SYSTEMATIC REVIEW: USE OF DIFFUSION – WEIGHTED MR, IN ORDER TO PREDICT SURVIVAL IN ADULT PATIENTS WITH A DIAGNOSIS OF ASTROCYTOMAS WITH A HIGH DEGREE OF MALIGNANCY

Revisión sistemática: uso de Imágenes por difusión en RM, para predecir supervivencia en pacientes adultos con diagnóstico de astrocitomas de alto grado de malignidad

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Summary

Objectives: The purpose of this study was to evaluate whether diffusion-weighted MR imaging (DWI) is an early biomarker of tumor response in high-grade astrocytomas, useful for early decision of treatment improvement and helpful tool for prognostic survival information. *Methods*: The search was conducted in the databases EMBASE, CENTRAL, MEDLINE. The selected articles were observational studies (case-control, cohort, cross-sectional) found no clinical trial , all participants had histopathologic diagnosis of high-grade astrocytomas, underwent surgical resection and / or radio - chemotherapy and monitoring response to treatment with DWI for at least 6 months. Data were independently extracted study type, participants, interventions, monitoring, outcomes (survival, progression / stable disease, death). *Conclusions*: Fifteen studies met the inclusion criteria. Among the techniques used for DWI to assess response to treatment, were histograms of apparent diffusion coefficient (ADC), finding in general a low ADC is a strong predictor of reduced survival and / or tumor progression and functional diffusion maps (FDM) that showed to be similar.

Resumen

Objetivos: Evaluar si la difusión en resonancia magnética (DRM) es un biomarcador temprano de respuesta tumoral en tumores gliales de alto grado de malignidad. Demostrar su posible utilidad en la toma de decisiones tempranas de tratamiento. Conocer su valor pronóstico en la sobrevida del paciente. *Métodos*: La búsqueda se realizó en bases de datos Embase, Central y MedLine. Los artículos seleccionados fueron estudios observacionales (casos y controles, cohortes, corte transversal). No se encontró ningún ensayo clínico. Todos los participantes tenían diagnóstico histopatológico de astrocitomas de alto grado (AAG) sometidos a resección quirúrgica y/o radioquimioterapia y seguimiento de respuesta al tratamiento con DRM por al menos 6 meses. Los datos extraídos de forma independiente fueron: tipo de estudio, participantes, intervenciones, seguimiento, desenlaces (sobrevida, progresión/estabilización de la enfermedad, muerte). *Resultados*: Quince estudios cumplieron los criterios de inclusión. Se encontraron varias técnicas de DRM para evaluar la respuesta al tratamiento, entre otras, los histogramas del coeficiente aparente de difusión (ADC). *Conclusiones*: Un ADC bajo es un fuerte predictor de menor supervivencia y/o de progresión del tumor; los mapas funcionales de difusión (MFADC) mostraron similares resultados.

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Introduction

It is estimated that 22,000 new cases of cancer in the Central Nervous System (CNS) were diagnosed in 2009 (including primary and secondary tumors). Close to 13,000 deaths due to this cause occurred in the United States (1).

In Colombia, 93 new primary cases of CNS tumors were diagnosed in the National Institute of Cancerology (INC), according to 2008 data (2).

Despite the emergence of new therapeutic techniques, the successful management of this pathology in children and adults is still unsatisfactory; particularly, glioblastoma represents a great challenge due to its moderate rate of response to practically all available standard therapies, with an average survival period between 12 and 18 months.

To the date, the age of the patient, its functional status and the histology of the tumor are considered as the most reliable prognosis indicators of survival.

It is unfortunate that the great neuroradiology advances which have occurred in the past few decades, such as an improvement in spatial resolution, tissue contrast, and the possibility of obtaining functional, metabolic, and micro-structural information, have not represented a significant impact in the prognosis of survival of patients with cerebral tumors (1).

These new imaging techniques have not been standardized or applied in a uniform manner in large clinical trials. Frequently, the image is used as a simple indicator of change in the size of the tumor, after therapy, through the objective or subjective evaluation of its dimensions. However, an early change in size is not a reliable indicator of the response.

There is an increasing awareness that a simple anatomical focus has significant limitations; tumors which cannot be measured, a poor reproducibility of the measures, and the presence or appearance of masses after therapy. The increasing use of cytostatic and anti-angiogenic therapies has led to the recognition that anatomical evaluation is not very sensitive to change which can relate to global therapeutic success.

A completely satisfactory method has not been developed in order to determine tumor response through images; currently, methods such as the RANO criteria and the McDonald criteria (3-5) are used (tables 1 and 2). The functional images or the volumetric evaluation with positron emission tomography (PET) or magnetic resonance (MR) have not been standardized. There is not sufficient evidence to abandon the anatomical evaluation of tumor charge.

Table 1. RANO response criteria

Type of response	Criteria
Complete response	The following conditions must all be met: 1. The complete disappearance of all lesions which are enhanced with the contrast medium, whether they can be measured or not. Disappearance must be maintained for four weeks. 2. No new lesions must appear. 3. The stability or reduction of high-signal lesions in T21/FLAIR2, which are not enhanced with the contrast medium. 4. The patient must be in better condition or must be stable from the clinical point of view. 5. The patient must not be required to take corticosteroids or take substitutive physiological dosages.
Partial response	The following conditions must be met: 1. The reduction in size must be greater than or equal to 50% (≥50%), compared to the basal MR3 or an MR in which a lesser-size tumor has been objectified, from the sum of products of the transverse diameters or of the measurable lesions which are enhanced with the contrast medium. The reduction must be maintained for at least four weeks. 2. No new lesions must appear. 3. The stability or reduction of high-signal lesions in T21/FLAIR2, which are not enhanced with the contrast medium. 4. The patient must be in better condition or must be stable from the clinical point of view. 5. The patient must not be required to take corticosteroids or take substitutive physiological dosages. 6. There must be no progression of non-measurable lesions.
Stable disease	The following conditions must be met: 1. That the RC4, PR5 or PE6. 2. The stability or reduction of high-signal lesions in T21/FLAIR2, which are not enhanced with the contrast medium. 3. In case there are dosages of corticosteroids which have increased in respect to the basal, a strict radiological clinical follow-up must be performed. If a radiological progression is confirmed, the date of progression will be the MR in which the dosage of corticosteroids has increased. 4. The dosage of corticosteroids must be lesser than or equal to the basal study.

Progression	One of the following conditions must be met. 1. An increase greater than or equal to twenty five percent (≥25%), compared to the basal MR or an MR in which a lesser-size tumor has been objectified from the sum of products of the perpendicular transverse diameters of the lesions which are captured by contrast. The patient must take a dosage of corticosteroids lesser than or equal to the one he/she took when undergoing the basal MR. 2. A significant increase of lesions which are not visibly enhanced in sequences with T21/FLAIR2 information which are not attributable to a co-morbidity (ischemia, RT7, infection etc.), with dosages o corticosteroids greater than or equal to the basal MR. 3. The appearance of a new lesion. 4. A clinical deterioration which is not attributable to different tumor causes or to changes in the dosages of corticosteroids. 5. An increase in the number or size of non-measurable lesions. 6. Death or serious clinical deterioration.

