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Assessment of stereotactic radiosurgery treatment response for brain metastases using MRI based diffusion index

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ABSTRACT

Introduction: To investigate the clinical predictive values of the apparent diffusion coefficient (ADC) as a biomarker in radiation response of brain metastases.

Method: Forty-one patients with brain metastases treated with stereotactic radiosurgery (SRS) were imaged at baseline, one month post SRS, and six months post SRS using diffusion weighted MRI. The mean of ADC for metastases and tumor volume was calculated. A diffusion index (DI) was generated using the sum of 1/ADC among all the voxels in a tumor. Tumor response status was determined by lesion volume measured at six month post-SRS, or the last available follow-up MRI. Logistic regression analysis was used to account for factors associated with tumor response at baseline and one month post SRS.

Results: A higher ADC mean distinguished responders from non-responders only at six month post SRS ($p < 0.05$). However, a lower DI distinguished a responder from non-responders on the baseline, one month post SRS and six months post SRS, indicating better diagnostic performance of the DI with regard to a non-invasive biomarker in monitoring SRS treatment response. A multivariate logistic regression analysis identified the DI as a predictor of tumor response at baseline and one month post SRS ($p = 0.002$ and $p = 0.001$, respectively). However, logistic regression analysis identified the ADC mean as a predictor of tumor response only at six months post SRS ($p = 0.019$).

Conclusion: Our results support the hypothesis that ADC and tumor volume generated DT at baseline, one month and six months post SRS may be a promising biomarker predicting brain metastases' response. Specifically, a lower DI at baseline and one month distinguished responders from non-responders.

1. Introduction

Brain metastases, the main cause of death for cancer patients, are common among malignant tumors in adults with an incident rate of up to 30% [1,2]. The main treatment options for brain metastases include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and/or surgical resection [3–5]. High radiation energy leads to tumor cell necrosis, while lower radiation energy leads to chromosome cleavage, organelle damage, as well as restraining cell division. This also has the secondary effect of tumor vascular endothelial cell hyperplasia, vascular wall thickening, and hyaline degeneration, followed by thrombosis and vascular occlusion [6,7]. SRS has several advantages over other treatment options for brain metastases and it is becoming the preferred treatment choice for brain metastases. One of the major advantages of SRS is a minimally invasive outpatient procedure with no significant recovery time. In addition, compared with WBRT, SRS provides more potent biologic doses of radiation, which may be beneficial, especially in tumor types considered to be radioresistant. Furthermore, potential neurologic toxicities associated with WBRT may be avoided with SRS. Currently, the candidacy for SRS is largely determined by the number of metastases and the best evidence for SRS is in patients with less than three to four lesions [1,8].

The evaluation of tumor response to radiotherapy depends mainly on morphological changes (i.e. size reduction or growth inhibition of the tumor) provided by a conventional MRI during long-term follow-ups, which could provide early evidence of treatment response [7,9–11]. Response criteria for tumors in general have been traditionally based on three-dimensional (3-D) volume-based assessments [12]. The most commonly accepted criteria for the evaluation of treatment response are the Response Evaluation Criteria In Solid Tumors (RECIST)

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guidelines [12]. However, the limitations of RECIST, and any linear dimension-based criteria for that matter, include generalizing the complexity of tumor structure to tumor volume, and the difficulty in estimating the maximum tumor volume for irregular or confluent lesions [13], as discrepancies in scan planes and patient positioning can result in erroneous measurements.

Non-invasive methods for monitoring tumor response to treatment are mainly imaging based. For example, diffusion-weighted MRI (DW-MRI) measures the impediment to diffusion of water molecules in tissue. The apparent diffusion coefficient (ADC), a quantitative parameter measured on a DW-MRI, is sensitive to changes in the number of water molecular between the intra-/extracellular space which is related to undergoing biologic changes in response to treatment [14]. Therefore, the purpose of this study is to determine if quantitative parameters from DWI are capable of predicting SRS treatment response in patients with brain metastases.

2. Methods

2.1. Patients

Demographic data is shown in Table 1. From 2014–2015, 41 consecutive patients (20 men, 21 women, mean age = 61.2 ± 6.5 years old) who underwent SRS were recruited for this study. The primary tumors were from lung (21), breast (10), renal (4), head and neck (4) and soft tissue (1) (Table 1). The clinical symptoms included headaches, dizziness, paralysis of limbs, nausea, vomiting, lethargy, etc. All patients were treated with SRS with a mean dose of 21 ± 5 Gy; the margin dose of the lesion ranged from 14 to 18 Gy, and the average target volume was 2.38 cm^3. As a part of the SRS procedure, all patients received local anesthesia to facilitate the painless application of the stereotactic head frame. This study was approved by the Institutional Review Board, and informed consent was obtained from all patients. This study was also compliant with all patient confidentiality regulations.

