

Case Report

Early intra-treatment diffusion weighted magnetic resonance imaging in patients with recurrent nasopharyngeal carcinoma treated with nivolumab

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ABSTRACT

Immune check point inhibitors have demonstrated promising efficacy in patients with recurrent or metastatic nasopharyngeal carcinoma (NPC) in phase I and phase II trials. Early identification of treatment response is important in these patients. This report aimed to document the early intratreatment diffusion weighted magnetic resonance imaging (DW-MRI) findings in NPC patients following treatment with the programmed cell death-1 inhibitor, nivolumab. Two consecutive patients with histologically confirmed recurrent undifferentiated NPC treated with nivolumab were prospectively recruited. Nivolumab was administered at a dosage of 3 mg/kg intravenously every 2 weeks. Patients underwent magnetic resonance imaging examinations at baseline, and at 3 and 5 weeks after commencement of treatment. Intratreatment changes in tumour volume and apparent diffusion coefficient (ADC_{mean}) were calculated. The endpoints were objective response by response evaluation criteria in solid tumors and survival. In patient 1, an intratreatment ADC increase at 5 weeks corresponded with anatomical tumour volume reduction and a better long-term survival outcome (progression free survival 1.3 years, overall survival 2.9 years). In patient 2, an intratreatment ADC decrease at 5 weeks corresponded to progressive disease and worse outcome (progression free survival 0.0 years, overall survival 0.9 years). Intratreatment ADC changes at 3 weeks were not associated with response outcome. These cases suggest that intratreatment changes in ADC at 5 weeks may potentially predict tumour response in patients treated with nivolumab. Dedicated studies are needed to clarify these findings and fully characterise patterns of treatment related ADC change.

Keywords: Nasopharyngeal carcinoma, Diffusion magnetic resonance imaging, Immunotherapy, Immune checkpoint inhibitors, Therapeutic response

INTRODUCTION

In recent years, immune check point inhibitors have emerged as a promising anticancer treatment, demonstrating clinical benefit in many solid tumours. Nasopharyngeal carcinoma (NPC) is frequently associated with Epstein-Barr virus (EBV) and upregulation of the programmed cell death-1 (PD-1)

receptor and its ligand, programmed death ligand-1 (PD-L1) ¹, and thus disruption of the PD-1 or PD-L1 mediated signalling by immune checkpoint inhibitors could increase tumour elimination by the immune system in this disease. Recently, humanized monoclonal antibodies against PD-1 such as pembrolizumab and nivolumab, have shown promising efficacy in patients with recurrent or metastatic NPC in phase I and phase II trials.²⁻⁴

However, the response and clinical benefit with these drugs may be only limited to a specific subset of patients.

Early identification of treatment response is important to allow modifications in the treatment regimen and minimization of unnecessary systemic toxicity associated with ineffective treatment. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a well-established functional MRI technique which can detect alterations in water mobility and tumour microstructural changes in response to treatment. Studies have shown that the response of many tumours, including NPC, can be detected by an early intratreatment increase in the apparent diffusion coefficient (ADC) value.^{5,6} Histologically, this is associated with cell death and reduction in cellular density in response to cytotoxic treatment. Non-responding tumours tend to have a lower% rise in ADC, or a fall in ADC during treatment.⁷ These typical patterns of tumour response have been shown in patients following conventional chemotherapy or chemoradiotherapy. There is a further need to understand the early DW-MRI changes in response to targeted immunotherapies, such as immune check point inhibitors due to their different mechanism of action. To our knowledge, in patients with NPC, it is unknown if treatment with immune check point inhibitors may induce early changes in DW-MRI that allow prediction of treatment response.

The aim of this preliminary report was to document the early DW-MRI findings in patients with NPC following treatment with the immune check point inhibitor, nivolumab.

