The Added Value of Diffusion Weighted MR Imaging for the Radiotherapy Treatment of Brain Tumors

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Abstract

The aim of this literature study is to investigate the added value of diffusion weighted MR imaging (DW-MRI) for the radiotherapy treatment of brain tumors. DW-MRI provides pathological information based on the mobility of water molecules. Because this technique provides different information than conventional anatomical MRI, it could be of added value in tasks where conventional MRI alone is not sufficient enough. DW-MRI can be used in different stages in the radiotherapy treatment process of brain tumors. This literature study discusses the added value of DW-MRI for delineation, prediction of therapy response and survival, and the discrimination between tumor recurrence and radiation injury. The literature shows a large variety of DW-MRI based measures to use in the different stages of therapy. DW-MRI could lead to more individual approaches and is able to predict therapy response in an early stage. However, DW-MRI is still in a exploratory stage and the literature does not only show consensus. This review will give an overview of recent results obtained with DW-MRI in the radiotherapy treatment process of brain tumors and will be concluded with a critical review of the added value of this advanced MR technique.

1. Introduction

Many advanced MR techniques, such as MR-spectroscopy, perfusion- and diffusion weighted MR imaging, have been developed in the last couple of years. An active field of research is to apply these new techniques to obtain functional information about the tumor characterization and tumor processes, which can lead to a better understanding of cancer. This information is different compared to the information obtained with the conventional MRI, which contains mostly anatomical information.

Diffusion weighted MR imaging (DW-MRI) has proven benefit within the diagnosis of brain pathologies and is therefore often included in diagnostic brain imaging protocols. However, it could also be beneficial for radiotherapy specific procedures such as delineating tumor volumes, predicting therapy response and survival, and differentiating between tumor recurrence and radiation injury. Because of the different aims in both application fields, the information needed during the radiotherapy treatment of brain tumors differs from the information needed for diagnosis. It will be interesting to know in which way the additional information obtained by DW-MRI contributes to the course of therapy.

The purpose of this literature study is to determine whether or not DW-MRI could be of an additional value within the different stages of the radiotherapy treatment process of brain tumors. The use of DW-MRI in those different stages will be discussed and critically reviewed. An early review about the role of DW-MRI (and perfusion MRI) in brain tumor characterization and assessment of treatment response has been conducted in 2006 by Provenzale *et al.* [1]. Their conclusion was that DW-MRI looked promising to get a better understanding of brain tumors and their response to treatment, but that the technique was still in a very preliminary stage. They also mentioned the lack of correlation between imaging and pathologic findings. It will be valuable to examine the development of DW-MRI since then and to determine what the status quo is of recent results obtained with DW-MRI in the radiotherapy treatment process of brain tumors. In this review we therefore revisit whether DW-MRI has an added value within the radiotherapy treatment process with the inclusion of histopathological findings.

1.1 Theory

DW-MRI provides information about the motion of water molecules. Typically, a pair of strong diffusion sensitive gradients is placed symmetrically around a refocusing pulse to measure the motion of water molecules. The higher the mobility of the molecules, the lower the remaining signal intensity. When the mobility is restricted, for example by cell membranes, the signal will be higher. The b-value summarizes the strength and duration of the used gradients and this determines the sensitivity to diffusion. The higher the b-

value, the stronger the diffusion weighting in the image. Typically used b-values are 1000 s/mm^2 and a b-value of 0 s/mm^2, which is similar to a T2-weighted image. To prevent long scan times a sequence based on echo planar imaging (EPI) is used, in which an entire slice is acquired after a single excitation. The water mobility is measured in at least three directions with DW-MRI to determine the diffusivity. An extended version of DW-MRI is called Diffusion Tensor Imaging (DTI), where the motion of water molecules is measured in at least six directions to be able to fill a tensor. In this way not only the diffusivity can be measured, but also the directionality of the motion. The diffusivity of water molecules in white matter will not be similar in every direction. The molecules have a preference to move along the tract instead of perpendicular to the tract (where the diffusion is more restricted). This phenomenon is summarized by the diffusion parameter Fractional Anisotropy (FA). Along with the FA, the Apparent Diffusion Coefficient (ADC) is used as a parameter to report the diffusion characteristics. The ADC describes the average diffusivity in all directions. The ADC determined by DW-MRI is considered to be mathematically equivalent to the mean diffusivity obtained with the use of DTI. By defining the diffusion parameters on a voxel-by-voxel basis, a parametric diffusion map can be created. To calculate these maps, the three eigenvalues (λ1, λ2 and λ3) of the eigenvectors from the measured tensor have to be determined. The maps can be calculated by using the following equations [2-**3**]:

$$MD = \frac{ADC_x + ADC_y + ADC_z}{3} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (1)$$

$$FA = \sqrt{\frac{2}{3}} \cdot \sqrt{\frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{\lambda_1^{\,2} + \lambda_2^{\,2} + \lambda_3^{\,2}}} \quad (2)$$

2. DW-MRI for delineation

Delineating the tumor to determine the target volume for radiation is the first and also a crucial step in the radiotherapy treatment process of brain tumors. What to irradiate is a difficult question. The tumor can be seen on conventional MR images, but the microscopic invasive tumor cells are not shown. Although the tumor can be determined with the use of different MR images such as T1-weighted contrast enhanced and T2-weighted images, there is still a lot of inter- and intra observer variation in delineating tumor tissue. In the literature can be seen that all kind of different advanced techniques are explored in order to reduce this uncertainty [1, 4-**6**]. Because of all the different methods used in recent studies, it can be concluded that there is no consensus yet on the best way to delineate the target volume for brain tumors. DW-MRI is one of the

advanced MR techniques, which is suggested to improve the delineation of tumor tissue [1,**6**].

