Investigation of the diffusion abnormality index as a new imaging biomarker for early assessment of brain tumor response to radiation therapy

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This work was in part presented at the 2nd Cancer Imaging and Radiation Therapy Symposium, February 8–9, Orlando, FL.

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Background. Diffusion MRI, although having the potential to be a biomarker for early assessment of tumor response to therapy, could be confounded by edema and necrosis in or near the brain tumors. This study aimed to develop and investigate the ability of the diffusion abnormality index (DAI) to be a new imaging biomarker for early assessment of brain metastasis response to radiation therapy (RT).

Methods. Patients with either radiosensitive or radioresistant brain metastases that were treated by whole brain RT alone or combined with bortezomib as a radiation sensitizer had diffusion-weighted (DW) MRI pre-RT and 2 weeks (2W) after starting RT. A patient-specific diffusion abnormality probability function (DAProF) was created to account for abnormal low and high apparent diffusion coefficients differently, reflecting respective high cellularity and edema/necrosis. The DAI of a lesion was then calculated by the integral of DAProF-weighted tumor apparent diffusion coefficient histogram. The changes in DAI from pre-RT to 2W were evaluated for differentiating the responsive, stable, and progressive tumors and compared with the changes in gross tumor volume and conventional diffusion metrics during the same time interval.

Results. In lesions treated with whole brain RT, the DAI performed the best among all metrics in predicting the posttreatment response of brain metastases to RT. In lesions treated with whole brain RT + bortezomib, although DAI was the best predictor, the performance of all metrics worsened compared with the first group.

Conclusions. The ability of DAI for early assessment of brain metastasis response to RT depends upon treatment regimes.

Keywords: cancer, diffusion abnormality index, DW-MRI, imaging biomarker.

Diffusion-weighted (DW) MRI has been shown to be an imaging biomarker for assessing tumor aggressiveness and early response to therapy in various cancers.1 The DW-MRI acquisition is rapid and noninvasive and uses neither exogenous contrast agent nor ionizing radiation. The apparent diffusion coefficient (ADC), quantified from DW-MRI, measures water mobility in tissue and is sensitive to cellular density, extracellular space tortuosity, and intactness of cellular membranes.1,2 However, quantification of an ADC change in the tumor is still a challenge and affects sensitivity and specificity of diffusion indices for early prediction of tumor response to therapy, mainly because the ADCs in a tumor manifest a heterogeneous distribution pattern,3,4 due to spatial variation in cellular density, cell structure, and water content. In a high cellular region, mobility of water molecules is restricted, and thus the ADC is low, while in a region with necrosis or edema, water molecules move more freely and hence the ADC is high. Animal studies have shown that the ADC in a tumor is inversely correlated with tumor cellularity.3 When a tumor responds to treatment, the ADC in the high cellular region could increase due to cell shrinkage followed by phagocytosis or necrosis.5 Also, the ADC in the edema region could decrease due to drainage of water as cells move into the region.6 Hence, the direction of the change depends upon where the ADC is measured and what the original value of the ADC is. Therefore, the heterogeneity in the tumor ADCs and the complex changes that occur after treatment suggest that a change in the mean ADC of a tumor may be a poor indicator for therapy response.
So far, several methodologies have been proposed to quantify the ADC changes in tumors, beyond a change in the mean ADC of a tumor, for response assessment. Functional diffusion mapping (fDM),3–7 probably the most common approach, measures the voxel-to-voxel interval changes in a pair of the coregistered ADC images acquired before and after the start of therapy. The voxels with an ADC change above a threshold are considered as a measure of response. Despite the promising results of the fDM-based approach and its modifications,8 the issue of voxel-to-voxel misregistration, particularly in the region where a tumor volume shrinks or grows during the interval of measurements, is not solved yet. Also, since the decrease/increase in regions of high cellularity or edema could have different interpretations, it is important to consider the initial ADC values to interpret subsequent changes correctly. Alternatively, analysis of the tumor ADC histogram has been proposed. A binormal distribution mixture model has shown that the mean value of the low-ADC distribution can predict therapy response in gliomas.9–11 Also, changes in mean, skewness, and kurtosis of the ADC histogram or the minimum value of the ADC in tumors have been related to survival and treatment outcome.12–20 However, these methods have not considered changes in the whole ADC histogram, including both regions with high cellularity and edema, in which each of a change could reflect a part of the process of a tumor response to therapy and therefore may lead to losing information from the analyses. Hence, it is highly desirable to develop a new methodology for quantifying the tumor ADCs to improve the performance of DW-MRI for therapy assessment.

