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Monitoring of Brain Tumor Response To Radio-Chemotherapy By DWI

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Abstract: *Imaging modalities are very attractive tools with respect to prediction of response to anticancer therapy due to noninvasive nature of these procedure, the possibility of repeating the test several times and the use of different imaging biomarkers. These modalities could be used before, during and after anticancer therapy to follow up and predict response, which could very helpful in individualizing therapy. The literature has been reviewed to assess the role of imaging techniques such as diffusion weight magnetic resonance imaging (DWMRI) in the prediction of the response to therapy. The initial search included Medline, Embase and PubMed. An initial criterion were to include studies where DWMRI was reported pre, during and/or post radiotherapy (irrespective of other treatments such as chemotherapy or surgery). Searching the search engine systematically recall a total of 410 articles. A total of 115 potentially relevant papers by reviewing the titles and abstracts. Reviewing the whole text of these articles retrieved a 29 paper where the presence of ADCs of brain tissues tumour pre and post chemoradiotherpay was considered as the inclusion criteria. These 29 papers were studied to evaluate the use of the selected imaging modalities as tools for predicting the prognosis of brain tumour patients as well as for predicting the future plan for therapeutic interventions of those patients. Almost all studies have revealed that ADC values, pre-treatment DWMRI and restriction DWI are of predictive outcomes. The studies included in this review were heterogeneous with respect to the locations of the tumours, treatment plans, the desired outcomes and parameters used in the assessment. However a conclusion that the studies imaging modalities can be of value in predicting response of brain tumour can be withdrawn as a result of reviewing the scientific literature.*

Key words: *Brian tumor , DWI , MRI ,Radio-Chemotherapy, Response***.**

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I. Introduction

There are growing concerns that size measurement has significant drawbacks in situations where tumors cannot be measured, where there is poor reproducibility, and where mass lesions persist after treatment Moreover, in brain tumors, radiological results following chemoradiation therapy may be misleading, where the increase in enhancement may be interpreted as disease progression (known as pseudoprogression) [2].As a result, advanced principles and new imaging methods are being tested to estimate treatment response including variations in tumor dimensions and density [3]With the continuous advance in cancer therapy, the use of innovated approaches to assess the response has become urgently needed. For example, drugs which act by inhibition of angiogenesis may reduce contrast enhancement ,this can be misleading because within few days, these drugs directly affect the size of the contrast enhance lesion (CEL)[4,5]on computed tomography (CT)/magnetic resonance imaging (MRI) scans, most of this effect is due to lower permeability to contrast media, rather than anticancer effect. In the era of evolving technology, if radioresistant areas can be identified early in the course of treatment, appropriate adaptive therapy strategies could also be considered to optimize the therapeutic ratio e.g. treatment escalation to poor responders; de-intensification for good responders and avoidance of treatment to non-responders .While primary radiotherapy with or without chemotherapy is the preferred treatment option in many centers to preserve organ function, response to therapy depends on tumour biology, including microenvironment characteristics, especially hypoxia which is associated with prognosis in brian tumor . Hypoxia is one such microenvironment characteristic which is known to be associated with poor oncological outcomes[6]

Hypoxia and GBM necrosis :There are compelling reasons to believe that hypoxia plays a role in GBM development, angiogenesis, and growth. The first, and most obvious, is the presence of intratumoral necrosis. In fact, the histological diagnosis of GBM depends on the presence of tumor necrosis and the cluster of cells that surround the necrotic areas known as pseudopalisading. All GBM tumors have intratumoral necrosis to a varying degree; it does not seem to be related to tumor size, as it is found in both small and large tumors. To complicate matters further, animal glioma models demonstrate that tumors <1mmin diameter are intensely hypoxic, poorly perfused, and possess sparse tumor vasculature. Larger tumors, 1–4 mm in diameter, were found to be better perfused with widespread vasculature and not significantly hypoxic .[7] This suggests that necrosis may not simply be due to inadequate vascular supply but instead may be a result of intrinsic molecular or genetic changes within the tumor .[8] Little is known of how this may take place, but microarray analysis of GBM necrosis identified specific genes and patterns of gene expression that may help elucidate the molecular basis of necrogenesis in the future .[9] On the other hand, although GBMis a highly vascularized tumor, this microcirculation is functionally very inefficient and may contribute to relative hypoxia and necrosis within a given tumor .[10-14]Direct and indirect measurements of tumor hypoxia in human GBM and attempts at correlating this with tumor blood flow and necrosis have not resolved this controversy .[15-18] It is possible that a combination of hypoxia and intrinsic tumor molecular biology are responsible for pseudopalisading necrosis . [19] Rong et al. have demonstrated that hypoxia and loss of the gene phosphatase and tensin homolog (PTEN) up-regulate tissue factor expression, which they postulate promotes microvascular thrombosis and subsequent intratumoral necrosis .[20] Studies have shown that the degree of necrosis within a GBM correlates inversely with patient outcome and survival [21-23] although our own group was unable to demonstrate this relationship in our patient series.[24] No studies have described whether the volume of resection of necrotic regions within these tumors influences response to either treatment or overall patient survival. Moreover, progression free survival (PFS) was believed to be suitable to decide whether or not cytotoxic therapy is efficacious. However, it was found that PFS and overall survival were not correlated, as described in extensive studies of bevacizumab therapy.To overcome these problems, functional imaging methods that describe cancer cells from the physiological point of view are slowing significance in the monitoring of response to treatments with new mechanisms of action, often foreseeing the response before changes in conventional measurements such as size . DWI presents substantial potential in the identification of the degree of tumour invasion. Variations in scalar diffusion measures adjacent to the tumour - such as apparent diffusion coefficient (ADC) and fractional anisotropy (FA) - correlate with histological estimates of tumour cellularity and tumour invasion in patients with high-grade (HGG) and low- grade gliomas (LGG) . **[25-31]** The classification of primary brain tumors depends on the tissue of phylogenic origin. Cancers originating from the neuroepithelium involve a subdivision of neoplasms known as "gliomas". About 40% of primary brain tumors are Gliomas. One of the most abundant groups of cells in the brain are glial cells and subdivided into four subgroups: astrocytes, oligodendrocytes, ependymal cells, and microglia . Gliomas are sub-classified depending on the cells from which they originate. Of these group, the most common in the clinical practice are astrocytomas, oligodendrogliomas, and oliogoastrocytomas. Astrocytomas are sub-classified into four-graded classification adopted by the World Health Organization (WHO), from the most benign grade I to the most malignant grade IV. Grade IV gliomas have high cellular density, marked nuclear atypia, elevated mitotic activity, presence of necrosis, and/or endothelial proliferation. Glioblastoma (GBM) is most frequently seen sub-type of grade IV glioma. Subdividing tumour into grades is important not only in treatment but also in prognosis, where the grade I tumors complete surgical resection can result in cure (Table 1). [32-34]