[1]T2 potentiated sequence, 2Fluid Attenuated Inversion Recovery (FLAIR), 3Magnetic resonance
4Complete response, 5Partial Response, 6Progression of the disease, 7Radiotherapy

Table 2. McDonald response criteria

Type of response	Criteria
Complete response	• The following conditions must all be met: • The complete disappearance of all lesions which are enhanced with the contrast medium, whether they can be measured or not, during four weeks or longer. • No new lesions must appear. • The patient must not be required to take corticosteroids or take substitutive physiological dosages. • The patient must be clinically stable
Partial response	• The following conditions must be met: • The reduction in size must be greater than or equal to 50% (≥50%), compared to the products of the maximum perpendicular diameters of all captured lesions during four weeks or longer. • No new lesions must appear. • The patient must take minor or stable dosages of corticosteroids. • The patient must be clinically stable or must be improving.
Stable disease	• The following conditions must be met: • Not complying with the complete response, partial response, or progression criteria. • The patient must be in stable condition or improving.
Progression	• At least one of the following conditions must be met: • There must be an increase greater than or equal to twenty five percent (≥25%) in the sum of the products of the perpendicular diameters of the lesions which are enhanced with the contrast medium. • The appearance of a new lesion.

With the purpose of overcoming the limitations of the anatomical evaluation, the use of advanced imaging techniques has been suggested in order to monitor the response to treatments with new action mechanisms which can predict the success of therapy before the conventional measures are altered. Within this scenario, functional imaging methods have also been used as response biomarkers at early stages, of the development of medications or compounds with new action mechanisms in order to observe if the physiology of the tumor is altered and therefore continue with the following phases (6,8).

Recent reports from the National Cancer Institute of the United States create great expectations in regards to the Diffusion in Magnetic Resonance (DMR) as a tool of great clinical importance (3).

The DMR was introduced in the mid 1960's by Stejskal and Tanner, and the first clinical usage was in the 1980's by De Bihan (9).

The DMR images are generally obtained through Echo Planar (EP) ultra-fast sequences. Their contrast depends on the random microscopic molecular movement of the tissue water.

This technique has been extensively used in clinical practice for the early diagnosis of CNS conditions which restrict the diffusion of water molecules; for example, the cytotoxic edema in an acute infarct, the elevated cellularity of certain tumors or the high viscosity of abscesses (9,10).

To summarize, the DMR is affected by the following factors: the exchange of water between the inter-cellular space and the tissue cellularity. In this case, the term Apparent Diffusion Coefficient (ADC) represents the constants of measured diffusion and are reported in cm2 or in mm2/sec.

The sensitivity of the MR imaging sequence or the mobility of water is determined by the intensity, the duration, and the direction of the intercalated pulse gradients within the imaging sequence (9,10).

Methodology

Design

Systematic revision. A comprehensive search of published studies and of electronic databases was performed without date or language restrictions and with the following key words:

"Magnetic Resonance Imaging/methods" (Mesh), "Diffusion Magnetic Resonance Imaging/methods" (Mesh), "Treatment Outcome" (Mesh), "Glioblastoma/therapy" (Mesh)" "Glioblastoma/diagnosis" (Mesh)

Inclusion and exclusion criteria

Types of studies

Random and non-random clinical trials from the III phase onwards were included, as well as cohort studies, the cases and controls, and transversal cut studies which had a response evaluator to the treatment with astrocytomas with a high degree of malignancy (AHDM), DMR images (figure 1) and an analysis of survival; with a follow-up of at least six months as diagnostic methods. Studies with less than ten participants were excluded.

Types of participants

Studies which included participants with an AHDM histopathologic diagnosis (WHO III Astrocytomas, WHO IV Glioblastoma [GB]) who underwent surgical resection and posterior RT, with a follow-up in response to treatment through DMR images (including base MR) were included. Studies in which participants had other pathologies, such as acquired immune deficiency syndrome, hepatitis B, an uncompensated congestive cardiac insufficiency, a cerebrovascular disease, a different or concomitant primary tumor with AHDM, or a CNS infection, were excluded.

Types of interventions

All patients with AHDM diagnosis during treatment with cytoreduction, radiotherapy (RT) and/or chemotherapy (CT).

Studies which included: DMR images as a diagnostic method of AHDM treatment follow-up, with description of the characteristics of the resonator, the resolution of images and analysis methods used for the interpretation of the results.

Result measures

- Apparent diffusion coefficient (ADC) in mm2/sec.
- Isolated restriction of the diffusion (high/low intensity).
- Progression of the disease versus pseudo-progression.
- Local recurrence of the primary tumor.
- No progression of the tumor (stable disease).
- Global survival (major and minor).
- Events which are adverse to treatment.

Sources of information

Several electronic searches in MEDLINE (From 1960-present) were performed, as well as in EMBASE (from 1980-present), in CENTRAL (The Cochrane Library, from 2008-present); In addition, manual searches in relevant magazines and in the reference lists of resulting documents were performed. Contact was established with some of the authors of the studies in order to know if they had knowledge of other non-published studies. There were no language restrictions. The age of the patients which was used as a base was 6 years onwards (attachment 1).

Collection techniques

Selection of studies

All relevant studies based on title and/or summary were selected; subsequently, each one of the researchers reviewed the selected studies in detail, verifying the compliance of established criteria for this revision. Disagreements where resolved through a consensus.

Data gathering

The following data were extracted from the studies by each one of the researchers and confirmed by a different researcher.

