to cohort 1 (11 women; median age, 42 years); and 5, to cohort 2 (3 women; median age, 48 years). Edited MR spectroscopy showed 100% specificity for detection of *IDH*-mutation and 91% specificity for the prediction of 1p/19q-codeletion status. Sensitivities for the prediction of *IDH* and 1p/19q codeletion were 69% and 33%, respectively. The median Cramér-Rao lower bounds values were 16% (13%–28%) for *IDH*-mutant and 572% (554%–999%) for *IDH* wild type tumors. The time between MR spectroscopy and surgery was longer for low-grade than for high-grade gliomas ($P = .03$), yet the time between MR spectroscopy and WHO diagnosis did not differ between grades ($P = .07$), possibly reflecting molecular analyses–induced delays in high-grade gliomas.

CONCLUSIONS: Our results, acquired in a clinic setting, confirmed that edited MR spectroscopy is highly specific for both *IDH*-mutation and 1p/19q-codeletion predictions and can provide a faster prognosis stratification. In the upcoming IDH-inhibitor treatment era, incorporation of edited MR spectroscopy into clinical workflow is desirable.

ABBREVIATIONS: CRLB = Cramér-Rao lower bound; 2HG = D-2-hydroxyglutarate; IDHi = IDH inhibitors; IQR = interquartile range; LW = linewidths; MEGA-PRESS = Mescher-Garwood point-resolved spectroscopy; NOS = not otherwise specified; PRESS = point-resolved spectroscopy; WHO = World Health Organization

Adult-type diffuse gliomas are classified into 3 tumor subtypes according to isocitrate dehydrogenase (*IDH*) mutation and chromosome 1p/19q-codeletion status.[1] Oligodendrogliomas, *IDH*-mutant and 1p/19q-codeleted, are, therefore, separated from astrocytomas, *IDH*-mutant and non-1p/19q-codeleted, and from glioblastomas, *IDH* wild-type. The integration of these 2 molecular markers into glioma classification outperforms histologically-based approaches in survival prediction[2,3] and allows distinct treatment decisions.[4] In the past, several *IDH*-targeted therapies have been developed. Recently, a randomized Phase III clinical trial has shown a significant increase in progression-free survival and time to the next treatment in grade 2 *IDH*-mutant gliomas treated with the IDH inhibitor (IDHi) vorasidenib compared with a placebo. Notably, a decrease in tumor volume and the tumor growth rate was observed in subjects treated

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SUMMARY

PREVIOUS LITERATURE: 2HG is a direct, downstream marker of isocitrate dehydrogenase (*IDH*) mutation in gliomas. Cystathionine is, to date, the only metabolite that was found to differ significantly in concentration in 1p/19q-codeleted gliomas from their non-1p/19q-codeleted counterparts. Edited 2HG MR spectroscopy enables reliable 2HG and cystathionine detection in a research context. Therefore, a wider translation of this technique into the clinical routine is advisable to improve the noninvasive diagnosis of gliomas and to propose target therapies as *IDH* inhibitors. This study aimed to explore the clinical impact of edited MR spectroscopy in the work-up of patients with diffuse gliomas.

KEY FINDINGS: Edited MR spectroscopy predicted both *IDH* mutation and 1p/19q codeletion via 2HG and cystathionine detection with high specificity in a clinical setting.

- MRI implemented with edited MR spectroscopy provided an earlier *IDH* diagnosis than the 2021 World Health Organization CNS analysis.
- Fast, accurate, noninvasive *IDH*-mutation detection can facilitate access to promising *IDH* inhibitors.

KNOWLEDGE ADVANCEMENT: This study shows the reliability and clinical value of in vivo edited MR spectroscopy for the noninvasive diagnosis of gliomas, and it suggests how the incorporation of this technique in clinical protocols can accelerate routine work-up for patients with diffuse gliomas.

with vorasidenib compared with subjects receiving a placebo, together with an excellent drug tolerance.[5] These emerging therapeutic opportunities reinforce and expand the clinical relevance of the noninvasive assessment of *IDH*-mutation status, allowing treating physicians to propose IDHi as a neoadjuvant treatment before a surgical procedure.

