Prognostic value of preoperative diffusion restriction in glioblastoma

Intérêt pronostique de la restriction de la diffusion dans le glioblastome

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Abstract

Introduction: Although glioblastoma (GBM) has a very poor prognosis, overall survival (OS) in treated patients shows great difference varying from few days to several months. Identifying factors explaining this difference would improve management of patient treatment.
Aim: To determine the relevance of diffusion restriction in newly diagnosed treatment-naïve GBM patients.
Methods: Preoperative magnetic resonance scans of 33 patients with GBM were reviewed. Regions of interest including all the T2 hyperintense lesion were drawn on diffusion weighted B0 images and transferred to the apparent diffusion coefficient (ADC) map. For each patient, a histogram displaying the ADC values within in the regions of interest was generated. Volumetric parameters including tumor regions with restricted diffusion, parameters derived from histogram and mean ADC value of the tumor were calculated. Their relationship with OS was analyzed.
Results: Patients with mean ADC value < 1415x10-6 mm2/s had a significantly shorter OS (p=0.021).
Among volumetric parameters, the percentage of volume within T2 lesion with a normalized ADC value <1.5 times that in white matter was significantly associated with OS (p=0.0045). Patients with a percentage >23.92% had a shorter OS.
Among parameters derived from histogram, the 50th percentile showed a trend towards significance for OS (p=0.055) with patients living longer when having higher values of 50th percentile. A difference in OS was observed between patients according to ADC peak of histogram but this difference did not reach statistical significance (p=0.0959).
Conclusion: Diffusion magnetic resonance imaging may provide useful information for predicting GBM prognosis.

Key words: Glioblastoma, Magnetic resonance imaging, Imaging diffusion MRI, Prognosis

Résumé

Introduction: Malgré le mauvais pronostic du glioblastome (GBM), la survie globale (SG) des patients varie de quelques jours à plusieurs mois. La connaissance des facteurs expliquant cette différence permettrait d'adapter le traitement.
Objectif: Etudier la valeur pronostique de l'imagerie de diffusion chez les patients atteints de GBM.
Méthodes: Les IRM de 33 patients atteints de GBM ont été revues. Des régions d'intérêt incluant tout l'hypersignal T2 tumoral ont été tracées sur la séquence de diffusion B0 et copiées sur la cartographie du coefficient apparent de diffusion (ADC). Un histogramme a été généré à partir des valeurs d'ADC incluses dans ces régions d'intérêt.
Des paramètres volumétriques incluant les zones tumorales avec restriction de la diffusion, des paramètres dérivés de l'histogramme ainsi que l'ADC moyen de la tumeur ont été calculés et leur liaison à la SG a été étudiée.
Résultats: La SG était liée de façon significative à l'ADC moyen (p=0,021), une valeur<1415x10-6mm2/s étant de plus mauvais pronostic.
Parmi les paramètres volumétriques, seul le pourcentage du volume tumoral avec un ADC normalisé <1,5 fois celui de la substance blanche normale était lié de façon significative à la SG (p=0,0045). Les patients avec une valeur >23,92% avaient une SG plus courte.
Sur l'histogramme, le 50ème percentile permettait de différencier les patients en fonction de la durée de SG. Cette différence était proche de la signification (p=0,055). Le pic d'ADC n'était pas significativement lié à la SG (p=0,0959).
Conclusion: L'imagerie de diffusion pourrait fournir des informations utiles sur le pronostic du GBM.

Mots clés: Glioblastome, Imagerie par résonance magnétique, Imagerie de diffusion par résonance magnétique, Pronostic

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Introduction

Glioblastoma (GBM) is the most aggressive and the most frequent primary brain tumor in adults (1). Despite its poor prognosis, considerable variability in overall survival (OS) between patients has been noticed leading to investigate the prognostic factors explaining this difference. Many studies evaluated the predictive value of different MRI parameters and promising results have been achieved (2–4).
The aim of this study was to evaluate the prognostic value of diffusion imaging in GBM.

