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Change in diffusion weighted imaging after induction chemotherapy outperforms RECIST guideline for long-term outcome prediction in advanced nasopharyngeal carcinoma

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Abstract

Purpose To investigate change in diffusion weighted imaging (DWI) between pre-treatment (pre-) and after induction chemotherapy (post-IC) for long-term outcome prediction in advanced nasopharyngeal carcinoma (adNPC).

Materials and methods Mean apparent diffusion coefficients (ADCs) of two DWIs (ADC_{pre} and $ADC_{post-IC}$) and changes in ADC between two scans (ΔADC%) were calculated from 64 eligible patients with adNPC and correlated with disease free survival (DFS), locoregional recurrence free survival (LRRFS), distant metastases free survival (DMFS), and overall survival (OS) using Cox regression analysis. C-indexes of the independent parameters for outcome were compared with that of RECIST response groups. Survival rates between two patient groups were evaluated and compared.

Results Univariable analysis showed that high ΔADC% predicted good DFS, LRRFS, and DMFS $p < 0.05$), but did not predict OS ($p = 0.40$). Neither ADC_{pre} nor $ADC_{post-IC}$ ($p = 0.07$ to 0.97) predicted outcome. Multivariate analysis showed that ΔADC% independently predicted DFS, LRRFS, and DMFS ($p < 0.01$ to 0.03). Compared with the RECIST groups, the ΔADC% groups (threshold of 34.2%) showed a higher c-index for 3-year (0.47 vs. 0.71, $p < 0.01$) and 5-year DFS (0.51 vs. 0.72, $p < 0.01$). Compared with patients with ΔADC%<34.2%, patients with ΔADC%≥34.2% had higher 3-year DFS, LRRFS and DMFS of 100%, 100% and 100%, respectively ($p < 0.05$).

Conclusion Results suggest that ΔADC% was an independent predictor for long-term outcome and was superior to RECIST guideline for outcome prediction in adNPC. A ΔADC% threshold of ≥ 34.2% may be valuable for selecting patients who respond to treatment for de-escalation of treatment or post-treatment surveillance.

Keywords Head and neck cancer, Diffusion weighted imaging, Outcome prediction, Nasopharyngeal carcinoma, RECIST guideline

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Introduction

Nasopharyngeal carcinoma (NPC) is sensitive to radiotherapy (RT) and can be cured by only RT when it is diagnosed at early stage with a favorable 5-year disease free survival (DFS) of over 90% [1, 2]. However, early-stage NPCs are usually overlooked as they rarely cause typical symptoms and so over 70% of patients have advanced NPC (adNPC) at diagnosis [1]. Patients with adNPC have disease with a greater likelihood of resistance to treatment and so the treatment of choice is now induction chemotherapy (IC) before the course of concurrent chemoradiotherapy (CCRT) [3]. However, there still have about 30% of these patients eventually develop disease recurrence after treatment [4]. The additional IC and full course of the CCRT increase risks of treatment-related toxicity, which is now one of the major causes of the decreased quality of life and even death after treatment. Therefore, early prediction of risk of recurrences in patients with adNPC would be beneficial because additional immunotherapy or targeted therapy and close post-treatment surveillance can be timely intervened for patients at high risk of disease recurrences while de-escalation of chemotherapy may be applied to patients at low risk of disease recurrence.

Pre-treatment MRI is the long-established imaging modality of choice for staging disease in the head and neck and the addition of diffusion weighted imaging (DWI), which is a short sequence, is easily accommodated in the MRI protocol [5, 6]. DWI can measure the random Brownian motion of water molecules within tissues. In previous head and neck squamous cell carcinoma (HNSCC) studies, DWI has shown the potential for the prediction of long-term post-treatment outcome [7–21]. Of many DWI parameters, change in mean values of apparent diffusion coefficient (ΔADC%) between pre- and intra-treatment scans is the most promising one for clinical practice because ΔADC% is less influenced by variability among scanners, techniques and scanning protocols. In NPC, the recent move to add upfront chemotherapy before CCRT requires a second MRI scan after tumor shrinkage to plan the radiotherapy field. This provides the opportunity to perform a second DWI examination to monitor treatment change in the tumor microenvironment. Although many studies have showed ΔADC% is valuable for the prediction of short-term outcome [22–24], there is little literature reported whether ΔADC% can also predict long-term outcome in NPC [25].

Therefore, in this study, we aimed to investigate the predictive value of DWI on the pre-treatment and post-IC scans and change in DWI after IC for long-term outcome in adNPC by correlating the mean values of ADC on the pre- and post-IC scans (ADC_{pre} and $ADC_{post-IC}$) and ΔADC% with long-term outcome. Furthermore, we compared the predictive values of the DWIs with that of treatment response to IC detected by anatomical change in tumour size using the internationally widely used RECIST guideline [26].

Materials and methods

Patients

This retrospective study was approved by the local institutional ethics review board, and the requirement for written consent was waived for this retrospective study. All study procedures complied with the tenets of the Declaration of Helsinki. Patients who fulfilled the following inclusion criteria were included in the study: (1) ethnic Chinese adult patients with new biopsy-proven NPC; (2) patients who had pre-treatment staging head and neck MRI from 2014 to 2022 showing stage III or stage IVa NPC in our institution; (3) patients treated with 2–3 cycles of IC followed by CCRT; and (4) patients who had a post-IC head and neck MRI (post-IC MRI) including DWI of the primary tumour using the same DWI protocol at both time points (pre- and post-IC MRIs). Patients were excluded from the analysis if: (1) patient was lost to follow-up; (2) MR images were severely degraded by motion artifacts or other artifacts; or (3) patient who had a history of another head and neck cancer or secondary primary tumours treated with different regimens. Some of the patients in this study was previously reported by Kwong et al. [27].