Many different approaches have been developed to predict *IDH* mutation.[6,7] In vivo MR spectroscopy emerged as the only method that can unequivocally establish the presence of an *IDH* mutation through detection of D-2-hydroxyglutarate (2HG),[8–10] its direct, downstream oncometabolite.[11] Conversely, other proposed methods indirectly identify *IDH*-mutational status through lesion feature analysis[12–14] or through the evaluation of possibly related pathologic processes.[15,16] In addition, MR spectroscopy can measure cystathionine, a metabolite that accumulates preferentially in 1p/19q-codeleted gliomas.[17,18] Therefore, MR spectroscopy can simultaneously visualize the 2 glioma diagnostic hallmarks.

Conventional MR spectroscopy can detect the 2HG peak at 2.25 ppm,[8,9] but at this chemical shift, the 2HG signal overlaps with other metabolites, such as glutamate, glutamine, and γ-aminobutyric acid, leading to a high possibility of false-positive results. Several strategies have been proposed to overcome this issue. Among these methods, edited MR spectroscopy is the only one that completely removes resonances overlapping with the 2HG signal at 4.02 ppm[19] and therefore selectively detects 2HG, potentially reducing the rate of false-positive findings. Compared with conventional MR spectroscopy techniques, edited MR spectroscopy has higher diagnostic accuracy[20] for *IDH* mutation. Edited MR spectroscopy also selectively detects cystathionine at 2.72 ppm,[17,21] which is, to date, the only metabolite that was found to differ significantly in concentration in 1p/19q-codeleted gliomas from their non-1p/19q-codeleted counterpart. Hence, edited MR spectroscopy has the potential to improve the noninvasive diagnosis of gliomas.[22] However, the combined value of the incorporation of highly-specific 2HG and cystathionine detection by edited MR spectroscopy in a clinical setting has not been demonstrated so far.

The use of edited MR spectroscopy should not aim to substitute a far more comprehensive pathologic evaluation and does not determine the CNS World Health Organization (WHO) grade, but it may speed up a targeted clinical work-up and, for example, accelerate access to IDH inhibitors. The elapsed time between the MRI examination and the final WHO diagnosis can last up to several weeks, especially for gliomas with noncanonical *IDH* mutations, which may delay patient care. Moreover, anticipating the specific glioma subtype before surgery is of paramount importance for neurosurgeons, because the glioma subtype influences the extent of surgical resection.[23] Edited MR spectroscopy has, therefore, a clear clinical relevance. Nevertheless, its incorporation into clinical practice is not straightforward, similar to other advanced MRI methods. The quality of acquired data is a first technical issue in a busy clinical environment because poor SNR and subtraction artifacts may severely hamper spectral editing and fitting,[24] leading to improper data interpretation.

In this study, we aimed to evaluate the specificity and sensitivity of edited MR spectroscopy for the prediction of both *IDH* mutation and 1p/19q codeletion in a clinical setting. In addition, we compared MR spectroscopy quality parameters in data acquired in this study (acquired in a clinical context) with those obtained in a previous study performed in a research setting in a similar population.[25] Finally, we measured the elapsed time between glioma subtype prediction via edited MR spectroscopy and WHO 2021 histomolecular diagnosis.

MATERIALS AND METHODS

Enrollment of Subjects

Two cohorts of adult subjects were recruited at our tertiary medical center (Pitié-Salpêtrière University Hospital, Paris, France) from February 2021 to July 2023.

Subject inclusion criteria for both cohorts were older than 18 years of age and an estimated lesion volume of >2 mL. Subject inclusion criteria for cohort 1 were the presence of a presumed low-grade glioma and surgery eligibility (biopsy or resection).

Subject inclusion criteria for cohort 2 were a histologic diagnosis of *IDH*-mutant diffuse glioma and progressive disease according to the RANO diffuse low-grade glioma criteria.[26]

The study adheres to the Declaration of Helsinki ethics principles and respects the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[27] The data were made available by the Clinical Data Warehouse of the Public Assistance Hospitals Paris (Assistance Publique Hopitaux Paris, Assistance Publique–Hôpitaux de Paris, reference number: 20211216174611), in accordance with the Ethical and Scientific Board of the Assistance Publique–Hôpitaux de Paris. According to regulations of the Assistance Publique-Hôpitaux de Paris and the Ethical and Scientific Board of our institution, institutional review board approval and written consent were waived because MRIs were acquired as part of the routine clinical care.