Methods

Patient population

Between January 2014 and June 2017, 201 consecutive patients with newly diagnosed GBM were reviewed. Inclusion criteria were: histologically proven GBM; surgical treatment with gross total resection; available preoperative MR exam; available post-operative follow up (with at least 12 months for living patients). Exclusion criteria were: subtotal resection or stereotactic biopsy; pediatric population; a preoperative MR exam with a missing or a poor quality diffusion sequence; GBM with a large hemorrhagic component; a follow up shorter than 3 months. As a result, 33 patients were included in the study.
After surgery, 19 patients had radiation therapy and chemotherapy (temozolomide), seven had radiation therapy alone and six patients had no adjuvant therapy. No data were available for one patient.

MR imaging and data post processing

MRI acquisition and post processing software

Preoperative MR data were acquired using a 3T (Siemens Magneto Verio) machine (n=20) and 1.5T machines (GE Signa HDxt, Philips Ingenia and Siemens Magnetom Aera) (n=13).
Imaging protocol included a diffusion-weighted (DW) sequence with the following acquisition parameters TR=2290-7500 ms, TE=64-109 ms, matrix =128-192x118-192, field of view = 224-259 mm, slice thickness = 4-5 mm, interslice gap= 0,7-1,2 mm, b values of 1000 s/mm2 and 0 s/mm2 . Apparent diffusion coefficient (ADC) map were generated using the software included in the MR machines. The protocol also included FLAIR and/or T2-weighted images, T2*-weighted images, precontrast and postcontrast T1- weighted images acquired in a transversal plane. All MR exams were moved to a Mac computer and opened with the Osirix software version v.7.5 (Pixmeo SARL, Switzerland).
For each MR exam, a radiologist with a four-year experience manually drew the limits of the tumor on each slice of the DW sequence (b=0 s/mm2) using the "ROI pencil" tool. Tumor was defined as the entire T2 lesion without distinguishing between peritumor edema and tumor infiltration and without excluding cystic and necrotic areas.
A visual assessment of anatomic sequences (T2-weighted or FLAIR images and postcontrast T1-weighted images) along the process was made to increase the accuracy of tumor delimitation (e.g. limits between the T2 lesion and subarachnoid spaces or ventricles). Areas of hemorrhage within tumor were detected on the T2*-weighted images and excluded from the ROI but micro-hemorrhage inside the tumor could not be excluded. A second radiologist with an eight-year experience verified and validated the ROIs
Consequently, on each MR exam, a set of ROIs including the tumor were drawn on the DW sequence (b=0 s/mm2) and then copied on the ADC map (figure 1). A histogram displaying ADC values inside the set of ROIs (and thus inside the tumor) was generated using the same software (Osirix). This histogram would serve as a reference.

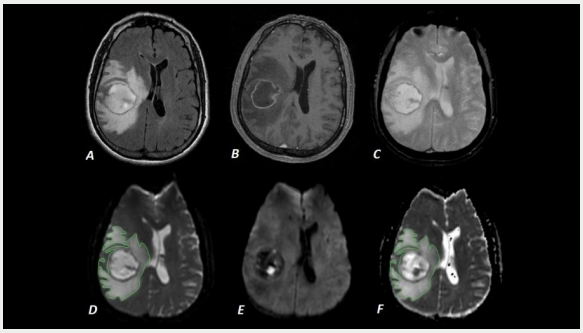

Figure 1. Axial magnetic resonance images in a patient with glioblastoma: Flair image (A), T1-weighted contrast enhanced image (B), T2*image (C), diffusion (b=0 s/mm^2) image with a ROI (green line) contouring the tumor (D), diffusion (b=1000 s/mm^2) image (E), ADC map image with the copied ROI (F).

Furthermore, for each patient, a ROI with a surface of 1.5cm2 was placed on the contralateral normal appearing white matter of centrum semiovale on the ADC map. Mean ADC value of this ROI was used to normalize ADC values within the tumor.

ROIs transfer and histogram generation

In order to make an automatic calculation of the study parameters, the following steps were taken by a neuroinformatics researcher with 12 years of experience in brain images processing:
-ROIs and ADC map images were transferred from Osirix to a personal computer
-They were converted to a standard neuroimaging format that can be used by the neurinformatics researcher: The free plugin «CreateROIMask» (www.sop.inria.fr/asclepios/software/pluginOsirix) was used to convert ROIs format to Analyse format and the free software «mricron» (http://people.cas.sc.edu/rorden/mricron/dcm2nii.html) was used to convert ADC map images from a DICOM format to a NifTI format.
-The converted ROIs and ADC map images were superimposed using a rigid registration implemented by the neuroinformatics researcher and the good alignment of the ROIs with the limits of the tumor on the ADC map was visually checked and corrected when necessary by the first radiologist.
-A histogram displaying ADC values inside the set of

ROIs (and thus inside the tumor) was generated for each patient using Python programming language and "matplotlib" with ADC values marked on the x-axis and number of voxels on the y-axis. This histogram was compared visually to the histogram generated using Osirix to ensure they were similar meaning that the process of transferring ROIs images and ADC maps, converting them into another neuroimaging format and superimposing them did not alter data (figure 2).