Image acquisition

MRI was performed on a Philips Achieva TX 3 T scanner (Philips Healthcare, Best, The Netherlands) or a GE 3 T scanner (GE HealthCare, Chicago, United States) with body coils for radiofrequency transmission and a 16-channel Philips neurovascular phased-array coil for reception. Patients underwent a pre-treatment MRI and post-IC MRI with DWI and anatomical imaging.

DWI was acquired using a fat-suppressed, single-shot spin-echo echo-planar imaging sequence. The imaging parameters were: repetition time/echo time, 2000/50 mesc; field of view, 230 mm × 230 mm; resolution, 1.7 mm × 2.1 mm; slice thickness, 4 mm; number of slices: 9; echo train length, 55; sensitivity encoding factor, 2; number of signals acquired, 4 and at least 2 b-values (0 and 1000 s/mm^2).

Anatomical MRI sequences included at minimum of (1) axial non-contrast-enhanced fat-suppressed T2-weighted images (non-CE FS-T2WI), (2) axial non-CE T1-weighted images (non-CE T1WI), and (3) axial contrast-enhanced with or without FS-T1WI.

Imaging analysis

DWI analysis

Olea Sphere (version 3.0; Olea Medical SA) was used for the diffusion post-processing steps by implementing a Bayesian probability-based algorithm using two b-values (0 and 1000 s/mm^2) to fit a mono-exponential diffusion model to calculate the conventional apparent diffusion coefficient (ADC).

The primary tumour on the pre- and post-IC ADC maps was contoured manually excluding any necrotic or cystic areas with reference to the corresponding anatomical images by a researcher with 10 years' experience in MRI of NPC. The mean values of pre- and post-IC ADC (ADC_{pre} and $ADC_{post-IC}$), and change in ADC between pre- and post-IC scans, which was defined as ΔADC% = [($ADC_{post-IC}$ - ADC_{pre})/ ADC_{pre} *100%] was calculated for further analysis. Intra- and inter-observer analyses for DWI were not analysed as previous NPC studies have shown the ICCs for ADC of > 0.90 [28–31].

Evaluation of treatment response to IC based on RECIST 1.1 guideline [26]

Treatment response to IC was evaluated according to the RECIST 1.1 criteria, using change in the maximum diameters of the primary NPC. Treatment response to IC was categorized into (1) complete response (CR), defined as disappearance of primary tumour, (2) partial response (PR), defined as at least 30% reduction in the maximum diameters of primary NPC, (3) progressive disease (PD), defined as at least 20% increase in the maximum diameters of primary NPC, or (4) stable disease (SD), defined as insufficient increase or reduction in the maximum diameters of primary NPC. Patients were then divided into a response group (CR or PR) and a non-response group (SD or PR) for the analysis.

Treatment

All patients were treated with IC followed by CCRT. The IC was administered intravenously once every 3 weeks for 2 or 3 cycles, with one of the IC regimens: (1) 1000mg/m^2 of body surface area (BSA) of gemcitabine on day 1 and 8 along with 80 mg/m^2 of body surface area of cisplatin on day 1, (2) with 175 mg/m^2 of body surface area of paclitaxel and 75mg/m^2 of body surface area of cisplatin on day 1; (3) with 75mg/m^2 of body surface area of docetaxel and 75mg/m^2 of body surface area of cisplatin on day 1, or (4) with 70 mg/m^2 of body surface area of paclitaxel on day 1, 8, and 15 and carboplatin area under the concentration-time curve (AUC) 5–6 mg/ml.min on day 1. The CCRT was given by administering 40 mg/m^2 of body surface area of cisplatin weekly or carboplatin target AUC of 2 mg/ml.min weekly for up to 7 cycles intravenously, concurrently with 66–74 Gy of radiation to the primary tumour and enlarged lymph nodes, and 50–60 Gy of radiation to regions at risk of microscopic spread given in 33–35 fractions.

Patient follow-up and endpoints

All patients underwent regular follow-up after treatment once every 3 months for the first 12 months, every 6 months for the next 24 months, and once yearly afterwards until diagnosis of recurrence or death. The disease-free survival (DFS), locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and overall survival (OS) were calculated from the date of the start of treatment to the date of any disease recurrence, locoregional recurrence, distant metastasis, and last date of follow-up or date of death, respectively.

Statistical analysis

Difference in ADC values between pre- and post-IC scans was evaluated using the paired student t-test. The diffusion weighted parameters (ADC_{pre}, $ADC_{post-IC}$, and ΔADC%) were correlated with DFS, LRRFS, DMFS and OS using univariable Cox regression. Significant parameters, together with age, sex, and T-category, N-category, overall stage, cycles of IC and cycles of concurrent chemotherapy were then added into multivariable Cox regression to identify the independent parameters for the prediction of outcome. Receiver-operating characteristic curve analysis and area under the curve (AUC) calculations of significant variables were used to identify the optimal thresholds by maximising the sensitivity plus specificity for the prediction of disease recurrence. The predictive performances of the independent parameters using the optimal thresholds for 3-year and 5-year DFS, LRRFS, DMFS and OS were compared with that of RECIST response groups using concordance statistics by the methods of both Harrel et al. and Uno et al. [32, 33]. The method of Harrel et al. provides an overall measure of differences, and the method of Uno et al. estimates differences from baseline to a specific time point [34], with 1000 bootstrapping to provide the biased-corrected c-index and corresponding 95% confidence intervals (CIs) [32, 35]. The survival rates between two groups of patients were evaluated using the Kaplan-Meier analysis, and differences in survival rates between two groups of patients were compared by log-rank test. A two-sided p-value of < 0.05 indicated statistical significance. All analyses were performed using the SPSS (24.0 version, IBM, NY, USA) statistical analysis software, SAS (9.4 version, SAS Institute Inc., Cary, NC).