Demographic (age, sex) characteristics were recorded for each subject, along with the type of surgery, the time between edited MR spectroscopy and surgery, and the time between edited MR spectroscopy and current WHO diagnosis.

MRI and Edited MR Spectroscopy Acquisition

MRI examinations were performed on a 3T Skyra MR scanner (Siemens) equipped with a 64-channel receive-only head coil. The spectroscopic VOI was placed in the suspected glioma on 3D FLAIR images (field of view = $256 \times 256 \times 192$ mm^3, spatial resolution = $0.5 \times 0.5 \times 1.0$ mm^3, TR/TE = 7000/374 ms, total scan time = 3 minutes, 25 seconds).

VOI dimensions were adapted to lesion morphology to maximize lesion coverage, minimize the contribution of normal brain tissue, and reduce common spectroscopic artifacts. VOI placement was performed by either a radiographer with 1–3 years of experience or a spectroscopy expert (Francesca Branzoli) with 10 years of experience in brain tumor MR spectroscopy.

Edited MR spectroscopy was acquired using a single-voxel Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) sequence (TR = 2 seconds, TE = 68 ms, number of complex points = 2048, bandwidth = 3 kHz, 128 edit-on and 128 edit-off scans acquired interleaved), as previously described.[25] The editing pulses were at 1.9 ppm for the edit-on scan and at 7.5 ppm for the edit-off scan. Water suppression was performed by using variable power with optimized relaxation delays (VAPOR) and outer volume suppression techniques.[28] B_0 shimming was performed by using the system 3D gradient-echo shim, operated in the "Brain" mode. Total scan time was around 12 minutes including preparation steps.

MR Spectroscopy Postprocessing

Spectra were analyzed at the Center for Neuroimaging Research (Paris Brain Institute), processed with Matlab (MathWorks), and quantified using LCModel v6.3-0G21 (http://www.lcmodel.com/), as detailed in Branzoli et al.[25] Briefly, single transients were frequency- and phase-aligned by using the total choline (tCho) signal at 3.22 ppm. The final spectra were obtained by subtracting the averaged spectra acquired for the edit-on and edit-off conditions. The basis set used for spectral fitting included 2HG, cystathionine, γ-aminobutyric acid, glutamate, glutamine, glutathione, *N*-acetylaspartate, and *N*-acetylaspartylglutamate. The Cramér-Rao lower bound (CRLB) threshold for 2HG and cystathionine detection was set to 20%. The linewidths (LW) of total creatine at 3.03 ppm were determined as the full width at half maximum of this peak in the edit-off spectrum.

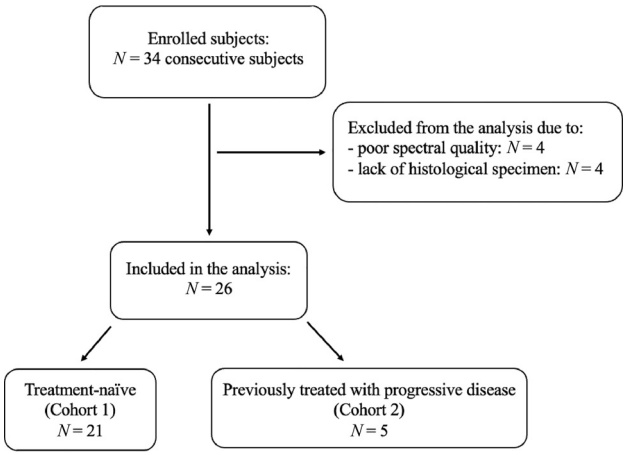

FIG 1. Flow chart of participants enrolled in the study.

MR spectroscopy spectra of insufficient quality (LW >10 Hz and/or poor water suppression preventing LW calculation) were excluded.

Tissue and Statistical Analysis

Immunohistochemical and molecular analyses were performed with standard techniques in the context of care. Histologic and molecular, integrated diagnosis according to the 2021 WHO classification was considered as a ground truth.