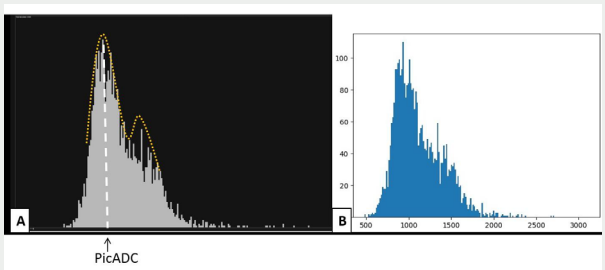

Figure 2. Two histograms of the same patient presenting ADC values distribution within a glioblastoma , the first generated with Osirix software (A) and the second using « matplotlib » library (B). The yellow dotted curve in (A) corresponds to a virtual curve drawn mentally by the radiologist to assess the ADC peak on the histogram (the first peak in this bimodal histogram).

Defining tumor regions with ADC restriction

Two thresholds were chosen to define ADC restriction based on literature (2,5) : 900 x 10^{-6}mm^2/s for absolute ADC values and a threshold of 1.5 times ADC value of normal appearing white matter for normalized ADC values.

Study parameters

Clinical parameters

The following data were collected: age, gender, duration of follow-up, overall survival and last contact status (dead or alive).

Imaging parameters

The following volumetric parameters were calculated:

- ***Vol<900***: tumor volume with ADC value≤900 (10-6m^2/s).
- ***%Vol<900***: the percentage of Vol<900 out of the whole tumor volume.
- ***VolADCn1.5***: tumor volume with normalized ADC value≤1.5 mean ADC value of normal appearing white matter.
- ***%VolADCn1.5***: the percentage of VolADCn1.5 out of the whole tumor volume.

Based on histogram analysis, the following parameters were also calculated:

- ***ADC10%, ADC25%, ADC50% and ADC75%***: corresponding respectively to the 10th, 25th, 50th and 75th percentiles of the distribution.
- ***ADC peak***: ADC value of the peak of histogram when there is only one peak (unimodal histogram) and of the first peak when there are two peaks (bimodal histogram).

In addition, ***mean ADC*** of the overall tumor was calculated. ADC peak value was calculated based on a visual method (figure 2) in which the peak of the histogram was detected by drawing mentally a virtual curve. For bimodal histograms, the ADC value of the first peak was noted. All other parameters were automatically calculated using an in-house code developed using Python programming language.

Statistical analysis

Data were analysed using SPSS software (version 19.0). Overall survival (OS) was determined from the day of surgical resection to the date of death or last contact at which the patient was known to be alive (censored). Surviving patients were followed up for at least 12 months. Mann-Whitney test and receiver operating characteristic (ROC) analysis were applied to determine the optimal cut-off value of each imaging parameter to differentiate between dead and living patients. For parameters with no statistically significant P value of Mann-Whitney test (P > 0.05), the median value was chosen as a cut-off. For each imaging parameter, study population was dichotomized according to the cut-off value and OS was analysed using the Kaplan-Meier method. Survival curves were compared using the log-rank test. For all analysis, a P value <0.05 was considered statistically significant.

Results

Patients' characteristics and outcomes

Patient age ranged from 37 to 73 years with a mean of 56 years. Among the 33 patients, 19 were men. At the last contact, 21 patients were dead, five were lost to follow-up and seven were still alive.

The mean survival time was 14 months with seven patients being censored. The surviving patients were followed up for at least 12.3 months with 30.7 months for the longest follow up. For lost to follow-up patients, the shortest follow-up duration was 3.25 months and the longest was 12.25 months.