In theory there is a difference in the mobility of water molecules in different tissues. Because of the variation in the water content within and around a tumor, due to variation in cellularity, necrosis and/or oedema, DW-MRI could provide additional information to the conventional MR images [1]. DW-MRI may therefore be helpful to differentiate between normal tissue and malignant tumor tissue. The molecules in tumors are more restricted, and the white matter tracts are more disrupted when malignant cells are present. Recent studies have shown a correlation between histology and diffusion parameters [**3,7**]. Different approaches are used within the literature to show this correlation, which indicates that a golden standard is not yet specified. Stadlbauer *et al.* have found a correlation between the diffusion parameters (FA and mean diffusivity) and the total cell number (CN), tumor cell number, and the ratio between those two histopathological parameters resulted in the percentage tumor infiltration. The mean diffusivity and the FA maps were calculated with the use of DTI [**3**]. For both FA and ADC, regression analysis showed a logarithmic correlation with total CN and with tumor CN. A linear relation was found between both diffusion parameters and the percentage tumor infiltration. FA showed a negative correlation with total CN (r = -0,802), tumor CN (r = -0,687) and tumor infiltration (r = -0,796). The relation found for ADC was positive and weaker than the correlation between FA and the histopathological findings. All correlations achieved statistical significance of $p < 0,001$ [**3**]. Another attempt to relate DW-MRI with existing biomarkers is done by a more physiologic approach, with the use of the Ki-67 labeling index. Ki-67 is a protein, which can be used as a marker for cell proliferation. The more malignant a tumor is, the higher the cell proliferation within the tumor and this results in a higher Ki-67 rate. A significant ($p < 0,001$) negative correlation for patients with malignant astrocytic tumors was found between minimum ADC and the Ki-67 labeling index with r = -0,562 [**7**].

Another group who's research is focussed on the differentiation between healthy and infiltrated tumor tissue is Price *et al.* [**6**]. This group uses measures derived from FA and diffusivity to characterize the tissue. The authors divided the diffusion into two components: the isotropic component, p, and the anisotropic component, q. These parameters are calculated by using the following equations, which deviate slightly from the commonly used ADC and FA: $p = \sqrt{3MD}$, and $q = \sqrt{(\lambda 1 - MD)^2 + (\lambda 2 - MD)^2 + (\lambda 3 - MD)^2}$ [**6**]. The diffusion parameters were compared between the affected side and the healthy side of the brain and validated with histopathological findings. 77 ROIs were examined in 20 patients. The performance of DTI to distinguish between normal, infiltrated and tumor tissue was compared with the performance of conventional MR images [**6**]. Both the isotropic and anisotropic

component were similar in normal tissue in both hemispheres. In infiltrated regions the isotropic component (p) was significantly increased, but the anisotropic component (q) did not change much compared to the contralateral hemisphere. For tumor tissue p had a marked increase, and q a marked decrease. These results are consistent with previous work of the same group [8]. Although one should note that the exact scaling of p and q is slightly different compared to the ADC and FA, the trend seen within the different regions is similar [**3,6**]. Distinguishing between the three different regions was done by classification thresholds [**6,**8]. Only the p and q values were used for discriminating between the different tissues, the mean FA values showed too much overlap to determine a proper threshold. DTI, T1- and T2- weighted images all misclassified one tumor region. However, DTI outperformed the other two techniques in the classification of the infiltrated region (1 misclassification vs. 8 and 9 misclassifications) [**6**]. This means that with the use of DTI the determination of tumor infiltration in peritumoral regions will improve.

Not only histopathology is used as classification to investigate the correlation with diffusion parameters. Classification based on conventional MRI is also used for this purpose [**9**]. ROIs were drawn within tumor tissue that enhanced on T1-weighted MRI, peri-enhancing brain tissue, which is represented by the hyper intense non-enhancing region seen on T2-weighted MRI, and within NAWM adjacent to the peri-enhancing region. The measured values within the ROIs were compared with values measured in mirrored ROIs at the non affected side of the brain. For the NAWM no statistical differences were found for both FA and ADC. In the peri-enhancing region significantly lower mean FA values were found in the affected side of the brain compared to the contralateral side ($p = 0,01$). For the same region the mean ADC values were significantly increased compared to the non affected side ($p < 0,01$). Within the tumor tissue the same trend was found; lower FA values and higher ADC values, with p-values of respectively $p < 0,001$ and $p < 0,01$ [**9**]. Stecco *et al.* also compared the diffusion parameters of a pre treatment scan with the values of a post treatment scan at the time of progression. The ROIs drawn in the enhancing tumor region at time of progression were divided into two groups: a group where the ROI was also enhanced on the pre treatment scan and a group where the ROI was not enhanced on the pre treatment scan. The same trend was acknowledged here: the ROIs, which were non enhancing at the pre treatment scan had significantly lower ADC values and higher FA values than the ROIs, which were already enhanced (and thus tumor) at the pre treatment scan. However, the non enhancing ROIs, which enhanced at time of progression had a significant higher ADC and lower FA than NAWM [**9**]. These results are consistent with the results found in other studies [**3,6-**8]. The reported values of the diffusion parameters in the different studies can be found in Table 1. The trend found in the behaviour of the diffusion parameters is also in consistency with the histopathological findings reported in a previously discussed study [**3**]; the larger the tumor infiltration,

the lower the FA and the higher the ADC. These results can be logically explained by the fact that tumor cells restrict the mobility of water molecules and they disrupt the white matter tracts. The parameters are also influenced by the presence of perilesional oedema, which results in the fact that these diffusion parameters alone cannot be used to determine tumor boundaries specifically [**9**].