Descriptive statistics were used to record study variables. Categoric data were reported as numbers (percentage), while continuous data were reported as medians with interquartile ranges (IQRs) or mean (SD), as appropriate. Significant differences were assessed with unpaired *t* tests.

RESULTS

Characteristics of Subjects

Thirty-four consecutive subjects were enrolled from February 2021 to July 2023 (Fig 1). Four subjects (12%) were excluded because of insufficient quality of MR spectra. A histologic integrated diagnosis was available for 26 of the 30 remaining subjects, because 4 subjects did not receive surgical treatment. Of these, 21 were treatment-naïve subjects and belonged to cohort 1 (11 women, 10 men; median age, 41.8 years; IQR = 33.6–51.7 years; 10 oligodendrogliomas, *IDH*-mutant and 1p/19q-codeleted; 6 astrocytomas, *IDH*-mutant; 4 glioblastomas, *IDH* wild type; and 1 astrocytoma not otherwise specified [NOS]) (Online Supplemental Data). The remaining 5 subjects belonged to cohort 2 (previously treated subjects with progressive disease) (3 women, 2 men; median age, 48.2 years; IQR = 47.5–57.1 years; 1 oligodendroglioma, *IDH*- mutant and 1p/19q-codeleted; 4 astrocytomas, *IDH*-mutant) (Online Supplemental Data).

Edited MR Spectroscopy is Highly Specific for IDH Mutation and 1p/19q-Codeletion Status

In the cohort 1, edited MR spectroscopy quantified the 2HG signal at 4.02 ppm with a CRLB of <20% in 11 of 16 *IDH*-mutant