WHO grade	WHO term	Histologic features	Age at diagnosis	Male/female ratio	Survival (years)
I	Pilocytic astrocytoma	Microcysts, Rosenthal fibers	10	1:1	Variable, Cures common
II	Diffuse astrocytoma	Mildly increased cell number or atypia	34	1.18:1	5(2-12+)
III	Anaplastic astrocytoma	Mitoses, prominent Atypia	41	1.8:1	2(1-5)
IV	Glioblastoma multiforme	Necrosis, endothelial proliferation	53	1.5:1	1(0.25-1.5)

Table 1 WHO classification of astrocytic tumors and their characteristic features.

II. Material And Methods

The aim of this study was to identify articles which evaluated the predictive/prognostic role of DWMRI. References for this review were identified by this **Search strategy :**A search on Embase, the Cochrane library, MEDLINE, Pubmed, Elsevier, Springer, free journals and Google scholar was conducted for studies using the key words: brain tumor or glioma or glioblastoma, GBM, diffusion magnetic resonance imaging, DWI, radio-chemotherapy, response. We supplemented electronic search by manually searching reference lists, reviews, and abstracts. References of all retrieved articles were manually searched for additional relevant manuscripts. Studies found through these search terms were assessed for potential eligibility by reading the abstracts first and then applying inclusion and exclusion criteria

Inclusion and Exclusion : We evaluated each study for inclusion in the systematic review on the basis of the following criteria: target population, patients with histologically proven astrocytoma (glioblastoma) and availability of ADC data. We included the studies that had ADC values. Only original articles that performed during the years 1990 to 2016 presented in English language that relevant to our objectives were considered for inclusion.Included articles were only those in which brain DWI was performed at baseline and prior to treatment; chemo or radiotherapy and reporting the role of DWI in the assessment of pathological response after radio-chemotherapy for brain tumor.To be eligible for this review, we decided that a study should consist patients with newly diagnosed or recurrent, histologically proven brain cancer undergoing chemo or radiotherapy who were imaged using DWI. We did not exclude studies if other imaging techniques were performed concurrently with DWI in order to evaluate treatment response.

Data Extraction : After this initial assessment, the publications were summarized using a standard extraction form. Each study was assessed for its number of subjects, the grade of astrocytoma, the DWI b and ADC value, and the method for ADC measurement.

Extracted data included: first author, year of publication, study design (retrospective or prospective), population size, mean patient age and range, cancer grade at inclusion, cancer histology, treatment regimen and imaging response assessment.While scoring the extraction forms, some studies were excluded if the study outcome proved not to contain information on response evaluation by DWI. Some variables that we depended on in choosing the reference articles to be reviewed were:

1.Article study type: like clinical trial, systematic review, meta-analysis, RCT (Randomization control trial), case control, review article, cross sectional and case report. Each study type has its own level of evidence. The higher level went to RCT, systematic reviews and meta-analysis, while lower one for descriptive studies like cross sectional and case reports.

2.The outcomes of patient were considered in review in term of response to treatment presented in reviewed articles before and after radio-chemotherapy.

3.Diffusion–weighted image, ADC value

Data analysis

We overviewed, organized and summarized literature key terms and concepts, research methodology and results. We reviewed eligible articles, categorized them according to study area of type, summarized their findings in tables and compared different means of ADC values and DWI restriction presented in studied literatures. Appropriate statistical test used when needed.All reported P-values ≤ 0.05 were considered statistically significant. The large heterogeneity observed in the included studies precluded us from pooling data, which is why we chose to use descriptive statistics in this review. We discussed difference between treatment response rates among brain tumor patients that being studied in reviewed studies and described main relevant characteristics of the patients when available

III. Results

This review summarizes the concepts and use of diffusion MR imaging as a prognostic indicator and a potential biomarker of treatment response in brain tumor. There are numerous clinical studies support the hypothesis that ADC serial change may be a biomarker of treatment response. Most clinical studies are single institution trials and involve modest patient numbers. Despite these limitations, DWI has shown promise as a tool for oncologic imaging of treatment response.