In this study, we aim to develop a diffusion abnormality index (DAI) to quantify the extent of diffusion abnormality of brain metastases compared with normal tissue for early prediction of tumor response to radiation therapy (RT). Brain metastases are the most prevalent form of intracranial cancer, exceeding the number of primary brain tumors and occurring in approximately 25% of all cancer patients.21 In our proposed approach, we assigned an abnormal diffusion probability to each voxel of the tumor based upon its ADC value relating to the normal tissue ADC distribution. Then, a DAI of the tumor is obtained by summing all the abnormal probabilities within the lesion. We tested whether an early change in the DAI could predict response of brain metastases in the patients who were treated by either whole brain radiation therapy (WBRT) alone or in combination with bortezomib as a radiation sensitizer.

**Materials and Methods**

**Patients**

Twenty-four patients who had brain metastases and were treated by WBRT were enrolled in an institutional review board–approved prospective MRI study (12 women and 12 men, ages 40–76 y; Table 1). Histology included melanoma (n = 14), non–small cell lung cancer (n = 6), renal cell carcinoma (n = 1), breast cancer (n = 2), and head and neck squamous cell carcinoma (n = 1). All patients received WBRT with a total dose of 30 Gy (16 patients) or 37.5 Gy (8 patients). Thirteen patients (the majority with melanoma metastases) participated in a phase II clinical trial and received...
bortezomib during WBRT as a radiation sensitizer. Each lesion was analyzed individually due to the intrapatient heterogeneous lesion response to therapy. If a patient had 3 metastases or fewer, all lesions were included. If a patient had more than 3 lesions, only the 3 largest lesions were analyzed. If a patient had more than 3 lesions larger than 0.5 cm³, all lesions larger than 0.5 cm³ were included. As a result, a total of 67 metastatic lesions were included in our dataset, of which 28 were treated with RT alone and the remaining lesions were treated with RT in combination with bortezomib as a radiation sensitizer.

**Image Acquisition and Preprocessing**

All patients had research MRI scans on a Philips 3T scanner prior to RT (Pre-RT), 2 weeks after the start of RT (2W), and 1 month after the completion of treatment (1M post-RT). After that, patients were followed up based upon clinical indication. Research MRI scans included pre- and post- gadoxetate disodium (Gd) diethylenetriamine pentaacetic acid volumetric T1-weighted images, 2D T2-weighted images, and diffusion-sensitive images. The DW images were acquired using a spin-echo echo-planar imaging sequence (resolution time/echo time $= 2636/46$ msec) with $b_0 = 0$, and diffusion weighting along 3 orthogonal directions, and $b_1 = 1000$ s/mm² to calculate the ADC images.

Using an in-house software package, all ADC images were coregistered to pre-RT post-Gd T1-weighted images by rigid transformation and mutual information to have a voxel size of $0.94 \times 0.94 \times 3$ mm³. After each lesion of interest was contoured by a radiation oncologist on the post-Gd T1-weighted images obtained Pre-RT, 2W, and 1M post-RT, the tumor volumes were transferred onto the ADC maps obtained at the same time point. For each patient, a volume of 3–4 cc of normal white matter or cerebellum tissue, depending upon the location of the tumor of interest, was also contoured on the pre-RT post-Gd T1-weighted images and transferred onto the Pre-RT ADC map to obtain a distribution of normal ADCs.

**ADC Image Analysis Framework**

**Histogram of ADCs in a tumor**

To analyze the ADC distribution in a tumor and a subsequent change during treatment, a histogram of ADCs in a lesion measured at each time point was generated with 150 evenly spaced bins that cover the ADCs of all lesions of interest. The ADC histogram, $H(ADC = x)$, of a lesion is calculated as:

$$H(ADC = x) = n_i : x - \epsilon \leq ADC_i \leq x + \epsilon$$  \hspace{1cm} (1)

where $n_i$ is the number of voxels within $[ADC_i; x] < \epsilon$, and $\epsilon = \sigma/4$, a smooth factor of $H$, where $\sigma$ is a standard deviation of the ADC distribution in the tumor. Then, the ADC histogram of each lesion at each scan is normalized to have an area under the histogram equal to one ($\int H(x)dx = 1$). The ADC histogram of normal tissue ($H_{\text{norm}}(ADC)$) is calculated in a similar fashion except that the peak is normalized to one (Fig. 1A). Compared with the normally distributed ADC histogram of normal tissue, the ADC histogram of a tumor spreads widely and is skewed and/or shifted (Fig. 1A).