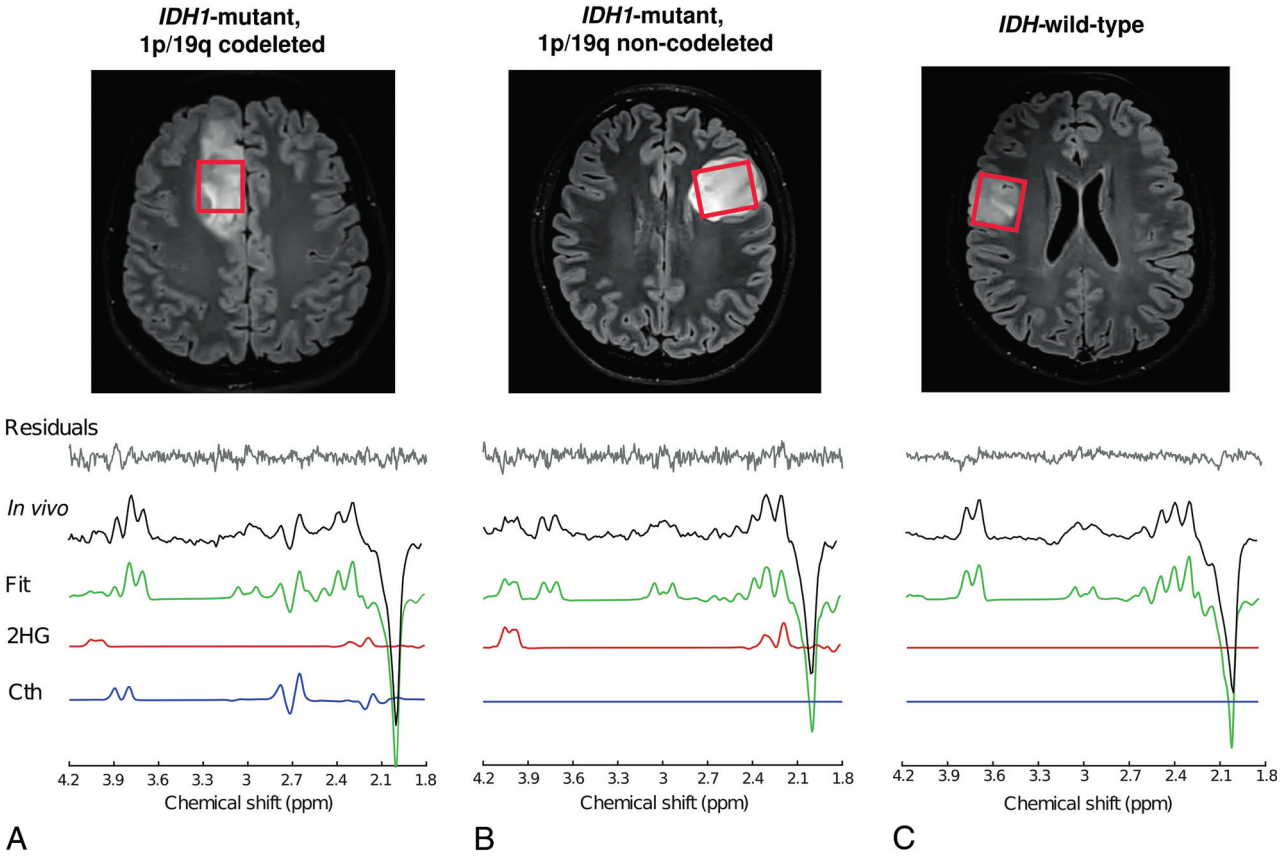

FIG 2. In vivo ^{1}H MEGA-PRESS spectra and VOIs. The location and size of the VOIs are shown on FLAIR images in *IDH1*-mutant, 1p/19-codeleted glioma (subject 1.1) (*A*); *IDH1*-mutant, 1p/19q noncodeleted (subject 1.2) (*B*), and *IDH* wild-type glioma (subject 1.5) (*C*). For each glioma subtype, in vivo MEGA-PRESS spectra (*black lines*) are shown together with LCModel fits (*green lines*), the 2HG and Cth contributions (*red and blue lines*, respectively), and residuals (*gray lines*). A line broadening of 2 Hz was applied to in vivo data. 2HG was detected in *A* and *B* (CRLB = 18% and 7%, respectively) and not detected in *C* (CRLB = 999%). Cth was detected in *A* (CRLB = 7%) and not detected in *B* and *C* (CRLB = 50% and 57%, respectively). Cth indicates cystathionine. Red boxes correspond to voxel placement.

gliomas (13 with a canonical R132H mutation, 3 with noncanonical *IDH* mutations, Online Supplemental Data). Conversely, the 2HG signal was not detected in the 4 *IDH* wild-type lesions and in 1 anaplastic astrocytoma NOS. Thus, the specificity and positive predictive value for *IDH* mutation prediction were both 100%, while the sensitivity and negative predictive value were 69% and 50%, respectively.

Concurrently, edited spectra allowed cystathionine quantification with a CRLB of <20% in 5 of 11 1p/19q-codeleted gliomas and in one 1p/19q-noncodeleted glioma. Of note, in this latter case a partial 1p chromosome gain was identified. Hence, the specificity and positive predictive value for 1p/19q-codeletion prediction were 91% and 80%, respectively, while the sensitivity and negative predictive value were 33% and 65%, respectively.

2HG and cystathionine were simultaneously detected with edited MR spectroscopy in 2 subjects with oligodendroglioma, *IDH*-mutant and 1p/19q codeleted. Cystathionine alone was detected in 2 oligodendrogliomas, *IDH*-mutant and 1p/19q-codeleted. Examples of edited spectra measured in the 3 glioma subtypes are shown in Fig 2, together with FLAIR images and VOIs. Figure 3 shows FLAIR images and edited spectra of subject 1.12 before and after treatment with ivosidenib, a selective inhibitor of the IDH1 enzyme. 2HG was detected at baseline with CRLB = 13%, while it was not detected 1 year after the beginning of the treatment (CRLB = 158%).

Reliable Edited MR Spectroscopy Data Can be Obtained in a Clinical Setting

MEGA-PRESS spectra ($n = 26$) had average total creatine LW of 6.0 (SD, 1.4) Hz; IQR = 5.0–7.0 Hz. This value is not significantly different from that obtained by Branzoli et al[25] in a previously performed study in a research setting (6.2 [SD, 0.7] Hz; IQR = 5.2–8.0 Hz).

For cohort 1, the median CRLB value of 2HG for *IDH*-mutant tumors was 16% (IQR = 13%–28%) and 999% for *IDH* wild-type tumors (IQR = 999%–999%). These values did not differ from the CRLB values acquired in a research environment for a similar cohort of treatment-naïve subjects: median value for *IDH*-mutant tumors = 18% (IQR = 15%–27%) and 999% for *IDH* wild-type tumors (IQR = 999%–999%; $P = .44$).[25]

The median VOI size was 8.0 mL for both studies (IQR = 6.9–10.3 mL in this study and IQR = 7.8−9.6 mL for the research setting study).

