European Journal of Radiology 116 (2019) 174–179

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Magnetic resonance diffusion-tensor imaging metrics in High Grade Gliomas: Correlation with IDH1 gene status in WHO 2016 era

Raffaele Augelli[a,*,1], Elisa Ciceri[a,1], Claudio Ghimenton[b], Giada Zoccatelli[a], Alessandra Bucci[a], Antonio Nicolato[c], Alberto Beltramello[d], Giampietro Pinna[c], Giuseppe K. Ricciardi[a]

[a] Neuroradiology Departments, Azienda Ospedaliera Universitaria Integrata Verona, Ospedale Civile Maggiore, Borgo Trento, Verona, Italy
[b] Pathology Departments, Azienda Ospedaliera Universitaria Integrata Verona, Ospedale Civile Maggiore, Borgo Trento, Verona, Italy
[c] Neurosurgery Departments, Azienda Ospedaliera Universitaria Integrata Verona, Ospedale Civile Maggiore, Borgo Trento, Verona, Italy
[d] Radiology Department, IRCCS "Sacro Cuore – Don Calabria" Hospital, Negrar, Verona, Italy

ARTICLE INFO

Keywords:
High-Grade Glioma
Diffusion tensor imaging metrics
Isocitrate DeHydrogenase mutation
Radial diffusivity
Fractional anisotropy
WHO glioma classification

ABSTRACT

Purpose: To evaluate any possible correlation between the presence of Isocitrate DeHydrogenase 1 mutation (IDH1m) and specific DTI (Diffusion Tensor Imaging) metrics, such as Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD) and Axial Diffusivity (AD).

Methods: We retrospectively analyzed 47 patients who underwent an advanced-MR study with DTI followed by surgical intervention with a subsequent histologic diagnosis of High-Grade Glioma (HGG) and immunohistochemical evaluation of IDH1 (Isocitrate DeHydrogenase) mutation status. For each DTI metrics we measured the ratio between tumor and normal tissue and we evaluated the correlation with IDH1 mutation.

Results: We observed a positive correlation with IDH1 status and RD and MD data. No correlation was demonstrated between IDH1 status and FA and AD.

Discussion: Our results support the hypothesis that the number of residual axonal fibers, extracellular matrix composition and the presence of colliquated tissue, may together contribute to a global RD increase in HGG, with a relatively higher increase in IDH1m tumors.

Conclusions: Our data are in favor of a need for multimodal advance evaluation of HGG. DTI metrics help to analyze IDH1 mutation status, in order to better characterize the lesions and to tailor treatment and follow up.

1. Introduction

The identification of glioma DNA biomarkers by means of DNA sequencing allows to classify tumor subtypes and correlate them with glioma biologic behavior and radio-chemo-therapy response [1]. Its role has been acknowledged by the new, recently published, WHO brain tumor classification [2]. This new classification identifies Isocitrate DeHydrogenase gene (IDH) mutation as the most important genetic marker in natural history of brain tumors; nowadays we tag glial neoplasm as IDH wild-type or IDH-mutated [3].

Moreover, WHO 2016 classification reviewed some glial entities, like "oligoastrocytoma", as oligodendroglial or astrocitary tumors depending on the presence of a particular genetic asset, in particular for the presence or absence of IDH mutation.

The presence of a somatic mutation on 132 codon of type 1 IDH (IDH1) has been demonstrated in 70% of anaplastic gliomas and in 30% of all high grade gliomas (HGG) (III and IV grade) [4]. Non mutated IDH1 gene, also known as IDH1 wild-type (IDH1wt), encodes for a carboxilase that converts isocitrate into alfa-cheto-glutarate, with NADPH production. This product reduces glutathione, an anti-oxidant agent in cellular metabolism. Absence of any enzymatic activity of proteins resulting from mutated IDH1 gene however, leads to a rise in 2-Hydroxi-Glutarate (2 H G), an onco-metabolite, which is thought to modify the methylation state of DNA [5]. IDH1 mutation (IDH1m) is an independent positive outcome predictor of histology type and tumor grade [4,6]. IDH1m low grade gliomas (LGG) are associated with a low frequency of switch to secondary glioblastomas (GBM). Moreover IDH1m HGG are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection [7]. Immunohistochemical analysis, and gene sequencing when available, currently remain the gold standard for the evaluation of genetic and epigenetic variables in brain tumors [6], although they can be performed only in

* Corresponding author at: Neuroradiology Department, University Hospital of Verona, Piazzale Stefani 1, 37126, Verona, VR, Italy.
E-mail address: raffaele.augelli@aovr.veneto.it (R. Augelli).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ejrad.2019.04.020
Received 10 February 2019; Received in revised form 8 April 2019; Accepted 29 April 2019

patients undergoing surgery or biopsy. In recent decades, many authors have tried to apply advanced MR imaging to determine genetic and/or epigenetic variables in brain tumors. Conventional MRI alone has shown lack of accuracy [8,9] in identifying any correlation with the presence of IDH1 mutation. Some studies on water-suppressed proton MR-spectroscopy in brain gliomas, have shown that in presence of IDH1 mutation, the levels of 2-HG are higher in tumors with wild-type IDH1 [10]. Caution is necessary however, when acquiring and analyzing in vivo MRS data. Reliable measurement of D-2HG requires customized MRS sequences and extensive post-processing [4,6]; for these reasons in clinical routine practice they are difficult to apply extensively [11].