1. Study Selection : After systematic search in scientific search engine, we retrieved a total of 410 articles. By assessing the titles and abstracts, we found 115 articles to be potentially relevant. After the full text assessment, 29 studies (table 2) met the inclusion criteria of having ADC values of brain tumor tissue pre and post chemoradiotherapy as mean or percent changes. Furthermore, eligible articles were submitted to further in depth reading, summarization and comparison in this systematic review.

2. Study Description and Patients Characteristics: Of the 29 included studies in this systematic review, 16 were prospective and 13 retrospective. A total of 1605 patients were involved in these studies aged 2 to 85

years. Among those patients, majority of brain tumor types were GBM. Studied lesions were either primary, recurrent or mixed with brain metastasis. The characteristics of included studies are illustrated in table 2.

Table 2. Main characteristics of included studies

Author	**Year**	**Study type**	**Patients No.**	**M/F**	**Age: Mean (±SD) OR Median (range)**	**Cancer type**
Chenevert et al.	2000	P	2	1/1	13-37	PNET, oligodendroglioma
Chenevert et al.	2002	R	2	1/1	56-64	anaplastic oligo-astrocytoma
Hien et al	2004	R	18	13/5	52 (14-77)	High grade glioma
Crawford et al.	2009	P	56	39/17	56 ± 12.8	GBM
Ellingson et al.	2015	P	64	34/30	57.3 ±11.2	GBM
Rahman et al	2014	R	91	51/40	56.3 (23–83)	Glioblastoma
Ellingson et al.	2014	R	132	NA	55.3 ± 9.9	GBM
Ellingson et al.	2011a	R	50	NA	NA	Malignant Glioma
Ellingson et al.	2011b	R	77	NA	NA	GBM
Ellingson et al.	2012	R	143	97/46	58.4 +11	Glioblastoma
Dessouky et al.	2010	P	46	24/22	43 (8–75)	Brain tumor
Elson et al.	2015	R	52	32/20	61 (32-85)	GBM
Lutz et al	2014	R	28	20/8	55.9 (33.8-70)	Glioblastoma
Gutierrez et al.	2013	R	18	10/8	10 (1.9-20.6)	Brain tumor
Hamstra et al.	2005	P	34	13/21	45 (20-75)	GBM, anaplastic astrocytoma
Hamstra et al	2008	P	60	NA	53 (20-75)	GBM, anaplastic astrocytoma
Jain et al.	2010	R	20	16/4	50.9 (32-67)	GBM, astrocytoma
Khayal et al	2010	P	37	27/10	56 (25-80)	GBM
Mardor et al.	2003	P	8	NA	NA	Brain tumor
Mardor et al.	2001	P	3	NA	NA	Malignant glioma.
Mardor et al.	2004	P	12	NA	NA	Brain tumor
Moffat et al.	2995	P	20	8/12	45 (8-67)	Brain tumor
Zulfiqar et al.	2013	P	181	112/69	7-79	GBM, anaplastic astrocytoma
Pope et al.	2011	R	121	78/43	58.5±9	Glioblastoma
Pope et al.	2012	R	97	64/33	54±12	GBM
Pope et al.	2009	P	82	52/30	54±14	GBM
Zhang et al.	2016	R	52	31/21	62 (28–80)	GBM
Mong et al.	2012	P	80	48/32	52.2 (20-82)	Malignant glioma
Tomura et al.	2006	P	19	NA	NA	Brain tumor

Role of DWI in assessing and predicting brain tumor response to treatment. We reviewed illegible 29 studies conducted in past 27 years where data on investigating the role of DWI is available in monitoring response to treatments in brain tumor. Table 3A and B shows main results of these studies regarding role of ADC values in predicting therapy response.

Table 3 : Results for the prediction of response to therapy based on the ADC parameters value in

Author	**Year**	**Therapy**	**b value sec/mm^2**	**Response evaluation/ progression assessment**	**Conclusion/ Predictor of response/ survival**	**Tumor type**
Chenevert et al.	2000	RT/Ch	0, 100, 1000	Macdonald criteria	Increase in ADC preceded tumor response suggesting that diffusion parameters could be serve as an early predictor of therapeutic response	Newly diagnose d tumor
Chenevert et al.	2002	RT/Ch	NA	Macdonald criteria	DWI has potential for assessment of treatment response as significant increase in ADC value is consistent with clinical assessment of response	Newly diagnose d tumor
Hien et al.	2004	RT±Ch	0, 1000	Clinical assessment/ histology	Mean ADCs of the recurrent tumors was lower than those of the nonrecurrence group	Recurrent tumor
Crawford et al.	2009	RT/Ch	1000	Survival time after start of treatment	Patients with more lesions presented with nADC less than 1.5 had worse survival	Newly diagnose d tumor

