Pediatric Brain Tumor Consortium Multisite Assessment of Apparent Diffusion Coefficient z-Axis Variation Assessed with an Ice–Water Phantom

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Rationale and Objectives: Magnetic resonance diffusion imaging can characterize physiologic characteristics of pediatric brain tumors used to assess therapy response. The purpose of this study was to assess the variability of the apparent diffusion coefficient (ADC) along z-axis of scanners in the multicenter Pediatric Brain Tumor Consortium (PBTC).

Materials and Methods: Ice–water diffusion phantoms for each PBTC site were distributed with a specific diffusion imaging protocol. The phantom was scanned four successive times to 1) confirm water in the tube reached thermal equilibrium and 2) allow for assessment of intra-examination ADC repeatability. ADC profiles across slice positions for each vendor and institution combination were characterized using linear regression modeling with a quadratic fit.

Results: Eleven sites collected data with a high degree of compliance to the diffusion protocol for each scanner. The mean ADC value at slice position zero for vendor A was 1.123×10^{-3} mm^2/s, vendor B was 1.0964×10^{-3} mm^2/s, and vendor C was 1.110×10^{-3} mm^2/s. The percentage coefficient of variation across all sites was 0.309% (standard deviation = 0.322). The ADC values conformed well to a second-order polynomial along the z-axis, (ie, following a linear model pattern with quadratic fit) for vendor–institution combinations and across vendor–institution combinations as shown in the longitudinal model.

Conclusions: Assessment of the variability of diffusion metrics is essential for establishing the validity of using these quantitative metrics in multicenter trials. The low variability in ADC values across vendors and institutions and validates the use of ADC as a quantitative tumor marker in pediatric multicenter trials.

Key Words: Diffusion phantom; MRI; pediatric brain tumors; quality assurance.

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Pediatric brain tumors are the most common type of solid tumor among children, the second most frequent childhood malignancy after leukemia, and the leading cause of death from solid tumors in this population (1). An estimated 4452 new cases of childhood malignant brain and central nervous system (CNS) tumors are expected to be diagnosed in 2014 (2). Efforts to accrue sufficient numbers of patients for investigating more effective treatment strategies must hinge largely on multicenter trials, a defining feature of the National Institutes of Health–funded Pediatric Brain Tumor Consortium (PBTC), established in 1999. The PBTC's primary objective is to rapidly conduct novel phase I and II clinical evaluations of therapeutic drugs, new biological therapies, treatment delivery technologies, and radiation treatment strategies in children from infancy to 21 years of age with primary CNS tumors. A second objective is to characterize reliable markers and predictors (direct or surrogate) of brain tumor responses to new therapies. A third

objective is to develop and coordinate innovative neuroimaging techniques. Through the PBTC's Neuroimaging Center, formed in May 2000, correlative imaging endpoints and research to evaluate new therapies are in progress (3).

Magnetic resonance imaging (MRI) is the leading imaging modality for evaluating a child with suspected brain tumor. It has unique multiplanar capabilities that offer detailed anatomic information with superior resolution and sensitivity. MRI is typically used for making a preoperative diagnosis and for guiding treatment planning including image-guided therapies such as surgery, chemotherapy, and radiotherapy. In addition, it is used for tumor follow-up, for evaluating disease progression, and for assessing both treatment response and effects of therapy.

Lacking with conventional MR is an assessment of physiological and functional information about the tumor. Advanced MRI techniques, including MR diffusion imaging, can elucidate and characterize the physiological characteristics of pediatric brain tumors and can be used to assess response to therapy. MR diffusion using predominantly echo-planar techniques has been useful in the characterization of tissue, tumor cellularity, tumor grading, tumor response to treatment, and distinction of tissue types (4–6). It has also been used as a biomarker for detecting early treatment response in brain tumor patients and thus is often incorporated into the imaging evaluation of these patients (7).

In addition to standardization of imaging acquisition protocols in the multicenter setting, assessment of the variability of imaging metrics owing to technical limitations is essential for establishing the precision of quantitative measurements of these metrics in multicenter trials. Our initial work focused on the assessment of imaging metrics using standard MR sequences and the American College of Radiology phantom (8). Other groups have realized the importance of quality assurance in cohort studies as currently performed in Europe (9). As diffusion imaging is an integral component of the majority of the PBTC multicenter trials, we sought to validate MR diffusion data from the 11 participating sites by using an ice–water phantom created for this purpose (10,11) and tested for the first time in a multicenter consortium.

MATERIALS AND METHODS

Data Collection

Eleven sites with a total of 15 scanners from three major vendors (vendors A, B, and C not necessarily in alphabetical order) participated in the study. An ice–water diffusion phantom (Fig 1) consisting of a sealed 29-mm diameter tube of distilled water within a larger plastic jug to contain ice cubes and tap water was distributed to each site along with instructions for its use and recommendations for a specific diffusion imaging protocol. Also included were instructions for preparing the ice–water diffusion phantom and allowing sufficient time for cooling of the central tube to approximately 0° Celsius (C) along its full length. The advantage of an ice–water–based diffusion phantom is to maintain the water at a known temperature, thereby establishing an absolute and well-known diffusion coefficient (eg, 1.1×10^{-3} mm^2/s for water at 0°C) along the length of the central tube (10). The recommended protocol included use of single-shot echo-planar imaging diffusion sequences using three orthogonal diffusion sensitization directions with one baseline and one high (1000 s/mm^2) b-factor for the generation of trace ADC images in the axial plane along the full length of the ice–water diffusion phantom. The recommended protocol and range of sequence parameters are listed in the top row of Table 1. Sites were instructed to scan the cooled phantom four times in succession to 1) confirm water in the measurement tube had reached thermal equilibrium with ADC values not showing a downward trend and 2) to allow for assessment of intra-examination ADC repeatability. Sites were requested to send vendor-generated ADC maps to the PBTC Neuroimaging Center for analysis.

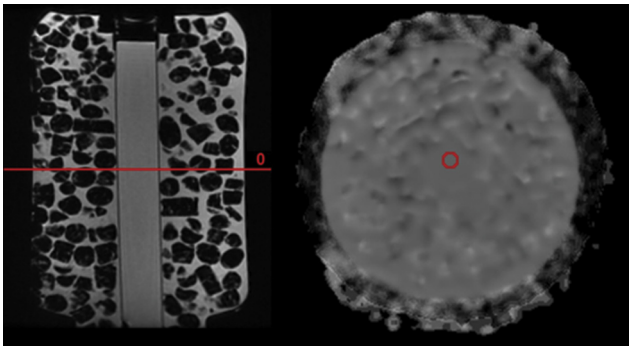

Figure 1. Representative sagittal T1 (left) and axial apparent diffusion coefficient (ADC; right) images of the diffusion ice-water phantom. *Red line* in the sagittal image shows the central slice along the tube to which ADC values were referenced, regardless of the actual slice positioning proscribed. In the ADC image, a typical region of interest within the distilled water tube used for data analysis is shown. (Color version of figure is available online.)

Data Analysis

A region of interest (ROI) analysis was used to determine the ADC value for each slice along the central tube. The range of ROI areas used was 53.1–62.2 mm^2, and the average ROI area was 59.4 mm^2. Because of differences in phantom positioning across sites, the true zero, or isocenter along each scanner's z-axis was determined from the localizer images. The central slice of the tube was repositioned to this origin for consistency of mean ADC values along the z-axis for all sites.

Statistical Considerations

Diffusion phantom ADC profiles along the z-axis across the slice positions for each vendor and institution combination