In a pre-clinical study, Chaumeil MM et al [12] investigated the value of ^{13}C-MRS of hyperpolarized [1-^{13}C]pyruvate for tumor detection and therapeutic response monitoring in HGG, with or without IDH1 mutation. Other authors demonstrated a potential role of DSC-MRI [13], 7T-SWI [14] and multimodal MRI [15] in IDH1 mutation detection.

Only recently Diffusion Tensor Imaging (DTI) metrics have been proposed to evaluate histology type [16,17] or grade [9,18–23] of primary brain tumors, utilizing Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD) and Axial Diffusivity (AD). Furthermore, their accuracy in discriminating tumor infiltration from perilesional edema [9,24] or differential diagnosis between primitive and metastatic tumors [25], has also been considered.

Our aim is to evaluate any possible correlation between the presence of IDH1m and specific DTI metrics (FA, MD, RD and AD) in groups of patients with HGG, preoperatively studied with DTI. We hypothesize that DTI could help in predicting IDH1 status in HGG in a non-invasive manner.

2. Materials and methods

2.1. Study population

Over a period of 16 months (Jan 2014–May 2015), we selected a group of brain tumor patients fulfilling the following criteria: 1) a complete MR examination with conventional and DTI sequences performed on a 3T MR unit; 2) surgical removal of the tumor after the MR examination (within 5 days); 3) a final diagnosis of HGG; 4) an immuno-histochemical evaluation of IDH1 mutation status.

These patients were classified in two groups: 1) patients with IDH1m; 2) patients with IDH1wt.

2.2. MRI acquisition

All patients underwent pre-surgical MR imaging with a 3.0T MR imaging unit (Achieva; Philips, Best The Netherlands); a body coil was used for transmission and 8-channel SENSE technology head coil was used for signal reception.

Acquisition parameters of 3D T2-weighted sequence, 3D FLAIR sequence, DTI sequence and 3D T1-weighted sequence are reported in Table 1.

2.3. DTI data processing

DTI imaging was processed on a separate workstation running OsiriX imaging software (Pixmeo SARL, Bernex Switzerland) version 5.6 (32-bit). DICOM data from the patients' brain MRI were anonymized and transferred to the computer. The DTI Map Plugin (version 1.6) was used to obtain maps of *Fractional Anisotropy* (FA), *Radial Diffusivity* (RD), *Mean Diffusivity* (MD) and *Axial Diffusivity* (AD), in order to calculate the ratio between tumor and normal tissue values in the contralateral semioval center (SOC). Using the image synchronization tool provided by OsiriX we traced 5 circular Regions-Of-Interest (ROI), with a maximum area of 0.12 ± 0.2 cm^2, on the solid part of any lesion (avoiding necrotic, hemorrhagic and cystic intralesional zones) and 5 ROI on the contralateral frontal part of the SOC, as shown in Fig. 1.

For each DTI metric, we calculated the arithmetical mean for minimum, mean and maximum value within each ROI, indicating them as *minFA*, *meanFA* and *maxFA* (for *Fractional Anisotropy*), *minMD*, *meanMD* and *maxMD*, (for *Mean Diffusivity)*, *minAD*, *meanAD* and *maxAD* (for *Axial Diffusivity*), *minRD*, *meanRD* and *maxRD* (for *Radial Diffusivity)*. Consequently we obtained the ratio between tumor value and SOC value, indicated as *min-ratio*, *mean-ratio* and *max-ratio* for each metric (ie $minFAtum / minFAsoc = minFA_{ratio}$).

2.4. Immunohistochemical evaluation

Formalin-fixed, paraffin-embedded sections were tested with a codon 132 IDH1 mutation-specific antibody (internal clone H09; Dianova, Hamburg, Germany).

Tumors with IDH1 (R132 H) mutation presented a cytoplasmic accumulation of the antibody, while IDHwt showed no accumulation (Fig. 2). Based on the low reported frequency of non-canonical IDH1 mutations and IDH2 mutations in malignant astrocytomas, these were not characterized due to tissue limitations.

For some non R132H mutated gliomas (namely young patients or cases with a component resembling oligodendroglioma) sequencing for different IDH1 and IDH2 mutations was performed.

2.5. Statistical analysis

The statistical analysis was conducted with SPSS 17.0 (SPSS Inc., Chicago, IL) with the support of the Clinical Research Unit of Our Hospital.

For each DTI parameter, Shapiro-Wilk test was performed on imaging data in order to evaluate if they were normally distributed.

Mann-Whitney was used in order to evaluate the statistical significance between ratio values observed in the IDH1m group versus those observed in the IDH1wt group (P-value < 0.01 was accepted for a statistically significant differences).

Receiver-Operating Characteristic (ROC) curves of the parameters with statistical significance were elaborated in order to find out the cut-off value for distinguishing between IDHm and IDHwt.

Table 1
Acquisition protocol parameters.