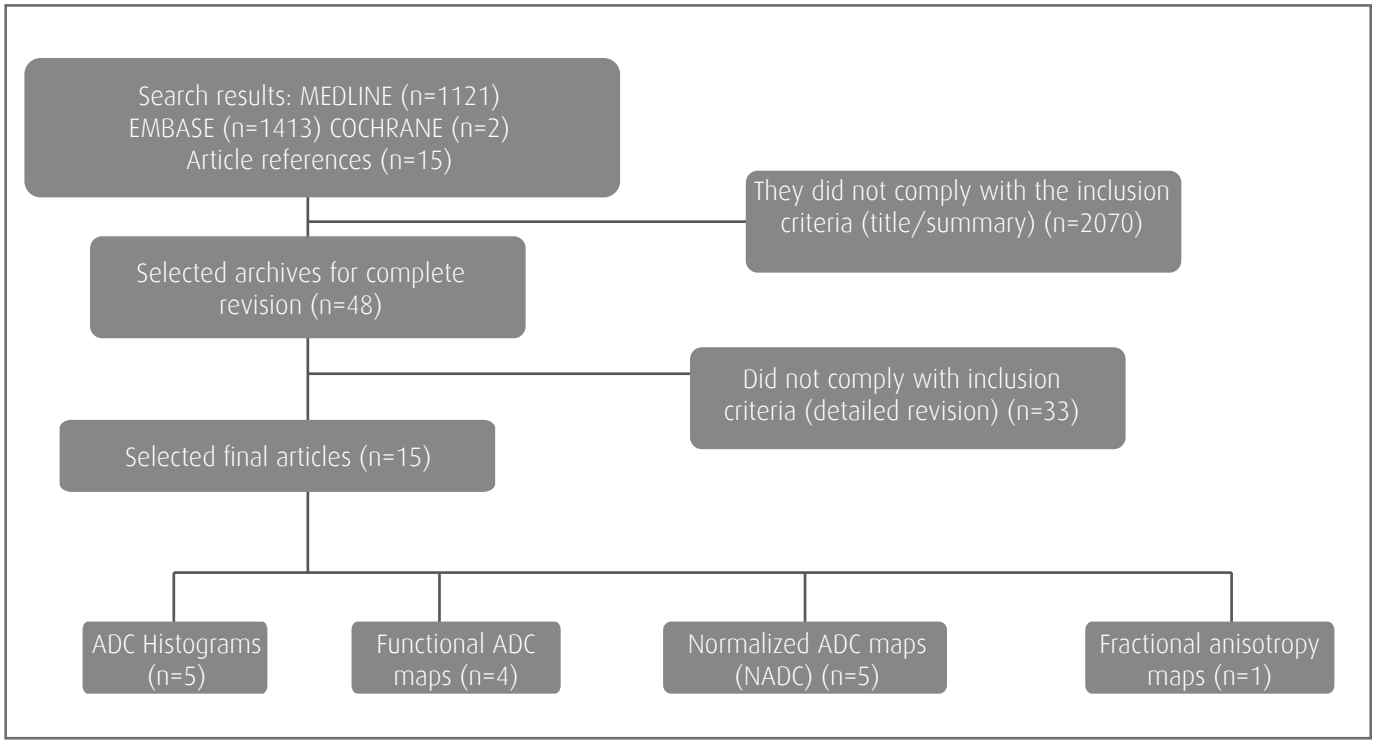
- Authors.
- Type of study.
- Methodology and methods: random, follow-up (duration, complete), blinding of the result methods.
- Participants: size of the sample, age, gender, AHDM type.
- Quantitative and qualitative evaluation of DMR (ADC, restriction of the diffusion).
- Treatment used.
- Response to treatment.
- Outcome: definition.
- Outcome measurement.
- Complications of the treatment: cerebral edema, perilesional necrosis, lesions due to radiation and other adverse cerebral incidents.

Quality of the studies

There is no current agreement regarding the criteria used to evaluate the quality of the prognosis or predictive studies (11): however, theoretical consideration and common points of several methodological aspects which are probably important to explore the internal validation of the articles were taken into account (12). The studies were considered to have good or regular intra-study quality if they presented 50% or more of the items; they were considered low quality if they presented less than 50%. The studies were considered undetermined if the researchers did not report the items on the article or if these were not clear (attachment 2).

Results

Figure 1. Search results



Features of the studies

The summary of the included studies are shown in tables 3 to 5.

Controlled or quasi-experimental studies were not found in the search. The process supplied fifteen eligible articles: two articles of cases and controls, twelve cohort studies and one transversal cut study.

All revised studies included female and male participants with an AHDM histopathologic diagnosis. The used diagnostic method to predict the response to treatment was based on DMR images. The number of included participants had an interval of 20 to 43 (average of 58 and median of 50). The follow-up lasted from 6 months-1 year for studies performed by Saraswathy, et al. (13), Khayal, et al. (14), Li, et al. (15), Jain, et al. (16). The remaining studies had a follow-up period of over two years. The characteristics of the participants were not explicitly described in the studies; the only ones which included age and other clinical conditions as possible response predictors were Hamstra, et al. (17,18), Tamasaki, et al. (19), Oh, et al. (20), Murakami, et al. (21) and Pope, et al. (22).

Most studies evaluated the imaging response to treatment from DMR, after a surgical resection and before the start of RT. There were two exceptions: Gupta, et al. (23), which used the base images which were obtained a month after RT was finished and Jain, et al (16), which did not specify the stage of treatment in which images began to be compared. All the MR images were obtained with 1.5 T, 3 T equipment, or both, in accordance with the standardized protocols of each one of the research sites, and included DMR, ADC and MR maps with contrast medium. The DMR images were acquired using sequences (EPI) spin echo, with values b= 0 and b = 1000 mm2/sec. Using the DMR images, ADC maps and fractioned anisotropy (FA) were obtained. The ADC maps were analyzed through histograms and with functional maps.

ADC Histograms

The technique used to calculate the apparent diffusion coefficient ADC for a given volume (voxel per voxel) used for the construction of the histogram differed between the authors. Pope, et al. (22,24), Yamasaki, et al. (19), and Gupta, et al. (23) only used the ADC values of the interest regions which corresponded to the portion of tumor re-enhancement; they excluded the regions of non-re-enhancement with high-intensity with T2 information, which represent an edema and/or an infiltrating tumor. Saraswathy, et al. (13), Murakami, et al. (21) included the high intensity regions in sequences with T2 information in their analysis.

Calculation of ADC functional maps

The functional diffusion map (FMADC) is a method used to evaluate the changes in ADC; Ellingson, et al. (25,26) staged each voxel into three categories, based on the change related to the ADC base line in regards to the post-treatment base line. The red voxels represented areas in which ADC (+) increased beyond a threshold of 0.4 mm2/ms (hypocellular voxels) and the blue voxels represented the areas in which ADC (-) reduced beyond a threshold of 0.4 mm2/ms (hyper-cellular

voxels), green ADC voxels (+/- 0.40 mm2/ms) which did not show changes. The total changes were expressed as ADC¬T= ADCR+ ADCB. This threshold has proven to have greater sensitivity and specificity for a progressive disease, and it is defined as a 95% confidence interval from a white and grey substance mix of normal appearance, evaluated from their reference time points (which range from one week until one year). Hamstra, et al. (17,18) used cut points of +/-50x10-5mm2/s.

Normalized ADC maps (NADC)

These are generated by dividing the ADC maps by the value of the median of the ADC within the T2ALL (any high-intensity image in T2 of the white substance, without differentiating between an edema, a tumor, etc.); The NEL (non-enhancing lesions) region refers to lesions which are not enhanced with the contrast medium, but only within the T2ALL area. The following formula was used to delimit these areas: NEL = (T2ALL – CEL). CEL refers to the lesions which are enhanced with the contrast medium; in this manner, the NEL area corresponded to a tumor invasion of the white matter, but not to the edema. Some authors did not use colors, but a greyscale; if the image restricted, it was seen as scale which ranged from grey-black; if the image did not restrict, it was seen from grey-white. Saraswathy, et al. (13), Li et al. (15), Oh et al. (20).