Sample size calculation

According to our previous study [27], we assumed a 3-year DFS of at least 90% for the low risk group and a 3-DFS of lower than 65% for the high risk group, and the median DFS for low risk group was around 48 months in

this study. In order to detect the 25% different of 3-year DFS with one-sided alpha level of 0.05 and power of 80%, at least 64 patients were required.

Results

Patients

There were 64 patients eligible for the analysis. The patient demographics, T- and N-categories, diffusion weighted parameters (ADC_{pre}, $ADC_{post-IC}$, and ΔADC%), RECIST response groups, treatment details, outcome, and length of follow-up time are shown in Table 1.

Table 1 Patient demographics, cancer staging, measurements, RECIST groups, and outcome

Characteristic	Numbers of patients (%)
Age	
Median age (range) (years)	54 (25 to 74)
Sex	
Male	51 (79.7%)
Female	13 (20.3%)
T-category	
T1	9 (14.1%)
T2	3 (4.7%)
T3	28 (43.7%)
T4	24 (37.5%)
N-category	
N0	3 (4.7%)
N1	11 (17.2%)
N2	24 (37.5%)
N3	26 (40.6%)
Overall stage	
Stage III	22 (34.4%)
Stage IVa	42 (65.6%)
DWI parameters	
ADC_{pre} ($\times 10^{-3}$ mm^2/s)	0.82 (0.58 to 1.04)[#]
$ADC_{post-IC}$ ($\times 10^{-3}$ mm^2/s)	1.05 (0.59 to 2.38) [#]
ΔADC%	28.6% (-8.2%–174.4%) [#@]
RECIST response	
Complete response	4 (6.3%)
Partial response	34 (53.1%)
Stable disease	26 (40.6%)
Progressed disease	0 (0%)
IC treatment	
Gemcitabin + cisplatin/ others	60 (93.8%)/ 4 (6.2%)
2 cycles/ 3 cylces	16 (25.0%)/ 48 (75.0%)
Concurrent chemotherapy	
Cisplatin/ others	57 (89.1%)/ 7 (10.9%)
Median cycles (range)	6 (2–7)
Outcomes	
Disease recurrence	16 (25.0%)
Locoregional recurrence	7 (10.9%)
Distant metastases	11 (17.2%)
Death	11 (17.2%)
Follow-up	
Median time (range)(months)	44.7 (16.5 to 111.0)

# indicates data shown as median values (range); @ value calculated by using (pre - post-IC)/pre × 100% and positive value indicates decrease in size after IC

DWI for the prediction of outcome in patients with adNPC

The $ADC_{post-IC}$ increased in 60/64 (93.8%) (from 0.4 to 174.4%) patients and decreased in 4/64 (6.2%) (from − 8.2% to -0.6%) patients. The difference in ADC values between pre- and post-IC scans was statistically significant (0.81 ± 0.11 vs. $1.10 \pm 0.29 \times 10^{-3}$ mm^2/s, $p < 0.01$).

There were 16/64 (25.0%) patients with disease recurrence and 48/64 (75.0%) patients without disease recurrence at the end of the follow-up period. The 3-year DFS, LRRFS, DMFS, and OS rates were 78.5%, 89.8%, 83.0%, and 94.6% respectively. The univariable analysis showed that high ΔADC% predicted good DFS (HR = 0.959, 95CI% = 0.932–0.987, $p < 0.01$), LRRFS (HR = 0.932, 95CI% = 0.882–0.986, $p = 0.01$), and DMFS (HR = 0.967, 95CI% = 0.936–0.999, $p = 0.04$), but did not predict OS ($p = 0.40$). Neither ADC_{pre} ($p = 0.07$–0.31) nor $ADC_{post-IC}$ ($p = 0.10$–0.97) predicted survival outcome.

Table 2 shows results from the multivariable cox regression analysis for the correlation of ΔADC%, together with age, sex, T- and N-category, overall stage, cycles of chemotherapy with outcome. Results showed that the ΔADC% was an independent predictor of DFS, LRRFS, and DMFS ($p < 0.01$ to 0.03), greater ΔADC% predicting better outcome (Table 2). Furthermore, age was an independent predictor of DMFS, old age predicting poor DMFS ($p = 0.01$); cycles of IC was an independent predictor of DMFS, higher cycles of IC predicting better DFS and DMFS (both $p < 0.01$); and cycles of concurrent chemotherapy was an independent predictor of DMFS, higher cycles predicting better DMFS ($p = 0.02$) (Table 2). Other variables did not predict any of the outcome ($p = 0.06$ to 0.77) (Table 2). Two representative examples of the patient with adNPC who had no recurrence after treatment and who had local recurrence after treatment predicted by the ΔADC% are shown in Figs. 1 and 2, respectively.