Imaging metrics result

Parameters cut-off value

ADC peak, mean ADC and %VolADCn1.5 were the only parameters with a significant P value (< 0.05) of Mann-Whitney test. For these parameters, ROC curves analysis was performed. The optimal cut-off for each parameter is shown in table 1.

Table 1. Optimal cut-off of parameters with a significant P value of Mann-Whitney test

Parameter	ADC peak	mean ADC	%VolADCn1.5
Cut-off value	1484 (10^{-6} mm^2/s)	1415 (10^{-6} mm^2/s)	23.92%
Sensibility	84.6%	65.4%	76.9%
Specificity	71.4%	100%	71.4%

The other parameters were dichotomized to the median value (table 2).

Table 2. Median value for different diffusion parameters

Parameter	Vol<900 (cm^3)	%Vol<900 (%)	VolADCn1.5 (cm^3)	ADC10% (10^{-6} mm^2/s)	ADC25% (10^{-6} mm^2/s)	ADC50% (10^{-6} mm^2/s)	ADC75% (10^{-6} mm^2/s)
Median	9.85	10	27.23	900	1100	1320	1650

Imaging parameters and survival analysis

Patients with a mean ADC value >1415 (10-6 mm^2/s) had a significantly longer OS (mean OS 19.6 months) compared with those with a value <1415 (10-6 mm^2/s) (mean OS 11.4 months) (log-rank, P = 0.021) (figure 3).

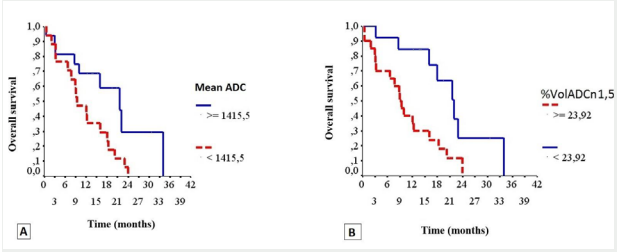

Figure 3. Overall survival curves based on mean ADC (A) and the percentage of tumor volume with normalized ADC value≤1.5 normal white matter value (%VolADCn1.5) (B).

Among volumetric parameters, only %VolADCn1.5 was significantly associated to survival (figure 3): mean OS was 21.6 months for patients with %VolADCn1.5 < 23.92% and 10.6 months for patients with %VolADCn1.5 > 23.92% (log-rank, P = 0.0045) (table 3).

Table 3. P value of log-rank test for volumetric parameters

Parameter	Vol<900	%Vol<900	VolADCn1.5	%VolADCn1.5
P value	0.499	0.101	0.781	0.0045

Among the 33 histograms, 20 were bimodal and 13 were unimodal. When the study population was split based on peak ADC cut-off (1484 (10^{-6} mm^2/s)), the survival curves were different with a longer OS for patients with an ADC peak > 1484 (10^{-6} mm^2/s). However, this difference was not statistically significant (log-rank, P = 0.096).

None of the ADC10%, ADC25%, ADC50% and ADC75% parameters were significantly associated with survival (table 4).

Table 4. P value of log-rank test for 10th, 25th, 50th and 75th percentiles

Parameter	ADC10%	ADC25%	ADC50%	ADC75%
P value	0.189	0.230	0.055	0.129

Figure 4 illustrates the example of two patients with short and long survival and the P values of the main imaging parameters.

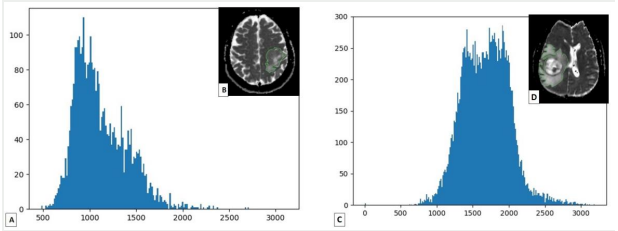

Figure 4. Example of two patients with GBM: the first (histogram (A), ADC map image (B)) with an overall survival of 2 months; ADC peak=912x10^{-6} mm^2/s; mean ADC =1125x10^{-6} mm^2/s; %VolADCn1.5= 62.9%; ADC50%= 1050 x10^{-6} mm^2/s. The second patient (histogram (C), ADC map image (D)) with an overall survival of 34 months; ADC peak=1400x10^{-6} mm^2/s, mean ADC =1677x10^{-6} mm^2/s, %VolADCn1.5=5.73%; ADC50%= 1680 x10^{-6} mm^2/s.