Fractional anisotropy maps

These describe the degree of anisotropy or restricted movement. A value closer to 0 is assigned if the voxel is spherical; and a value close to 1 if the voxel is ellipsoid, which tends to be lineal. In other words, a value of 0 means that the diffusion is isotropic, that is to say, it does not have any restrictions of moving freely in all directions. A value of 1 expresses that the diffusion occurs throughout a single axis, that is to say, it is not free to move in other directions (27). The only study which used this measure was Saraswathy, et al. (13).

All the participants of the studies underwent surgical resection, whether it was total, partial or biopsy: in addition to chemotherapy and radiotherapy. In turn, the studies of Pope, et al. (22,24), Gupta, et al. (23), Ellingson, et al. (25,26), and Jain, et al. (16) analyzed patients according to the usage or non-usage of an anti-angiogenic therapy such as bevacizumab (BVZ).

The studies include the following outcomes: progression of the disease, mortality, survival, complete, partial response, and non-response to the established treatment.

Risk of bias in the included studies

The search for articles which met the inclusion criteria did not show experimental studies, only observational studies; subsequently, clinical heterogeneity was very marked.

The publication biases which are inherent to these types of studies (prognosis) caused difficulty to identify all the studies, and the negative results (non-significant) which could not be published. There was an attempt to control this by performing a comprehensive search in three databases, as well as carrying out a manual search of magazines. It was proven that most studies were retrospective cohorts, with a great variation in the different measurement techniques, and of statistical methods adjusted by variables as well as an inadequate description of quantitative information with a variation in the presentation of outcomes.

The internal validity of the studies showed that only one of them had good quality and that the rest had intermediate or low quality. Therefore, using the global quality of these studies, one cannot precisely suggest that DMR is an early predictor of response to treatment in patients with AHDM. A great variety of other clinical, imaging, or therapeutic factors can predict a poor response to treatment; however, evidence is insufficient to suggest that other factors may alter the precision of the test.

Outcomes

The studies were classified according to the diagnostic technique which was calculated to evaluate the response to treatment.

ADC histograms

Two case studies and controls (22,24) were found with this technique, as well as four retrospective cohorts (19,21,23,28).

Pope, et al. (22,24) established an ADC cut point in the average. Significant differences were found between the high ADC values (ADCH ≥ 1,200) and low tumor ADC values (ADCL≤ 1,200) (median of 459 days versus 315 days of log-Rank test [p<0.008]). In patients treated initially with BVZ (cases), high values of ADC were found to be associated with greater global survival compared to a high ADC without BVZ (Hazard ratio [HR]: 2.1 p= 0.02). In cases of recurrent GB, the risk of 6-month progression with a low ADCL compared to a high ADCH was an HR of 4.1 (IC 95%: 1.6, 10.4), and there was a reduction of 2.75 times in the mean progression time.

For the control group, this survival stating was not significant. It was only significant for patients who started BVZ by recurrence of the tumor (HR: 2-4, p=0.02). Additionally in the Pope, et al. (22) study, the change in the tumor volume was a significant predictor at the sixth month of progression (p = 0.004), while the average ADC, the size of the tumor and the age during recurrence were not significant (p=0.787, 0.203 and 0.155, respectively).

Murakami, et al. (21) and Yamasaky, et al. (19) studies also dichotomized the ADC variable (ADC > 1 and ADC ≤ 1) and observed that the minor values of the average ADC presented greater mortality compared to a high ADC. In the univariate factor with the Log-rank test, it was revealed that the only significant global survival factor was ADCL (p< 0.01). The following factors had no prognostic value: the age of the patient (≥50 years), the gender, the duration of symptoms ([≤ 3,0 months], Karnofsky KPS [≥ 80]), or the subtotal surgical removal of the tumor.

The greatest survival predictors were ADCL and the partial surgical resection of the tumor, and were also the strongest predictors for global survival (HR: 3.15, p= 0.05; HR: 19.187, p= 0.01, respectively). These findings were comparable to the ones described in the study, where the multivariate analysis demonstrated that the ADC values, greater than the average, had a survival increase which was 10 times greater than (5.113, 21.396) (p<0.001) the low ADC values.

The minimum ADC was significantly lesser in patients with GB than the Anaplastic Astrocytomas (AA) (p = 0.001). Other evaluated predictive variables were age, neurological functions, Karnofsky, a histopathologic diagnosis, the re-enhancement of tumor components; these were all significant.

Gupta et al. (23) observed that the restriction of diffusion, along with low ADC values precede the re-enhancement of contrast in tumor images, with a probability of 0.48 (IC 95%, 0.288 to 0.675), independently from the BVZ treatment. Twenty three (85.2%) patients presented a re-enhancement with the contrast medium of the tumor in the restriction location of the diffusion, after a median of 3.0 months (IC 95%, 2.6 to 4.1 months). No significant statistical correlation was detected between the magnitude of the ADC reduction from the start and an increase in free survival of the tumor (HR: 0.542; p=0.75) or global survival (HR: 0.03; p =0.19). The Higano, et al. group (28) classified participants into two groups, according to the progression or stabilization of the disease two years after having started treatment. The minimal average ADC of the group with progressive disease was significantly lower than the one of the stable group. The minimum cut ADC 0.9 presented a sensitivity of 79% and a specificity of 81% (p= 0.002).

Tabla 3. Histogramas del ADC

Author, year	Methodology	*Sample (k)*	DMR (variable)	Treatment	Response to treatment	Outcome COX analysis	Conclusions
WB. Pope, 2011 (24)	Cases-controls. Retrospective follow-up April 2005/ November of 2008.	Cases: 59 Controls: 62	ADC < 1.2 ADC ≥ 1.2	Case: BVZ, TMZ, RT. Control: No BVZ only of there is recurrence	(93%) total mortality: 85/121. Mortality cases: 38/59 Mortality controls: 47/62 RR: control (55/62, Case: 34/55)	ADCb: median 459 days ADCa: median 315 days (p < 0.008) Cases: ADCh HR: 2.1 (p= 0.02)/ ADCb (p= 0.055) Controls: ADC no staging survival (p= 0.22)	The analysis of the histogram of the ADC before treatment can stage a free survival in the progression of patients treated with BVZ.
Fumiyuki Yamasaki, 2010 (19)	Retrospective cohort, Feb. 1998/January of 2006, follow-up (3.6-54.5 months; average, 16.6 months), physical and neurological exam	*n = 33 patients (range 10-76 years) high degree GB*	ADC < 1 ADC ≥ 1,0	Proportion of tumor resection: Biopsy ≤ 50%; PR = 50-95 %; SR = 96-99%; TR ≥ 99%	ADC ≤ 1 (23/33) 30.4% ADC > 1 (10/33) 60% p = 0.05 (rate of survival at 1.5 years)	PR HR = 19.187 p = 0.01 ADCMIN HR = 3.15 p 0.05	ADCMEDIUM, ADCMIN and ADCMAX, which are statistically significant prognostic factors ADCMIN most sensitive predictive factor global survival.
A. Gupta, 2011 (23)	Retrospective, January 2005/ March 2010, follow 8.7 ms (0.9-188) with clinical test and images	*n = 27 (34-74 years) all ADC ↓. Patients with GB*	ADCMEDIUM ↓ (0.44-0.97) SD0, 13 RD (yes and no)	BVZ 15 not BVZ 12	RD precedes the re-enhancement of the tumor. Median of 3.0 months (IC of 95%, 2.6 to 4.1 months), ADCMEDIUM: reduced to 22.9% in respect to the basal value (p= 0.001).	The probability of 3 month survival was 0.481 (IC 95%, 0.288-0.675). The probability at 12 months was 0.521 (IC 95%, 0.345-0.788).	Development of a focus of restriction of the diffusion during treatment can precede the development of a new re-enhancement of the tumor.