2.2. MR data acquisition

All patients underwent MRI scans at three time points: baseline (one day before radiotherapy), early-mid-treatment (one month after start of radiotherapy), and post-treatment (six months after radiotherapy). MRI scans were performed on all participants using a 3T MRI scanner (Siemens TrioTim) and a 12-channel head coil. All patients were supine, with their heads fixed by a sponge. Axial spin-echo T1-weighted images were acquired with TR/TE = 360/8 ms, slice thickness = 1.5 mm, field of view (FOV) = 26 cm × 26 cm, matrix size = 256 × 256, number of excitations (NEX) = 4. Fast spin-echo T2–weighted images were acquired with TR/TE = 2800/90 ms, slice thickness = 3.0 mm, interslice gap = 0, FOV = 26 cm × 26 cm, matrix size = 288 × 256, and NEX = 4. DWI was performed before administration of a contrast agent in the transverse plane by using a single-shot SE-planar imaging sequence with diffusion gradients in three orthogonal directions, and two diffusion weightings (b = 0 s/mm and 1000s/mm). DWIs were acquired with TR/TE = 6000/70 ms, slice thickness = 3.0 mm, FOV = 26 cm × 26 cm, matrix size = 128 × 128, NEX = 4. Finally, a volumetric three-dimensional gadolinium-enhanced T1 fast-spoiled gradient echo (FSPGR) was acquired with TR/TE = 8.5/4.2 ms, flip angle = 20°, FOV = 22 cm × 22 cm, matrix size = 270 × 270, slice thickness = 1.5 mm and NEX = 1. An initial loading dose of 3 mL of gadobenate dimeglumine (MultiHance; Bracco, Milan, Italy) was administered which, after five minutes, was followed by another bolus injection with the remaining dose (for a total of 0.3 mL/kg or 1.5 times a single dose) during image acquisition.

Table 1
Showing patient demographics data.

	Responders (n = 25)	Non-responders (n = 16)	p Value
Age, y mean(SD)	60.0 (8.6)	62.3 (9.4)	> 0.0.5
Sex, male, n (%)	17 (68)	10 (63)	> 0.05
Total radiation dose (SD)	19.8 (5.0)	22 (4.9)	> 0.05
Primary tumor site n (%)			
Lung	15(60)	6 (38)	> 0.05
Breast	5 (20)	5 (31)	> 0.05
Genitourinary	2 (8)	2 (13)	> 0.05
Head and neck	2 (8)	2 (13)	> 0.05
Sarcoma	1 (4)	1 (6)	> 0.05
Mean total volume (cc) of treated metastases (SD)	3.4 (0.7)	3.8 (0.8)	> 0.05

2.3. MRI data processing

DWI images were processed using DTI Studio v2.4 [15] (Johns Hopkins University, Baltimore, MD) to generate eigenvalues (λ_1, λ_2 and λ_3). ADC values were created for quantitative analysis by applying the following equation:

$$ADC = (\lambda_1 + \lambda_2 + \lambda_1)/3 \quad (1)$$

2.4. Imaging analysis

Regions of interest (ROIs) were drawn manually for the tumor-enhanced regions of the tissues in the axial Gd-enhanced T1-weighted images. ROIs in the tumors included areas with maximal degrees of contrast enhancement on Gd-enhanced T1-weighted images while avoiding necrosis, cystic areas, hemorrhage and calcification. ROIs were set in all slices of tumor that included the tumor parenchyma to the full extent.

Mean ADC value (ADCi) and the cross-sectional area (areai) of the tumor ROI on each slice (i representing the slice number) was calculated using Image J software (NIH, USA). Subsequently, the ADCmean of the entire tumor was calculated as the weighted average for all ADCi values in each tumor using Eq. (1):

$$ADC \ \text{mean} = \frac{\sum_i (ADC_i \times Area_i)}{\sum_i Area_i} \quad (1)$$

We calculated weighted averages as this is mathematically identical to calculating averages of ADC values directly from all voxels within the entire tumor volume. The volume of the tumor on DWI images was calculated using Eq. (2):

$$\text{Tumor volume} = \sum_i Area_i \times (\text{slice thickness} + \text{gap}) \quad (2)$$

We also introduced the concept of a diffusivity index (DI), which is the sum of 1/ADC among all the voxels in a tumor calculated via the home-made MATLAB script using Eq. (3):

$$DI = \text{tumor volume}/ADCmean \quad (3)$$

where the volume of the tumor is calculated using Eq. (2); where the DI is the mean of 1/ADC for all voxels on each ROI area. This equation would be mathematically identical to calculating the sums of 1/ADC values directly from all voxels within the entire tumor volume.

2.5. Tumour response evaluation

Tumor response was assessed based on the volumetric T1 post-gadolinium MRI using three-dimensional (3-D) volume-based criteria [16]: (l) complete response (CR) − lesions disappeared completely or little traces remained; (2) partial response (PR) − lesions were reduced