Sequence	TR (ms)	TE (ms)	TI (ms)	ST (mm)	NEX	N° gradients	Matrix	AcqTime
T1-3D[a]	8.13	3.69	–	1	1	–	240 × 240	10'8"
T2-3D	2800	221.2	–	1.6	1	–	184 × 182	6'32"
FLAIR	4800	299.9	1660	1.6	1	–	228 × 228	5'48"
DTI	8.114	94.4	–	2	3	32	128 × 128	12'32"

TR (repetiton time), TE (echo time), TI (inversion time), ST (slice thickness), NEX (number of excitations), AcqTime (acquisition time).
[a] Pre/post Gadovist ® (0.1 ml/kg) administration.

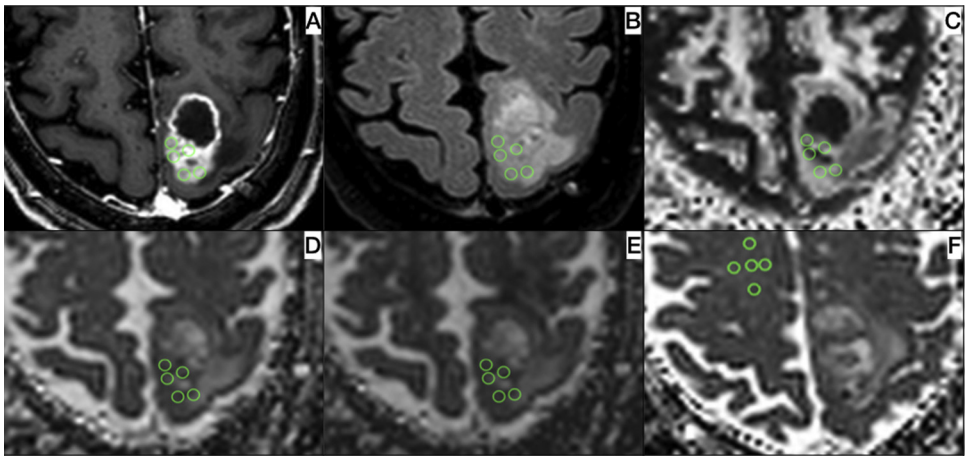

Fig. 1. 3T MR Axial images and parametric maps in a patient with left parietal HGG.
A-E: 5 ROIs placed on tumor tissue in left parietal lobe; A: T1-weighted axial image, after Gadolinium administration; B: axial FLAIR image; C: FA map; D: MD map; E: RD map; F: 5 ROIs placed on contralateral (right) SOC, in the same patient, MD map.

3. Results

3.1. Demographics

A total of 283 patients with intracranial neoplasm were studied in our department by means of preoperative MR (Jan 2014-May 2015). Among these, 84, with suspected cerebral glioma underwent advanced MR-DTI examination, followed by surgery excision (days between MR-DTI study and surgery: mean = 2.87; range: 1–5).

We excluded 37 patients:

- pts with MRI artifacts preventing an accurate DTI metric maps reconstruction;
- pts with a non-glial brain tumor at histopathology evaluation;
- pts with histology of LGG
- pts without IDH1 analysis.

The final population analyzed in our study was made up of 47 patients (20 F and 27 M), with a mean age of 53.6 (range: 25–75; median: 55).

According to 2016 WHO classification, our series included grade III glioma in 18 patients (13 M; 5 F) and grade IV glioma in 29 (15 F; 14 M). IDH1 was mutated in 10 patients (21.3%; IDH1m group) and non-mutated in 37 patients (78.8%; IDH1wt group):

- IDH1m group: 8/10 glioma grade III (80%) and 2/10 glioma grade IV (20%);
- IDH1wt group: 10/37 glioma grade III (27%) and 27/37 glioma grade IV (73%).

3.2. DTI metrics

We observed positive correlation within the data concerning RD and MD.

RD parameter: P-value < 0.0001 for minRDratio and meanRDratio and < 0.0011 for maxRDratio. Cut-off of 3.151, 2.389 and 2.023, respectively; Area-Under-Curve (AUC) 0.895 for $minRD_{ratio}$, 0.878 for $meanRD_{ratio}$ and 0.824 for $maxRD_{ratio}$. Significance level resulted < 0.0001, < 0.0001 and 0.0001 respectively (Fig. 3).

MD parameter: P-value 0.005 for $minMD_{ratio}$, 0.018 for $meanMD_{ratio}$ and 0.089 for $maxMD_{ratio}$. Cut-off of 1.639, 1.641 and 1.49, respectively; AUC of 0.895 for $minMD_{ratio}$, 0.743 for $meanMD_{ratio}$ and 0.678 for $maxMD_{ratio}$. Significance level of 0.0003, 0.0064 and 0.1035 respectively (Fig. 4).

No correlation was demonstrated for FA (P-value of 0.0465 for $minFA_{ratio}$, of 0.376 for $meanFA_{ratio}$, and of 0.539 for $maxFA_{ratio}$) and AD (P-value of 0.07 for $minAD_{ratio}$, of 0.159 for $meanAD_{ratio}$, and of 0.582 for $maxAD_{ratio}$). In fact, even if we observed a global reduction of FA in tumor versus non-pathologic tissue, with a tendency for a lower reduction in the IDH1m group versus the IDH1wt group, these differences did not reach an acceptable level of statistical significance. We observed no correlation between AD ratio values and IDH1m as the values were extremely variable.