Ellingson et al.	2015	RT/Ch/ anti-angiogenic	0, 1200	RANO criteria± biopsy	A high volume fraction of increasing ADC after therapy was associated with shorter PFS, while a high volume fraction of decreasing ADC was associated with shorter OS.	Recurrent tumor
Rahman et al.	2014	bevacizumab ± chemotherapy	0, 1000	RANO criteria	Smaller pretreatment volume, (≤20 cc) with a combined baseline ADC factor of >0.8, had the longest median OS.	Recurrent tumor
Ellingson et al.	2014	Bevacizumab or chemotherapy	0, 1000	MRI criteria or clinical assessment or biopsy	Patients with highest mean ADC_L (>1.2 µm2 /ms) showed a significant longer PFS and OS	Recurrent tumor
Ellingson et al.	2011a	Bevacizumab or temozolomide	0, 1000	Neurological assessment (KPS) and Macdonald criteria	‘‘fDM Responders’’ had a significantly longer median survival and time to progression compared with ‘‘fDM Non-Responders’’	Newly diagnosed tumor
Ellingson et al.	2011b	bevacizumab ± chemotherapy	0, 1000	MRI criteria or clinical assessment or biopsy	Traditional and graded fDMs were predictive of OS, where the larger the volume of tissue with decreased ADC, the shorter the OS.	Recurrent tumor
Ellingson et al.	2012	RT/Ch	0, 1000	Clinical assessment	fDM is a sensitive imaging biomarker for predicting survival in glioblastoma, suggesting patients exhibiting a large volume of tissue with decreased ADC are statistically more likely to have a short PFS and OS.	Newly diagnosed tumor
Dessouky et al.	2010	RT/Ch	0, 1000	Neurological assessment and Macdonald criteria	non-responding tumors at 3 weeks (low volumes with increased ADC% by fDM) greatly had a shorter survival (mean 8.7 months) compared to those with responding tumors (larger volumes with increased ADC% by fDM)(mean 35.6 months)	Newly diagnosed tumor
Elson et al.	2015	RT	NA	MRI criteria or clinical assessment or biopsy	Absence of an ADC hypointensity was a significant predictor of favorable PFS	Recurrent tumor
Lutz et al.	2014	RT/Ch or bevacizumab	0, 1000	RANO criteria	Decreased mean ADC between baseline and follow up exam indicates tumor progression	Newly diagnosed tumor
Gutierrez et al.	2013	RT/Ch	0, 1000	RANO criteria	Higher fDM ratio, higher regional ADC increase, larger fiADC, and steeper slopes among responders	Newly diagnosed tumor
Hamstra et al.	2005	RT ±Ch	0, 1000	Macdonald criteria	Low diffusion by fDM (sum of diffusion change Vt= ≤6.57%) at week 3 predict PD at week 10 which associated with poor survival	Newly diagnosed tumor
Hamstra et al	2008	RT±Ch	0, 1000	Macdonald criteria	Greater increases in fDM VI correlate with better prognosis	Newly diagnosed tumor
Jain et al.	2010	bevacizumab /Ch	0, 1000	Macdonald criteria, KPS index	Progressive negative percent change of ADC in nonresponders	Recurrent tumor
Khayal et al.	2010	RT/Ch/ anti-angiogenic	1000	Neurological assessment and Macdonald criteria	Significantly higher percent nADC changes from mid- to post-RT observed within the CEL, NEL, and T2ALL for progressors (16%, 13%, and 14%) vs nonprogressors (4%, 3%, and 3%)	Newly diagnosed tumor
Mardor et al.	2003	RT	5, 1000, 4000	Macdonald criteria	Increase in ADC in responders preceded tumor response	Newly diagnosed tumor

Mardor et al.	2001	Convection-enhanced Taxol	5, 1000	Conventional imaging T2	Changes in ADC preceded tumor response and greater increase in ADC in patients receiving more treatment	Recurrent tumor
Mardor et al.	2004	RT	5, 1000	Macdonald criteria	Negative correlation: a lower ADC was found in the group with the best response	Newly diagnose d tumor
Moffat et al.	2005	RT/Ch	0,1000	Macdonald criteria	Positive correlation: responding lesions had a higher percentage with increase in ADC values	Newly diagnose d tumor
Zulfiqar et al.	2013	RT/Ch	0,1000	Clinical and radiological evaluation, survival time	Low ADC values is independent predictor for poor prognosis	Newly diagnose d tumor
Pope et al.	2011	Bevacizumab	0,1000	RANO criteria	Low ADC is associated with longer PFS and OS	Newly diagnose d tumor
Pope et al.	2012	Bevacizumab	0,1000	RECIST, Macdonald criteria	Low ADC is associated with worse PFS and OS	Recurrent tumor
Pope et al.	2009	Bevacizumab	0,1000	Macdonald criteria	Low ADCL is associated with worse 6 months PFS	Recurrent tumor
Zhang et al.	2016	Bevacizumab	0,1000	RANO criteria	Greater volume of low-ADC lesions predicted shorter OS	Newly diagnose d tumor
Mong et al.	2012	Bevacizumab	0,1000	Survival analysis	Restricted-diffusion lesions associated with improved outcomes	Newly diagnose d tumor
Tomura et al.	2006	Stereotactic RT	0,1000	Macdonald criteria	Positive: ADC rose after treatment. A higher nADC was found in lesions without recurrence	Newly diagnose d tumor

RT: radiotherapy, Ch: chemotherapy, SRT: stereotactic radiotherapy, OS: overall survival, PFS: progression free survival. fDM: functional diffusion map, nADC: normalized ADC, PD: progressive disease, ADC: apparent diffusion coefficient, KPS, Karnofsky performance score.

Table (4) points estimate

Author	**Year**	**Odd ratio**	Hazard ratio	
Hien et al.	2004	No.	No. No.	
Ellingson et al.	2015	No.	No. No.	
Rahman et al.	2014	No.	Yes	
Ellingson et al.	2014	No.	Yes	
Ellingson et al.	2011b	No.	No.	
Elson et al.	2015	No.	No. No.	
Jain et al.	2010	No.	No No.	
Mardor et al.	2001	No.	No. No.	
Pope et al.	2012	Yes	Yes	
Pope et al.	2009	Yes	Yes	
Chenevert et al.	2000	No.	No.	
Chenevert et al.	2002	No.	No.	
Crawford et al.	2009	No.	No.	
Ellingson et al.	2011a	No.	Yes	
Ellingson et al.	2012	No.	Yes	
Dessouky et al.	2010	No.	No.	
Lutz et al.	2014	No.	No.	
Gutierrez et al.	2013	No.	No.	
Hamstra et al.	2005	No.	Yes	
Hamstra et al	2008	No.	Yes	
Khayal et al.	2010	No.	No.	
Mardor et al.	2003	No	No	
Mardor et al.	2004	No.	No.	
Moffat et al.	2005	No.	No.	
Zulfiqar et al.	2013	Yes	No.	
Pope et al.	2011	No.	Yes	

Zhang et al.	2016	No.	Yes	
Mong et al.	2012	No.	No.	
Tomura et al.	2006	No.	No.	