Shuichi Higano, 2006 (29)	Retrospective cohort, follow-up after 2 years, physical and neurological exam. April 1999 / January 2003	*n= 37 patients (range between 7 and 75 years of age) 22 GB, 15 AA*	ADCMIN for GB and AA	Surgery 30, biopsy 7 (1 GB, 6 AA), all RT and CT	GE: 19 patients (13 AAs, 6 GBs) PD: 16 patients (2 AAs, 14 GBs) 2 GBs censured due to death by pneumonia	Average ADCMIN (0.834 x 10-emm2. Sec-1) of AA (p= 0.001) PD: ADCMIN (0.80 x 10-3mm2. Sec-1) was lesser than (1.037 x 10-3mm2. Sec-1) of GE (p= 0.001). ADCMIN cut 0.9, S = 79%, E= 81% (p = 0.002)	The minimum ADC of AHDM supplies additional information about the prognosis of malignancy after treatment.
Ryugi Murakami, 2007 (21)	Retrospective cohort, June 1996 / November 2003, follow-up with clinical exam and images	*n= 79 (16 to 76 years) AA: 29, GB: 50 (ADCb: 39, ADCa: 11)*	ADCMIN ≤1 ACD > 1 ADCMED 0.897 +/- 0.217	Surgery, RT and CT	AA ADC ≤ 1 (3/29(ADC > 1 (26/29(Global survival after 2 years: ADCb 33% ADCa 92% P < 0.01 GB ADC ≤ 1 (39/50) ADC > 1 (11/50) Global survival after 2 years: ADCb = 13 %, ADCa = 64% P< 0.01	ADCMIN ≤ 1 HR = 10.459 (5.113, 21.396) (p< 0.001)	The minimum pre-treatment ADC in the MR is a clinical prognosis biomarker for the survival of patients with AHDM.
Whitney B. Pope 2009 (22)	Cases and controls August 2006 / January 2008	Cases N = 41 (53 +/- 15) controls n = 41 (53 +/- 12)	ADC = <1,2 ADC = ≥ 1,2	Case: BVZ n = 28 (first), RE n = 7 (second), n = 6 (third)	Cases: PD = 37/41	HR cases = 4.1 IC 95% 1.6, 10.4 controls HR = 1.8; IC 95% 0.9, 3.7	Analysis of the ADC histogram can stage progression and free survival in GB RE.

ADC: apparent diffusion coefficient. BVZ: bevacizumab. TMZ: temozolamide. RT: radiotherapy. HR hazard ratio. N: sample. GB: glioblastoma. PR: partial response ADCMIN: minimal apparent diffusion coefficient. ADCMAX: maximum apparent diffusion coefficient. ADCMEDIUM: medium apparent diffusion coefficient. S: sensitivity. E: specificity. HDA: High-degree astrocytoma. ADC↓: low apparent diffusion coefficient. SD: standard deviation. AA: anaplastic astrocytomas. RD: restriction of the diffusion. SG: stable group. PD: progression of the disease, RD: recurrence of the disease. ADCb: apparent diffusion coefficient in point b. PR: partial resection. TR: total resection.

ADC functional maps (FMADC)

Two retrospective cohorts (17,25), a prospective cohort (18), and a transversal cut study (26) were found in the studies which used this technique as a DMR quantification method.

Hamstra, et al. (17,18) evaluated both participant groups with AHDM diagnosis, in different time spaces: with samples obtained independently (n = 34, n = 60, respectively). They proved that, after three weeks of follow-up, the percentages of change in the volume in the evaluated areas were different between the response groups which were favorable to treatment and those with no response. However, for the Hamstra study, et al. (17), only the percentage of total change in the values of tumor diffusion (VT) with a threshold of 6.57% was the greatest predictor of the progression.

Through crossed validation, a sensitivity of 75% was obtained at this point (IC 95%, 45-92), and a specificity of 93% (IC 95%, 66-99); with an analysis of the ROC curve which suggests a threshold of less than 4.7% as a non-response, and over 4.7% as a response. When performing the multivariate analysis (Cox) in order to predict 1-year survival, between the age, the degree of the tumor, the resection of the tumor and FMADC, only FMADC was a significant predictor (p = 0,001; AUC=0,723;

Sensitivity of 69.7 % [IC 95 %, 51.3 to 84.4]; specificity of 75.0 % [IC 95%, 50.9 to 91.2]; positive predictive value [PPV] of 82.1 %, negative predictive value [NPV] = 60.0 %).

The changes in FMADC after three weeks were closely related to the radiological change after ten weeks; however, this premise was only significant for the Hamstra stud, et al. (17), (p= 0.04). The Ellingson study, et al. (25) suggests that the patients who present a reduction (compared to the start) in the ADC value four weeks after finalizing treatment (20% in the regions of high T2 FLAIR sequence high signal regions or 15% in areas of re-enhancement with a contrast medium [T1-CEL]), have a greater risk of progression of the disease and a lower survival period [T1 + C1 > 15 % HR = 3,15 (p = 0,0001)]. The greatest predictor of survival in patients in treatment with BVZ were FMADC; in which FMADC "responding" had a longer survival period compared to "non-responding" (Log-Rank, p= 0.008).