**Diffusion abnormality probability function**

Next, we developed a diffusion abnormality probability function (DAProF) to characterize the whole tumor ADC histogram based upon the normal tissue ADC distribution of each patient. The $H_{\text{norm}}(ADC)$ divides the tumor ADC histogram into 3 segments with low, normal, and high ADCs (Fig. 1). The first and last are related to high cellular density and edema + necrosis, respectively. Therefore, for each patient, a DAProF can be defined as $1 - H_{\text{norm}}(ADC)$, and filtered by a Kaiser band-pass filter at the center of the peak of $H_{\text{norm}}(ADC)$ to reduce noise influence in the computation at 2 tails where the ADC approaches positive or negative infinity (or zero) as:

$$DA \text{ProF} = BPF \cdot (1 - H_{\text{norm}}(ADC))$$ \hspace{1cm} (2)

Equation (2) denotes that the tumor ADCs are abnormal except in the areas where the ADC values are in the range of those of normal tissue. In Eq. (2), 90% of the confidence interval of $H_{\text{norm}}(ADC)$ is used to define the bandwidth of the band-pass filter. Considering that changes in the low-ADC (high cellularity) tumor region could be associated with therapy response differently, a weighting factor $\alpha (< 1)$ is used to weight low and high ADC contributions unequally in the DAProF as:

$$DA \text{ProF} = \begin{cases} \text{DAProF}_{\text{low}} = BPF \cdot (1 - H_{\text{norm}}(ADC)) & \text{ADC} \leq ADC_{\text{norm}} \\
\alpha \cdot BPF \cdot (1 - H_{\text{norm}}(ADC)) & \text{ADC} > ADC_{\text{norm}} \end{cases}$$ \hspace{1cm} (3)

where $ADC_{\text{norm}}$ is the ADC at the peak of the normal tissue histogram. Finally, the DAProF is normalized to one at the peak. Note that DAProF$_{\text{norm}}$ is patient specific.

**Diffusion abnormality index**

To quantify the extent of diffusion abnormality in a tumor at a specific scan time ($\tau$), the DAI is defined as:

$$DAI_{\tau}(\tau) = GTV_{\tau} \cdot \int H_{\tau}(x) \text{DAProF}_{\tau}(x)dx$$ \hspace{1cm} (4)
where GTV, and \( H(x) \) denote the gross tumor volume (GTV) and the normalized tumor ADC histogram at time \( \tau \), respectively. As a result, the DAI is a summation of diffusion abnormality from all voxels of a tumor. It is worthwhile to note that the DAI is minimum for normal tissue. A low or high ADC abnormality index can also be obtained by replacing \( \hat{D}AProF_{\alpha} \) by \( \hat{D}AProF_{\text{high}} \) or \( \hat{D}AProF_{\text{high}} \) in Eq. (4). Finally, a change in the DAI from Pre-RT to 2W is calculated as:

\[
\Delta \text{DAI}_{\text{pre} \rightarrow 2w} = \frac{\text{DAI}_{\text{pre} \rightarrow 2w} - \text{DAI}_{\text{pre}}}{\text{DAI}_{\text{pre}}} \times 100
\]

(5)

In response to therapy, the ADCs in the region with high cellularity may increase due to cell shrinkage or necrosis, and the region of edema may decrease due to the drainage of water as cells move into the region. However, Eq. (5) combines the 2 contributions into a single metric for assessing tumor response to a specific therapy regimen.

