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Quantitative diffusion-weighted magnetic resonance imaging assessment of chemotherapy treatment response of pediatric osteosarcoma and Ewing sarcoma malignant bone tumors

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ABSTRACT

Objective: Assessment of tumor response to chemotherapy is essential in managing malignant pediatric bone tumors prior to resection.
Subjects and methods: Pre-chemotherapy and post-chemotherapy osteosarcoma and Ewing sarcoma cases (n = 18) were analyzed with apparent diffusion coefficient (ADC) values measured by two readers.
Results: Treated tumors demonstrated significantly greater ADC values compared to untreated tumors ($p < 0.001$). Intraclass correlation coefficients ranged between 0.858 and 0.935. No significant tumor volume differences were observed. Regression analysis demonstrated average ADC as the best predictor of treatment.
Conclusions: Our study suggests that ADC values may be useful for evaluating chemotherapeutic response of malignant pediatric bone tumors.

1. Introduction

Malignant bone tumors in children are treated with chemotherapy prior to definitive surgical resection. An important component of management involves the assessment of treatment response to chemotherapy prior to surgery in ameliorating recurrence risk. Presently, prognosis of non-metastatic osteosarcoma is determined largely based on histological response and completeness of resection [1,2]; post-chemotherapy magnetic resonance imaging serves an adjunct role in assessing treatment response, generally on the basis of imaging appearance on fluid sensitive and post-contrast imaging sequences with a focus on global tumor volume reduction. Metabolic imaging with FDG PET/CT is also sometimes employed to ascertain residual hypermetabolic tumor, but can result in substantial cumulative radiation doses in children [3]. One of the main challenges in assessing treatment response on conventional magnetic resonance imaging is that tumor volume may not significantly decrease following chemotherapy due to tumor necrosis, resulting in a stable or paradoxically increased tumor volume [4]. In addition, the osteoid component of osteogenic tumors such as conventional osteosarcoma does not appreciably change on fluid-sensitive and contrast-enhanced sequences [4]. Anatomic musculoskeletal MRI also does not provide information regarding viability of tumor tissue [5].

Diffusion-weighted imaging has a well-established role in neuroimaging to provide information regarding the mobility of water molecules within tissues for assessment of acute infarct as well as tumors such as gliomas [6]. There is evidence that diffusion-weighted imaging is capable of ascertaining tumor cellularity [7]. Tumor tissue is expected to be highly cellular with associated impedance of water movement, whereas necrotic tissue is acellular and allows free diffusion of water [7]. Therefore, diffusion-weighted imaging can provide information regarding tumor cellularity as a surrogate indicator of treatment response on the basis of a quantitative value, apparent diffusion coefficient (ADC). This value is expected to increase in the setting of adequate treatment response as an indicator of tumor necrosis with decreased restriction of water diffusion due to increased cellular permeability and decreased cellularity [7,8].

On the basis of cellularity corresponding to an ADC value, some have promoted the use of these diffusion-based measurements as surrogate markers of treatment response following cytotoxic and radiation therapy [8]. Studies of osteosarcoma patients demonstrated increased ADC

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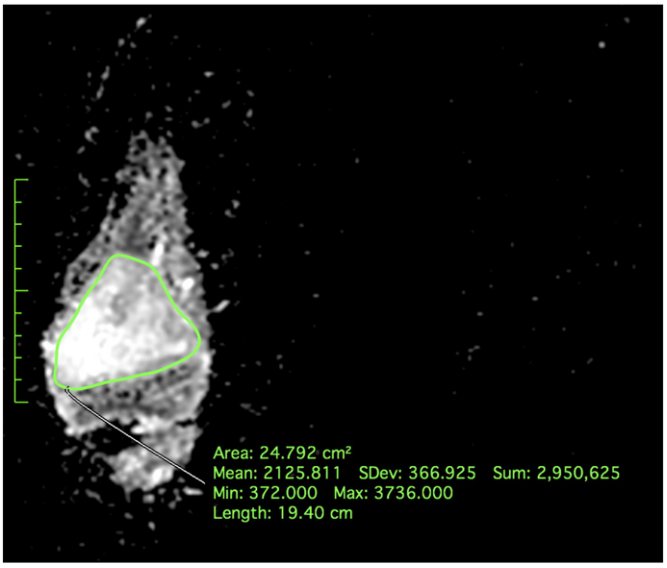

Fig. 1. Sample measurement of ADC values in a treated osteosarcoma case. For each case, a freehand region-of-interest was drawn on the image with greatest tumor dimensions. The tumor area, mean ADC, minimum ADC, and maximum ADC were obtained.

values following successful treatment with chemotherapy [9,10]. Similarly, a small study of pediatric osteosarcoma patients noted greater increases in ADC values following chemotherapy in patients who had less viable residual tumor than those with larger areas of viable tumor [4].