Table 4. ADC functional maps

Author, year	Methodology	Sample *(k)*	DMR (variable)	Treatment	Response to treatment	Outcome COX analysis	Conclusions
Daniel A. Hamstra, 2005 (17)	Retrospective Cohort, Feb. 1999 / Sept. 2004, follow-up 11 m	*n = 34 gliomas II/IV (58, +/- 11 years) GB 27. AA: 7 two groups PE, SG, RE*	FMADC, VOLUME %	Surgery, RT, 70G, CT	PD in 15/27 (52%) SG 12/27 /41%), RD 2/27 (7%)	Changes in total diffusion (VT) 3 weeks PD: 5.7 +/- 1.4% SG/RD: 17.8 +/- 2.7%; (p 0.001) VT: 6.57% greater predictor [S: 75 % (IC 95 %, 45 to 92). E: 93 % (p < 0,001)	Through the use of FMADC, early staging was related to a shorter global survival in a group of progression of the disease compared to the stable one.
Benjamin M. Ellingson, 2012 (25)	Retrospective cohort, January 2007/ September 2010, IM previous to treatment, 1 week, 10 weeks post-treatment 4 end; with McDonald criteria	*n = 143 GB (58,4 ± 11 years)*	ADC(↑/↓) = ADC(↑) + ADC(↓) FMADC Sequences: FLAIR and T1 + C1	Surgery, CT (TMZ), BVZ if there is recurrence and RT.	Mortality: 118/143	Survival predictor % ADC (↓) Pre-Tx T1 + C1 > 15 %; HR: 3,15; (p = 0,0001)	Patients with a reduction in ADC in a fraction of the volume > FLAIR pre-treatment showed a greater statistical probability of progression than patients with a lower volume fraction.
Daniel A. Hamstra, 2008 (18)	Prospective cohort Nov. 2000 / November 2006, radiological response.	*n = 60 (58,4 ± 11 years)*	ADC↑ [FMADC-VI] ADC↓ [FMADC-VD] ADC no↑/↓ [mFMADC-VT]	21 cycles of RG (60 Gy) + TMZ	FMADCVI > 4,7% In 3 weeks (n = 31) Response to treatment FMADC - VI ≥ 4,7 % no (n = 29)	VI after 3 weeks (p.0002) fDM-VI (≥ 4.7 % vs < 4.7 %) HR: 2.7 (1.5-5.9); p = 0,003	Compared to a conventional neural image, the combination with FMADC is an early predictor of the survival and the radiological response to treatment.
Benjamin M. Ellingson, Mark Malkin, 2010 (26)	Transversal cut, follow-up, clinical and McDonald	*n* = 50	FMADC response FMADC no response	BVZ (*n* = 20) TMZ (*n* = 30)	Stable disease vs. progressive	FMADC responding had a longer survival compared to non-responding FMADC (p = 0.00008)	The results suggest that FMADC applies to regions of FLAIR abnormality as an early progression biomarker, survival without progression and global survival.

ADC: apparent diffusion coefficient. FMADC: functional map of ADC, DMR: Diffusion in magnetic resonance. BVZ: bevacizumab. TMZ: temozolamide RT: radiotherapy. GB: glioblastoma. AHDM: high-degree astrocytoma, PR: partial response ADC↓: low apparent diffusion coefficient. AA: anaplastic astrocytomas. VT: percentage of total change in the values of tumor diffusion. VI increase ADC. VD reduction ADC. ADC (↑/↓): change/recovery of the inversion to the attenuated fluids (FLAIR) and improvement in contrast (T1 + C). ADC ↓: apparent low diffusion coefficient. RD: restriction of the diffusion. SG: stable group, PD: progression of the disease RD: recurrence of the disease. RT: radiotherapy. G: Grays. CT: chemotherapy. S: sensitivity, E: specificity. IM: images. Pre-Tx: pre-treatment.

Normalized ADC maps (NADC)

Different studies have used this technique (13-16, 20), which analyzes the percentage of change in the different CEL, NEL, T2ALL and nADC regions, in order to predict a response to treatment.

Khayal, et. Al. (14) evaluated the changes in volumes and the parameters of diffusion within the regions which are enhanced with a contrast-medium (CEL), and those which are not enhanced (NEL) at the start of radiotherapy (RT), at the middle point of the treatment and after the treatment. The results indicated that the post-radiotherapy intermediate changes were significantly different between the patients who progressed in a period of six months, faced with those which were free of progression. This study also used FA; the percentage of change in normalized fractional anisotropy (nFA), from the intermediate RG and the post-radiotherapy in CEL and NEL, which was significant (p = 0.0396 and 0.0421, respectively), with a greater reduction in the progressives faced with the non-progressives (25% and 22%, respectively).

Li, et al. (15) observed that the patients who lived over two years had stable changes in the median nADC, in the regions T2ALL and

NEL, between pre-RT and post-RT. However, this difference was not statistically significant when using the Cox regression model. However, it did show that the minor nADC values (median and percentile 10) within the enhancement region with the contrast medium (CEL), the larger nADC values (median, percentile 10) within the region of T2 high intensity (T2ALL), and those which are not enhanced with the contrast medium (NEL), were associated with a poor survival period.

Joonmi Oh, et al. (20) evaluated the MR parameters, evidencing that the patients with high volumes of metabolic and anatomical abnormalities (volume CNI2), and low nADC, presented a shorter survival period compared to low levels of ADC in the regions of high signal in sequences with T2 information (11.2 and 21.7 months, respectively; p= 0.004).

Lastly, Rajan Jain, et al. (16) staged the patients according to the progression or non-progression of a tumor mass. They found that the group of patients who had a progressive disease presented a progressive negative change between the measurements of the region with enhancement and restriction of the diffusion (CEL / ADC), and the region without re-enhancement with restriction to the diffusion (NEL/ADC); which suggests an increase in the restriction of the diffusion in both regions, which is possibly attributable to hyper-cellularity and therapeutic failure.

These changes were statistically significant for the measurements after three months in NEL (p= 0.023) after six weeks (p= 0.054), and after a year has passed (p = 0.078), compared to basal values, even though during the same period of time, the volume of the enhancement region CELvol showed a significant reduction, even for progressors. These changes were also observed when comparing the percentage of change in measurements NEL/ADC after six weeks, after three months, and after one year (p = 0.047, p = 0.025 and p = 0.064, respectively). This difference in measurements indicates that the usage of only the CELvol measurement can over-estimate the response in these patients: especially, in early tumor progressions, in which NEL / ADC can be used as an initial biomarker of the image.