**Evaluation**

**DAI for Prediction of Response**

**Endpoint**

Considering that there are no standard and validated criteria for treatment response in brain metastases, we adopted the criteria proposed by Lin et al.\(^{22}\) to define the responsive, stable, and progressive lesions. In the Lin study, the patients had brain scans every 8 weeks. Objective response was defined as either complete response or >50% reduction in the volumetric sum of all measurable CNS lesions. Progressive disease was defined as >40% increase in the volumetric sum of all evaluable CNS lesions. In our study, clinical MRI follow-up scans after 1M post-RT were not available for all patients due to short survival time of some patients. However, for the patients for whom the brain scans were available, there was a good correlation between the tumor volume change at 1M and 3M post-RT \((\Delta \text{GTV}_{\text{pre} \rightarrow 3M \text{-post} = 1.23 \times \Delta \text{GTV}_{\text{pre} \rightarrow 1M \text{-post}}, \ r = 0.64)\). Also, the previous studies indicate that brain metastases exhibit little pseudo-response and pseudo-progression 1M post-RT.\(^{23}\) We used our data and verified that there was little pseudo-response or pseudo-progression in brain metastases treated by either WBRT alone or WBRT with bortezomib. Hence, a percentage change in GTV from Pre-RT to 1M post-RT, \( \Delta \text{GTV}_{\text{pre} \rightarrow 1M \text{-post}} \), was used as a measure of tumor response to therapy. However, given that the volumetric changes were measured 4 weeks after the completion of treatment (instead of every 8 wk by Lin et al.\(^{23}\)), we scaled the tumor volume change 1M post-RT by a factor of 1.23 from the Lin' definitions. Also, we considered each lesion individually because we assessed individual lesion response to RT. Therefore, from Pre-RT to 1M post-RT, of the 28 lesions treated with RT alone, 15 had a decrease in GTV larger than 40%, defined as responsive; 7 had an increase in GTV larger than 32%, defined as progressive; and the remaining 6 were defined as stable. For the 39 lesions treated by RT in combination with bortezomib, 7 lesions were responsive, 11 lesions were progressive, and 21 lesions were stable by applying the same criteria.

**Predictive model**

First, we optimized \( \alpha (<1) \) in \( \Delta \text{DAI}_{\text{pre} \rightarrow 2w} \) in each treatment group by maximizing the group difference between the responsive and progressive lesions using the Mann–Whitney U-test. If multiple \( \alpha \) produced similar P-values, we chose \( \alpha \) with the best differentiation between the responsive and stable groups. Using the optimal value of \( \alpha \), we further tested whether \( \Delta \text{DAI}_{\text{pre} \rightarrow 2w} \) could differentiate responsive from stable tumors, and stable from progressive tumors in both treatment groups. \( P < .05 \) was considered significant. Next, we tested sensitivity and specificity of \( \Delta \text{DAI}_{\text{pre} \rightarrow 2w} \) for its predictive value in classifying the responsive, stable, and progressive lesions by receiver operating characteristic (ROC) analysis (ROCKET software).\(^{24} \) Also, we compared the performance of \( \Delta \text{DAI} \) for predicting posttreatment response with the ADC metrics previously published by others, such as a mean of the low ADC distribution from the binormal ADC distribution mixture model\(^9–11\) and skewness and kurtosis of tumor ADC histograms,\(^{13} \) and conventional metrics, such as a percentage change in GTV, pretreatment minimum ADC, a minimum ADC change, and a change in the mean of tumor ADCs from Pre-RT to 2W. The significant differences of the areas under the ROC curves (AUCs) among the metrics were compared by t-test, for which the standard errors and the difference between the 2 AUCs were calculated by the method proposed by DeLong et al.\(^{25} \) We also used the leave-one-out technique to measure the prediction risk of \( \Delta \text{DAI} \).

**Results**

**Association of DAI With Response**

The best separation of the group difference between the responsive and progressive tumors resulted in \( \alpha \) values of 0.7 and 0.2 for lesions treated with RT alone and in combination with bortezomib as a radiation sensitizer, respectively, suggesting that decreases in abnormality associated with high ADCs (edema/necrosis) may have different roles in response assessment, depending on the treatment regimen and tumor type. For lesions treated with RT alone, as anticipated, the DAI showed a significantly greater decrease from Pre-RT to 2W in the responsive tumors than the progressive ones (\( P < .0002 \), but also the stable lesions (\( P < .0003 \)) or the nonresponsive tumors (including both progressive and stable; \( P < .0004 \); Table 2). For the volumetric change observed during the same period, the percentage decrease in GTV in the responsive group differed significantly from the stable group (\( P < .02 \)), the progressive group (\( P < .0002 \)), and the group of combined progressive and stable tumors (\( P < .0002 \)). For the metrics that are often found in literature, their performances for differentiation of responsive, stable, and progressive lesions are summarized in Table 2. As seen, skewness and kurtosis were able to differentiate between the responsive and progressive lesions, but worse than the percentage changes in the GTV and DAI for the RT-alone group. The mean of the low ADC distribution determined from the binormal Gaussian mixture model could not differentiate the responsive tumors from progressive or stable ones.