To examine whether ΔADC% being the independent variable for outcome was resulted from the overfit of the confounding variables in the multivariable analysis, we then performed the multivariable analysis by only fitting the ΔADC%, together with T- and N- categories, which are two confounding variables closely relate to long-term outcome in NPC. Results showed that ΔADC% was an independent predictor for DFS, LRRFS, and DMFS ($p < 0.01$ to 0.03) (Supplementary Table 1).

Performances of RECIST groups and ΔADC% for the prediction of outcome

The optimal ΔADC% threshold using the maximised sensitivity and specificity for the prediction of disease recurrence was 34.2%. There were 39 patients categorised to

Table 2 Multivariable Cox regression analysis for the correlations of significant measurement, patient demographics, cancer staging, and treatment details with outcome

	DFS		LRRFS		DMFS	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
ΔADC%	0.945 (0.910–0.980)	**< 0.01**	0.887 (0.793–0.991)	**0.03**	0.923 (0.871–0.978)	**< 0.01**
Age	1.070 (0.994–1.152)	0.08	0.928 (0.804–1.070)	0.30	1.241 (1.061–1.451)	**0.01**
Sex (female as ref.)	1.926 (0.401–9.255)	0.41	2.935 (0.268–32.109)	0.40	5.051 (0.411–62.112)	0.21
T-category	2.458 (0.976–6.187)	0.06	2.887 (0.533–15.632)	0.22	0.923 (0.871–22.164)	0.08
N-category	1.828 (0.0.944–3.538)	0.08	0.757 (0.243–2.355)	0.63	2.447 (0.985–6.077)	0.06
Overall stage	0.168 (0.024–1.193)	0.08	1.644 (0.061–4.585)	0.77	0.560 (0.094–1.525)	0.09
Cycles of IC	0.115 (0.023–0.565)	**< 0.01**	7.110 (0.304–16.565)	0.22	0.110 (0.055–0.211)	**0.01**
Cycles of Concurrent chemotherapy	0.771 (0.527–1.129)	0.18	1.708 (0.675–4.324)	0.26	0.459 (0.245–0.858)	**0.02**

DFS = disease free survival, LRRFS = locoregional recurrence free survival, DMFS = distant metastases free survival, IC = induction chemotherapy, ADC = apparent diffusion coefficient

ΔADC% < 34.2% and 25 categorised to ΔADC% ≥ 34.2% groups (ΔADC% groups). Table 3 shows the c-indexes of the ΔADC% groups and that of RECIST groups (response vs. non-response groups) for the prediction of DFS, LRRFS, DMFS, and OS. Compared with the RECIST groups, the ΔADC% groups showed a higher c-index for 3-year (c-index: 0.47 vs. 0.71, $p < 0.01$) and 5-year DFS (c-index: 0.51 vs. 0.72, $p < 0.01$) (Table 3), but there were no statistical differences in c-indexes between RECIST groups and the ΔADC% groups for 3-year and 5-year LRRFS, DMFS and OS ($p = 0.13–0.89$) (Table 3). For the RECIST groups, the Kaplan-Meier curves showed no statistical differences in DFS, LRRFS, DMFS and OS between responder and non-responder groups ($p = 0.07–0.85$) (Fig. 3). For the ΔADC% groups, compared with those with ΔADC% < 34.2%, patients with ΔADC% ≥ 34.2% had statistically higher 3-year DFS of 100% ($p < 0.01$), LRRFS of 100% ($p = 0.03$) and DMFS of 100% ($p < 0.01$), but there was no statistical difference in OS between ΔADC% groups (Fig. 3).

Discussion

This study investigated the role of DWI obtained from the pre- and post-IC MRI scans for the prediction of long-term outcome in patients with adNPC. Our results showed that percentage change in ADC between pre- and post-IC scans (ΔADC%) was the only diffusion weighted parameter that correlated with DFS, LRRFS, and DMFS, high ΔADC% (greater % increase in ADC on the post-IC scan) predicting good outcome. Neither ADC_{pre} nor $ADC_{post-IC}$ predicted survival using any of the endpoints in this study. After adjusting confounding factors (age, gender, T- and N-categories, overall stage, and treatment), ΔADC% remained independently predictive of DFS, LRRFS and DMFS. When compared with RECIST response groups (responder vs. non-responder), the ΔADC% groups which was grouped by using the optimal ΔADC% threshold of 34.2% improved the predictive values showing a c-index increased from 0.47 to 0.71 and from 0.51 to 0.72 for 3-year and 5-year DFS, respectively. The finding indicated a reduction in the restriction of water molecules in the primary tumor after IC is a stronger indicator of long-term outcome than shrinkage in size.

In previous HNSCC studies [10–16, 18, 21], ΔADC% has shown consistent predictive values for long-term outcome and so is the most promising one for clinical practice. In these HNSCC studies, most of studies only focused on the post-treatment locoregional recurrence because that the locoregional recurrence is the main cause of death in patients with HNSCC [11, 13–16]. For NPC, although many studies have showed ΔADC% is valuable for the prediction of short-term response evaluated within 6 months after treatment on the primary tumour bed [22–24, 36], only one focused on long-term outcome [25], which showed that ΔADC% is also valuable for the prediction of long-term outcome. Results from our study provided additional confirmation in that ΔADC% also predicted long-term outcome. In keeping with the trend of ADC change for the prediction of outcome reported previously [22–25, 36], our study showed that great ΔADC% (i.e. great increase in ADC on the post-IC scan) predicted better long-term outcome. One of the possible explanations is that anti-tumour treatment

