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Orbital benign and malignant lymphoproliferative disorders: Differentiation using semi-quantitative and quantitative analysis of dynamic contrast-enhanced magnetic resonance imaging

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ABSTRACT

Objectives: To assess the value of dynamic contrast-enhanced MR imaging (DCE-MRI) in differentiating benign from malignant orbital lymphoproliferative disorders (OLPDs).
Methods: Thirty-nine patients with orbital lymphoproliferative disorders (21 malignant and 18 benign) underwent DCE-MRI scan for pre-treatment evaluation from March 2013 to December 2015. Both semi-quantitative (TTP, AUC, $Slope_{max}$) and quantitative (K^{trans}, k_{ep}, v_e) parameters were calculated, and compared between two groups. Receiver operating characteristic (ROC) curve analyses were used to determine the diagnostic value of each significant parameter.
Results: Malignant OLPDs showed significantly higher k_{ep}, lower v_e, and lower AUC than benign OLPDs, while no significant differences were found on K^{trans}, TTP and $Slope_{max}$. ROC analyses indicated that v_e exhibited the best diagnostic performance in predicting malignant OLPDs (cutoff value, 0.211; area under the curve, 0.896; sensitivity, 76.2%; specificity, 94.9%), followed by k_{ep} (cutoff value, 0.853; area under the curve, 0.839; sensitivity, 85.7%; specificity, 89.9%).
Conclusion: DCE-MRI and specially its derived quantitative parameters of k_{ep} and v_e are promising metrics for differentiating malignant from benign OLPDs.

1. Introduction

Orbital lymphoproliferative disorders (OLPDs) constitute ten to fifteen percent of orbital masses [1]. They represent a broad spectrum of benign and malignant diseases, including lymphoid hyperplasia, atypical lymphoid hyperplasia, ocular adnexal lymphoma and idiopathic inflammatory pseudotumor [1,2]. Along with these, IgG4-related ophthalmic disease is becoming increasingly recognized and classified into benign OLPD group based on recent surveillance [3,4]. Differentiation of benign and malignant OLPDs is very crucial, because of the different treatment strategy and prognosis [5,6]. Orbital lymphomas are amenable to low-dose radiation therapy, while the benign mimics often exhibit a good response to corticosteroid therapy. The value of using clinical criteria for differentiating benign and malignant OLPDs is limited, because they often share similar clinical presentation [1,7,8]. Therefore, to find an efficient method to differentiate these two entities is in urgent need.

Recently, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) which utilizes fast T1-weighted imaging following a bolus injection of gadolinium contrast agent, has been increasingly used to assess the hemodynamic information of various tumors [9–11]. It allows noninvasive assessment of vascular permeability and blood flow, and has the potential to detect and characterize tumors, as well as evaluate treatment response [12,13]. Previous studies have confirmed that DCE-MRI and its derived quantitative metrics were helpful for predicting orbital malignancy [14,15]. However, they did not focus on the OLPDs, and enrolled several other orbital disorders. Few studies that specially used the DCE-MRI to discriminate benign from malignant OLPDs have been reported till now. In addition, they processed the DCE-MRI data using the model-free method, however we know that the main drawback of the model-free analysis is that they do not necessarily correlate with the physical essence [12]. Besides the model-free method, another method is the model-based

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Table 1
Patient characteristics and pathologic findings of OLPD cases.

Variable	Malignant OLPDs (n = 21)	Benign OLPDs (n = 18)	P value
Age	63.10 ± 14.83	50.39 ± 14.37	0.010
Gender (M/F)	14/7	13/5	0.742
Histologic subtypes			
	MALT lymphoma (17)	IIP (8)	
	DLBCL (2)	RLH (6)	
	Follicular lymphoma (2)	IgG4-related disease (4)	

Note: M indicates male; F, female; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; IIP, idiopathic inflammatory pseudotumor; RLH, reactive lymphoid hyperplasia. Data in parentheses indicates the number of the corresponding patients in our study.

calculation which is preferable as it provides greater pathophysiological insight [16].

Therefore, the aim of this study was to assess the value of DCE-MRI derived perfusion parameters, including both semi-quantitative and quantitative measurements, for differentiating benign from malignant OLPDs.

2. Materials and methods

2.1. Patient population

Our institutional review board approved this study and waived the informed consent requirement due to the retrospective nature. From March 2013 to December 2015, fifty-eight consecutive OLPDs patients underwent orbital MRI examination for pre-treatment evaluation. Nineteen patients were excluded because of the following exclusion criteria: no available DCE-MR images (n = 12), no adequate imaging quality (n = 1), lesions with diameter less than 1 cm (n = 2), secondary lymphoma (n = 1), prior history of corticosteroid or radiation therapy before MRI scan (n = 3). Finally, 39 OLPDs patients (21 malignant and 18 benign, 27 men and 12 women, mean age, 57.23 ± 15.79 years old) were enrolled in our study.