Table 5. Normalized ADC maps

Author, year	Methodology	Sample *(k)*	DRM (variable)	Treatment	Response to treatment	Outcome COX analysis	Conclusions
Suja Saraswathy, 2009 (13)	Retrospective cohort, follow-up 1 year (3 to 5 weeks posXx, 1 week after CT), McDonald criteria	*n = 68 (27 to 78 years) AHDM*	nADC	Total surgery: 25; partial resection: 34, biopsy: 9. All CT and RT	Total resection survival 22 months. Subtotal resection or biopsy survival of 16 months.	WM (1,0), CEL (1,4 ± 0,4), NEL: (1,3 ± 0,3), T2ALL (1,4 ± 0,3) NADC <1,5 (n = 65) vol cc/voxels 15,4 ± 15,8 (p = 0,006)	ADC maps are valuable to evaluate the special extension of the tumor, as well as define the objective of the focal therapy and the personalization of the treatment planning.
Inas S. Khayal, 2010 (14)	Prospective cohort followed by 6 months McDonald criteria	*n = 37 (25 to 80 years) AHDM*	nADC	Total surgery: 10, partial resection: 24, biopsy: 3. All CT and RT	After 6 months PD: 19; SG: 18	% change ADCmedpost-RT PE/SG CEL (p = 0,0221), NEL (p: 0,0192), T2ALL (p = 0.0069). CEL (p = 0,0396) NEL (p = 0,0421)	A better normalization of the ADC values in pre and post-RG (p = 0.001) in non-progressors of the disease.
Yan Li, 2011 (15)	Prospective cohort, followed by a year; McDonald criteria and clinical deterioration	*n = 64 (27 to 77 years of age)*	nADC	Surgery, CT and RT-TZ	Progression: 47/64 (23/47 second surgery). After one year of follow-up 20/47 CT alone, 24 CT + QX	Variable depending on time. Small NADC y CEL (p = 0.008 y 0.016); Large NADC T2ALL (p = 0.018 y 0.011) NEL (p = 0.027 a 0.011)	This study suggests that the derivative quantitative variables of an anatomical and physiological magnetic resonance supply useful information for the prediction of results with patients with GB.
Joonmi Oh, 2004 (20)	Retrospective cohort, AHDM follow-up during 2 years with clinical exam and images.	*n = 28 (14.6 to 79.5)*	nADC T1 CEL <1.6 ≥1.6 nADC T2 < 1.5 ≥ 1.5	Surgery all RT and QT	Survival	ADCnT1CE<1,6 (11,2 -+ 4,1 mes) ADCnT1CEL≥1,6 (17,1± 4,3) p = 0.400 T2 <1,5 (11,2+1,6) T2 ≥ 1,5 (21,7 ± 1,8) p = 0.004	The Pre-RT volume of the metabolic alteration and the CADC value within the T2 region can be valuable in the prediction of results in patients with GB.

Rajan Jain, 2010 (16)	Retrospective cohort, follow-up during 1 year in a clinic and McDonald criteria	*n = 20 (32 a 67), GB = 16 c/u = A, AA, AO, AOA. 12 NPRO, 8 P, 9*	%ADCmed/ CEL, % change ADC/NEL	BBVZ only (n = 5) BVZ+ Irinotecan (n = 14) BVZ+ Irinotecan+ Temodar (n = 1)	PE GB 7/12, AA 1/12 SG GB 9/12 AA3/12	SG: % ADCmed/CEL 1 año/previo 20,52 ± 42.90 average13, PD: -15,42 ± 30,12 md -15,1 (p = 0,064) SG: 6 weeks % ADCmed/NEL2,93 ± 12.94 average 0,9 PD: -13.82 ± 24,89 average-5.0 (p = 0,047)	ADC/CEL and ADC/NEL increase slightly when PD are present and they progressively reduce in SG. These findings suggest that it can be used as an early response biomarker.

ADC: NEC: Necrosis areas which are marked post-contrast. T2ALL: high-signal lesion in T2 in FLAIR sequences in order to exclude the resection cavity. NEL (non-enhanced lesion) = T2ALL – (CEL + NEL). AA: Anaplastic astrocytoma. BVZ: bevacizumab. TMZ: temozolamide. RT: radiotherapy. GB: glyoblastoma. PR: partial response. ADCmed: Medium apparent diffusion coefficient. AHDM: high-degree astrocytoma. ADC↓: low apparent diffusion coefficient. SD: Standard deviation. AA: anaplastic astrocytomas. SG: stable group. PD: progression of the disease. RD: recurrence of the disease. PostQx: post-surgical. CT: chemotherapy. RT: radiotherapy. NADC: normalized apparent diffusion coefficient. TMZ: temozolamide.

Discussion

Currently, the follow-up of patients in AHDM treatment is performed by using the McDonald criteria and RANO (4, 5) which are based in bidimensional measures in contrasted MR images, in which progression occurs if there is an increase over 25% in the enhancement areas (29). The efficiency of these criteria is reduced when using new therapies, such as CT with temozolamide and antiangiogenic medications (BVZ), which modify the physiology of enhancement of the contrast medium when altering the hematoencephalic barrier (30).

New methods based on MR imaging diffusion techniques are being studied, with the hypothesis that the tumor areas which restrict diffusion (low ADC) precede in their appearance to the areas which are enhanced with the contrast medium (which are the base of the current methods of evaluation), which seem to be a very efficient method when evaluating the real tumor volume, distinguishing it from the areas of pseudo-response or pseudo-progression (23,29,30).

The results of the reviewed articles in this work coincide in the sense that they prove that the DMR images can play a very important role in the evaluation of patients who undergo AHDM treatment.

The tumor areas which restrict in diffusion (low ADC levels) are related to a lower survival period and with shorter free periods of progression; it is also a predictor of a greater risk of progression of the disease (21,22,24,25,28).

In addition, the presence of areas which restrict the diffusion precedes the appearance of areas which are enhanced with the contrast medium in the images of post-treatment follow-up, which can serve as an early marker of failure during treatment (17,23)

Most of the developed techniques perform measurements before and after this, with quantitative values such as DC histograms, nADC maps or FMADC (14,17,18,26). Similarly, one can say that the subjective evaluation of the restriction to the diffusion is also a useful method. Quantitative values of the magnitude of these measurements is not necessary (8).

The presence of areas which do not restrict the diffusion (high ADC) is related to a higher total survival period, as well as a better response to treatment (BVZ), and with greater periods of survival free of progression (17,22,23).

The areas with low ADC values precede the appearance of areas with new enhancement in the same location, up to three months (17,23). This leads to an effort to develop and propose new response criteria to the treatment of AHDM, as well as identifying other MR findings, different to the enhancement areas with contrast medium, especially in cases where antiangiogenics are used (15,22,23).

The images through diffusion are sensitive to the alterations¬ in the Brownian movement of the water particles; the low ADC values are co-related with a high cellularity, a high degree and index of Ki-67 proliferation in the cerebral gliomas (23).

Likewise, said images are performed routinely as part of each cerebral MR study; therefore, the recognition of these areas of low ADC values has a wide and potential impact in the routine clinical care of patients with AHDM. Likewise, they are related to the findings described in other new MR evaluation techniques, such as the presence of areas with high volumes of metabolic abnormality (VNCI2, NCI), in spectroscopy studies, and with high values of relative cerebral blood volume (rCBV) in perfusion studies, showing shorter survival values than in groups of patients which do not present these characteristics.

Frequently, if the place of the elected biopsy is not optimal, AHDM classification can be incorrect due to the fact that these tumors are histologically heterogeneous. Therefore, the ADC helps to identify the areas of greater cellularity within a tumor, which can be useful for selecting the site of the biopsy (28).