2021 WHO Diagnosis Impacts Current Preoperative Triage

In cohort 1, the time between MRI implemented with edited MR spectroscopy and surgery (5 stereotactic biopsies, 16 resections) was 42 days (median, IQR = 97–4 days) and was longer in low- than in high-grade tumors ($P = .03$). The time between *IDH* assessment status via edited MR spectroscopy and the 2021

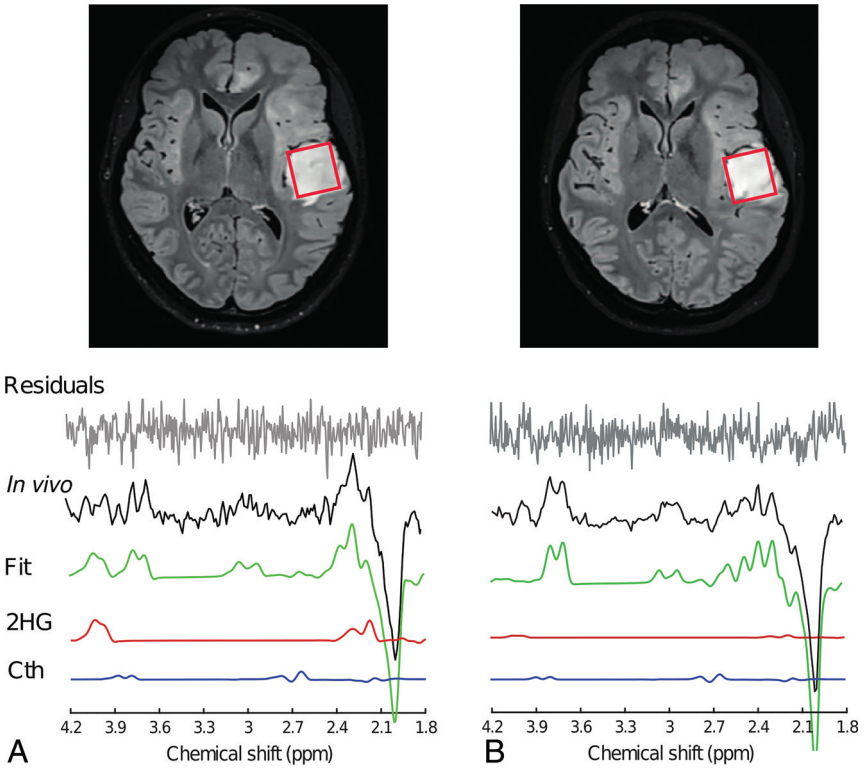

FIG 3. In vivo ^{1}H MEGA-PRESS spectra and VOI in a subject (1.12) treated with ivosidenib, a selective inhibitor of the IDHi enzyme. The location and size of the VOIs are shown on FLAIR images at baseline before IDHi treatment (*A*), and 1 year after treatment (*B*). For each time point, in vivo MEGA-PRESS spectra (*black lines*) are shown together with LCModel fits (*green lines*), the 2HG and Cth contributions (*red and blue lines*, respectively), and residuals (*gray lines*). A line broadening of 2 Hz was applied to in vivo data for better visualization only. 2HG was detected only at baseline (CRLB = 13% and CRLB = 158% before and after treatment, respectively), while Cth was never detected (CRLB = 161% and 68%). Cth indicates cystathionine. Red boxes correspond to voxel placement.

WHO diagnosis was 77 days (median, IQR = 117–35 days) and did not differ between low- and high-grade tumors ($P = .07$).

2HG Detection at Progression

In cohort 2, 2HG was detected in 3 of 5 *IDH*-mutant tumors. Conversely, cystathionine was not detected in the sole oligodendroglioma. For this population, the sensitivity and specificity of edited MR spectroscopy cannot be assessed because a pathologic evaluation was not available after edited MR spectroscopy.