Table 1: Reported values of diffusion parameters in different studies (mean ± SD) ADC x 10^{-3} mm^2/sec, FA: scalar value between 0 and 1

Study	# patients	Diffusion parameters	Tumor	Infiltrated	NAWM
Stadlbauer *et al*	20	Mean ADC	1,557 ± 0,353	-	0,826 ± 0,089
		Mean FA	0,179 ± 0,046	-	0,389 ± 0,046
Price *et al*	17	P ratio[1]	1,36 ± 0,71	1,32 ± 0,05	1,02 ± 0,02
		q ratio[1]	0,62 ± 0,04	1,18 ± 0,09	1,12 ± 0,06
		Mean FA ratio[1]	0,60 ± 0,06	0,86 ± 0,12	0,97 ± 0,06
Stecco *et al*	20	Mean ADC	1,46 ± 0,55	1,21 ± 0,31	0,99 ± 0,31
		Mean FA	0,24 ± 0,15	0,30 ± 0,16	0,45 ± 0,15

[1]: Ratio between values in affected hemisphere and unaffected hemisphere

For the validation of diffusion parameters based on histopathology one of the most important factors is the registration between the images to be sure that the locations are similar. The registration of the biopsy and the diffusion images is difficult because of distortions in the diffusion images due to susceptibility artefacts [1]. Multiple studies used fiducial skin markers for registration with the biopsy locations [**3,6**]. Besides the skin markers Stadlbauer *et al.* also averaged the diffusion parameters within a region around the determined location, to take into account small uncertainties [**3**]. No co-registration was used in the study performed by Stecco *et al*. [**9**].

Literature, which focuses on the more practical implementation of DW-MRI in the treatment planning of radiotherapy is not much present. A planning study with seven patients is done by Jena *et al.* They suggest to use an individually treatment region with the use of DW-MRI data [**10**]. The planning study was performed hypothetically to determine the possible gain in treatment. The patients were not treated based on the individual treatment regions determined by DW-MRI. Two different plans are generated for the included patients. The standard plan was acquired with an isotropic margin of 2.5 cm around the contrast enhanced Gross Target Volume (GTV) to create the Clinical Target Volume and was bound by the skull. The CTV margin is necessary to take into account the invisible microscopic invasive tumor cells in the surrounding area of the tumor. This standard plan is compared to a plan with individually created margins based on DTI. Thresholds based on the FA maps were used to discriminate between normal and infiltrated tissue. The area with sufficient lower FA was marked as the Image-Based high-risk volume (IHV) [**10**]. Around the IHV an extra margin is added to include

microscopic infiltrations, which cannot be seen on DTI, and this results in the individual CTV. In most patients the IHV did not extend beyond the standard CTV. The individualized CTV with extra security margin did extend beyond the standard CTV in some patients. This approach of creating planning target volumes resulted overall in smaller treatment volumes. The accepted dose to be given is highly restricted by the healthy tissue within the CTV of the standard planning techniques. With the use of individualized non uniform margins the planning target volume would be restricted around infiltrated tissue, and therefore the dose could be increased to get a similar Normal Tissue Complication Probability (NTCP). This dose escalation is most successful for patients with a small localized tumor. Although the dose escalation is not suitable for all patients, the IHV can be of added value to reduce the chance of relapse [**10**]. The group of Krishnan *et al.* examined the use of individually treatment regions with the use of tractography [11]. The reasoning behind the planning study of Jena *et al.* is very interesting, but it has to be noted that in the more recent years no other studies are performed with the same approach. DTI is not yet been clinically accepted for this kind of purposes, and although individualization of treatment volumes is a hot topic within the radiation treatment, there is still no consensus about how to incorporate it and with what kind of techniques. To be able to use these individual approaches clinically, large (costly) randomized trials will be necessary to validate the power of these methods.

3. DW-MRI to predict therapy response and survival

Treatment results can be determined by follow-up with clinical examination and conventional MRI after the completion of the therapy [12]. With the development of more advanced techniques, which can provide pathological information, the question arises if the treatment response and survival can already be predicted in an early stage of the treatment process. The advantage of being able to predict the response in an early phase is that the treatment plan may be adjusted during treatment when the current approach does not seem to work. Different DWI-based measures have been suggested to predict therapy response and survival in the literature. Minimal ADC-values [**7,13**], the average ADC value [14] and the functional diffusion map [**15-17**] are all used to examine the possibility of determining treatment response in an early stage. A comparison of all these different methods is made in the following sections.

3.1 Minimal ADC

As discussed before there is a correlation between the ADC and the cellularity of the tumor. The minimal ADC should therefore correspond to the area with the highest cell density and thus the region with the highest proliferation. This region should be

considered as most malignant area in the tumor and can therefore play an important role in the prognosis [**7,13**]. Two independent groups examined the prognostic value of the minimal ADC values in DW-MR images acquired before the start of the treatment. A correlation between two year follow up and pre treatment minimum ADC was found. Lower pre treatment minimum ADC resulted in poorer prognosis [**7,13**]. Based on follow-up findings of clinical examination and conventional MRI, two years after initial treatment, the patients were divided into two groups: stable and progressive disease. Minimal ADC values of 1,037 ± 0,196 and 0,800 ± 0,131 x 10^{-3} mm^2/sec (mean ± SD) were found respectively for the stable and the progressive group. The minimal ADC of the progressive group was therefore significantly lower ($p < 0,001$) than the minimal ADC of the stable group [**7**]. Receiver Operating Characteristic (ROC) analysis was used to determine the threshold, which was able to discriminate between the two groups. The determination of the best threshold is a process where a trade off between sensitivity and specificity has to be made. In this case the best threshold was defined as the threshold value, which maximized the sum of both measures. Discrimination between stable and progressive disease based on a threshold of 0,90 x 10^{-3} mm^2/sec, resulted in a sensitivity of 79% and a specificity of 81%. The outcome of the stable group, with a minimum ADC > 0,90 x 10^{-3} mm^2/sec, was also significantly better than that of the progressive group ($p = 0,002$) [**7**]. These results were confirmed by the research of Murakami *et al*. [**13**]. They used a threshold value of 1,0 x 10^{-3} mm^2/sec to investigate the correlation between the minimum ADC and the survival rate. The patients with a minimum ADC value of ≤ 1,0 x 10^{-3} mm^2/sec at the pre treatment scan had a two year survival of 14%, compared to a two year survival of 84% in the patients with a pre treatment minimum ADC > 1,0 x 10^{-3} mm^2/sec. The threshold value of 1,0 x 10^{-3} mm^2/sec was not determined by ROC analysis, but was chosen because all patients who died within one year had a minimal ADC value below that threshold [**13**].