CASE REPORT

Two consecutive patients with histologically confirmed recurrent undifferentiated NPC planned for treatment with the immune checkpoint inhibitor nivolumab were prospectively recruited. These patients were also separately included in the phase II NCI-9742 trial which assessed the clinical activity and biomarker response to nivolumab but not the treatment imaging changes.⁴ Treatment with nivolumab was at a dosage of 3 mg/kg intravenously every 2 weeks on a 4 week cycle. Patients underwent MRI examinations of the head and neck and distant liver metastases prior to nivolumab treatment (baseline imaging), and at 3 weeks, and 5 weeks after treatment (one week following the 2nd and 3rd nivolumab doses respectively).

Imaging protocol

MRI was performed using a Philips Achieva TX 3.0-T scanner (Philips Healthcare) with a body coil for radiofrequency transmission and a 16-channel Philips neurovascular phased-array coil for reception for head and neck and dedicated body coil for liver. DWI was acquired using a fat-suppressed, spin-echo, echo-planar imaging sequence with parameters of number of slices, 9;

repetition time/echo time, 1900/45 ms; field of view, 230×230 mm; section thickness, 4 mm; and 6 b-values of 0, 200, 400, 600, 800 and 1000 s/mm² for nasopharynx and parameters of number of slices, 35; repetition time/echo time, 2650/50 ms; field of view, 360×300 mm; section thickness, 5 mm; 3 b-values of 0, 300, 600 s/mm² for liver. Anatomical MRI included a fat-suppressed T2-weighted turbo spin-echo sequence and a T1-weighted turbo spin-echo sequence.

Imaging analysis

Olea Sphere (version 3.0; Olea Medical SA) was used for all the post-processing steps by implementing a Bayesian probability-based algorithm using six b-values (0, 200, 400, 600, 800, 1000 sec/mm²) for the primary tumour and 3 b-values (0, 300, 600 sec/mm²) for liver metastases to fit a mono-exponential diffusion model to calculate the conventional ADCs. On the ADC maps, the region of interest was manually drawn around the whole primary NPC and the largest liver metastatic tumour by a researcher with 4 years of experience of NPC MRI. The mean values of ADC for these two entities were obtained. The total volumes of the malignant entities were obtained by manually outlining the cross-sectional area of the abnormalities on each slice, summing the cross-sectional areas, and multiplying by the slice thickness of 4 for the primary tumour and 5 mm for the liver metastasis.

Change in ADC

Changes in ADC (Δ ADC) and percentage of ADC changes (% Δ ADC) were calculated as follows:

$$\Delta\text{ADC} = \text{ADC}_{\text{mean}(t)} - \text{ADC}_{\text{mean}(t-1)};$$

$$\%\Delta\text{ADC} = \frac{\text{ADC}_{\text{mean}(t)} - \text{ADC}_{\text{mean}(t-1)}}{\text{ADC}_{\text{mean}(t-1)}} \times 100$$

where $\text{ADC}_{\text{mean}(t)}$ refers to the ADC_{mean} obtained at a time point (t), and $\text{ADC}_{\text{mean}(t-1)}$ refers to the ADC_{mean} obtained at the prior imaging time point (t-1). Considering ADC repeatability, a change in ADC of 25% or greater was considered outside the expected ADC variability, and assessed as reflecting true changes in tumour ADC. A change in ADC of less than 25% was assessed as within the range of expected ADC variability.

Endpoints

The primary end points objective response by the response evaluation criteria in solid tumors criteria, and duration of progression free survival and overall survival. Patients were assigned to one of the following categories at each of the follow up intervals: complete response, partial response, stable disease, progressive disease, or inevaluable response. The best overall response was recorded for each patient. Clinical follow up data was used to calculate the duration of progression free survival

and overall survival, taken as the length of time after commencement of nivolumab to disease progression or death from any cause respectively.

