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Diffusion weighted magnetic resonance imaging of pre and post treatment nasopharyngeal carcinoma

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ABSTRACT

Objectives: To evaluate the utility of different Apparent Diffusion Coefficient (ADC) values on Diffused Weighted Magnetic Resonance Imaging (DW-MRI) for nasopharyngeal carcinoma (NPC).
Study design and setting: A retrospective cohort study in a single tertiary medical center.
Subjects and methods: The study group consists of patients with pathology proven NPC that underwent DW-MRI prior or/and following a non-surgical chemo radiation treatment between the years 2007 and 2017. ADC thresholds were analyzed and compared for primary (pre-treatment) and expected post-irradiation NPC cases and healthy controls.
Results: We recruited 144 patients who underwent 195 MRI's for NPC. 25 DW-MRI were performed before (primary, active NPC) and 56 following (no residual NPC) treatment. 45 out of 225 patients who had brain DW-MRI for other reasons (control group) had measurable nasopharynx tissue (N = 33, adjusted for age and gender). The mean ADC of NPC prior to treatment ($0.69 \pm 0.13 \times 10^{-3}$ mm^2/s) was significantly lower (ANOVA, $P < 0.001$) compared to the mean ADC of the adjusted controls ($1.11 \pm 0.25 \times 10^{-3}$ mm^2/s) and post-treatment ($1.49 \pm 0.28 \times 10^{-3}$ mm^2/s) groups. An ADC threshold of 0.805×10^{-3} mm^2/s had 94% and 93.9% sensitivity and specificity rates, respectively and an odds ratio of 175[95%CI(23.25–1000)], comparing ADC levels of pre-treatment NPC patients and adjusted control group. An ADC threshold of 0.965×10^{-3} mm^2/s yielded 100% positive and negative predicted values distinguishing pre-treatment and post-treatment NPC patients (free of disease). There was no statistical association between ADC levels and tumor volume/stage, nodal stage or group staging.
Conclusions: ADC levels have distinct values in newly diagnosed and follow up of NPC.

1. Introduction

Nasopharyngeal cancer is one of the most common head and neck cancers in Asia and Africa. Local control and overall survival exceeding 90% and 80% at 5 years, respectively, can now be achieved [1].

Nasopharyngeal carcinoma (NPC) size and extension (T) is better demonstrated on Magnetic Resonance Imaging (MRI) compared to other imaging modalities [2]. MRI plays an important role in tumor staging, delineating target volumes and tumor recurrence. Yet, standard MRI sequences cannot distinguish between NPC and benign etiologies, in particular lymphoid hypertrophy, posing a diagnostic challenge for both the clinician and the radiologist [3,4]. Moreover, since the current mainstay of therapy for NPC includes radiation therapy [5].which alters the internal architecture and the cellular structure [6], the identification of either residual disease or tumor recurrence becomes even more challenging.

Diffusion-weighted imaging (DWI) detects the random motion of water molecules, which is the Brownian motion of water protons in biologic tissues [7]. It has been used for years to identify subtle brain parenchyma pathologies [8]. The extent of tissue cellularity and the presence of intact cell membranes help in determining the impedance of water molecule diffusion [9]. Extracranial diffuse weighted magnetic resonance imaging is gaining increasing importance, including various head and neck regions [10]. On recent studies, DWI correlated with

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retinoblastoma [11], lung cancer [12], breast cancer prognosis [13] and esophageal cancer treatment response [14]. Apparent diffusion coefficient (ADC) is a quantitative parameter expressing the impedance of diffusion of water molecules. It has been previously established that a neoplasm with densely packed malignant cells represents a greater impairment to diffusion and has a lower ADC.

Previously, a universal ADC cutoff value of $1.2 \times 10^{-3}\,mm^2/s$, differentiating benign and all head and neck cancers, was suggested [15]. However, we aimed to address ADC in a non-Chinese population for both pre and post treatment scenarios (not just for pre-treatment [16] or post-treatment recurrence diagnosis [17].

2. Material and methods

2.1. Ethical considerations

The study was conducted at a single tertiary center following the approval of the institutional review board (0693-16-HMO) according to the World Medical Association Declaration of Helsinki, 2008.

2.2. Study design

A retrospective analysis and chart review were performed, collecting demographic data, disease parameters, and treatment description, for patients with pathology documenting epithelial nasopharyngeal carcinoma.

2.3. Participants

All patients with a histology proven NPC treated between January 1st, 2007 and 31st of December 2017 were included in the study.

The control group consisted of patients with DWI MRI scans performed for either brain or ocular reasons and with no known nasopharyngeal abnormalities. Patients with MRI scans performed without diffuse weighted sequence were excluded, as well as patients with nasopharyngeal tissue (tumor or normal) less than 4 mm in diameter, as the region of interest (ROI) could not be measured reliably [18].