In both studies the prognostic value of the minimal ADC was compared with other prognostic factors such as age, extent of surgery, performance status, and if the tumor is enhanced on a T1-weighted MR image or not. The minimum ADC was found to be the most important prognostic factor [**13**]. Only the ADC values within the tumoral region were used to determine the prognostic factor of pre treatment minimum ADC values. It would be possible that the peri-enhancing region around the tumor has an even stronger relation with prognosis because of the infiltration of microscopic tumor cells [**7**]. There are still some doubts nowadays about the underlying biophysical processes measured with minimal ADC [18], and therefore the technique is not yet accepted as clinical care by everyone.

The average pre treatment ADC is another DWI-based measure, which is considered to be predictive for treatment response [14]. Because of the different patient population (mostly metastases) and a different scanning protocol (0,5 T and no EPI), the results

cannot be compared directly, but it is interesting to see that the results are the opposite of the results obtained with the minimal ADC discussed earlier. An explanation for this phenomenon could be that when determining the average ADC over the whole tumor, the high ADC values of necrotic areas will influence the mean ADC of the tumor. Therefore highly necrotic tumors will have a higher pre treatment ADC. The study shows that the tumors with low pre treatment mean ADC values respond better to radiation therapy [14]. The influence of necrotic tissue on the ADC values could be reduced by excluding necrotic areas in determining the ROIs. Another aspect examined in the study of Mardor *et al.* is the use of higher b-values (4000 s/mm^2), but the results obtained by conventional and high b-values had a similar predictive value [14].

3.2 Functional diffusion map

When using the mean or minimal ADC values to predict response, the values are either averaged over a large volume or represent only a local area of the tumor. This means that the heterogeneity of a tumor is not taken into account with the use of these kind of methods. Therefore the research group of the university of Michigan introduced an alternative approach in which regional alterations in diffusion can be quantified: the functional diffusion map (fDM) [**15-16**]. With this approach the ADC change in the tumor is calculated between a pre treatment scan and a scan after the start of the therapy on a voxel-by-voxel basis. The fDM demonstrates the ADC changes between both scans by a colored overlay image. An increase in ADC is indicated in red, a decrease in ADC is indicated in blue and when no significant change was measured this was defined with the color green. After administration of therapy, different underlying biological processes can alter the ADC values. A successful treatment will lead to a lower cell density caused by necrosis and/or apoptosis. This tumor cell death will result in an increase in ADC. Cell swelling and reorganization of tissue can lead to a decrease in diffusion. Together with (hypoxic) cells, which are less radiosensitive, this leads to a very heterogeneous therapy response within the tumor [**15**].

Currently the radiological response criteria are used most often to define the treatment response of brain tumors and are also known as the Macdonald criteria. These criteria are determined by two-dimensional tumor measurements on CT/MRI and the use of steroids [12]. With the use of these criteria patients are divided into four categories: 1) complete response; all enhancement is disappeared and the use of steroids is stopped, 2) partial response; stable or decreased use of steroids and a deduction in tumor volume of more than 50% at least 4 weeks after the end of therapy, 3) progressive disease; the presence of any new lesion and/or an increase in tumor volume of more than 25%, and 4) stable disease; when a patient cannot be classified in the other three categories [12, **15**]. Although the Macdonald criteria are widely used in determining treatment response, there are some known limitations due to the fact that not only tumor tissue

can cause enhancement on T1-weighted images. Other limitations are the challenge to measure irregularly shaped tumors, and the observer dependency of the measurements [12]. Because of these limitations some updated response criteria are suggested. Wen *et al.* expect that when pathological techniques such as DW-MRI are more established they could be incorporated in the response criteria [12].

Multiple studies performed by the research group of the university of Michigan examined the use of the fDM for predicting the therapy response in an early stage of the treatment process [**15-17**]. Based on the pre treatment DW-MRI and a scan acquired within the radiotherapy treatment period, ADC changes were determined and fDMs were created within a manually defined tumor region. Tumor volume change may have happened in the time between scans, so only voxels which were assigned as tumor in both scans were used. All voxels within the tumor volume are represented in a scatter plot, where the ADC values of the mid treatment scan are shown as a function of the ADC values measured on the pre treatment scan [**15-17**]. An indication of the fDM analysis process is summarized in Figure 1.

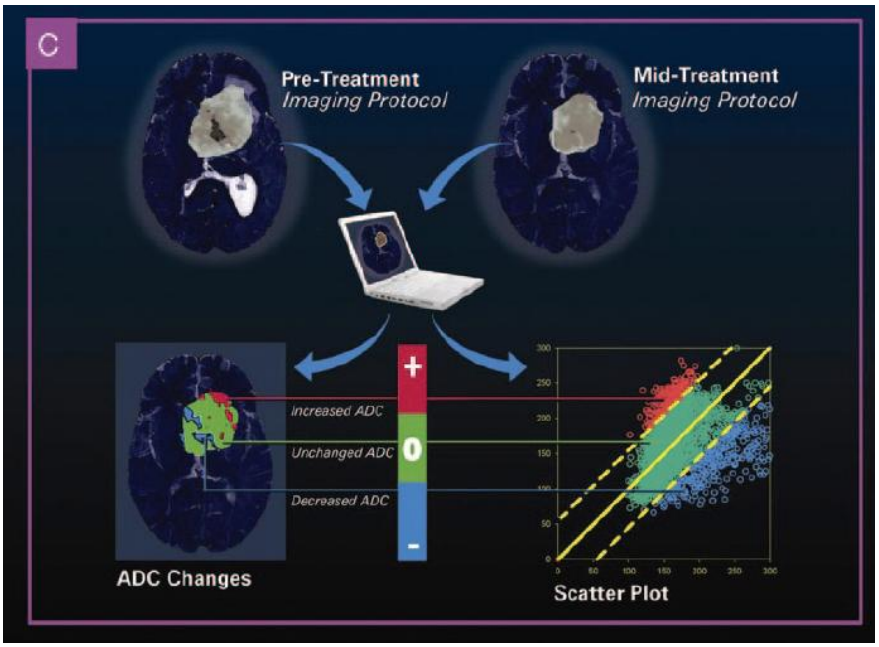

*Figure 1: Summary of the fDM analytical process. The ADC values of the mid treatment scan are compared with the pre treatment scan. All voxels within the tumor volumes can be represented in a scatter plot. Significant changes in ADC within these voxels are color coded; red = increase, blue = decrease and green = unchanged ADC. The figure originates from [**15**].*