DISCUSSION

This study highlights the reliability and value of edited MR spectroscopy in a clinical context and, for the first time, explicitly points out how this technique can accelerate routine glioma work-up. Both in preoperative and in recurrent gliomas, edited MR spectroscopy predicted *IDH*-mutation status with 100% specificity and 100% positive predictive value, as confirmed elsewhere.[25,29] No other advanced MRI technique has this diagnostic performance for the characterization of *IDH* mutation.[19]

The long TE (97 ms) single-voxel point-resolved spectroscopy (PRESS) sequence has been previously evaluated at 3T in a clinical practice, with lower specificity (77%[30] and 81%[31]) except for 1 study that reported a specificity of 100%.[32] However, measurement of 2HG with the long-TE PRESS technique may provide false-positive results, especially in necrotic areas.[33]

After the exclusion of 4 of 34 spectra (12%), MR spectroscopy data quality was comparable with that in previous results obtained in a research setting, thus encouraging a wider clinical translation, but also suggesting the need for quality control.

In opposition to specificity and positive predictive value, sensitivity and negative predictive values were low (69% and 50%) but within previously reported parameters.[25] Indeed, in our data set, we defined a CRLB cutoff of 20% for 2HG detection, as previously suggested,[34] to minimize edited MR spectroscopy uncertainties. In a study conducted in a research environment with the same sequence,[25] the sensitivity was very similar (60%) with the same CRLB cutoff set at 20%. In addition, we did not detect false-positive cases even with a CRLB of 50% (Online Supplemental Data), in contrast to a previous clinical study reporting false-positive results using a CRLB <30% threshold.[34] This finding can be due to multiple reasons, such as a difference in data quality and/or spectral analysis. Limited scanner time in a busy clinical context can lead to inaccuracy in VOI placement, possibly causing spectral artifacts that may increase the risk of detecting false-positive results. Therefore, a more conservative CRLB threshold may be more beneficial to avoid false-positive data, even at the cost of an increased number of false-negatives. In fact, we believe that in vivo noninvasive tumor stratification should focus on specificity and positive predictive values.

Fast, early, and accurate detection of pivotal prognostic markers, such as *IDH* mutation and 1p/19q codeletion, can promptly guide efficient subsequent clinical work-up. If a 2HG resonance is detected with a technique that provides a 100% positive predictive value, a maximum safe surgical resection can be directly planned, thus avoiding brain biopsy. A 100% specific 2HG visualization could also accelerate access to emerging tailored therapeutic strategies.[5] IDHi treatment is accessible for patients with progressing *IDH*-mutant tumors, but it is also a safe and valuable antitumor treatment option at diagnosis, especially in non-surgically-accessible subjects, in whom it allows delaying chemotherapy or radiation therapy toxicity. Figure 3 shows the pharmacologic effect of ivosidenib, a selective inhibitor of the IDH1 enzyme, in a young patient noneligible for surgery and highlights the key role that edited MR spectroscopy can play during IDHi therapies.

Of note, the 2HG oncometabolite accumulates independent of the *IDH*-mutation type[11] while immunohistochemistry detects

only the canonical *IDH* mutation (IDH1R132H). According to the fifth edition of the WHO classification of CNS tumors, DNA sequencing analysis is needed in case of immunohistochemistry negativity in diffuse gliomas with histologic grade 2 or 3 at any age, or in case of histo-molecular aspect (necrosis, microvascular proliferation, *TERT* promoter mutation, *EGFR* gene amplification, combined gain of whole chromosome 7 and loss of chromosome 10) of glioblastoma in subjects younger than 55 years of age.[1] DNA sequencing visualizes noncanonical *IDH1* and *IDH2* mutations but, at the same time, lengthens the diagnostic evaluation in subsequent glioma workflow. In our cohort 1, 3 subjects had noncanonical *IDH* mutations (subjects 1.2, 1.7, 1.11). For 2 of these 3 individuals (subjects 1.2 and 1.11), edited MR spectroscopy detected a 2HG peak and, therefore, diagnosed an *IDH*-mutant glioma 1.5 and 7 months earlier than histomolecular analysis, respectively. Of note, 1 of 3 brainstem gliomas have an *IDH* mutation, which is a noncanonical *IDH1* mutation in most cases,[35] outlining the importance of a noninvasive diagnosis in this high-surgical-risk location. Thus, edited MR spectroscopy can rapidly identify rarer diseases[36] that often have a delayed diagnosis.