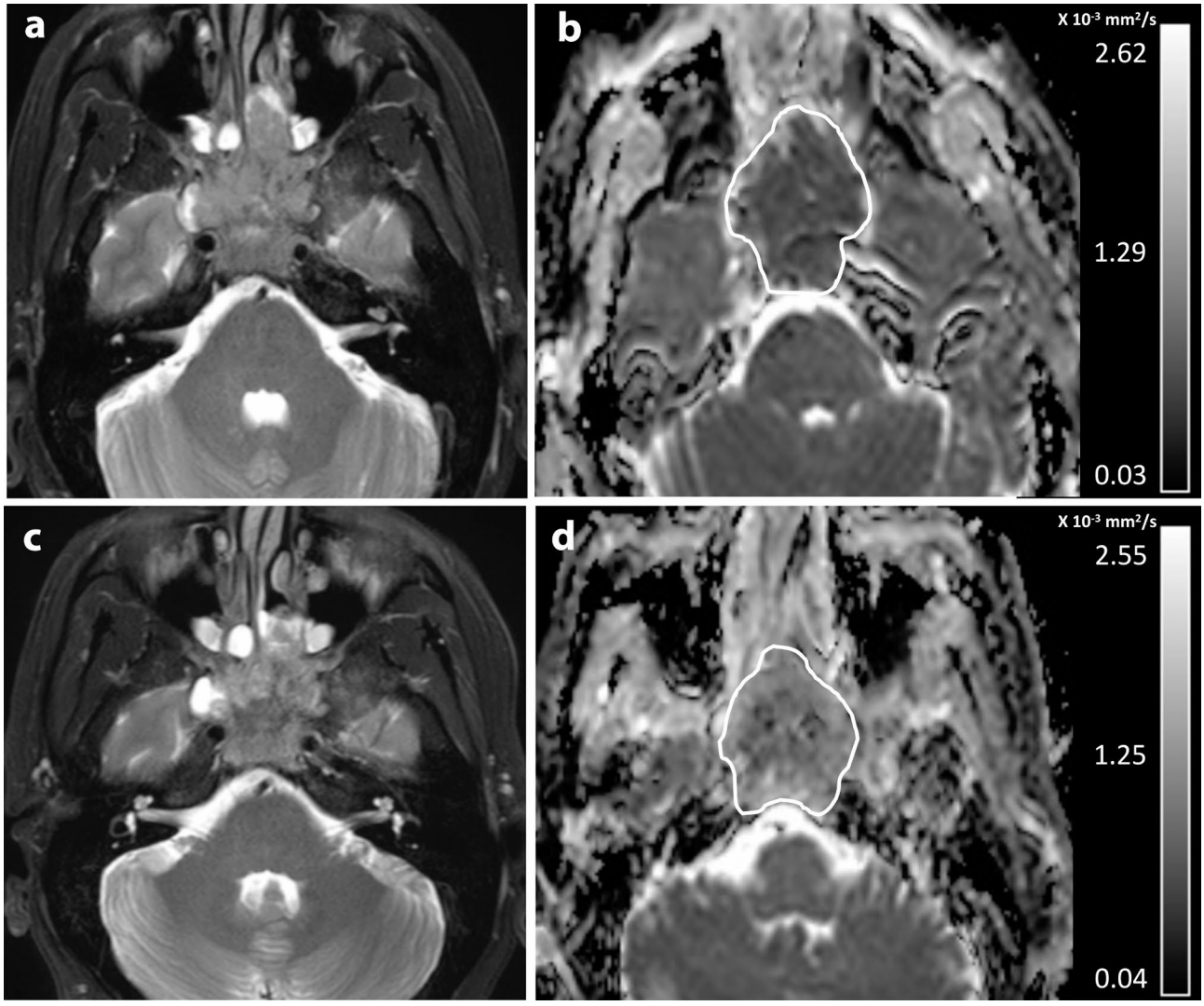

Fig. 1 Pre-treatment (**a**-**b**) and post-IC (**c**-**d**) MRIs of a patient with stage T4 NPC that had no recurrence 36 months after treatment. The axial images comprise T2-weighted fat-suppressed images (**a** and **c**) and ADC maps (**b** and **d**). The mean ADC_{pre} and $ADC_{post-IC}$ extracted from the primary NPC (white contours) on the ADC maps were 0.81×10^{-3} mm^2/s, and 1.14×10^{-3} mm^2/s, respectively and the ΔADC% was 40.7%. The good long-term outcome was predicted by a high percentage increase in mean ADC value (ΔADC% of ≥ 34.2%) on the post-IC DWI compared with that on the pre-treatment DWI.

can result in tumour cell necrosis, which is reflected by the increase in ADC values, and great increase in ΔADC% may reflect tumour cells which are sensitive to treatment, thus being likely to response to treatment and be cured.