All voxels with the same classification were added together to determine the volumes with increased and decreased ADC values. These volumes were normalized with the total tumor volume at the scan three weeks after start of therapy. The obtained fDM tumor volumes are: V_R (increased ADC), V_B (decreased ADC) and $V_{T,}$ which is the sum of

V_R and V_B and represents the total percentage of the tumor with significant change in ADC values [**15-16**].

First, the group of the University of Michigan focussed on the correlation between the fDM and the radiological response based on the Macdonald criteria. Significant differences in fDM volumes have been found for the different radiological response groups. The responding group had a significant higher volume of increased ADC than the stable and progressive group [**15,17**]. Whereas the progressive group showed the lowest total volume of changed ADC of all groups [**15-16**]. Additionally, ROC analysis was applied on a larger and more homogenous patient group, to refine the threshold value to differentiate between the different response groups [**16**]. The fDM was able to accurately predict progressive disease (as early as three weeks after start of treatment) with a V_T threshold value of ≤ 6,57% (sensitivity of 75% and specificity of 81%) [**16**]. Secondly, the research extended to be able to correlate the predictive ability of the fDM with overall survival and time-to-progression (TTP). The group, which was classified as progressive by fDM at three weeks after start of the treatment, turned out to have a shorter overall survival and TTP. The median overall survival and TTP were respectively 8,2 and 4,3 months for the progressive group, and for the non progressive group 18,2 and 7,3 months [**16**]. These results are confirmed in a later study, where a threshold value of 4,7% for V_R turned out to be a significant predictor of one year survival ($p < 0,001$) [**17**]. However, it has to be noted that a different fDM volume is used for the classification of progressive disease, compared to earlier work (V_R vs. V_T) [**15-17**]. This discrepancy is a result of the fact that the correlation found between radiological response and decreasing ADC values in earlier work [**15-16**], could not be confirmed by the results of the later study, which used the one year survival as an end point [**17**]. To test the predictive value of the fDM three weeks after start of treatment, the performance of the fDM was compared with other techniques and prognostic factors. ROC analysis revealed that the fDM was a better predictor for radiological response and survival than either the mean ADC, Cross Diameter Product (CDP), or tumor volume at the same time point [**16-17**]. In addition, the fDM also outperformed other prognostic factors such as age, tumor location, pathologic grade and surgical extent in the prediction of overall survival. For the TTP only the pathologic grade and the fDM were predictive [**16**].

One of the main reasons to investigate a technique such as the fDM, is the ability to predict survival in an early stage in the treatment process. To get insight in the predictive power of the fDM during treatment, Hamstra *et al.* examined the usefulness of the fDM at different time points (1,3 and 10 weeks after start of therapy) [**17**]. A comparison between these time points showed that the fDM performs best at three weeks after the start of therapy. A similar trend can be seen for the change in mean ADC, where the strongest correlation with survival was also found at the scan acquired

three weeks after start of treatment [**17**]. At that time point, higher ADC values were reported for the patients with a more favourable prognosis [**17,19**]. The research of Kayal *et al.* did not focus on the fDM, but examined the behaviour of multiple parameters (e.g. volume change, normalized ADC and normalized FA) at different time points. A comparison between progressive and non progressive patients revealed that the difference between both groups is most distinct in the period between the mid- and post treatment scan for the percentage change of all parameters [**19**]. This result is remarkable to see, since the scan during treatment is currently not typically performed. Together with the previously described correlation between the fDM, based on the scan three weeks after start of therapy, and overall survival this could be an indication that a DW-MRI during the treatment may be of clinical use for the assessment of therapy response.

Another method, which showed significant correlation with survival was the use of Macdonald criteria at 10 weeks after the start of therapy. This means that both fDM and the radiological response correlate with the overall survival. The advantage of fDM is that it can be determined in an earlier stage in the treatment process. Using a combination of both techniques in the prediction of overall survival resulted in the most robust predictive method [**17**].

It has to be noted that the fDM is not usable when the residual tumor is smaller than 4 cc in the postoperative scans [**17**]. This is due to the fact that a large tissue shift can occur when only a small tumor cavity is left after surgery. This phenomenon makes coregistration of image voxels over time very difficult and challenging. The study of Kayal *et al.* confirmed the importance of this threshold [**19**]. Their whole patient population had a residual cavity at or below the threshold value of 4 cc. When using the fDM they did not find any significant differences between progressive and non progressive patients [**19**].