For the lesions treated with RT combined with bortezomib, the DAI change from Pre-RT to 2W was still able to differentiate between the responsive and progressive lesions (\( P < .03 \)), but not between the responsive and stable lesions (Table 3). However, the performance of DAI worsened for the lesions treated by RT + bortezomib compared with the first group, also evidenced by several overlaps between responsive, stable, and progressive lesions (Fig. 2E). However, other commonly used diffusion metrics could not differentiate the responsive from progressive groups.
Finally, Fig. 2 shows the box plots of the significant metrics ($\Delta$DAI, $\Delta$GT, $\Delta$Skewness, and $\Delta$Kurtosis) listed in Tables 2 and 3 for responsive, stable, and progressive lesions treated with RT alone or in combination with bortezomib.

### Discussion

In this study, we developed a diffusion abnormality index based upon diffusion-weighted MRI to study the potentials of DW-MRI for early assessment of brain metastasis response to radiation therapy. The development of the DAI considers underlying physiology of abnormal ADCs in a tumor, including high cellularity and edema. The DAI weights the abnormal ADC contributions from high cellularity and edema. The DAI weights the abnormal ADC contributions from high cellularity and edema differently for predication of therapy response. We evaluated the performance of the DAI in patients who had brain metastases and were treated by either WBRT alone (mostly radiation-sensitive lesions) or in combination with bortezomib as a radiation sensitizer (radiation-resistant lesions). Compared with other ADC metrics published previously and conventional metrics, the DAI showed a greater potential in prediction of the volumetric response of brain metastases to RT. However, it also revealed that the diffusion-based metrics alone may have limited power for prediction of response in certain treatment regimens. Also, our

### Performance of the DAI for Prediction of Response

We evaluated the performance of $\Delta$DAI for prediction of responsive or progressive tumors post-RT as well as the metrics proposed by others and reached significance or marginal significance in Tables 2 and 3, such as $\Delta$GT, $\Delta$Skewness, and $\Delta$Kurtosis. The AUC and SEMs are summarized in Table 4. For WBRT alone, DAI could predict responsive lesions from stable and progressive ones, or progressive lesions from stable and responsive ones with an AUC of 0.96 or greater. However, for WBRT + bortezomib, the performance of DAI was worsened as well as the other diffusion metrics tested, indicating that the sensitivity of DW-MRI for response assessment varies with treatment regimens. As an example, for the lesions treated with RT alone, the ROC analysis showed that the AUCs for prediction of responsive lesions were 0.96 ± 0.03 (±SEM), 0.92 ± 0.05, 0.75 ± 0.09, and 0.73 ± 0.09 for $\Delta$DAI, $\Delta$GT, $\Delta$Skewness, and $\Delta$Kurtosis, respectively (Fig. 3). A pairwise comparison of the ROCs of the 2 metrics revealed that $\Delta$DAI is a better predictor, but not significantly, than $\Delta$GT ($P < .15$). For 92% sensitivity, $\Delta$DAI achieved 87% and 73% specificity, respectively. In addition, the leave-one-out analysis resulted in $\alpha = 0.698 ± 0.009$(SEM) for the lesions treated by RT alone, and $\alpha = 0.186 ± 0.04$ for the tumors treated by combining RT with bortezomib, indicating that there is no significant bias in the $\alpha$ value selection and that $\alpha$ is a treatment-specific parameter in the DAI. Finally, exclusion of melanoma metastases from the first treatment group resulted in an AUC of 0.93 ± 0.08, indicating that the results from the first group are not predominated by the 2 melanoma cases.

### DAProF Map

Examples of maps of the ADC and the DAProF for a responsive lesion with RT alone and a progressive one treated with RT + bortezomib at Pre-RT and 2W are shown in Fig. 4. From Pre-RT to 2W, the DAI decreased ~31% for the responsive lesion but increased ~75% for the progressive one. For the responsive lesion, the low and high ADC components in the DAI decreased ~65% and 21%, respectively. For the progressive lesion, the low ADC component in the DAI increased 411% but the high ADC component decreased 20%.