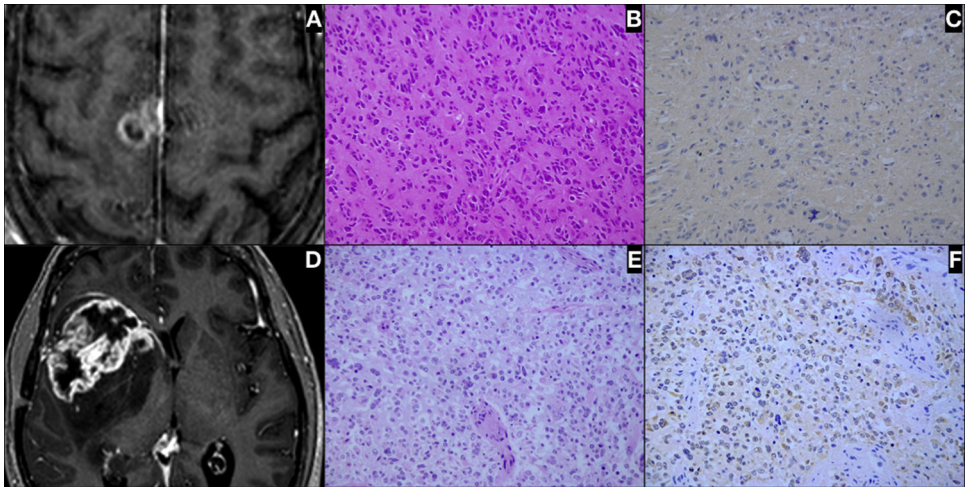

Fig. 2. Immunohistochemical demonstration of IDH mutation state in two different GBM cases.
(A–C) *IDH* wild type GBM: A) partially necrotic GBM in right supplementary motor area,
B) haematoxylin and eosin stain showing presence of pleomorphic cells, C) immunohistochemical absence of IDH1 132H expression (no IDH1 R132H staining). In this case **minRDratio resulted 2.628**.
(D–F) *IDH* mutant GBM: D) extensively necrotic right deep frontal and insular GBM, E) haematoxylin and eosin stain showing presence of vascular proliferation, F) cytoplasmic positivity for IDH1 132H (positive IDH1 R132H staining appearing as light yellow interstice). In this case **minRDratio resulted 4.411**.

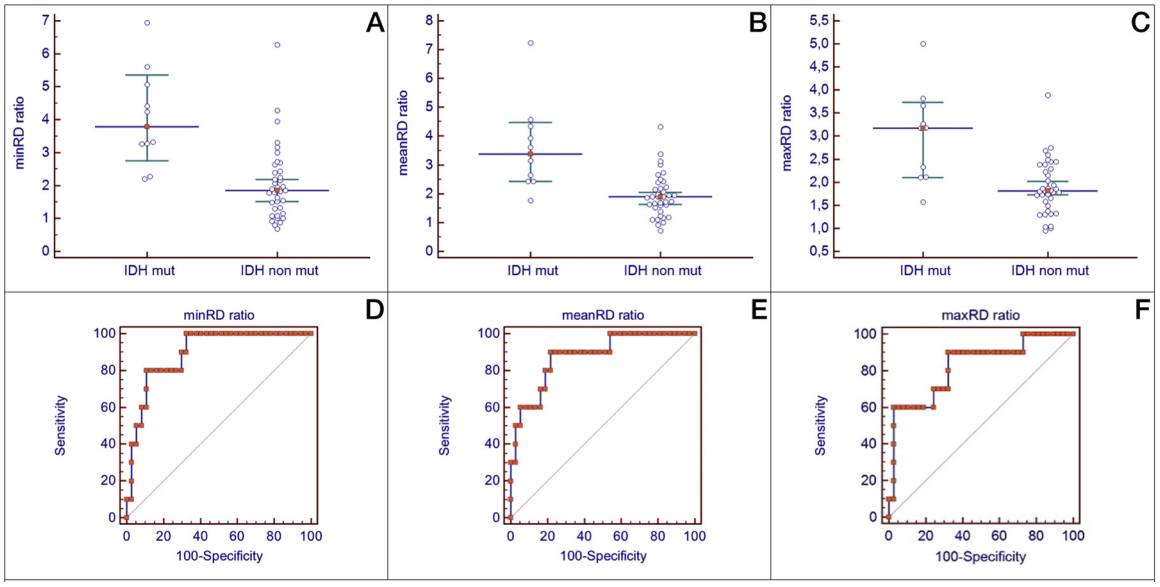

Fig. 3. Correlation findings between IDH1 state and RD.
A-C: Dot-plot graphs for $minRD_{ratio}$ (A), $meanRD_{ratio}$ (B) and $maxRD_{ratio}$ (C) values in IDH1m group compared to IDH1wt group. D–F: ROC curve obtained for $minRD_{ratio}$ (D), $meanRD_{ratio}$ (E) and $maxRD_{ratio}$ (F) values.

4. Discussion

In this study, we retrospectively analyzed DTI parametric maps in a population of 47 HGG.

Among the parameters evaluated, RD and MD correlated with the presence of the IDH1 mutation.