- Mardor et al 2001[35] studied three patients with recurrent malignant glioma received intratumoral convection-enhanced Taxo. They showed clear increase in ADC within the first 24–48 h after the treatment was begun. The response was clearly detected in the DWI before it could be detected by the conventional imaging methods.

- Hien et al. 2004[36] Post treatment study. They found that recurrence and nonrecurrence neoplasm could be differentiated by using mean ADC values and ADC ratios. ADC ratios in the **recurrence g**roup showed lower **values (1.43 ± 0.11**) than those of the **nonrecurrence** group (1.82 ± 0.07, P < .001). Mean ADCs of the recurrent tumors (1.18 ± 0.13 × 10-3 mm/s2) was lower than those of the nonrecurrence group (1.40 ± 0.17 × 10-3 mm/s2, P < .006).

- Rahman et al. 2014[37] they assessed by histogram analysis, the ADC factor was still significantly associated with OS in both subgroups, baseline enhancing volume ₌20 cc (HR = 0.40,p = 0.01) and patients with baseline enhancing tumor B20 cc .first recurrence and For patients with bevacizumab monotherapy, ADC parameters were able to stratify the sample for survival. For patients at second and third recurrence and for patients with concurrent therapy in combination with bevacizumab neither ADC parameter was able to stratify patients for survival .while **Ellingson et al. 2014**[38] reported Cox multivariate regression analysis accounting for the interaction between bevacizumab- and non-bevacizumab-treated patients suggested that the ability of the lower Gaussian curve to predict survival is dependent on treatment (progression-free survival, P ₌.045; overall survival, P ₌.003). Patients with recurrent glioblastoma multiforme with a mean lower Gaussian curve from ADC histogram analysis > 1.2m have a survival advantage when treated with bevacizumab **Elson et al. 2015**[39] they reported recurrent GBM to investigate the association of pre-radiotherapy ADC abnormalities with patterns of recurrence and survival. They found that the median PFS (with 95 % CI) for patients with an ADC hypointensity versus without was 3.2 versus 8.0 months (p = 0.013) and a trend toward reduced OR of 11.3 versus 18.9 months (p = 0.059). This suggests that this abnormality represents an adverse prognostic feature.

Ellingson et al. 2011b[40] The researchers suggested that the use of graded fDM allowed for slightly improved stratification of patients regarding survival compared with the traditional fDM approach . Patients with a volume of tissue having a decrease in ADC ranging within 0.25 and 0.4 mm2/ms larger than the median of 12 cc within FLAIR ROIs were more likely to have poor survival than those with lower volumes (P = .0024) with sensitivity and specificity of 79% and 57% to predict 6-month OS and 58% and 67% predicting 12-month OS respectively. Also they found similar survival pattern within contrast-enhancing ROIs when patients having a volume of tissue exhibiting a decrease in ADC within the range of 0.25 and 0.4 mm2/ms larger than the median of 1.5 cc had a significantly shorter survival compared with patients having a lower volume (P, .0001) with sensitivity and specificity of 86% and 59% to predict 6-month OS, and 62% and 74% predicting 12-month OS respectively.

- Ellingson et al. 2015 [41] **(1)** they reported fDM analysis were not significant predictors for PFS when accounting for age and gender. patients with a large volume fraction of pre-treatment enhancing tumor with increasing ADC had slightly worse PFS (median PFS = 167 vs. 98 days); however, this was not statistically significant, . and Results also suggest patients with a large volume fraction **of pre-treatment** enhancing tumor with decreasing ADC at follow-up, had a slightly **shorter PFS**(median PFS =107vs.240 days), but this was also not statistically significant .A high volume fraction of increasing ADC **after therapy** was associated with shorter PFS, while a high volume fraction of decreasing ADC was associated with shorter OS.

Pope et al. 2009[42] they reported that using whole enhancing tumor ADC histograms , can demonstrated that in bevacizumab-treated group, those with less ADCL significantly had worse 6 months PFS versus greater values (HR, 4.1 (95% Cl: 1.6, 10.4), There was no significant difference in baseline ADC between both patients groups (P = .10). **Pope et al. 2012**[43] **They found that Low ADC-L was associated with worse survival.** The hazard ratios for 6-month PFS, overall PFS, and OS in patients with less versus greater than mean ADC-L were 3.1 (P = 0.001), 2.3 (P = 0.002), and 2.4 (P = 0.002), respectively. **Low ADC-L was associated with worse outcome.**

- Jain et al. 2010[44] They reported that change was significant for NEL ADC measurements at 3 months (P = 0.023) and strong trends at 6 weeks (P = 0.054) and 1year/last (P = 0.078) as compared to baseline despite the significant reduction in CELvol even for progressors during the same time period.

- Chenevert et al, 2000[45] One patient classified as stable disease and ADC map indicates a 10% increase in ADC 12 weeks from the start of therapy. During tumor regrowth, the mean ADC value declined dramatically. The second one showed a peak diffusion increase of 86% at 6 weeks and classified as responder. Clinical outcomes were classified as complete response , partial response , stable disease , and progressive disease .