2.4. Primary endpoints

Establishing ADC cutoff values differentiating pre-treatment NPC and normal nasopharynx or radiated post-treatment nasopharynx (with neither residual disease nor tumor recurrence).

Investigating a potential association between ADC level and disease stage and prognosis.

2.5. Magnetic resonance imaging (MRI)

MRI was obtained on either Siemens 1.5T Avanto, Siemens 3T TrioTeam, or Philips 3T Ingenia. The imaging protocol included axial T2-weighted (T2W) fat-suppressed (FS) short tau inversion recovery (STIR) images, and axial T1-weighted spin echo (T1W SE) images. Data analyzed included qualitative (visual assessment - T1 enhancement, T2 signal intensity compared to nasal conchal signal) and quantitative (ADC level, tumor volume) parameters.

2.6. ADC measurements

For DWI a multi-slice single-shot echo-planar imaging sequence was used with the following parameters: matrix 96X96, TR/TE = 4000 ms/78 ms, FOV (field of view) 490 × 230mm, B value 0, 500, 1000 s/mm^2. (B value depicts the diffusion gradient strength). The DW MRI was acquired with adequate morphologic images with the same field of view, orientation and section thickness for best overlay and anatomic localization. ADC calculation was performed separately by R.E and S.D on a Philips portal (IntelliSpace Portal 8.0) workstation while being blinded to the clinical scenario (subgroups of patients: healthy, pre-treatment NPC, post-treatment nasopharynx, non-epithelial nasopharyngeal malignancies). According with previous publications [10,18], considering the complexity of performing DW imaging acquisitions in the head and neck region a round solid region of interest (ROI), with at least 4 mm diameter, was placed in the nasopharynx tissue. Cases with nasopharynx tissue less than 4 mm in size were therefore excluded. Cystic and necrotic regions were excluded as well because of the high ADC value that results from necrosis. The ADC levels were measured (S.D.) while being blinded to the patients' subgroup (clinical status). For accuracy purpose, an experienced radiologist (R.A.) verified all measurements.

2.7. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software version 24. Results and their interpretation were independently reviewed by a statistician. Chi-square or Fisher's exact tests were used for comparison of qualitative parameters, and the Odds ratio with its 95% Confidence interval (CI) was presented for each comparison. The student t-test and Mann-Whitney test were used for quantitative parameters and the ANOVA test for the comparison of more than two subgroups. Pearson coefficient was used for measuring the linear correlation between two parameters. The ROC curve, implicating sensitivity/specificity pair corresponding to different ADC cutoffs, using the area under the curve (AUC), was used for chosen cutoffs. Cox regression model was used for demonstrating the association of different survival parameters and ADC levels. P value of 0.05 or less was considered as statistical significant.

3. Results

One hundred and forty-four NPC patients, who underwent 195 MRI scans, were treated in our medical center during the study period. Of them, 93 patients who had no DWI protocol and eight non-measurable nasopharyngeal tissue cases were excluded (Fig. 1). The study group consisted of 25 patients with pre-treatment NPC. The post treatment group consisted of 28 patients with no residual or tumor recurrence that underwent 56 DWI MRI scans. Of these two study groups, 10 patients underwent pre- and post-treatment NPC DWI MRI scans. Of 225 patients with brain or ocular pathology that underwent DWI MRI scans (control group), only 45 (20%) had a measurable (> 4 mm) tissue in the nasopharynx. For gender and age adjustment with the study group, only 33 patients were included in the adjusted control group. Regardless, age (R = 0.472) and gender (p = 0.497) had no association with ADC levels. No ADC difference was demonstrated between the original ($1.11 \pm 0.25 \times 10^{-3}\,mm^2/s$) and the age and gender adjusted control groups ($1.10 \pm 0.25 \times 10^{-3}\,mm^2/s$). There was no epidemiological, clinical, imaging, or survival difference between the pre- and post-treatment study subgroups (Table 1). The mean tumor volume among the NPC pre-treatment subgroup was 43.7 mm^3 (3.4–115.95 mm^3). Almost half (12/25) of these patients had advanced T3-T4 disease (AJCC 8th edition [19]). The mean nodal category was N2, where nodal spread was noticed in most of our patients; N1 (3/25), N2 (14/25) and N3 (1/25). The median follow up time for the post treatment group was 4.2 years (9 months–38 years).

The ADC level of the pre-treatment NPC study group ($0.69 \pm 0.13 \times 10^{-3}\,mm^2/s$), the post- treatment group ($1.49 \pm 0.28X10^{-3}\,mm^2/s$) and the adjusted control group ($1.10 \pm 0.25 \times 10^{-3}\,mm^2/s$), differed significantly ($P < 0.001$) (Table 2).

