Kurtosis analysis for DWI improves prediction of short-term response in head and neck cancer

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Introduction

Diffusion Weighted Imaging (DWI) allows the measurement of water diffusivity [1]. It has been shown that DWI can be used as a predictive biomarker and can also assess early detection of response to therapy in head and neck squamous cell carcinoma (HNSCC) [2]. Recently, it was demonstrated that non-Gaussian fitting, using the kurtosis analysis [3], of the diffusion signal decay curves obtained over an extended range of b values can better characterize tumors than mono-exponential fitting [4]. The present study investigates the added value of non-Gaussian analysis of DWI for the prediction of the short-term response to chemoradiation therapy in patients with advanced HNSCC.

Material and Methods

Patients 23 newly diagnosed HNSCC patients with metastatic nodes (M/F: 17/6, age: 56±10y, primary cancer: 7 base of tongue, 13 tonsil, 3 nasopharynx, table 1) underwent a clinical MRI examination, which included DWI. Three to four months after completing chemo-radiation treatment, a short-term response assessment was performed based on WHO criteria [5]. Patients were divided into 2 groups; complete response (no evidence of disease on clinical and imaging exam) and incomplete clinical response (measurable disease). *MRI* MRI was performed on a 1.5 Tesla GE Excite scanner using an 8-channel neurovascular phased-array coil. The protocol consisted of MR imaging covering the entire neck or oral cavity/tongue or nasopharynx using T2-weighted and T1-weighted images. DWI images were obtained by using single-shot spin-echo echo-planar imaging. Parameters: TR = 4000 ms, TE = 85-98 ms, averages = 4, slice/gap thickness = 5.0/0 mm, field of view = 20-26 cm, matrix =128x128, and 3 diffusion sensitizing directions. The b values were 0, 50, 100, 500, 750, 1000, and 1500 s/mm^2. *Data analysis* Image processing was performed using Matlab and SPM5. Six b=0 images were aligned using affine transformation in SPM5. Subsequently, all corresponding DWI images with a b-value > 0 s/mm^2 were transformed using the identical parameters. An averaged b=0 image was obtained after realignment. Gaussian smoothing was applied on all images with a FWHM of 3 mm. For each patient, masks were created using MRIcro, to select regions of interest (ROI) of the neck nodes. ROIs were manually drawn by an experienced neuro-radiologist on the averaged b=0 image. Fits were performed on a voxel-by-voxel basis with a Marquardt-Levenberg algorithm, using: $\ln[S(b)]=\ln[S(0)]-b \cdot D_{app}+1/6 \cdot b^2 \cdot D_{app}^2 \cdot K_{app}$, where S is the signal intensity, b is the b value (s/mm^2), D_{app} is the apparent diffusion coefficient (10^{-3}mm^2/s), and K_{app} is the apparent kurtosis coefficient [4]. In addition to non-Gaussian fitting, mono-exponential fitting was performed using (K_{app}=0, yielding ADC$_{mono}$). A histogram analysis was performed on all pixels within the ROI, which yielded the mean and standard deviation (std) of the distribution of all pixels. *Statistical analysis* To assess the predictive value of DWI for short-term response, logistic regression analysis was performed in SPSS 17.0 using the parameters mean(ADC$_{mono}$), std(ADC$_{mono}$), mean(D_{app}), std(D_{app}), mean(K_{app}), and std(K_{app}). The forward stepwise (LR) method of analysis was used (variable entered if $P <$ 0.10, variable removed if $P >$ 0.15). After creation of the multivariate model the predicted probabilities were saved. An ROC curve was constructed with these probabilities to assess the accuracy of the multivariate model for the prediction of short-term response.

Results

At short-term response evaluation, 19 patients had complete response and 4 patients had incomplete clinical response. Examples of parametric maps for a patient with CR and a patient with ICR are shown in figure 1. The logistic regression analysis of the DWI data indicated that std(D_{app}) (p = 0.068) was the only significant predictors of short-term response. The short-term responses could be predicted correctly in 20 patients (87%, sensitivity is 100%, specificity is 25%) using std(D_{app}), and the area under the ROC curve was 0.632 [95% CI 0.29 0.97]. No parameter derived from the standard mono-exponential fitting was a significant predictor.

Discussion

Kim et al. [2] recently reported in 40 HNSCC patients that ADC$_{mono}$ was a prediction marker of early response (median 12 months). We did not see such a relationship for ADC$_{mono}$, which could be due to our lower number of patients and shorter follow up duration. However, we did demonstrate that the apparent diffusion parameter derived from the kurtosis analysis, std(D_{app}), is a significant, though relatively weak, predictor of short-term response to therapy in HNSCC. The sign of the regression coefficient (β) for std(D_{app}) in the logistic regression analysis shows us that higher std(D_{app}) values are associated with worse prognosis. Standard deviation measures describing the width of the pixel histogram distribution are indicative of the tumor heterogeneity [6]. Our results therefore suggest that the more heterogeneous the node, the more unfavorable the outcome, which is in agreement with literature [7]. Interestingly, the standard deviation of the apparent diffusion coefficient parameter derived from the standard mono-exponential fitting (ADC$_{mono}$) is not a significant predictor. It seems that the kurtosis analysis yields a better and more sensitive estimation of the apparent diffusion coefficient (D_{app}).

Conclusion

Kurtosis analysis for DWI improves prediction of short-term response in head and neck cancer over standard mono-exponential fitting.

References

[1] Koh, AJR Am J Roentgenol 2007 188:1622; [2] Kim, Clin Cancer Res 2009 15(3):986; [3] Jensen, Magn Reson Med 2005 53:1432; [4] Jansen, AJNR 2010 31:741; [5] Rengan, Am J Clin Oncol 2008 31(465); [6] Lee, Ultrasound Med Biol. 2006 32:1817; [7] Jackson, Clin Cancer Res 2007; 13:3449.

Characteristic	Chemoradiation therapy (N=23)
Age	
18-69 yr	21
≥70 yr	2
Sex	
Male	17
Female	6
Clinical Stage	
III	2
IV	21
Primary tumor location	
Oropharynx	20
Nasopharynx	3

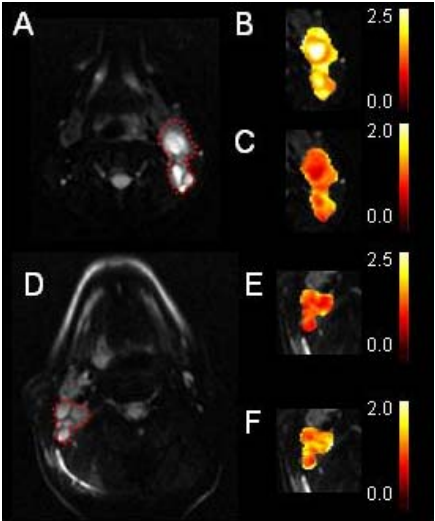**Table 1.** Clinical characteristics of the HNSCC patients.

Figure 1. Realigned mean b=0 images, of a patient with CR (F/27y, primary tonsil) (A-C), and with ICR (M/70y, primary base of tongue) (D-F). The red dotted lines (A and D) indicate the metastatic nodes. Overlays of D_{app} (10^{-3} mm^2/s) (B and E), and K_{app} (dimensionless) (C and F) were obtained from the diffusional kurtosis analysis.