The results reported about the fDM are mostly investigated by researchers of the same group at the University of Michigan and therefore the experiments were done with an overlapping group of patients. A standard threshold of $0{,}55 \times 10^{-3}$ mm^2/sec was used to determine if the ADC change was significant. This threshold value was based on the 95% coincidence interval of the ADC values of normal white and gray matter determined on three different scans of five patients [**15-17]**. This threshold was chosen without comprehensive examination. An independent study of Ellingston *et al.* investigated some of the assumptions, which has been made with the use of the fDM [**20**]. The authors found a significant correlation between ADC measurements and cellularity, which is consistent with the findings of previously discussed studies [**3,6-**8]. To examine if the fDMs are influenced by the normal variation of ADC values over time, the ADC values were measured in different tissue types at different time points. No significant

correlation among the time between the DW-MRI scans and the change in ADC could be found. This finding indicates that the fDM does not change over time [**20**]. Furthermore, the influence of different threshold values to determine whether or not the ADC has changed significantly was verified. With the use of 95% coincidence interval analysis different thresholds were determined for a variation of tissue mixtures based on the ADC values of 69 patients. Subsequently five different thresholds (the standard used threshold of 0,55 x 10^{-3} mm^2/sec included) were used to create fDMs of 33 patients to examine the influence of the different threshold values on the predictive value of tumor progression. With ROC analysis no statistical differences in the AUC values could be found between the different threshold values. Because of the slightly better AUC score, a threshold value of 0,4 x 10^{-3} mm^2/sec is preferred by the authors. All threshold values were able to discriminate between progressive and stable disease and performed better than chance **[20]**. These findings indicate that the outcome of the fDM analysis will not be influenced by the threshold chosen for significant increase/decrease.

4. DW-MRI to differentiate between tumor recurrence and radiation injury

When treating brain tumors with radiation therapy, not only tumor cells will be irradiated, but also healthy tissue. The radiation dose given on healthy tissue causes radiation effects in the normal brain tissue. The examination of these radiation effects is challenging because the radiation effect will not be similar for every patient. Radiation injuries, which can occur within three months after the start of the therapy are pseudo progression and treatment necrosis. Pseudo progression imitates progression, but those patients recover spontaneously without any treatment [21]. It is important to be able to differentiate between radiation injury and progressive disease because the treatment strategies of both phenomena deviate a lot. Discriminate pseudo progression and treatment necrosis from tumor recurrence is very difficult because these processes all appear the same on conventional MRI. This is also one of the limitations of the widely used Macdonald criteria. Therefore is in the updated response criteria proposed to only classify a new enhancing lesion within three months as tumor recurrence when the enhancement is outside the radiation field, or if histological examination confirms it to be tumor tissue [12]. The current gold standard for discrimination between tumor recurrence and radiation injury is to take a biopsy. However, this is an invasive method with unnecessary risks for patients who might not have a recurrent tumor. Hence the use of a non invasive approach would be preferred. Since DW-MRI is a non invasive technique, which provides different information than conventional MRI, the use of this technique for discrimination between tumor recurrence and radiation injury is examined by multiple groups [**22-26**].

To differentiate between radiation injury and recurrent tumor tissue the minimal, maximal and mean ADC could be used. When using a combination of all these three measures, the heterogeneity of the enhanced lesion can be taken into account [**22**]. Based on histopathology and/or clinical follow up, the patients are divided into two groups: radiation injury or tumor recurrence. Comparing the diffusion parameters for both groups, a significantly lower maximal ADC was found in the tumor recurrence group. The mean ADC was also lower for this group, but that did not reach significance. No notable difference between radiation injury and tumor recurrence was found for the minimal ADC values [**22**]. However, the trend of having a lower average ADC value in the tumor recurrence group did reach significance in other studies [**23-**24]. Xu *et al.* examined multiple diffusion parameters obtained with DTI. The average ADC and FA values were not only measured within the contrast enhancing lesion, but also within peri-enhancing oedema. With the use of the values measured within NAWM in the contralateral hemisphere a ratio for ADC and FA was determined as follows: value lesion/normal value [**23**]. The ADC ratio of the lesion showed a similar correlation as the mean ADC, and thus was lower for the recurrence group [**23-**24]. The mean FA and FA ratio on the other hand were both significantly lower for the radiation injury group, with p-values of 0,0025 and 0,0015, respectively. The measured FA values of the recurrent group were lower than those measured in NAWM [**23**]. These results indicate that necrotic tissue has a larger impact on the disruption of white matter tracts than the presence of a recurrent tumor has. These results suggest that FA can be used for discriminating between both patient groups. None of the measured diffusion parameters determined within oedema showed significant differences between both groups. This indicates that the peri-enhancing region is not useful for the discrimination between radiation injury and recurrence. ROC analysis was applied to the ADC and FA ratios to determine the best diagnostic threshold value for the differentiation between both groups. Both ratios were able to accurately differentiate between the two groups, with an AUC of 0,86 and 0,85 respectively for the ADC and FA ratio. The best diagnostic threshold based on the ADC ratio was 1,65. For the FA ratio the best determined threshold was 0,85. Either threshold was able to accurately classify, 30 out of 35 patients. This means that the diagnostic classification accuracy was 85,7%. Based on either the ADC or the FA ratio recurrence could be diagnosed with a sensitivity of 85% and a specificity of 86.7% [**23**]. Approaches, which make use of a combination of MR-spectroscopy and DW-MRI to discriminate between radiation injury and tumor recurrence are recommended [24].

Most results reported in the literature are consistent with the theory that tumor tissue restricts the diffusion of the water molecules and will therefore have lower ADC values than the necrotic tissue [**22-**24]. However, the literature does not only show consensus about the diffusion parameters. Opposite correlations are reported by Sundgren *et al.* [**25**]. They found significant higher mean ADC values in the recurrence group than in the

radiation injury group. The ADC ratio showed a trend of higher values in the recurrence group, but that did not reach significance. And where Xu *et al.* reported significant lower FA values in the case of tumor recurrence [**23**], Sundgren *et al.* did not found significant differences in FA values within the contrast enhanced lesion between both groups. It has to be noted that Sundgren *et al.* did found significant (p = 0,03) higher FA ratios in the NAWM of the radiation injury group (0,89 ± 0,15) compared to the recurrence group (0,74 ± 0,14) [**25**]. The trend of the diffusion parameters in the peri-enhancing lesion area reported by Sundgren *et al.* is opposite to the trend observed in the study of Xu *et al.*, but in both studies the results did not reach significance. This confirms the suggestion that the peri-enhancing region is not suitable for distinguishing between recurrence and radiation injury. The absolute values of the diffusion parameters (within the contrast enhanced lesion) reported in the discussed studies and their levels of significance (p-values) are listed in Table 2.