The area under the curve (AUC) of the ROC graphs were used for ADC cutoffs analysis. An ADC cutoff of $0.805 \times 10^{-3}\,mm^2/s$, differentiating pre-treatment NPC and the adjusted control groups, producing 94% sensitivity and positive predictive value (PPV), 93.9% specificity and negative predictive value (NPV), with a striking odds ratio of

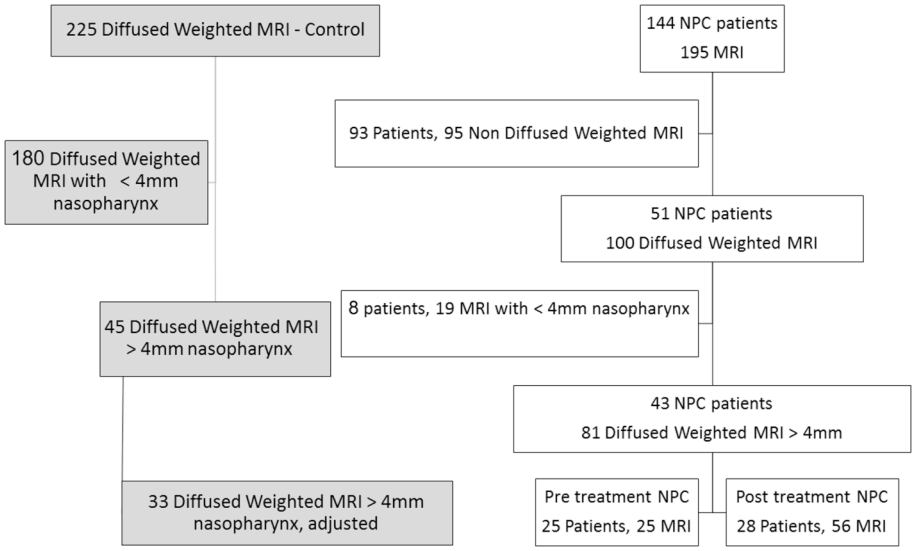

Fig. 1. Study scheme.
Aberrations: NPC: Nasopharyngeal carcinoma, MRI: Magnetic Resonance Imaging, mm: millimeters, Pre-treatment group of patients with pathology proven nasopharyngeal carcinoma, Post-treatment group of patients with no residual disease, Control group of patients adjusted for age and gender.

Table 1
Demographics, epidemiologic data, and disease description of patients treated between the years 2007–2017.

Characteristic		Pre-treatment group (N = 25)	Post-treatment group (N = 28)
Male		17 (68%)	20 (71.4%)
Female		8 (32%)	8 (28.6%)
Immune deficiency		3 (12%)	4 (14.3%)
Mean age at DW-MRI (years)		47.68	49.43
Keratinizing NPC		1 (4.8%)	0 (0%)
Differentiated nonkeratinizing NPC		8 (38.1%)	5 (29.4%)
Undifferentiated nonkeratinizing NPC		12 (57.1%)	12 (70.6%)
Stage (AJCC 8th edition)	1	3 (12.5%)	1 (4.2%)
	2	3 (12.5%)	3 (12.5%)
	3	8 (33.3%)	8 (33.3%)
	4	10 (41.7%)	12 (50%)
Spread to bone	No	24 (96%)	27 (96.4%)
	Yes	1 (4%)	1 (3.6%)
Chemotherapy	Yes	21 (87.5%)	26 (93%)
	No	3 (12.5%)	2 (7%)
Recurrence	No	23 (92%)	25 (89.3%)
	Yes	2 (8%)	3 (10.7%)
Death (overall)	No	23 (92%)	24 (85.7%)
	Yes	2 (8%)	4 (14.3%)
T1 enhancement	Yes	25(100%)	
T2 signal	Low	25 (100%)	

Aberrations; DW-MRI: Diffused Weighted Magnetic Resonance Imaging, AJCC 8th edition [19], T1 enhancement with gadolinium, T2 signal compared to nasal conchae.

175[95%CI (23.25–1000)]. Only two patients in the pre-treatment NPC group (out of 25) had an ADC value higher than $0.805 \times 10^{-3}\,mm^2/s$. Only four patients in the adjusted control group of (out of 45) had an ADC value lower than $0.805 \times 10^{-3}\,mm^2/s$.

An ADC value cutoff of $0.965 \times 10^{-3}\,mm^2/s$, differentiating pre-treatment NPC and post-treatment (no residual or tumor recurrence), demonstrated 100% sensitivity, specificity, PPV and NPV. None of the patients with NPC (pre-treatment) had an ADC value higher than $0.965 \times 10^{-3}\,mm^2/s$. None of the patients in the post-treatment group had an ADC value lower than $0.965 \times 10^{-3}\,mm^2/s$.