Discussion

Diffusion-weighted imaging (DWI) is a technique that reflects microscopic water motion within tissues and thus provides information about tissues microarchitecture. Diffusion restriction happens when there are barriers to water motion such as high cellularity and macro proteins (6–8). In glial tumors, high cellularity is a factor of aggressiveness and poor prognosis (9,10). Therefore, it is assumed that DWI, by reflecting tumor cellularity in GBM, could provide information about its prognosis and many methods using ROIs including parts or the whole tumor to study diffusion parameters were reported in literature.

Because DWI is subject to geometrical distortion artefact, we chose DW images with b=0 s/mm^2 as the T2-weighted sequence for drawing ROIs to guaranteed that the obtained ROIs would match the tumor edges when copied on the ADC map (11). In literature, many studies used T2 FSE or Flair images to draw the ROIs but had to use some in-house software to align these sequences with the ADC map (12,13).

We found that mean ADC could be used as a prognostic factor. Our results are consistent with those of a study including GBM treatment-naïve patients in which mean ADC value in enhancing regions correlated with survival (14). However, in a study including postoperative MR exams, Elson et al (15) found no significant association between mean ADC and survival (P = 0.083).

Instead of mean ADC, some studies assessed the prognostic value of the minimum ADC (3,16,17). This factor would be a better indicator of tumor cellularity and aggressiveness. Giving the fact that we could not exclude zones of micro-hemorrhage inside the tumor when drawing the ROIs and knowing that hemorrhage causes a susceptibility artefact on diffusion-weighted images, calculating minimum ADC value would have been inaccurate (7). Because hemorrhage is a common component of GBM, the used method for calculating minimum ADC in literature consisted in detecting tumor areas with the lowest ADC by visual inspection, placing focal ROIs on these regions and calculating the minimum ADC. We think this method does not offer a good reproducibility and does not allow the study of the whole tumor tissue leading to a sampling bias.

In our study, none of the percentile parameters was significantly associated with OS. In literature, results are contradictory. Crawford et al (2) and then Saraswathy et al (18) studied the prognostic value of the 10th percentile respectively on preoperative and postoperative MR exams. In the first study, it was associated with OS in the enhancing component but not in the non-enhancing part. In the second study, it had no prognostic value in both enhancing and non-enhancing components. In both studies, the 50th percentile had no prognostic value. In

another study including 112 patients, the 25th, 50th and 75th percentiles were all associated to OS on preoperative MR exams (14).Those contradictory results could be explained by the non-uniformity of the used methods of study.

Histogram gives a global view of ADC values distribution inside the tumor. High values are thought to reflect cystic/necrotic components while low values reflect cellular components (12). When a histogram has a bimodal distribution, the first curve (low ADC values) is thought to represent the cellular and thus aggressive component of the tumor (figure 5) and peak ADC of this curve could reflect this aggressiveness. ADC peak was not associated to OS in our study. This could be partly explained by the fact that we included histograms with unimodal distribution meaning with one ADC peak. Indeed, we think that in unimodal histograms, cellular components and cystic/necrotic components are entangled and ADC peak is thus less representative of the aggressive part. In a study including preoperative MR exams and comparing two groups of patients with different adjuvant treatment, ADC peak was not significantly associated to OS in both groups, which is consistent with our results (19). Other studies evaluated this parameter on postoperative MR exams. In some of them, ADC peak had a prognostic significance (4,12,20), in others, it did not (21,22).

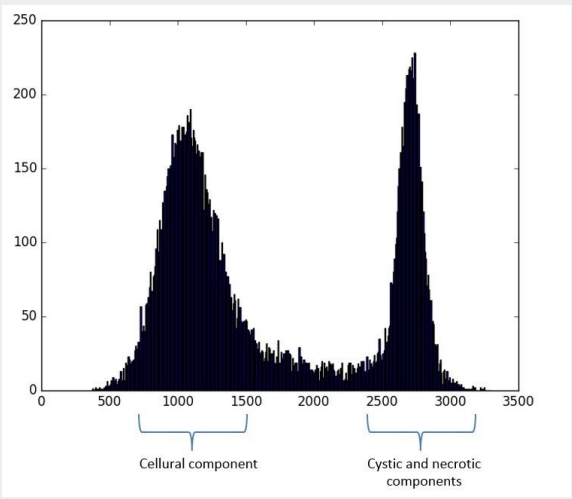

Figure 5. Histogram representing ADC values distribution within a glioblastoma. Abscissa: ADC values (10^{-6} mm^2/s), ordinate: number of voxels.