*Table 2: Absolute values of diffusion parameters of the enhanced lesion in different studies (mean ± SD) ACD: x $10^{-3}mm^2$/sec, FA: scalar value between 0 and 1, significance is marked with *.*

Study	# patients	Diffusion parameters	Tumor Recurrence	Radiation injury	p-value
Asao *et al.*	17	minimal ADC	1,07 ± 0,18	1,04 ± 0,31	> 0,05
		maximal ADC	1,68 ± 0,37	2,30 ± 0,73	0,0398 *
		mean ADC	1,37 ± 0,25	1,68 ± 0,46	> 0,05
Xu *et al.*	35	mean ADC	1,23 ± 0,20	1,54 ± 0,17	0,0002 *
		ADC ratio[1]	1,34 ± 0,15	1,62 ± 0,17	0,0013 *
		mean FA	0,24 ± 0,05	0,14 ± 0,03	0,0025 *
		FA ratio[1]	0,45 ± 0,03	0,32 ± 0,03	0,0015 *
Zeng *et al.*	55	mean ADC	1,20 ± 0,08	1,39 ± 0,09	< 0,01 *
		ADC ratio[1]	1,42 ± 0,10	1,69 ± 0,08	< 0,01 *
Sundgren *et al.*	28	mean ADC	1,27 ± 0,15	1,12 ± 0,14	0,01 *
		ADC ratio[1]	1,54 ± 0,23	1,40 ± 0,26	0,07
		mean FA	0,15 ± 0,05	0,17 ± 0,04	0,13
		FA ratio[1]	0,55 ± 0,17	0,52 ± 0,19	0,55

[1]: Ratio between values in affected hemisphere and unaffected hemisphere

There are various possible reasons for the discrepancy between the results of the different studies: 1) the manual placing of the ROIs to measure the values of the diffusion parameters. As discussed before the values of ADC and FA can vary between tissue types, and could therefore be influenced by the location of the placed ROI [**20**]. When necrotic tissue is included in the ROI, this will elevate the ADC values and could therefore also cause discrepancy between results. Sundgren *et al.* mentioned explicitly that the necrotic tissue was excluded from ROIs [**25**]. Although mentioned less explicitly, Xu *et al.* also used ROIs with avoidance of necrotic tissue [**23**]. So albeit the methodology of drawing/placing the ROIs could lead to discrepancies between studies, the inclusion

of necrotic tissue in ROIs would not be the most obvious reason for discrepancy in this case. 2) The small cohort of patients in each study. This results in the fact that the patient population is very important for the results. Different tumor types (high/low grade) can result in different ADC/FA values and can therefore cause deviations among different studies. 3) The therapy received can make a huge difference. 4) The large variety of follow-up times. The DW-MRI scans were in all studies made after initial identification of the enhancing lesion or during follow-up, which means that along the patient group the scans were made at different time points. Although there is a large variation in all discussed studies, the range reported by Sundgren *et al.* is rather large (5-120 months) compared to for example the range mentioned by Xu *et al.* (6-52 months). Finally, 5) Sundgren *et al.* reported that the new enhanced lesion on average occurred later for the recurrence group (57,5 months) than for the radiation injury group (17,7 months) [**25**].

With the use of DTI Nagesh *et al.* investigated the dependency between the diffusion parameters and the scanning moment within the treatment process in patients with radiation injury [**26**]. DTI scans were acquired before the start of the radiotherapy treatment and at 5 different time points in the period of 3-45 months after the start of radiation. A significant time dependency for both mean diffusivity and FA was found. The mean diffusivity showed a linearly increase over time and the FA values showed a linearly decrease over time [**26**]. Different linear temporal relationships for different tissue types (genu and splenium) were reported, which leads to the conclusion that the radiation effects are heterogeneous within the brain [**26**]. The time dependency curves of mean diffusivity and FA in two different tissue types is shown in Figure 2.

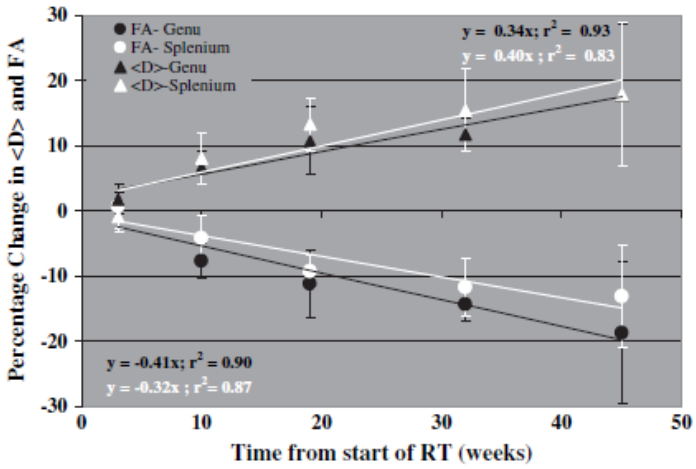

*Figure 2: Time dependency curves of FA and mean diffusivity within two different tissue types (genu and splenium). The figure originates from [**26**].*

The results based on diffusion eigenvalue analysis, where the parallel component is sensitive for axonal injury and the perpendicular component is sensitive for demyelination, suggest that radiation injury exists mainly of demyelination. The authors also suggest that the diffusion parameters are dependent on the given dose [**26**].

Pre treatment DTI scans could also be used to predict different recurrence patterns [27]. The pre treatment DTI scans were used to determine abnormalities in diffusion and anisotropy. Regions were determined based on these abnormalities and were used as an overlay on scans obtained at time of recurrence. When the abnormal diffusion area exceeds the abnormal anisotropy area in all directions with more than 0,5 cm, it could be indicated as a diffuse recurrence pattern. If the abnormal diffusion area only exceeds the abnormal anisotropy area along one direction, it would most likely develop as a local recurrence pattern. When both abnormal areas are quite similar this could be an indication of a minimal recurrence pattern [27]. Prediction of these different recurrence patterns could lead to a more individual treatment approach [**10,** 27].