The Pearson correlation and Mann-Whitney analyses demonstrated no association between ADC level and tumor volume ($R = 0.02$, $p = 0.923$), T stage ($R = -0.081$, $p = 0.699$), N stage ($R = -0.365$, $p = 0.08$) and group staging ($p = 0.454$) among the pre-treatment NPC subgroup of patients. Moreover, Cox regression analysis demonstrated no association between survival and ADC levels ($p = 0.693$).

Table 2
Apparent Diffusion Coefficient on Diffused Weighted Magnetic Resonance Imaging for the different subgroups of patients.

ADC Level $\times 10^{-3}\,mm^2/s$	Pretreatment group 25 patients, 25 DW-MRI	Post treatment 28 patients, 56 DW-MRI	Control 33 patients, 33 DW-MRI
Mean	0.69	1.49	1.11
Median	0.71	1.48	1.10
Minimum	0.32	1.07	0.6
Maximum	0.86	2.33	1.76
Standard Deviation	0.13	0.28	0.25

Aberrations; ADC: Apparent Diffusion Coefficient, Pre-treatment group of patients with pathology proven nasopharyngeal carcinoma, Post-treatment group of patients with no residual -disease, Control group of patients adjusted for age and gender.

4. Discussion

4.1. Key findings

We have defined ADC threshold values assisting in the diagnosis of NPC in comparison with healthy control and post-radiation patients with no residual disease. These may assist with the diagnosis of primary NPC and tumor recurrence, respectively. We have focused on a single head and neck site (nasopharynx) and homogeneous non-Asian origin population as opposed to other study groups, who have investigated a general ADC level for all head and neck tumors [10,15,20]. Whereas, other researchers either analyzed pre-treatment NPC [16], or the diagnosis of tumor recurrence [17,21], we have demonstrated significant lower ADC levels among pre-treatment NPC patients compared to healthy and post-radiation patients.

ADC levels reflect water molecular diffusion and cells density. Therefore, malignant tumors characterized by hypercellularity, hyperchromatism and high nucleus-cytoplasm ratio [22] and have low mean ADC levels ($0.69 \pm 0.13 \times 10^{-3}\,mm^2/s$) compared to other study groups. ADC levels contribute to the conventional T1 and T2 MRI sequences where all NPC, treated and pre-treated, had enhanced T1 following IV gadolinium injection [4] and low T2 signal.

We have first demonstrated no age or gender effect for ADC calculation. Still for the sake of comparison, we have matched the control group for any potential confounder.

We deliberately calculated two separate ADC cutoffs for two different clinical situations; $0.805 \times 10^{-3}\,mm^2/s$ for naïve patients (compared to healthy controls) and $0.965 \times 10^{-3}\,mm^2/s$ for post-treatment patients with no residual or tumor recurrence (compared to patients with NPC). In this way, using the appropriate threshold in the specific clinical situation we can achieve better ADC cutoffs with very high accuracy. We believe that physiologic parameters are essential specifically for the post-treatment scenario as a purely morphologic MRI can be misleading in the setting of tissue alterations or non-active masses [23].

In contrast to previous data [24] we did not establish an association between ADC levels and tumor extent (volume and T stage), nodal spread, and group staging. These may emphasize the importance of various histological factors, such as lymphvascular invasion (LVI), perineural invasion (PNI), and tumor differentiation, that do not affect ADC. Moreover, tumor extent (stage) reflected by dural involvement and lateral pterygoid muscle spread is not related to cellularity (ADC value). For the same reasons, we argue for no correlation between ADC levels and survival, yet, the small subgroup of patients that have died of disease does not allow us to make a firm conclusion. In contrast to other cancer sites [25] we did not demonstrate any association between ADC values and NPC nodal spread; either by comparing nodal negative (N0) and positive (N+) disease, or comparing low tumor burden (N1) with high tumor burden (N2-3). Therefore, we successfully depicted the ADC role for pre-treatment NPC diagnosis and tumor recurrence, but failed to demonstrate ADC biomarker potential role in risk stratification.

4.2. Study drawbacks

We are aware of the study retrospective nature, using different MRI scanners and the relatively small sample (e.g. no survival analysis). We believe the strict patients' homogeneousness, the meticulous measurements performed by two examiners blinded to the patient medical history and avoiding inconclusive statements, where the statistics power is low, overcome these confines.

5. Conclusions

Herein, we present the role of diffusion weighted MRI for nasopharyngeal carcinoma tissue characterization by two separated ADC cutoff for two distinct clinical scenarios (pre and post-treatment recurrence diagnosis), producing a more sensitive and specific tailored thresholds.

Future investigations for other specific head and neck cancer sites, with larger scale study groups, are needed. Supplementary studies are required to elucidate the association of ADC as an outcome and treatment response predictor.

Conflicts of interest

There is no conflict of interest or financial support.

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