Several ΔADC% thresholds have been proposed in the previous head and neck cancer studies for the prediction of long-term outcome [13–16, 22–25]. These thresholds ranged widely (14 – 60%) possibly because of differences in prediction scenarios and time-intervals between pre- and inter-treatment DWI scans. Nevertheless, all of these proposed thresholds are similar to or above the intrinsic variability of DWI (about ΔADC% of 15%). In our study, we identified the optimal ΔADC% threshold of 34.2% by considering the predictive power for disease recurrence. We showed that patients with a ΔADC% of ≥ 34.2% had 100% survival rates for 3-year DFS, LRRFS, DMFS and OS, which indicated this group of patients did not have locoregional recurrence or distant metastases at least 3 years after the treatment. We believe that the ΔADC% of ≥ 34.2% could be clinically useful to confirm NPC patients, who do not need additional adjuvant chemotherapy or advanced treatment or close post-treatment follow-up. This group of patients would avoid complications and side effects from the unnecessarily additional treatment. Meanwhile, medical resources can be precisely allocated to other patients particularly in areas with limited resources. Nevertheless, it is worthy to note that the use of ΔADC% of ≥ 34.2% standard alone identified only about 50% of patients (25/48, 52%) who had

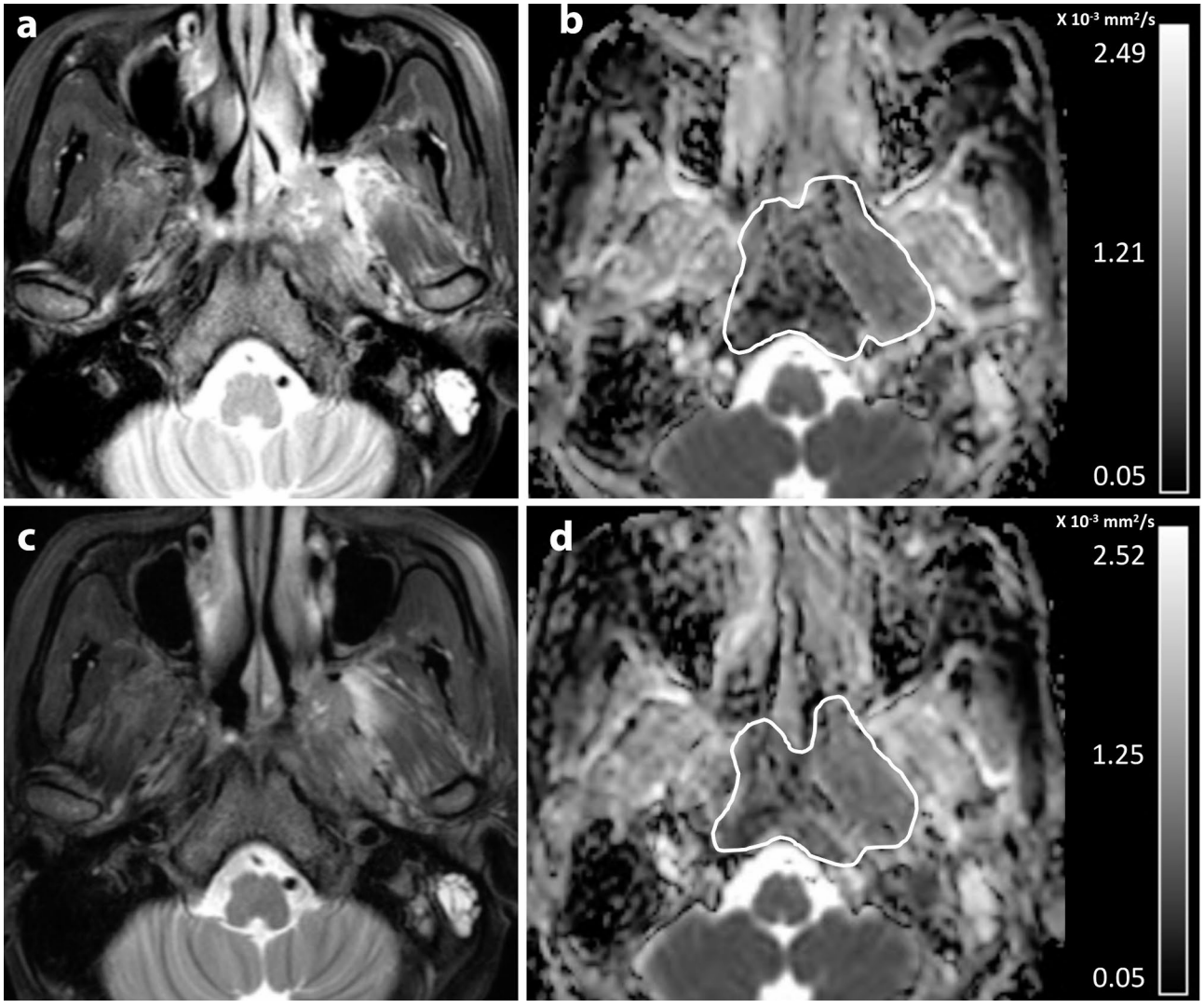

Fig. 2 Pre-treatment (**a**-**b**) and post-IC (**c**-**d**) MRIs of a patient with stage T3 NPC that had recurrence 28 months after treatment. The axial images comprise T2-weighted fat-suppressed images (**a** and **c**) and ADC maps (**b** and **d**). The mean ADC_{pre} and $ADC_{post-IC}$ extracted from the primary NPC (white contours) on the ADC maps were 0.89×10^{-3} mm^2/s, and 0.99×10^{-3} mm^2/s, respectively and the ΔADC% was 11.2%. The poor long-term outcome was predicted by a low percentage increase in mean ADC value (ΔADC% of < 34.2%) on the post-IC DWI compared with that on the pre-treatment DWI.

no disease recurrence. There still has space to improve the performance to maximise the numbers of patients to benefit from the precise medical management. Therefore, other predictors that play complementary role to this DWI parameter are suggested to be included in the future clinical practice to identify patients at low risk of disease recurrence particularly from those who have ΔADC% of < 34.2%.