- Chenevert et al. 2002[46] They mentioned that the sensitivity of DWI for detection of therapeutic-induced changes depends on the dynamic range, which can be observed by measurements of ADC. The early

ADC increase in is consistent with partial therapeutic response while nonresponsive tumor revealed no significant increase in diffusion values throughout the treatment protocol.

- **Crawford et al. 2009**[47] They showed that low 10th percentile ADC values were associated with poor survival

- **Mardor et al 2004**[48] pretreatment evaluated the clinical efficacy of DWI and high DWI, acquired up to b = 4000 sec/mm2 to amplify sensitivity to diffusion properties, . They found that lesions with low baseline ADC tend to significantly correlate with later therapy response better than those with higher values ($p<0.02$). There was a clear correlation between the volume of the lesions and their mean ADC values, up to a value of 2.4×10-3mm2/sec, where it plateaus. Viable tissues are associated with low water mobility;therefore, viable tumors appear dark on ADC and RD maps.

Moffat et al. 2005[49] **(2)** They noted that more tumor volume with increased ADC at three weeks of treatment were classified as PR by radiological assessment after completion of treatment. Values for fDM that predict PD patient were (VR=0.9%, VB=1.1% and VG=98.0%), SD patient (VR=2.7%, VB = 17.8%, and VG = 79.5%) revealing significant differences with 100% sensitivity and specificity to differentiate between these patients.

- **Ellingson et al. 2011a**[50] they reported the baseline, post-surgical, pre-chemotherapy ,Results indicate that the rate of change in fDMs is an early predictor of tumor progression, time to progression and overall survival with two types of treatments, suggesting the application of fDMs in FLAIR abnormal regions may be a significant advance in brain tumor biomarker technology. fDM Responders'' had a significantly longer survival compared to ''fDM Non-Responders''and fDM Responders'' had a significantly longer time to progression compared with ''fDM Non-Responders''

- **Mardor et al 2003**[51] They determined that all responding lesions showed increase in ADC values (1.2 ± 0.2) compared to nonresponding lesions (0.9 ± 0.1) with either no change or decrease. These changes in ADC measured one week after initiating treatment were correlated with later tumor response or no response ($P<.006$) determined by standard MRI seven weeks post-therapy. This correlation was increased to $P<.0006$ when high DWI was used.

- **Hamstra et al 2005**[52] (fDM), which were correlated with the radiographic response, time-to-progression (TTP), and overall survival (OS), The percentage of the tumor undergoing a significant change in the diffusion of water (V) was different between patients with progressive disease (PD) vs. stable disease (SD) ($P < 0.001$). Patients classified as PD by fDM analysis at 3 weeks were found to have a shorter TTP compared with SD (median TTP, 4.3 vs. 7.3 months; $P < 0.04$). By using fDM, early

patient stratification also was correlated with shorter OS in the PD group compared with SD patients (median survival, 8.0 vs. 18.2 months; $P <0.01$).

- **Hamstra et al. 2008** [53] investigated the role of fDM in predicting treatment response. They found that Three-week meanADC was associated with 1-year survival, with those exhibiting increased ADC (median=3.4%) compared with a decreased ADC (median, =1.5%) in those who died (P = .03) Their results demonstrated that the percentage of tumor with increasing diffusion (fDM-VI) was associated with survival one year from diagnosis. No correlation was found between survival and decreasing diffusion (VD) or sum of diffusion (VT).

- **Dessouky et al. 2010**[54] They reported at 3 weeks after initiation of therapy, the percentage of tumor volume with significant increase in diffusion (increase in ADC value) was the strongest predictor of treatment response than the changes in whole-tumor volume and mean ADC values determined at the same time point as compared to their pre-therapy values.

- **Ellingson et al. 2012**[55] By fDM study they suggesting patients exhibiting a large volume of tissue with decreased ADC are statistically more likely to have a short PFS and OS. They confirmed that pretreatment %ADC decrease >15% within contrast enhancing and > 20% within FLAIR regions was a statistically significant predictor of OS (Cox regression, hazard ratio =3.15; P= .0001) and PFS (Cox regression, hazard ratio = 2.63, P = .0003) respectively.

- **Lutz et al. 2014** [56] investigated whether ADC histogram analysis can differentiate between patients presenting T2-progress from those presenting stable T2-signal in glioblastoma.They found that 11 patients with a T2-progress presented a change of the tumor ADC distribution to lower ADC values and three patients to higher ADC (P =0.04). In contrast, there was no significant change on ADC histograms in the control group (P = 0.3).

- **Gutierrez et al. 2013**[57] They identified that the best fDM ratio to differentiate between responders and nonresponders (P = .01) was found using the fixed threshold of 0.4×10^{-3}mm2/s.

- **Tomura et al**. 2006[58] They noticed that nADC of the tumors was significantly greater at 2-4 weeks after STI (1.91 ± 1.67) than before STI (1.40 ± 0.99). There was a significant difference in the nADC at 2-4 weeks after STI between the responder (2.52 ± 1.93) and non-responder (1.00 ± 0.36) groups when evaluated later at 8-12 weeks after STI.

- Pope et al. 2011[59] They found a significant difference in PFS between low ADC tumors and high ADC tumors in bevacizumab-treated group (median, 459 versus 315 days; P=.008) and better OS though this was not quite statistically significant (P = .055). ADC values did not stratify PFS and OS in the control group.