This study sought to validate the role of diffusion imaging in the management of pediatric conventional osteosarcoma and extend this technique to Ewing sarcoma in comparing ADC values before and following treatment with chemotherapy. We hypothesized that ADC values would significantly increase following treatment due to cytotoxic effects of chemotherapy on the primary tumor.

2. Subjects and methods

2.1. Study participants

Retrospective review of patient medical records during a four-year period (between January 2013 and January 2017) identified consecutive cases from a quaternary care pediatric hospital (<blinded>) via a clinical text search engine utilizing the terms “osteosarcoma”, “osteogenic sarcoma” or “Ewing sarcoma.” Inclusion criteria consisted of: primary diagnosis with documented pathology of conventional osteosarcoma or Ewing sarcoma; patient age between 1 and 25 years; and MRI including diffusion-weighted imaging sequences performed before and/or following chemotherapy administration. Exclusion criteria consisted of: pathology other than conventional osteosarcoma or Ewing sarcoma (e.g., surface osteosarcoma); age >25 years; and MRI performed without diffusion-weighted imaging or performed following primary tumor resection.

Patients' medical records and imaging data were reviewed for relevant clinical data and anonymized. The University of Pittsburgh Institutional Review Board reviewed and approved this HIPAA-compliant study (PRO16030133) by the expedited review procedure authorized under 45 CFR 46.110 and 45 CFR 46.404 for the inclusion of children.

2.2. Image acquisition

MRI was performed using system-wide standard sequences, which included coronal and axial diffusion-weighted imaging. Echo-planar two-dimensional diffusion-weighted imaging was performed at 1.5 T (GE Signa HDxt, n = 11; sequence parameters – TR: 3000, TE: 77–100, matrix: 256 × 256, FOV: 30 cm, slice thickness 5.0 mm, slice gap 5.0 mm; $b = 0$, 700–1000) or 3.0 T (GE Discovery MR750w, n = 5, Siemens Skyra, n = 2; sequence parameters – TR: 3000–9900, TE: 78–99, matrix: 256 × 256, FOV: 30 cm, slice thickness 5.0 mm, slice gap 5.0 mm; $b = 0$, 800), depending on scanner availability with coil-use determined by anatomic region imaged.

2.3. Image analysis

Tumor volumes were calculated based on the previously interpreted imaging studies according to a standard ellipsoid volume calculation of maximal tumor dimensions. ADC map images were extracted, anonymized and diagnosis blinded prior to imaging analysis. Two radiology residents with four and seven years' experience in imaging interpretation independently performed measurements of tumor ADC values using open-source software, (Osirix Lite, Version 8.0.2, Pixmeo SARL, Bernex, Switzerland). For each case, a single ADC image with greatest tumor size was selected, and a freehand region-of-interest was drawn around the visualized tumor as exemplified in Fig. 1. Images with excessive image noise or error values within tumor were not selected. From these regions-of-interest, the measurement area, minimum ADC, mean ADC and maximum ADC were calculated.

2.4. Statistical analysis

Comparisons of demographic and ADC values between pre-chemotherapy and post-chemotherapy groups were performed using a Student's *t*-test for equality of means. Reliability analysis of measures was performed using single measures intraclass correlation coefficient (ICC) calculation according to a two-way mixed effects model. Linear regression analysis was conducted using stepwise analysis of variance with chemotherapy treatment as the dependent variable and tumor volume, ADC values, measurement area, age and gender as inputs. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Macintosh, Version 23.0. Armonk, New York).

Table 1
Summary of study participants.

	Pre-chemotherapy (n = 8)	Post-chemotherapy (n = 10)	Comparison (*p*-value)
Age, yrs (SD)	11.3 (2.7)	12.3 (4.3)	0.537
Sex, male:female	5:3	6:4	0.920
Diagnosis	4 osteosarcoma	6 osteosarcoma	
	4 Ewing sarcoma	4 Ewing sarcoma	
Tumor site	4 femur	7 femur	
	1 humerus	1 humerus	
	1 tibia	1 pelvis	
	1 cervical spine	1 tibia	
	1 mandible		
Tumor volume, mL (SD)	999 (750)	1037 (992)	0.929
Chemotherapy time, wks (SD)	0 (0)	9.9 (0.6)	*<0.001*

Italic data indicate statistical significance (<0.05).