This study has some limitations in the interpretation of the results, which are caused by the variability of the ADC values which were calculated in the studies. Said variability reflects the differences in the bobbin systems and in the image generators which were used in the markers of the instruments and in the applied field intensities (31). The minimal ADC cut values can also be affected. Therefore, it is suggested that the optimal absolute ADC is established through wider studies; the semi-quantitative usage of ADC and its relation with the contralateral side can help to eliminate variables. It is necessary to perform new studies in order to standardize ADC or the evaluation methods.

Even through this systematic revision proves that the low ADC is one of the most important prognosis factors, due to the heterogeneous nature of AHDM; other variables, such as the characteristics of the patients, the type of tumor and the treatment strategies must be taken into account in order to perform the studies.

Conclusions and recommendations

The preliminary data support the importance of the diffusion images, by signaling lesions with low ADC as potential precursors of a

tumor progression, and which must be included in the process of taking clinical decisions in this group of patients.

The presence of low ADC isolated lesions in a subgroup of patients with AHDM precede the development of enhancement of the concordant lesions in the same area: that is to say, a progression. Ample prospective trials are required to confirm these findings. However, this systematic revision supports the important role of diffusion potentiated images.

A larger number of studies must be performed. Ideally, these studies must have a histopathologic correlation of the areas which present low ADC values in MR.

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Attachment 1

(((“Magnetic Resonance Imaging/methods”[Mesh]) OR “Diffusion Magnetic Resonance Imaging/methods”[Mesh] OR (ADC*[TW] AND MAPP*[TW]) OR (diffusion[TW] AND restrictio*[TW]) OR MRI[TW] OR (apparent*[TW] AND diffusion[TW] AND coefficient*[tw]) OR (apparent*[TW] AND diffusion[TW] AND coefficient*[tw] AND HISTOGRAM*[TW])) AND ((“Treatment Outcome”[Mesh] OR (treatment*[TW] AND outcome*[tw]) OR “Neoplasm Recurrence, Local”[Mesh] OR ([TW]) OR “Disease Progression”[Mesh] OR PSEUDOPROGRESSION*[TW] OR (DISEASE[TW] AND PROGRESSION*[TW]) OR (STABLE[TW] AND DISEASE[TW])) AND (“Glioblastoma/drug therapy”[Mesh] OR “Glioblastoma/radiotherapy”[Mesh] OR “Glioblastoma/surgery”[Mesh] OR “Glioblastoma/therapy”[Mesh] OR “Brain Neoplasms/drug therapy”[Mesh]) OR “Brain Neoplasms/therapy”[Mesh] OR “Angiogenesis Inhibitors/therapeutic use”[Mesh] OR “Antibodies, Monoclonal, Humanized/therapeutic use”[Mesh]) AND (“Follow-Up Studies”[Mesh] OR “Cohort Studies”[Mesh] OR “Incidence”[Mesh] OR “mortality” [Subheading] OR prognos*[tw] or predict*[tw] or course[tw]) AND (“Glioblastoma/diagnosis”[Mesh] OR “Brain Neoplasms/diagnosis”[Mesh] OR BRAIN NEOPLASM*[TW])) Filters: Humans; Aged: 6+ years

Attachment 2

Strategy of Medline search format PubMed

COCHRANE search strategy

Index test set (Prueba Diagnóstica)
#1 MeSH descriptor **Diffusion Magnetic Resonance Imaging** explode all trees with qualifier: **MT** #2 MeSH descriptor **Magnetic Resonance Imaging** explode all trees with qualifier: **MT** #3 MRI #4 adc map* #5 diffusion restrict* #6 MeSH descriptor diffusion coefficient #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
Target condition set (Predicción de respuesta)
#8 MeSH descriptor **Treatment Outcome** explode all trees #9 treatment* outcome* #10 MeSH descriptor **Disease Progression** explode all trees #11 stable* diseas* #12 MeSH descriptor Neoplasm Recurrence, Local explode all trees with qualifier: DI #13 pseudoprogression #14 stable* diseas* #15 neoplasm* recurrenc* #16 (#8 OR #9 OR#10 OR#11 OR#12 OR#13 OR #14 OR #15) #17 MeSH descriptor **Angiogenesis Inhibitors** explode all trees with qualifier: **TU**. #18 MeSH descriptor **Antibodies, Monoclonal, Humanized** explode all trees with qualifier: **TU** #19 MeSH descriptor **Glioblastoma** explode all trees with qualifier: **DT** **Target condition set (Predicción de respuesta)** #20 MeSH descriptor **Brain Neoplasms** explode all trees with qualifier: **TH** #21 (#17 OR#18 OR#19 OR#20) #22 (#16 AND #21)
Patient description set (Enfermedad del paciente)
#23 MeSH descriptor **Glioblastoma** explode all trees with qualifier: **DI** #24 MeSH descriptor **Brain Neoplasms** explode all trees with qualifier: **DI** #25 BRAIN NEOPLASM* #26 (#23 OR#24 OR#25)
Characteristics of studies (Tipos de estudio)
#27 MeSH descriptor Cohort Studies explode all trees #28 MeSH descriptor Incidence explode all trees #29 mortality” [Subheading] #30 MeSH descriptor **Follow-Up Studies** explode all trees #31 prognos* #32 predict* #33 course #34 (#27 or #28 OR #29 OR #30 OR #31 OR #32 OR #33)
Combined sets
#35 7 and 22 and 26 and 31 (limits humans,6+ years)

Estrategia de búsqueda EMBASE

Index test set (Prueba diagnóstica)
1 ‘nuclear magnetic resonance imaging’/exp 2 ‘diffusion weighted imaging’/exp 3 ‘mri’/exp 4 adc NEAR/5 map* 5 ‘diffusion’/exp AND coefficient* 6 diffusion NEAR/5 restrict* 7 or/1-6
Target condition set (Predicción de respuesta)
8 ‘treatment outcome’/exp 9 treatment* AND outcome* 10 Neoplasm Recurrence, Local”/exp 11 NEOPLASM*[TW] AND RECURRENCE* 12 ‘disease course’/exp 13 pseudoprogression 14 STABLE AND DISEASE* 15 or/8-14 16 ‘angiogenesis inhibitor’/exp/dd_dt 17 ‘monoclonal antibody’/exp/dd_dt 18 ‘glioblastoma’/exp/dm_dt 19 ‘brain tumor’/exp/dm_th **Target condition set (Predicción de respuesta)** 20 or/16-19 21 15 and 20
Patient description set (Enfermedad del paciente)
22 ‘glioblastoma’/exp/dg 23 ‘brain tumor’/exp/dg 24 BRAIN NEOPLASM* 25 or/22-24
Characteristics of studies (Tipos de estudio)
26 “Cohort Studies”/exp 27 “Incidence”/exp 28 Follow-Up Studies/exp 29 “mortality” [Subheading] 30 prognos* 31 predict* 32 course 33 or/26-32
Combined sets
34 7 and 21 and 25 and 33 (limits humans, 6+ years)