### Table 2: Association of the different diffusion metrics with response in lesions treated by WBRT alone

<table>
<thead>
<tr>
<th>Metric (Pre-RT to 2W)</th>
<th>Lesion Response Groups</th>
<th>R &amp; S vs P</th>
<th>R vs S &amp; P</th>
<th>R vs S</th>
<th>S vs P</th>
<th>R vs P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$DAI&lt;sub&gt;0.7&lt;/sub&gt;</td>
<td>.0001</td>
<td>.0004</td>
<td>.003</td>
<td>.001</td>
<td>.0002</td>
<td></td>
</tr>
<tr>
<td>$\Delta$GT</td>
<td>.0001</td>
<td>.0002</td>
<td>.02</td>
<td>.001</td>
<td>.0002</td>
<td></td>
</tr>
<tr>
<td>$\Delta$Skewness</td>
<td>.05</td>
<td>.027</td>
<td>.23</td>
<td>.53</td>
<td>.024</td>
<td></td>
</tr>
<tr>
<td>$\Delta$Kurtosis</td>
<td>.043</td>
<td>.042</td>
<td>.33</td>
<td>.36</td>
<td>.028</td>
<td></td>
</tr>
<tr>
<td>$\mu$</td>
<td>.83</td>
<td>.40</td>
<td>.33</td>
<td>.94</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>$\Delta$MinADC</td>
<td>.33</td>
<td>.89</td>
<td>.33</td>
<td>.23</td>
<td>.52</td>
<td></td>
</tr>
<tr>
<td>MinADC&lt;sub&gt;preRT&lt;/sub&gt;</td>
<td>.91</td>
<td>.81</td>
<td>.84</td>
<td>1</td>
<td>.88</td>
<td></td>
</tr>
<tr>
<td>$\Delta$Low-ADC (BNGM)</td>
<td>1</td>
<td>.11</td>
<td>.04</td>
<td>.29</td>
<td>.62</td>
<td></td>
</tr>
<tr>
<td>Low-ADC&lt;sub&gt;preRT&lt;/sub&gt; (BNGM)</td>
<td>.16</td>
<td>.35</td>
<td>.96</td>
<td>.36</td>
<td>.18</td>
<td></td>
</tr>
</tbody>
</table>

The group differences between responsive (R), stable (S), and progressive (P) tumors treated with RT. For each metric, the absolute or percentage change from Pre-RT to 2W were evaluated and the best performance is reported. $\Delta$ change from Pre-RT to 2W; $\mu$ mean of tumor ADC; Min; minimum; Low-ADC (BNGM), the mean of the low ADC distribution in the binormal Gaussian mixture model<sup>9–11</sup>; kurtosis: intervoxel ADC kurtosis.

### Table 3: Association of the different diffusion metrics with response in radiosensitive lesions treated by WBRT + bortezomib as a radiation sensitizer

<table>
<thead>
<tr>
<th>Metric (Pre-RT to 2W)</th>
<th>Lesion Response Groups</th>
<th>R &amp; S vs P</th>
<th>R vs S &amp; P</th>
<th>R vs S</th>
<th>S vs P</th>
<th>R vs P</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$DAI&lt;sub&gt;0.2&lt;/sub&gt;</td>
<td>.0005</td>
<td>.52</td>
<td>.79</td>
<td>.0005</td>
<td>.034</td>
<td></td>
</tr>
<tr>
<td>$\Delta$GT</td>
<td>.0105</td>
<td>.86</td>
<td>.63</td>
<td>.0074</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>$\Delta$Skewness</td>
<td>.21</td>
<td>.78</td>
<td>.36</td>
<td>.23</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>$\Delta$Kurtosis</td>
<td>.35</td>
<td>.84</td>
<td>.67</td>
<td>.28</td>
<td>.86</td>
<td></td>
</tr>
<tr>
<td>$\mu$</td>
<td>.98</td>
<td>.62</td>
<td>.59</td>
<td>.93</td>
<td>.79</td>
<td></td>
</tr>
<tr>
<td>$\Delta$Min</td>
<td>.67</td>
<td>.36</td>
<td>.42</td>
<td>.87</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>Min&lt;sub&gt;preRT&lt;/sub&gt;</td>
<td>.98</td>
<td>.89</td>
<td>.91</td>
<td>.93</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>$\Delta$Low-ADC (BNGM)</td>
<td>.60</td>
<td>.72</td>
<td>.71</td>
<td>.57</td>
<td>.86</td>
<td></td>
</tr>
<tr>
<td>Low-ADC&lt;sub&gt;preRT&lt;/sub&gt; (BNGM)</td>
<td>.96</td>
<td>.57</td>
<td>.49</td>
<td>.87</td>
<td>.86</td>
<td></td>
</tr>
</tbody>
</table>