4.1. Radial diffusivity and mean diffusivity

Values of RD (minRD, meanRD and maxRD) in the tumor were higher than those in healthy brain tissue, so their ratio was always higher than 1. In HGG with IDH1m gene, the above values and the ratio between tumor and normal tissue values were relatively higher than HGG with IDH1wt. Nowadays few data are available about RD variation in normal tissue or about HGG. Server et coll. found that RD values, together with ratio values, were higher in LGG than in HGG; other authors agree with these conclusions [9,26,27]. The altered RD can be explained by axonal disruption and demyelination, as reported in Klawiter and coll. study [28]. In our population, minMD values were higher than those in healthy brain tissue, with an increased $minMD_{ratio}$ in the IDH1m group; our results confirm the conclusion of Tan and coll. [20], who found an ADC-value higher in the case of IDH1m versus IDH1wt in grade IV gliomas. However, the authors observed a different behavior in grade II and III, with lower ADC value in IDH1m lesions.

4.2. Fractional anisotropy

As regards FA values, we observed a decrease in FA values in tumors but we failed to find statistically significant differences between IDH1m and IDH1wt groups. Up to now, Server et al. [9] concluded that minFA

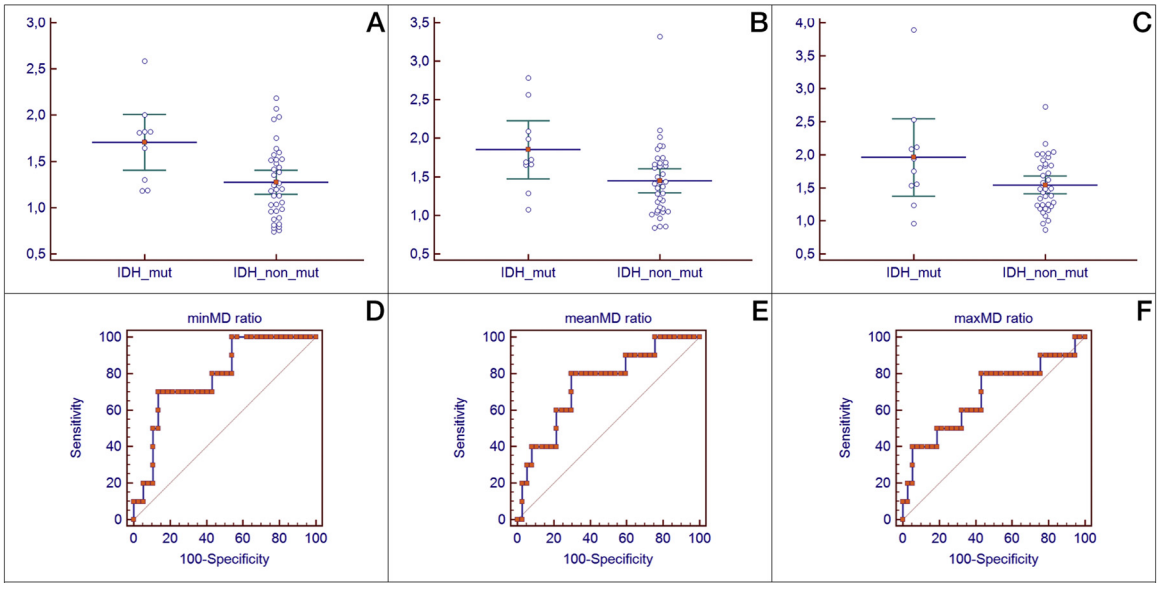

Fig. 4. Correlation findings between IDH1 state and MD.
A-C: Dot-plot graphs for $minMD_{ratio}$ (A), $meanMD_{ratio}$ (B) and $maxMD_{ratio}$ (C) values in IDH1m group compared to IDH1wt group. D-F: ROC curve obtained for $minMD_{ratio}$ (D), $meanMD_{ratio}$ (E) and $maxMD_{ratio}$ (F) values.

values (rather absolute than relative to normal appearing tissue) in grade III lesions were different from grade IV. Tan and coll. found lower values of maximum FA in gliomas compared to normal appearing tissues. In their study [20], lesions with IDH1m showed a lesser degree of decreased FA values compared to wild-type ones, but differences were less evident as the histological grade increased. In fact, they found no significant differences in FA between IDH1m and IDH1wt tumors when comparing grade III WHO versus grade IV tumors. Inoue and coll., in agreement with other authors, reported higher FA values in HGGs compared to LGGs [25,29–31], although the mechanism behind higher FA values in the former remains complex and controversial. Beppu and coll. found a correlation not only between increasing FA value, but also between cellular density and neo-angiogenesis processes [25,29,30], while Stadlbauer observed an inverse trend [18]. In his study, Smitha hypothesized that tumor infiltration could produce disorganization of the nervous fibers resulting in a reduction in FA ratio between lesion and normal tissue [23]. Changes in FA are still a matter of debate.

4.3. Data interpretation

The justification for the correlation observed in our study between the presence of IDH1m (in about 1/3 of HGG) and increase in the values of RD and MD, may lie within the biological function carried out by IDH1, or the modifications that it induces in tumor tissue. The presence of an IDH1wt gene, as described above, is associated with the normal expression of the protein, with normal metabolism of cancer cells, and a more aggressive tumor compared to those with IDH1m. In the latter case, the protein is not produced, cell metabolism is impaired and the tumor is usually less aggressive. The increase in MD and RD observed may depend on less compact tissue and consequently a more isotropic movement of water molecules in IDH1m versus IDH1wt. RD, linear indicator of diffusivity along a perpendicular plane of diffusion tensor, was the most correlated parameter among DTI metrics. RD may increase instead of AD because perpendicular components of water diffusion may be more influenced by tumor tissue than axial ones. This may be secondary to a global reduction of fibers within the tumor.