Among volumetric parameters, %VolADCn1.5 was significantly associated with OS. Normalization of ADC values is performed to minimize ADC measurement variation related to the use of different MR machines and protocols (15,13). In one study, this parameter showed a trend towards significance but the used cut off for defining diffusion restriction was 1.3 times that in white matter and not 1.5 (15).

The other volumetric parameters were not associated with OS. In literature, the results are once again contradictory. Wen et al (23) evaluated the prognostic value of tumor volumes with ADC< 900 $x10^{-6}$ mm^2/s (Vol (ADC<900 in T2L)) and 1000 $x10^{-6}$ mm^2/s (Vol (ADC<1000 in T2L)) in two groups of patients receiving a different adjuvant treatment on MR exams before the adjuvant treatment (baseline) and during follow-up. In one group, both parameters were associated with OS at 1-month follow up MR exam but not at the other exams. In the other group, Vol (ADC<900 in T2L) was associated with OS at follow-up scans but not at the baseline scan while Vol (ADC<1000 in T2L) was associated with OS only at the 4-month follow-up scan. The author explains these results by postoperative ischemic effects, changes induced by radiotherapy and the different mechanisms of action of adjuvant treatments. In another study including patients with recurrent GBM, volumetric parameters within T2 volume were not associated with OS while parameters within the enhanced volume had significant association with OS (24).

In addition to diffusion imaging, many studies investigated the prognostic value of other MRI parameters including morphologic parameters (e.g., the volume of the whole T2 lesion or the volume of the enhancing component), perfusion parameters (e.g., relative cerebral blood volume) and MR spectroscopy parameters (e.g., Choline-to-N-acetylaspartate ratio) (2, 18, 25). The results are promising but need further investigation.

This work had some limitations. Indeed, it was a retrospective study including a small number of patients. Moreover, MR exams were made on different MR machines.

Conclusion

Diffusion imaging could be a valuable biomarker for predicting prognosis of GBM but the variation in the used methods in literature limiting the comparison of results should be addressed and further studies with standardized methods should be done.

List of abbreviations:
ADC : Apparent diffusion coefficient
DWI: Diffusion-weighted imaging
GBM: Glioblastoma
MRI: Magnetic resonance imaging
OS: Overall survival
ROI: Region of interest

Reference

1. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev 2014;23:1985–96.
2. Crawford FW, Khayal IS, McGue C, Saraswathy S, Pirzkall A, Cha S, et al. Relationship of pre-surgery metabolic and physiological MR imaging parameters to survival for patients with untreated GBM. J Neurooncol 2009;91:337–51.
3. Nakamura H, Murakami R, Hirai T, Kitajima M, Yamashita Y. Can MRI-derived factors predict the survival in glioblastoma patients treated with postoperative chemoradiation therapy? Acta radiol 2013;54:214–20.
4. Ellingson BM, Gerstner ER, Smits M, Huang RY, Colen R, Abrey LE, et al. Diffusion MRI phenotypes predict overall survival benefit from Anti-VEGF monotherapy in recurrent glioblastoma: Converging evidence from phase II trials. Clin Cancer Res 2017;23:5745–56.
5. Chen Z, Ma L, Lou X, Zhou Z. Diagnostic value of minimum apparent diffusion coefficient values in prediction of neuroepithelial tumor grading. J Magn Reson Imaging 2010;31:1331–8.
6. Le Bihan D, Iima M. Diffusion magnetic resonance imaging: What

water tells us about biological tissues. PLoS Biol 2015;13:1–13.