- Mong et al. 2012[60] They found that mean ADC values were generally stable with time (mean, 5.2 ± 12.6% change from baseline). The volume of restricted diffusion increased by median of 23% from baseline by 6 months. Patients with restricted-diffusion lesions had significantly greater TTP (P=.013), TTS (P = .008), and OS (P = .010) than matched controls.

- Khayal et al 2010[61] They found that the percent change in the nADC from mid to post-RT showed significant differences between progressors and nonprogressors within CEL (P = .0221), NEL (P = .0192), and T2ALL (P = .0069). Significantly higher percent changes were observed within the CEL, NEL, and T2ALL for progressors (16%, 13%, and 14%) vs nonprogressors (4%, 3%, and 3%).

- Zhang et al. 2016[62] They found that median OS was 9.1 months (95% CI: 7.2–14.3). At the second post-bevacizumab scan, the volume of the low-ADC lesion (median: 12.94 cm3) was inversely associated with OS, with larger volumes predicting shorter OS (HR=1.014 [95% CI: 1.003–1.025], P=.009)

In a meta-analysis conducted **by - Zulfiqar et al. 2013[63]** They found that the mean survival rate below the respective ADC cutoff points (ranged $0.6\text{-}1\times10^{-3}$ mm2/s) was 22.7% and ADC value has an inverse relationship with malignant astrocytoma survival (Mantel-Haenszel odds ratio=12.441, p = 0.0001). Their results showed that the survival of WHO grade IV GBMs tumor with ADC below the cutoff was significantly poorer than above the ADC value (Mantel-Haenszel odds ratio= 6.690; p < 0.0001) and for WHO grade III anaplastic astrocytomas (Mantel-Haenszel odds ratio=23.204; p = 0.004)

Discussion :This review summarizes the results of studies investigated the role of diffusion imaging in the prediction and monitoring of various kinds of treatments of brain tumors. The review includes the results of 29 studies evaluating the predictive role of functional imaging (DWMRI) performed before, during or after treatment in brain tumor High values of ADC refer to water motion without restriction while low ADC values indicate a certain degree of restriction of water molecules motion. The factors affecting the b value (The diffusion sensitivity) are intensity, duration, and time interval between the diffusion-sensitizing gradients. A usual b-value used in clinical settings extends between 900 to 1000 s/mm2. The greater the b-value, the greater the sensitivity of the diffusion imaging is in obtaining better contrast and detecting spaces with restricted water motion. **[64]**

To apply fDM clinically, it is important to use and choose b-value properly. The National Cancer Institute Diffusion MRI Consensus Conference , [65] recommends to use three or more b-values (0,>100, and>500 s/mm2) for ADC to be estimated adequately. Unfortunately,the retrospective nature of the clinical trials used in this study makes its recommendations not implementable. multiple b values are utilized for additional precise quantification**. [66]** When multiple b values are used, the (TE) time , which is the highest of b, is usually constant for all values b for better estimation. **.[67]** The SNR of the sequence is grossly affected by the b value selection. When the b value is increased, the SNR of the sequence reduces and at very high values the SNR becomes very low so as to make the quantification unreliable. At the same time low b value will not generate an image whose contrast characteristics are truly based on diffusivity of water molecules. So optimal b value is a balance between the SNR required for quantification and the diffusion contrast of the image. So , diffusion-weighted imaging, which has become rather popular at 1.5T lately. [68] Unfortunately, many studies presented in this systematic review were performed retrospectively and so many of the consensus recommendations could not be implemented.

Functional imaging such as DWMRI have become more commonly used imaging technique as a diagnostic tool and in staging and follow up of brain tumors. It is increasingly aimed at further use this technique in individualizing the tumor treatment. There are a number of limitations facing the clinical trials studying the role of DWMRI in prediction of treatment outcomes before, during and after therapy. Of these limitations are inadequate sample sizes, conflicts in trails conclusions insufficient follow up and heterogeneous characteristics of studied cases. This modality is not available in all radiotherapy (RT) cenetrs, while FCT and FMR are available in most RT centers but they are not sufficient to RT plans.

Brain tumors follow up becomes increasingly complicated. Ordinary MR imaging is not very beneficial to monitor the treatment of this tumor. Drugs and radiotherapy may exert changes on BBB with subsequent effect on enhancement that could be misleading. [69] . Brain was the most commonly studied organ with DWI research owing to its immobility, homogeneity from the magnetic point of view and large ratios of signal to noise. [70] . The imaging protocol should {1} describe the tumor tissue, {2} pinpoint the tumor, {3} display the size of the tumor, and {4} identify if the tumor is malignant or not.

Response of solid tumor to treatment is monitored using the principle ‘‘response evaluation criteria in solid tumors’’, however an ideal method is yet to be developed. [71] Response to CNS cancer therapy is dependent on assessment of anatomical changes of the tumor size by CT or MRI, [72] these changes happen later than the physiological changes. In addition, the decrease in tumor size can be misleading and may be not

correlated with the response because of edema and necrosis. For the above reasons, functional imaging markers can play essential roles in the evaluation of response to therapy early in time. Examples on these markers changes in tumor metabolites, diffusion, or perfusion characteristics.[49] Using conventional CT and MRI in the evaluating the response of CNS tumors to treatment need about 6 weeks of treatment and another several weeks for follow up. [72] Taking into account the short survival periods of less than 52 weeks of these patients, the waiting time for evaluation using the conventional methods is very long. So From , **[35] (3)** ,[54] , **[53]** ,[52] , [49] **,[51]** , Diffusion-weighted imaging-MRI can be of crucial role to evaluate microstructural changes that happen within relatively short period of time. Radiological response approaches like T1W post contrast precedes changes in tumor size as an indication of tumor response to therapy and in period of time ranging (1day-3weeks) compared to (2- 10weeks).