On the other hand, we consider that the lack of correlation between FA reduction and the IDH mutation status we observed could be secondary to the higher variance of FA compared with RD and MD, in the analyzed cases. Nonetheless the higher dependency of FA on the extracellular matrix composition, when compared to isotropic parameters, may justify the absence of a significant correlation. We hypothesize that the number of residual axonal fibers (reduced when compared to normal tissue), extracellular matrix composition and the presence of colliquated tissue, may together contribute to a global RD increase in HGG, with a relatively higher increase in IDH1m tumors.

4.4. Future directions

We believe that our observations present a very high clinical value, even though further studies are needed to explain how DTI metric variations are related to histologic changes, such as tumor cell density, neo-angiogenesis, perilesional edema and lesion size, via a detailed anatomopathological characterization. Therefore we strongly agree with Ma et al., who stated that only an integrated evaluation of DTI metrics would make a better glial tumor classification possible.

In this perspective recently interesting data have been published, deriving from the application of machine-learning approach in tumor biomarkers identification [32,33].

5. Conclusions

Our study demonstrates a high grade of correlation between *Radial Diffusivity* and the presence of IDH1m gene. A valid correlation of *Mean Diffusivity* was also observed.

We believe that advanced MR imaging techniques are an excellent means of characterizing High Grade Gliomas and, in the near future, they will enable us to predict prognostic factors such as those described above. However, to date, only an integrated and multi-parametric MRI evaluation can support or dismiss some kind of diagnostic hypothesis based solely on conventional imaging.

Further studies are required to confirm or exclude the association of IDH1 status with DTI metrics in a wider range of population. This association would further support the need to integrate advanced MRI techniques and specific gene sequencing to characterize cerebral lesions.

Conflicts of interest and financial disclosure agreement

The authors declare that they have no conflict of interest.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

All the patients gave their informed consent prior to their inclusion in the study.

The study was reviewed and approved by local scientific committee before study initiation and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Acknowledgment

We thanks dr Cristina Mazzi for her help in reviewing statistical analysis.

References

[1] D. Ricard, A. Idbaih, F. Ducray, M. Lahutte, K. Hoang-Xuan, J.-Y. Delattre, Primary brain tumours in adults, Lancet Lond. Engl. 379 (2012) 1984–1996, https://doi.org/10.1016/S0140-6736(11)61346-9.

[2] D.N. Louis, A. Perry, G. Reifenberger, A. von Deimling, D. Figarella-Branger, W.K. Cavenee, H. Ohgaki, O.D. Wiestler, P. Kleihues, D.W. Ellison, The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary, Acta Neuropathol. (Berl.) 131 (2016) 803–820, https://doi.org/10.1007/s00401-016-1545-1.

[3] H. Yan, D.W. Parsons, G. Jin, R. McLendon, B.A. Rasheed, W. Yuan, I. Kos, I. Batinic-Haberle, S. Jones, G.J. Riggins, H. Friedman, A. Friedman, D. Reardon, J. Herndon, K.W. Kinzler, V.E. Velculescu, B. Vogelstein, D.D. Bigner, IDH1 and IDH2 mutations in gliomas, N. Engl. J. Med. 360 (2009) 765–773, https://doi.org/10.1056/NEJMoa0808710.

[4] D.W. Parsons, S. Jones, X. Zhang, J.C.-H. Lin, R.J. Leary, P. Angenendt, P. Mankoo, H. Carter, I.-M. Siu, G.L. Gallia, A. Olivi, R. McLendon, B.A. Rasheed, S. Keir, T. Nikolskaya, Y. Nikolsky, D.A. Busam, H. Tekleab, L.A. Diaz, J. Hartigan, D.R. Smith, R.L. Strausberg, S.K.N. Marie, S.M.O. Shinjo, H. Yan, G.J. Riggins, D.D. Bigner, R. Karchin, N. Papadopoulos, G. Parmigiani, B. Vogelstein, V.E. Velculescu, K.W. Kinzler, An integrated genomic analysis of human glioblastoma multiforme, Science 321 (2008) 1807–1812, https://doi.org/10.1126/science.1164382.

[5] M. Aghili, F. Zahedi, E. Rafiee, Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review, J. Neurooncol. 91 (2009) 233–236, https://doi.org/10.1007/s11060-008-9706-2.

[6] Cancer Genome Atlas Research Network, Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas, N. Engl. J. Med. (2015), https://doi.org/10.1056/NEJMoa1402121.

[7] J. Beiko, D. Suki, K.R. Hess, B.D. Fox, V. Cheung, M. Cabral, N. Shonka, M.R. Gilbert, R. Sawaya, S.S. Prabhu, J. Weinberg, F.F. Lang, K.D. Aldape, E.P. Sulman, G. Rao, I.E. McCutcheon, D.P. Cahill, IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection, Neuro-Oncol. 16 (2014) 81–91, https://doi.org/10.1093/neuonc/not159.