For patients with adNPC, the IC is routinely used to shrink the size of tumours to secure more critical tissues from the RT treatment and to diminish the micro disseminated tumour cells to decrease the risk of disease recurrence. The size of tumour shrinkage may be a predictive value for long-term outcome because tumour without shrinkage after IC may be resistant to treatment, thus being at risk of recurrence afterwards. Some previous head and neck cancer study investigated tumour responses to IC evaluated by using the RECIST guideline for the prediction of long-term outcome [37, 38]. In keeping with the results reported by Zeng et al. [38], our results showed that RECIST response groups did not predict outcome. However, conflicting results were reported [37]. The possibly explanation for the discrepancy is that the unidimensional measurement recommended by the RECIST guideline may not accurately reflect shrinkage of head and neck cancer during treatment.

In this study, we also investigated the predictive values of DWI on the pre-treatment scan for the prediction of long-term outcome. In keeping with our previous findings [39–41], this study showed that ADC_{pre} did not

Table 3 C-index of the RECIST groups and ΔADC% groups for 3- and 5- year DFS, LRRFS, DMFS and OS

	DFS		LRRFS		DMFS		OS	
	C-index (95%CI)	**P-value**	**C-index (95%CI)**	**P-value**	**C-index (95%CI)**	**P-value**	**C-index (95%CI)**	**P-value**
3-year								
RECIST groups	0.47 (0.41–0.52)	Ref.	0.72 (0.60–0.85)	Ref.	0.54 (0.44–0.64)	Ref.	0.45 (0.33–0.58)	Ref.
ΔADC% groups	0.71 (0.68–0.75)	**< 0.01**	0.70 (0.66–0.73)	0.89	0.71 (0.67–0.74)	0.13	0.69 (0.63–0.75)	0.29
5-year								
RECIST groups	0.51 (0.45–0.58)	Ref.	0.69 (0.56–0.84)	Ref.	0.57 (0.48–0.66)	Ref.	0.53 (0.43–0.64)	Ref.
ΔADC% groups	0.72 (0.68–0.77)	**< 0.01**	0.70 (0.68–0.73)	0.78	0.71 (0.68–0.75)	0.22	0.60 (0.52–0.68)	0.68

RECIST groups = responder group vs. non-responder group

ΔADC% groups = ΔADC% < 34.2% group vs. ΔADC% ≥34.2% group

DFS = disease free survival, LRRFS = locoregional recurrence free survival, DMFS = distant metastases free survival, OS = overall survival, ADC = apparent diffusion coefficient