In this study, *IDH*-mutation status was obtained >2 months earlier through edited MR spectroscopy than the WHO diagnosis. This multifactorial interval differed according to the suspected tumor grade before surgery ($P = .03$), but not after surgery, suggesting that in our clinical center surgery triage, due to MRI protocols, is efficient, while the histomolecular diagnostic approach can be improved because there is possibly a clinical impact of the time needed for the examination of the surgical samples through pathologic and molecular analysis, especially DNA profiling techniques. This elapsed time delays clinical care in patients with diffuse gliomas, while a 100% specific 2HG assessment may shorten this gap.

In addition to 2HG detection, edited MR spectroscopy protocol also identifies the cystathionine multiplet at 2.72 ppm. Cystathionine measurements are linked to serine- and cystathionine-pathway genes located on 1p chromosome, as cell models with 1p deletion have shown.[18] In addition, cystathionine levels are linked to the oligodendroglioma tumor subtype.[18,22] In rarer cases, cystathionine is also seen in astrocytomas, with poorly understood mechanisms. Most interesting, in our study, the only astrocytoma with cystathionine signal had a partial gain of chromosome 1p, extending the possible mechanisms of cystathionine accumulation. Therefore, the use of edited MR spectroscopy in the clinic may improve knowledge regarding neurochemical alterations in gliomas.

In a pretherapeutic stage, a fast detection of *IDH*-mutational status may accelerate access to IDHi in patients in whom a complete surgical resection is difficult at diagnosis but may be practicable after IDHi treatment.

The feasibility of 2HG detection in recurrent lesions, as illustrated from the results in cohort 2, may help the treating physician select the best candidates for IDHi, avoiding additional surgical intervention. Furthermore, 2HG spectroscopy may investigate on glioma evolution, because little is still known on the epigenetic evolution of *IDH* gliomas at advanced disease stages.

Under IDHi, in vivo evidence of a 2HG decrease can be used to pharmacodynamically confirm target engagement[37] (Fig 3) and to explore mechanism of acquired resistance (because the occurrence of a re-emerging peak may point to improper medication adherence or the development of resistance mutations). In patients with *IDH*-mutant gliomas under standard of care treatment, 2HG MR spectroscopy may monitor treatment efficacy[38] by observing a progressive reduction in 2HG levels with time that can occur earlier than other radiologic changes detected with conventional MRI sequences,[29] while in postsurgical patients, it can help in the discrimination between gliosis and recurrence.

Therefore, the information acquired through edited MR spectroscopy can strongly impact the management of patients with diffuse glioma.

Limitations

A first limitation of this study is that an unsuppressed water reference was not acquired for all subjects, therefore not providing 2HG concentration on the Online Supplemental Data. A second limitation is the monocentric nature of the study. A third limitation is the small number of patients with negative *IDH*-mutant status. Given that edited MR spectroscopy strength relies on 100% specificity in 2HG detection, further studies with a greater number of true-negative patients are warranted. A fourth limitation is the assistance of an MR spectroscopy expert (Francesca Branzoli) in most data acquisitions and in all data analyses. A correct voxel placement (proper lesion coverage, avoidance of artifacts area) is crucial for acquiring informative spectra and is done manually, potentially bringing multiple sources of error. Voxel dimensions have also been manually adapted according to lesion location and size. An automated acquisition planning method was proposed that improves lesion coverage compared with manual voxel placement,[39] but it is not yet available on MRI scanners.

A fifth, relevant limitation for edited MR spectroscopy incorporation in the clinic is that postprocessing software requires technical expertise and no automatic postprocessing pipeline exists yet.

Last, edited spectra are not embedded in the hospital-wide PACS system.

CONCLUSIONS

2HG and cystathionine detection through edited MR spectroscopy is highly specific, clinically feasible, and accelerates individual glioma management significantly. In the future, access to emerging IDHi will increase, thereby increasing the need for edited MR spectroscopy. Thus, a wider implementation of this technique in the routine setting is desirable. We hope our encouraging results accelerate its clinical adoption.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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