5. Discussion and conclusion

Various approaches to use DW-MRI within the radiotherapy treatment of brain tumors are suggested in the literature. DW-MRI could be used for three different tasks during the treatment process: delineation, prediction of therapy response and survival, and to differentiate between radiation injury and tumor recurrence. The DW-MR images are currently implemented in the diagnostic radiological brain imaging protocol to obtain additional pathological information, but those images are not yet integrated in the radiotherapy process. It is remarkable to see that a broad variety of DWI-based measures are used within the different studies. This indicates that the underlying biophysical processes measured with DW-MRI are not fully understood yet, and that there is no consensus about what the most important DWI-based markers are. In general, the discussed research results were obtained with a small number of patients. Studies based on a larger cohort of patients are necessary to be able to ensure the additional value of DW-MRI in the different stages of the radiotherapy treatment.

Provenzale *et al.* mentioned in an earlier review the lack of correlation between histopathological findings and imaging results [1]. In the more recent studies, discussed within the current review, this correlation is more present. Within the literature there is consensus about the correlation between the diffusion parameters and malignant tumor cells. The higher the cellularity, the higher the ADC and the more disrupted the white matter tracts, the lower the FA. Despite this consensus a lot of factors could influence these parameters, such as necrosis and oedema. The absolute values of the diffusion parameters are variable when different scanning protocols and scanners are used, and

are even diverse between different tissue- and tumor types. This makes the comparison of the results between studies more difficult. Most literature focussed on the grading and the characterization of the tumor type, which is useful in diagnosing tumors, but that is a passed stage when radiotherapy is already the treatment of choice. An advantage of using additional DW-MRI for delineation of the tumor is that, as opposed to conventional MRI, infiltrated areas can be shown. This can lead to a more individual approach of defining a non uniform target volume for radiation. In this way you could extend the target volume to areas at high risk of recurrence. Although there is more interest in individualizing target volumes in the last couple of years, it requires a long-term research process with a large amount of patients to validate the strength of using these kind of individual approaches. It has to be noted that very little (recent) data exist on how to best implement DW-MRI into the delineation of the target volume. This could indicate that DW-MRI might not be the preferred method for this task.

A correlation has been found between DW-MRI and treatment response and survival. An advantage of the use of DW-MRI for this purpose is that it is possible to predict treatment response and survival in an early stage of the treatment process. Even as early as pre treatment measurements could give an indication of the course of the treatment. This could again lead to a more individual approach and the treatment plan could then be adapted when no response is expected based on the measurements. In the literature a variation of approaches are suggested for the prediction of tumor response. There is no consensus yet on which ADC measurement represents the tumor the best. The question arises whether the minimum, median, mean, or maximal ADC gives the most realistic representation of the tumor characteristics. The different approaches used makes comparison of results challenging. The introduction of the fDM allows to show the heterogeneity of the tumor. Although this method shows some promising results in the early prediction of response, there are also some drawbacks for this technique. First, the registration of images over time can be very challenging because of deformations within the brain during treatment. Therefore you cannot be absolutely sure that you compare the same tissue at both scans. Because of the coarse resolution of DW-MRI voxels and the large tissue shift in the brain after surgical intervention, the fDM is not suitable for patients with a smaller residual tumor than 4 cc. Secondly, the research on fDM is mostly done by one group, and their results are based on an overlapping patient group [**15-17**]. Another group showed that the results obtained with fDM are independent of the chosen threshold value for significant increase/decrease [**20**]. However, it is remarkable to see that even with an overlapping patient group no consistent threshold value could be determined for the discrimination between progressive and stable disease. There was also an inconsistency in the methodology used, since different fDM volumes were found best for the discrimination between groups in all studies [**15-17**]. So despite the promising opportunities of being

able to predict treatment response in an early stage, some drawbacks has to be overcome before it can be used in clinical practice.

The differentiation between radiation injury and tumor recurrence cannot be made with conventional MRI because both pathologies appear the same on T1- and T2-weighted images. There is a difference in water mobility between both pathologies and therefore DW-MRI is able to discriminate between both patient groups. Although most reported results are consistent, there are also opposite results presented. Because of these ambiguities, more comprehensive research has to be done to get a better understanding of the correlation between the diffusion parameters and the presence of tumor recurrence or radiation injury.

Future research should focus on the validation of the findings so far with a larger cohort of patients. Multi-institutional studies could be of added value because the diffusion parameters are dependent on multiple factors and the approach used in studies deviates a lot, which makes it difficult to compare the results of different studies. Hopefully this multi-institutional approach with a large number of patients will lead to consensus. Most studies published so far are done retrospectively. Therefore more prospective studies are warranted to get a better insight in the possibilities of DW-MRI within the radiotherapy treatment process. Taking all literature in consideration, we think DW-MRI has the least potential for delineation. The development of diffusion based target volumes has stagnated. Whereas the use of DW-MRI in predicting therapy response and survival, and its use in discriminating between tumor recurrence and radiation injury has been further developed in the last couple of years.

In conclusion, DW-MRI is able to obtain additional information within the radiotherapy treatment process of brain tumors compared to conventional MRI. The use of pathological information (obtained by DW-MRI) looks promising due to the fact that it is a non invasive technique that can be used for tasks, which are not feasible with conventional MRI. Because the two modalities generate different information, the DW-MRI may be used as additional information, but it will not totally replace the conventional MRI during treatment. DW-MRI can be used in early stages of the treatment process and this may lead to more individual treatment approaches. However, DW-MRI is still in a very exploratory stage, and comprehensive prospective research in a multi-institutional setting with a large number of patients will be necessary to get consensus and to validate the findings so far.

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