The spectrum of OPLDs included: 1) malignant lesions (n = 21; 14 men and 7 women; mean age, 63.10 ± 14.83 years old): recorded as MALT lymphoma (n = 17), DLBCL (n = 2), and follicular lymphoma (n = 2). 2) Benign lesions (n = 18; 13 men and 5 women; mean age, 50.39 ± 14.37 years old): recorded as idiopathic inflammatory pseudotumor (n = 8), reactive lymphoid hyperplasia (n = 6), and IgG4-related ophthalmic disease (n = 4). Detailed demographic and pathologic information of our study population are displayed on Table 1. The final diagnosis was made based on the surgically pathological results in 35 patients, on the follow-up after steroid treatment in 4 patients with inflammatory pseudotumor.

2.2. MRI scan

MR images were obtained using a 3T MR scanner (Verio; Siemens, Germany) with a 12-channel head coil. All patients underwent conventional unenhanced axial T1-weighted imaging (repetition time [TR]/echo time [TE], 600/10 msec), axial T2-weighted imaging (TR/TE, 4700/79 msec) with fat saturation, and coronal T2-weighted imaging (TR/TE, 3500/79 msec) with fat saturation.

Then the dynamic images were obtained by using a two-dimensional (2D) turbo fast low angle shot (FLASH) sequence with integrated parallel acquisition technique (iPAT). Gadolinium-diethylene triamine pentaacetic acid (Magnevist; Bayer Schering Pharma AG, Berlin, Germany) was intravenously bolus injected via a power injector at the rate of 4 mL/s at the dose of 0.1 mmol/kg, followed by a 20-mL bolus of saline administered at the same injection rate. Before the dynamic acquisition, an unenhanced T1 map based on a dual flip angle of 5° and 12° was obtained by using the same sequence, which allows conversion of the changes of MR signal intensity into those of the gadolinium concentration during passage of the contrast agent [17].

The DCE acquisition consisted of 5 baseline sets and 90 contrast-enhanced sets of images (total: 95 dynamics) without delay between acquisitions. The temporal resolution was 3.3 s, and the total acquisition time was 5 min 15 s. The other detailed imaging parameters for the DCE imaging were as follows: TR/TE, 474.66/1.43 msec; flip angle (FA), 12°; Average, 1; field of view (FOV), 230 mm; matrix, 128 × 128; section thickness, 4.5 mm; number of sections, 7. After DCE-MRI scan, post-contrast axial, coronal and sagittal T1-weighted images were obtained.

2.3. Imaging processing

DCE-MR images were processed using a dedicated postprocessing software program (Omni-Kinetics; GE Healthcare) which supplies pharmacokinetic calculation on a pixel-by-pixel basis. The current tracer-kinetic modeling for quantitation of DCE images was based on a two-compartment modified Tofts model [18]. In terms of the arterial input function (AIF), it was extracted by manually drawing a small circle region of interest (ROI) on one side of carotid artery located proximal to the tumor [19]. Whole-tumor ROIs were manually drawn over DCE-MR images, and then voxel-wise perfusion maps, containing both model-free (semi-quantitative) and model-based (quantitative) parameters were automatically generated. Semi-quantitative parameters included AUC (Area under the gadolinium dynamic curve in mmol*min), TTP (Time from contrast arrival to peak in min) and $Slope_{max}$ (Maximum concentration-time ratio in min^{-1}). Quantitative parameters included K^{trans} (the volume transfer constant between the plasma and the extracellular extravascular space [EES] in min^{-1}), v_e (the volume fraction of the EES in ml/ml), and k_{ep} (the rate constant from EES to blood plasma in min^{-1}, which equals the ratio K^{trans}/v_e) [12,13].

In terms of the ROIs placement, they were outlined on all slices by encompassing as much as tumor area, while the visual necrotic, hemorrhagic areas and surrounding blood vessels were excluded with reference to the conventional MR images. To minimize the effect of partial volume, the edges of lesions were avoided. If bilateral lesions occurred, the lesion with the larger diameter was included for analysis.

All the quantitative measurements were performed independently by two neuro-radiologists (reader 1: with 6 years of experience; reader 2: with 4 years of experience) who were blinded to the clinical information, pathological results and study design. The measurement results of these two readers were used to evaluate the inter-observer reproducibility. Meanwhile, to evaluate the intra-observer reproducibility, all the DCE-MR images were assessed again by the reader 1, spaced at least one month. The average of the two measurement results of reader 1 was adopted into statistical analysis.