The group differences between responsive (R), stable (S), and progressive (P) tumors treated with RT. For each metric, the absolute or percentage change from Pre-RT to 2W were evaluated and the best performance is reported. $\Delta$ change from Pre-RT to 2W; $\mu$ mean of tumor ADC; Min; minimum; Low-ADC (BNGM) = the mean of the low ADC distribution in the binormal Gaussian mixture model<sup>9–11</sup>; kurtosis: intervoxel ADC kurtosis.
results indicate that the diffusion-related physiological change in the tumor may occur earlier than the morphological change in response to RT. The DAI developed and tested in this study could also be applied to other tumor types and treatment regimens after recalibration, such as glioblastoma and head and neck cancers and anti-angiogenesis therapy. The DAI has the potential

Table 4. The results of the ROC analysis of the significant metrics shown in Tables 2 and 3

<table>
<thead>
<tr>
<th>Metric (Pre-RT to 2W)</th>
<th>Lesion Response Groups</th>
<th>AUC ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R &amp; S vs P</td>
<td>R vs S &amp; P</td>
</tr>
<tr>
<td>WBRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔDAI₀.7</td>
<td>1 ± 0.0</td>
<td>0.96 ± 0.03</td>
</tr>
<tr>
<td>ΔGTV</td>
<td>1 ± 0.0</td>
<td>0.92 ± 0.05</td>
</tr>
<tr>
<td>ΔSkewness</td>
<td>0.74 ± 0.11</td>
<td>0.75 ± 0.09</td>
</tr>
<tr>
<td>ΔKurtosis</td>
<td>0.75 ± 0.11</td>
<td>0.73 ± 0.09</td>
</tr>
<tr>
<td>WBRT + Btz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔDAI₀.2</td>
<td>0.86 ± 0.07</td>
<td>0.55 ± 0.11</td>
</tr>
<tr>
<td>ΔGTV</td>
<td>0.77 ± 0.09</td>
<td>0.52 ± 0.12</td>
</tr>
<tr>
<td>ΔSkewness</td>
<td>0.58 ± 0.09</td>
<td>0.53 ± 0.12</td>
</tr>
<tr>
<td>ΔKurtosis</td>
<td>0.64 ± 0.09</td>
<td>0.51 ± 0.12</td>
</tr>
</tbody>
</table>

For each metric, the area under the ROC curve in distinguishing the corresponding groups of lesions are calculated and presented. Abbreviations: Δ, change from Pre-RT to 2W; Btz, bortezomib; R, responsive; S, stable; P, progressive.

Fig. 2. Box plots of ΔDAI (A and E), ΔGTV (B and F), ΔSkewness (C and G), and ΔKurtosis (D and H) for responsive, stable, and progressive lesions treated by WBRT alone (top) or in combination with bortezomib as a radiation sensitizer (bottom). The top row shows that ΔGTV and ΔDAI₀.7 differentiate the responsive lesions from the stable and progressive ones treated by WBRT, while ΔDAI₀.2 differentiates the responsive and stable lesions from the progressive ones when bortezomib is used as a radiation sensitizer.
to be a robust imaging biomarker to extract response-related information from DW-MRI for early assessment of tumor response and therapy outcome.

In the development of the DAI, we found that the weighting factor, $\alpha$, is different for different treatments and tumor types. For instance, when brain metastases were treated with WBRT alone, the changes in abnormality associated with high ADCs contributed substantially to response assessment. In this case, both a decrease in cellularity and a decrease in edema could indicate treatment response. However, in the treatment of melanoma metastases to the brain by the combination of RT and bortezomib, we realized that a decrease in abnormality associated with high ADCs is less important for response assessment. Also, we found that the performances of all tested ADC metrics, including the DAI, were worse in the latter group than in the first group. This could be due to the effect of bortezomib on the lesion.\textsuperscript{26,27} Since bortezomib could alter vascular properties of the tumor, a change in vascular characteristics of the tumor could also be an important part of tumor response to therapy, and hence a perfusion change could be added into the DAI to improve the response assessment.

Whether different brain metastasis pathologies affect the predictive ability of the DAI for therapy response needs to be further investigated. It seems that the results from the first group did not