DWI depict infarction post-surgically which could be misdiagnosed as recurrence of tumor where endothelial barrier disrupted resulting in contrast enhancing in the follow-up. The DWI signal and the equivalent ADC also reveal the microstructure of a tumor .[73] DWI has been studied in many clinical studies involving brain tumors because of the role of this modality to describe tumors of diverse varieties and to identify first signs of progression and to follow up treatment. The role of ADC values have been stated as valuable means in differentiating high-grade gliomas and edematous brain from normal tissue. [74] An significant drawback of Fmri studies is that the main result in some of the trials (8 of 29) was response to treatment rather than long term oncological results (e.g. LRFS, DFS, OS). More extensive studies in this field is required because the connection between tumour hypoxia and response to treatment has been well recognized in the literature for long time, and direct measurment of tumour oxygenation have been proven to relate to long-term survival. [75] However, DW-MRI trials conducted pre-treatment have been shown to be beneficial in predicting responses to therapy. Since DWMRI is not commonly used as part of the primary work-up in brain tumor (unlike another studies), this is probable to have influence on available data. Even though the predictive usefulness has been revealed in many clinical trials, fmri may be the finest imaging biomarker in serial evaluation due to no hazard of additional radiation exposure, compared to another modality. Prospective trials with reasonably larger sample sizes, homogeneous patient population , and similar primary treatments (PS or PRT) are still essential using the novel molecular measurement parameters before using these outcomes into broader clinical settings. To recognize poor or good responders during therapy, an important tumour response should be accomplished but enough time to perform adaptive therapy is also mandatory. Furthermore, most trials did not state important information necessary for evaluating the clinical usefulness of biomarkers such as hazard ratio/risk ratio/odds ratio with 95% confidence interval. This may be because of the small sample size of the trials table(4) .which commonly seen in clinical oncology and because The point estimate you choose depends on the "nature" of the outcome of interest like Binary Variables like response, progression, > 50% reduction in tumor size and Time-to-Event (Survival) Variables examples: time to progression, time to death, time to relapse , It is therefore very appropriate to use these point estimate, It is essential that all outcome endpoints are verified and negative associations are also published so that comparisons can be made. Due to these restrictions, results are controversial and interpretations are difficult. Therefore, a minimum group of features that should be stated in any trials assessing the prognostic/predictive usefulness were suggested so that comparisons can be made in future. These features include study type, patients characteristics, Tumour characteristics, Treatment, Follow up (in months), Outcome Endpoints, Methodology Results. In recurrence diseases , there are contradictory outcomes to some degree, where some trials showed an increase in ADC with necrosis and some showed that the therapy induced necrosis without reference to the value of the ADC and some indicated that necrosis can be a factor of the complexity of the measurement of the ADC particularly post-trenatmet, and this harmonious with trials which have suggested that the extent of necrosis within a GBM relates inversely with patient outcome and survival [21-23] , and another trial was incapable to show this association in their patient series [24]

(4)and [56] **(5)**The results of this trials cannot be accepted completely because of the inaccurate grading represents a risk for the patient, since it could lead to an unsuitable therapy . [76] So conventional histopathologic diagnosis has important restrictions: It is an invasive technique that has natural sampling error, particularly for difficult-to-access tumors candidate only to stereotactic biopsy, and incapability to estimate remaining tumor tissue after surgery . [77]

This review has some important limitations. Publication bias which need attention in systematic review where small studies with less favorable results tend to be less frequently published. Hence, overestimation of current positive findings is potential. The lack of uniformity among reviewed studies prevented us from performing a meta-analysis. Therefore, we chose to perform a systematic review of the selected studies and described observed findings instead of performing a meta-analysis that uses statistical tests. Variations in study objectives, treatment regimens, response assessment criteria, patient sample size and brain cancer subtypes precluded us from developing more specific conclusions. The population size of the majority of studies is

relatively small. Only five studies had a sample size more than 50 subjects and majority of the studies were single-center studies.

One of the major pitfalls of DWI is related to the intrinsic sensitivity of the technique to lesions containing high magnetic susceptibility such as blood products, calcium or metal, and bone or air. The susceptibility artifact caused by the paramagnetic or ferromagnetic material can cause spurious signal changes on MR image that simulate pathologic process such as infarct or abscess and hence the interpretation of diffusion-weighted images must be done by concomitant review of anatomic MR images. This is particularly true in the immediate postoperative state, when there is usually a combination of blood products and surgical material within the surgical bed that can cause prominent susceptibility artifacts on DWI. [78]

IV. Conclusion

In conclusion, significant clinical evaluations have been performed that support the hypothesis that DWI parameters are early surrogate biomarkers for brain tumor response and can stratify patients according to response and short and long term survival. Predicting the response based on fDM analysis may be applicable across many different primary brain tumors. Currently, most modern MRI machine have diffusion protocols as a standard part of their operation. The time required for diffusion scans would add only 30–60 sec to the standard MRI evaluation in addition to a single scan at three weeks after treatment. [52] In addition, fDM analysis offers the potential to evaluate different response between patients and the heterogeneity of response within an individual tumor allowing for tailoring therapy between patients or even within individuals

The result of this review encourages to incorporate DWI technique in routine brain tumor patient evaluations for response and survival as its acquisition is non- invasive, does not necessitate ionizing radiation in its application and does not require exogenous contrast agents, beside its quantitative approach that might be obtained relatively fast.

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