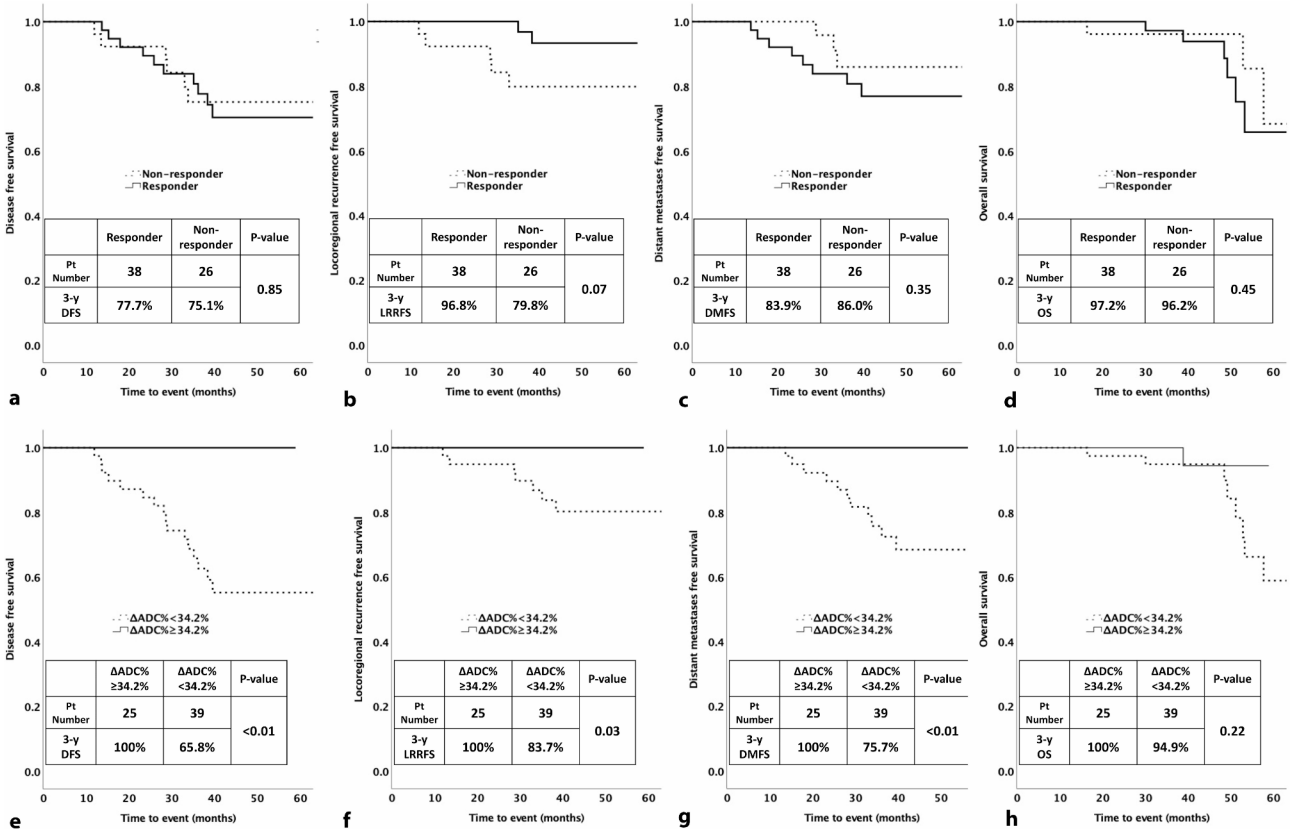

Fig. 3 shows Kaplan-Meier curves of the RECIST groups (response and non-response) (**a**-**d**) and the ΔADC% groups (< 34.2% and ≥ 34.2%) (**e**-**h**) for the prediction of disease free survival (DFS) (**a** and **e**), locoregional recurrence free survival (LRRFS) (**b** and **f**), distant metastases free survival (DMFS) (**c** and **g**), and overall survival (OS) (**d** and **h**). Differences in all survivals between RECIST groups were not statistically significant ($p = 0.07$ to 0.85)(**a**-**d**) and that between the ΔADC% groups were statistically significant ($p < 0.01$ to 0.03), except that in OS ($p = 0.22$). Compared with those with RECIST responder, patients with a ΔADCV% of ≥ 34.2% showed a great in 3-year DFS (100% and 77.7%, respectively), in 3-year LRRFS (100% and 96.8%, respectively), in 3-year DMFS (100% vs. 83.9%, respectively) and in 3-year OS (100% and 97.2%, respectively

predict any of the long-term outcome, although some other studies showed conflicting results [42–44]. We further investigated predictive value of mean ADC on the post-IC for long-term outcome in NPC, which showed that absolute $ADC_{post-IC}$ was not a predictor. Interestingly, we found that patients with old age were more likely to have distant metastases, possibly because that the biological degeneration of immune system in elderly

increases the risk of residual tumour cells escaping from the self-immune surveillance. In terms of treatment, we showed that the increase in the cycles of chemotherapy predicted better outcome, probably due to the benefits from chemotherapy to decrease the risk of distant metastases. However, there have conflicting results been reported [45–48], possibly resulted from the retrospective design of the study. Therefore, further prospective studies dedicate to the investigation of the role of cycles of chemotherapy for outcomes are suggested.

This study has limitations. First, this study only included patients with adNPC and treated with IC + CCRT. The predictive value of ΔADC% for long-term outcome in patients who treated only by RT or CCRT remains unknown. Second, this study only focused on the assessment of the primary tumour, and metastatic nodes were not considered in the analysis. Third, although the median follow-up time of patients without relapse in this study was long (44.7 months), it is possible that a few patients may still relapse with a longer follow-up time. Fourth, the study was restricted to only one intra-treatment time point, and it is unknown if this is the optimal time for early DWI assessment. Fifth, this study did not include other recently proposed imaging-related methods, such as the volumetric analysis [27] to evaluate treatment response as unlike RECIST guideline, these methods are yet widely applied to clinical practice. Furthermore, we wish that our study could provide another option to accurately predict long-term outcome in adNPC in which volumetric analysis is time-consuming. Six, as this is one of the first NPC studies that investigated the predictive value of ΔADC% for long-term outcome, we only included patients who had the same DWI protocols performed in both pre- and post-IC MRIs to minimise the potential biases from the intrinsic variability of scanning protocols. Therefore, the generalisibility of findings from this study requires further external prospective validation studies to examine before ΔADC% is applied to clinical practice. Furthermore, plasma Epstein-Barr virus DNA levels were not included in the analysis because not all patients had this test routinely at different phases of treatment.

Conclusion

Results suggested that percentage change in DWI on the pre-treatment and post-IC scan (ΔADC%) independently predicted long-term outcome and was superior to RECIST response groups for the prediction of treatment outcome in patients with adNPC. A great increase in ΔADC% (i.e. a great percentage of the increase of ADC values between pre- and post-IC MRIs) predicted good outcome and the ΔADC% achieved better performances for the prediction of DFS compared with RECIST response groups. A ΔADC% threshold of ≥ 34.2% may be of valuable for identifying patients without disease recurrence after treatment, who can potentially benefit from the reduced post-treatment surveillance and exemption of additional treatment (i.e. adjuvant chemotherapy).

Abbreviations

ADC	Apparent Diffusion Coefficient
CR	Complete Response
DFMS	Distant Metastases Free Survival
DFS	Disease Free Survival
DWI	Diffusion Weighted Imaging
LRRFS	Locoregional Recurrence Free Survival
NPC	Nasopharyngeal Carcinoma
OS	Overall Survival
PR	Partial Response
PD	Progressed Disease
SD	Stable Disease

Supplementary Information

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Supplementary Material 1

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Author contributions

Guarantors of integrity of entire study: QYH Ai. Study concepts/study design: QYH Ai. Data acquisition: HS Leung, EP Hui, BBY Ma, AD King. Data analysis: QYH Ai, HS Leung, FKF Mo, K Mao, LM Wong, and YY Liang. Data interpretation: QYH Ai, FKF Mo, and K Mao. Literature research: QYH Ai, K Mao, and YY Liang. Manuscript drafting: QYH Ai. Manuscript editing: All authors. Approval of final version of submitted manuscript: all authors.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Written informed consent was waived by the Institutional Review Board. Institutional Review Board approval was obtained (ref. no. CRE-2022.545).

Consent for publication

N.A.

Competing interests

The authors declare no competing interests.

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