7. Schaefer PW, Grant PE, Gonzalez RG. Diffusion-weighted MR Imaging of the Brain. Radiology 2000 Nov;217:331–45.
8. Padhani AR, Liu G, Mu-Koh D, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion-Weighted Magnetic Resonance Imaging as a Cancer Biomarker: Consensus and Recommendations. Neoplasia 2009;11:102–25.
9. Ferris SP, Hofmann JW, Solomon DA, Perry A. Characterization of gliomas: from morphology to molecules. Virchows Arch 2017;471:257–69.
10. Kiss R, Dewitte O, Decaestecker C, Camby I, Gordower L, Delbecque K, et al. The combined determination of proliferative activity and cell density in the prognosis of adult patients with supratentorial high-grade astrocytic tumors. Am J Clin Pathol 1997;107:321–31.
11. Wu W, Miller KL. Image formation in diffusion MRI: A review of recent technical developments. J Magn Reson Imaging 2017;46:646–62.
12. Pope WB, Qiao XJ, Kim HJ, Lai A, Nghiemphu P, Xue X, et al. 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 2012;108:491–8.
13. Cui Y, Ren S, Tha KK, Wu J, Shirato H, Li R. Volume of high-risk intratumoral subregions at multi-parametric MR imaging predicts overall survival and complements molecular analysis of glioblastoma. Eur Radiol 2017;27:3583–92.
14. Choi YS, Ahn SS, Kim DW, Chang JH, Kang S, Kim EH, et al. Incremental Prognostic Value of ADC Histogram Analysis over MGMT Promoter Methylation Status in Patients with Glioblastoma. Radiology 2016;1:151913.
15. Elson A, Bovi J, Siker M, Schultz C, Paulson E. Evaluation of absolute and normalized apparent diffusion coefficient (ADC) values within the post-operative T2/FLAIR volume as adverse prognostic indicators in glioblastoma. J Neurooncol 2015;122:549–58.
16. Hilario A, Sepulveda JM, Perez-Nuñez A, Salvador E, Millan JM, Hernandez-Lain A, et al. A prognostic model based on preoperative MRI predicts overall survival in patients with diffuse gliomas. Am J Neuroradiol 2014;35:1096–102.
17. Higano S, Yun X, Kumabe T, Watanabe M, Mugikura S, Umetsu A, et al. Malignant Astrocytic Tumors: Clinical Importance of Apparent Diffusion Coefficient in Prediction of Grade and Prognosis. Radiology 2006;241:839–46.
18. Saraswathy S, Crawford FW, Lamborn KR, Pirzkall A, Chang S, Cha S, et al. Evaluation of MR markers that predict survival in patients with newly diagnosed GBM prior to adjuvant therapy. J Neurooncol 2009;91:69–81.
19. Pope WB, Lai A, Mehta R, Kim HJ, Qiao J, Young JR, et al. Apparent diffusion coefficient histogram analysis stratifies progression-free survival in newly diagnosed bevacizumab-treated glioblastoma. Am J Neuroradiol 2011;32:882–9.
20. Chang W, Pope WB, Harris RJ, Hardy AJ, Leu K, Mody RR, et al. Diffusion MRI Characteristics After Concurrent Radiochemotherapy Predicts Progression-Free and Overall Survival in Newly Diagnosed Glioblastoma. Tomography 2015;1:37–43.
21. Wen Q, Jalilian L, Lupo JM, Molinaro AM, Chang SM, Clarke J, et al. Comparison of ADC metrics and their association with outcome for patients with newly diagnosed glioblastoma being treated with radiation therapy, temozolomide, erlotinib and bevacizumab. J Neurooncol 2015;121:331–9.
22. Kondo M, Uchiyama Y. Apparent diffusion coefficient histogram analysis for prediction of prognosis in glioblastoma. J Neuroradiol 2018;45:236–41.
23. Wen Q, Jalilian L, Lupo JM, Li Y, Roy R, Molinaro AM, et al. Association of diffusion and anatomic imaging parameters with survival for patients with newly diagnosed glioblastoma participating in two different clinical trials. Transl Oncol 2015;8:446–55.
24. Rahman R, Hamdan A, Zweifler R, Jiang H, Norden AD, Reardon DA, et al. Histogram analysis of apparent diffusion coefficient within enhancing and nonenhancing tumor volumes in recurrent glioblastoma patients treated with bevacizumab. J Neurooncol 2014;119:149–58.
25. Boonzaier NR, Larkin TJ, Matys T, van der Hoorn A, Yan JL, Price SJ. Multiparametric MR imaging of diffusion and perfusion in contrast-enhancing and nonenhancing components in patients with glioblastoma. Radiology 2017;284:180-90.