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Example of ROC curves of $\Delta$DAI, $\Delta$GTV, $\Delta$Skewness, and $\Delta$Kurtosis for predicting nonresponsive tumors (including both stable and progressive tumors) treated with radiation therapy alone.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Example of changes in tumor cellularity map in a responsive and a progressive lesion. T1-weighted images at Pre-RT and 2W (top rows), ADC maps at Pre-RT and 2W (middle rows), and maps of diffusion abnormality probability functions at Pre-RT and 2W (bottom rows) for a responsive and a progressive lesion. The images of a responsive case (with a volume of 3.7 cc) are shown in 2 left columns and the images of a progressive one (with a volume of 4.1 cc) are shown in 2 right columns. From Pre-RT to 2W, the DAI decreased $\sim 31\%$ for the responsive lesion and increased $\sim 75\%$ for the progressive one. For the responsive lesion, treated by RT alone, $\alpha = 0.7$, but for the progressive lesion where bortezomib was used, $\alpha = 0.2$.}
\end{figure}
change with or without the 2 melanoma cases. The DAI could be extended to assess other treatments on other tumors. For an anti-angiogenesis treatment of a brain tumor, such as glioblastoma, a high ADC abnormality reduction indicates the treatment effect on the abnormal leaky vasculature, but a low ADC abnormality decrease suggests the effect on the tumor. This hypothesis will be tested in the future.

The DAI proposed in this study has several advantages in comparison with FDM. The most common approach in the study of ADC maps. Foremost, the DAI does not rely on voxel-to-voxel image registration accuracy, which the FDM-based analysis depends solely upon. Hence, anatomical alteration of a tumor after starting therapy—for instance, a change in edema, surgical cavity, and/or tumor growth or shrinkage—does not have an adverse effect on the DAI. In addition, we incorporate the tumor volume into the DAI, and thus a change in DAI represents both physiological and morphological changes in a tumor, which could increase the sensitivity of the DAI for tumor response to therapy. Furthermore, the FDM-based analysis only considers an absolute change in the ADC, regardless of the origin of the ADC, whereas an increase or a decrease in the low or high ADC region has a very different underlying implication. An ADC increase in the region with abnormal low diffusion and a decrease in the region with abnormal high diffusion both are positive indications for a tumor response to therapy, thereby accounted for in the DAI. Also, it is important to point out that although a change in the DAI of a tumor does not depend upon voxel-level accuracy of registration of images acquired before and after the start of therapy, spatial information of diffusion abnormality of a tumor is available at any given measurement (Fig. 4), which could be used for visualization or provide guidance for intensified treatment.

The DAI has also several advantages in comparison with other histogram-based approaches. In some of these techniques, only the low-ADC portion of the tumor histogram is used for therapy assessment. We have shown that a reduction in the abnormal high ADC in the edema region is also an important indicator for response prediction. Hence, combining the changes in both abnormal low and high ADC regions has the potential to produce a better predictor for assessing response to various treatments. The indices based upon the skewness and kurtosis of the tumor ADC histogram neglect diffusion physiology in a tumor and may not be able to capture the complex change patterns in a heterogeneous tumor for response assessment. Also, in the development of the DAI, we used the ADC histogram in a region of interest of either normal white matter or cerebellum to define the DAProF. Most regions of interest were on the contralateral side of the lesion under study. The optimal control ADC histogram could be further studied in future work.

One very important point regarding our study is to use GTV change as the endpoint in evaluation of response of brain metastases to RT. Currently, none of the standard response criteria, such as Response Evaluation Criteria In Solid Tumors, World Health Organization, Macdonald, Revised Assessment in Neuro-Oncology, have been validated for assessment of brain metastasis response to RT. Hence, development of standard criteria in evaluation of response assessment tools for brain metastases is an urgent need but is beyond the scope of this study. Overall survival is the most important endpoint in testing any anticancer drugs in phase III trials. However, control of brain metastases, which is the goal of RT, may or may not be translated into improvement of overall survival, depending upon the control of active extracranial diseases. The latter is frequently coexistent with intracranial diseases. Our primary goal in this study was to develop a means of early assessment of the individual response of brain metastases to RT as a local treatment regimen. Currently, WBRT and stereotactic radiosurgery are 2 routine treatments for brain metastases. Patients who have noncontrolled intracranial cancers have poorer survival. A recent study has shown that WBRT produces a decrease in neurocognitive status compared with stereotactic radiosurgery. Therefore, more and more patients are receiving focal treatment for brain metastases. As WBRT is being done less, more patients are developing new lesions after treatment of the initial lesions, and thus are being treated to new lesions over time. Thus, the need for developing a tool for early assessment of the brain metastasis response to therapy will become more and more important as patients receive more and more focal treatment. However, the DAI needs to be further validated using an independent dataset. The DAI could be extended to other tumor types, such as glioblastoma, for early assessment of tumor response to therapy.

Funding
This work was supported by grants R01 NS064973 and R21 CA113699 from the National Institutes of Health.

Conflict of interest statement. None declared.

References