[8] W.B. Pope, X.J. Qiao, H.J. Kim, A. Lai, P. Nghiemphu, X. Xue, B.M. Ellingson, D. Schiff, D. Aregawi, S. Cha, V.K. Puduvalli, J. Wu, W.-K.A. Yung, G.S. Young, J. Vredenburgh, D. Barboriak, L.E. Abrey, T. Mikkelsen, R. Jain, N.A. Paleologos, P.L. Rn, M. Prados, J. Goldin, P.Y. Wen, T. Cloughesy, Apparent diffusion coefficient histogram analysis stratifies progression-free and overall survival in patients with recurrent GBM treated with bevacizumab: a multi-center study, J. Neurooncol. 108 (2012) 491–498, https://doi.org/10.1007/s11060-012-0847-y.

[9] A. Server, B.A. Graff, R. Josefsen, T.E.D. Orheim, T. Schellhorn, W. Nordhøy, P.H. Nakstad, Analysis of diffusion tensor imaging metrics for gliomas grading at 3 T, Eur. J. Radiol. 83 (2014) e156–165, https://doi.org/10.1016/j.ejrad.2013.12.023.

[10] P. Metellus, B. Coulibaly, C. Colin, A.M. de Paula, A. Vasiljevic, D. Taieb, A. Barlier, B. Boisselier, K. Mokhtari, X.W. Wang, A. Loundou, F. Chapon, S. Pineau, L. Ouafik,

O. Chinot, D. Figarella-Branger, Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis, Acta Neuropathol. (Berl.). 120 (2010) 719–729, https://doi.org/10.1007/s00401-010-0777-8.

[11] W.B. Pope, R.M. Prins, M. Albert Thomas, R. Nagarajan, K.E. Yen, M.A. Bittinger, N. Salamon, A.P. Chou, W.H. Yong, H. Soto, N. Wilson, E. Driggers, H.G. Jang, S.M. Su, D.P. Schenkein, A. Lai, T.F. Cloughesy, H.I. Kornblum, H. Wu, V.R. Fantin, L.M. Liau, Non-invasive detection of 2-hydroxyglutarate and other metabolites in IDH1 mutant glioma patients using magnetic resonance spectroscopy, J. Neurooncol. 107 (2012) 197–205, https://doi.org/10.1007/s11060-011-0737-8.

[12] M.M. Chaumeil, M. Radoul, C. Najac, P. Eriksson, P. Viswanath, M.D. Blough, C. Chesnelong, H.A. Luchman, J.G. Cairncross, S.M. Ronen, Hyperpolarized (13)C MR imaging detects no lactate production in mutant IDH1 gliomas: implications for diagnosis and response monitoring, Neuroimage Clin. 12 (2016) 180–189, https://doi.org/10.1016/j.nicl.2016.06.018.

[13] W. Tan, J. Xiong, W. Huang, J. Wu, S. Zhan, D. Geng, Noninvasively detecting Isocitrate dehydrogenase 1 gene status in astrocytoma by dynamic susceptibility contrast MRI, J. Magn. Reson. Imaging JMRI (2016), https://doi.org/10.1002/jmri.25358.

[14] G. Grabner, B. Kiesel, A. Wöhrer, M. Millesi, A. Wurzer, S. Göd, A. Mallouhi, E. Knosp, C. Marosi, S. Trattnig, S. Wolfsberger, M. Preusser, G. Widhalm, Local image variance of 7 Tesla SWI is a new technique for preoperative characterization of diffusely infiltrating gliomas: correlation with tumour grade and IDH1 mutational status, Eur. Radiol. 27 (2017) 1556–1567, https://doi.org/10.1007/s00330-016-4451-y.

[15] B. Zhang, K. Chang, S. Ramkissoon, S. Tanguturi, W.L. Bi, D.A. Reardon, K.L. Ligon, B.M. Alexander, P.Y. Wen, R.Y. Huang, Multimodal MRI features predict isocitrate dehydrogenase genotype in high-grade gliomas, Neuro-Oncol. 19 (2017) 109–117, https://doi.org/10.1093/neuonc/now121.

[16] E. Roldan-Valadez, C. Rios, D. Cortez-Conradis, R. Favila, S. Moreno-Jimenez, Global diffusion tensor imaging derived metrics differentiate glioblastoma multiforme vs. normal brains by using discriminant analysis: introduction of a novel whole-brain approach, Radiol. Oncol. 48 (2014) 127–136, https://doi.org/10.2478/raon-2014-0004.

[17] S. Wang, S.J. Kim, H. Poptani, J.H. Woo, S. Mohan, R. Jin, M.R. Voluck, D.M. O'Rourke, R.L. Wolf, E.R. Melhem, S. Kim, Diagnostic utility of diffusion tensor imaging in differentiating glioblastomas from brain metastases, AJNR Am. J. Neuroradiol. 35 (2014) 928–934, https://doi.org/10.3174/ajnr.A3871.

[18] A. Stadlbauer, O. Ganslandt, R. Buslei, T. Hammen, S. Gruber, E. Moser, M. Buchfelder, E. Salomonowitz, C. Nimsky, Gliomas: histopathologic evaluation of changes in directionality and magnitude of water diffusion at diffusion-tensor MR imaging, Radiology 240 (2006) 803–810, https://doi.org/10.1148/radiol.2403050937.

[19] S. Van Cauter, J. Veraart, J. Sijbers, R.R. Peeters, U. Himmelreich, F. De Keyzer, S.W. Van Gool, F. Van Calenbergh, S. De Vleeschouwer, W. Van Hecke, S. Sunaert, Gliomas: diffusion kurtosis MR imaging in grading, Radiology. 263 (2012) 492–501, https://doi.org/10.1148/radiol.12110927.

[20] W.L. Tan, W.Y. Huang, B. Yin, J. Xiong, J.S. Wu, D.Y. Geng, Can diffusion tensor imaging noninvasively detect IDH1 gene mutations in astrogliomas? A retrospective study of 112 cases, AJNR Am. J. Neuroradiol. 35 (2014) 920–927, https://doi.org/10.3174/ajnr.A3803.

[21] J. Zamecnik, The extracellular space and matrix of gliomas, Acta Neuropathol. (Berl.) 110 (2005) 435–442, https://doi.org/10.1007/s00401-005-1078-5.

[22] L. Ma, Z.J. Song, Differentiation between low-grade and high-grade glioma using combined diffusion tensor imaging metrics, Clin. Neurol. Neurosurg. 115 (2013) 2489–2495, https://doi.org/10.1016/j.clineuro.2013.10.003.

[23] K.A. Smitha, A.K. Gupta, R.S. Jayasree, Total magnitude of diffusion tensor imaging as an effective tool for the differentiation of glioma, Eur. J. Radiol. 82 (2013) 857–861, https://doi.org/10.1016/j.ejrad.2012.12.027.

[24] E.J. Lee, K.J. Ahn, E.K. Lee, Y.S. Lee, D.B. Kim, Potential role of advanced MRI techniques for the peritumoural region in differentiating glioblastoma multiforme and solitary metastatic lesions, Clin. Radiol. 68 (2013) e689–697, https://doi.org/10.1016/j.crad.2013.06.021.

[25] S. Wang, S. Kim, S. Chawla, R.L. Wolf, W.-G. Zhang, D.M. O'Rourke, K.D. Judy, E.R. Melhem, H. Poptani, Differentiation between glioblastomas and solitary brain metastases using diffusion tensor imaging, NeuroImage 44 (2009) 653–660, https://doi.org/10.1016/j.neuroimage.2008.09.027.

[26] X. Liu, W. Tian, B. Kolar, G.A. Yeaney, X. Qiu, M.D. Johnson, S. Ekholm, MR diffusion tensor and perfusion-weighted imaging in preoperative grading of supratentorial nonenhancing gliomas, Neuro-Oncol. 13 (2011) 447–455, https://doi.org/10.1093/neuonc/noq197.

[27] M.L. White, Y. Zhang, F. Yu, S.A. Jaffar Kazmi, Diffusion tensor MR imaging of cerebral gliomas: evaluating fractional anisotropy characteristics, AJNR Am. J. Neuroradiol. 32 (2011) 374–381, https://doi.org/10.3174/ajnr.A2267.

[28] E.C. Klawiter, R.E. Schmidt, K. Trinkaus, H.-F. Liang, M.D. Budde, R.T. Naismith, S.-K. Song, A.H. Cross, T.L. Benzinger, Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords, NeuroImage 55 (2011) 1454–1460, https://doi.org/10.1016/j.neuroimage.2011.01.007.

[29] T. Beppu, T. Inoue, Y. Shibata, N. Yamada, A. Kurose, K. Ogasawara, A. Ogawa, H. Kabasawa, Fractional anisotropy value by diffusion tensor magnetic resonance imaging as a predictor of cell density and proliferation activity of glioblastomas, Surg. Neurol. 63 (2005) 56–61, https://doi.org/10.1016/j.surneu.2004.02.034 discussion 61..

[30] M. Kinoshita, N. Hashimoto, T. Goto, N. Kagawa, H. Kishima, S. Izumoto, H. Tanaka, N. Fujita, T. Yoshimine, Fractional anisotropy and tumor cell density of the tumor core show positive correlation in diffusion tensor magnetic resonance imaging of malignant brain tumors, NeuroImage 43 (2008) 29–35, https://doi.org/10.1016/j.neuroimage.2008.06.041.

[31] T. Inoue, K. Ogasawara, T. Beppu, A. Ogawa, H. Kabasawa, Diffusion tensor imaging for preoperative evaluation of tumor grade in gliomas, Clin. Neurol. Neurosurg. 107 (2005) 174–180, https://doi.org/10.1016/j.clineuro.2004.06.011.

[32] P. Korfiatis, T.L. Kline, L. Coufalova, D.H. Lachance, I.F. Parney, R.E. Carter, J.C. Buckner, B.J. Erickson, MRI texture features as biomarkers to predict MGMT methylation status in glioblastomas, Med. Phys. 43 (2016) 2835–2844, https://doi.org/10.1118/1.4948668.

[33] Y. Li, Z. Qian, K. Xu, K. Wang, X. Fan, S. Li, T. Jiang, X. Liu, Y. Wang, MRI features predict p53 status in lower-grade gliomas via a machine-learning approach, Neuroimage Clin. 17 (2018) 306–311, https://doi.org/10.1016/j.nicl.2017.10.030.