Case 1

Clinical history

A 71-year-old man with AJCC/UICC stage 4, T2N0M1 non keratinizing undifferentiated nasopharyngeal carcinoma with lung metastases, was initially treated with

neoadjuvant conventional chemotherapy and radiotherapy achieving complete remission. Five months after treatment, he presented with blood stained post nasal drip. MRI showed locoregional recurrence with small volume primary tumour and unilateral nodal disease. Local recurrence was subsequently confirmed with rhinoscopy and nasopharyngeal biopsy. Computed tomography of the chest, abdomen and pelvis demonstrated recurrent lung metastases. He was commenced on nivolumab and had a subsequent response to nivolumab which lasted well over 12 months.

Table 1: Intratreatment tumour volume, ADC and clinical endpoints in case 1 (responder).

	Tumour volume (cm ³)	Tumour volume change (%)	ADC _{mean} (x10 ⁻³ mm ² /s)	ΔADC (x10 ⁻³ mm ² /s)	%ΔADC	Overall ADC change*	Overall objective response	Progression free survival (years)	Overall survival (years)
Baseline	5.00	N/A	0.74	N/A	N/A	N/A	N/A		
3 weeks	4.40	-12.00	0.76	0.15	2.01	Static	PR	1.30	2.90
5 weeks	3.20	-27.30	1.19	0.44	57.09	Increase	PR		

*Taking into account expected ADC variation; PR=partial response, N/A=not applicable

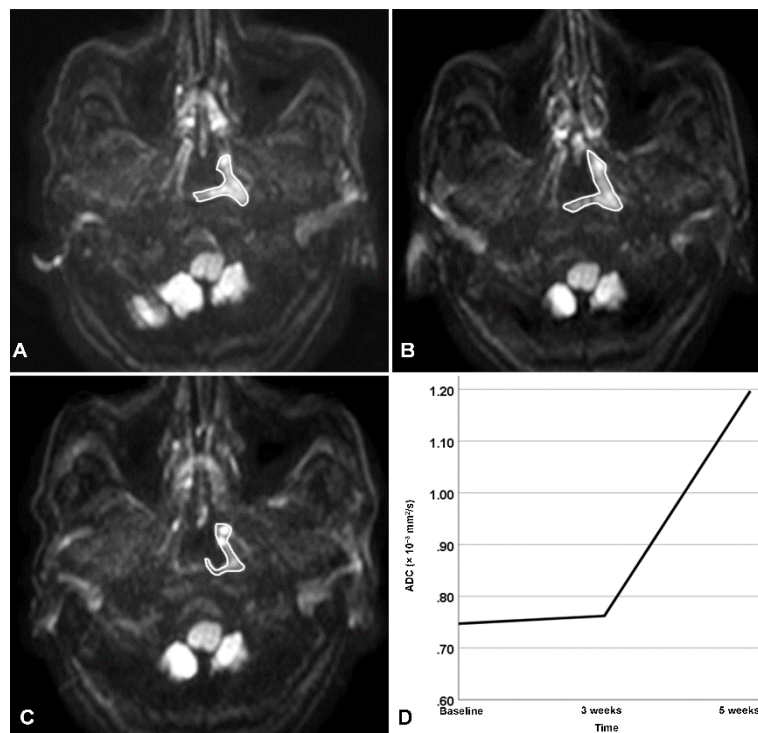


Figure 1: DWI images (b-value = 1000 sec/mm²) of the primary recurrent nasopharyngeal tumour in case 1 obtained at (a) baseline, (b) 3 weeks, (c) 5 weeks after commencement of nivolumab and (d) tumour ADC changes during treatment.

The ADC_{mean} was static at 3 weeks and increased at 5 weeks.

Change in ADC and response

The recurrent primary tumour volume at baseline was 5.0 cm³, and baseline ADC_{mean} of the tumour was 0.786x10⁻³ mm²/s. The intratreatment ΔADC and %ΔADC are shown in Table 1 and Figure 1. The tumour

ADC_{mean} showed no significant change at 3 weeks, but had increased at 5 weeks. The patient achieved reduction in the volume of the local tumour and stable pulmonary metastatic disease at 3 weeks and 5 weeks. The duration of progression free survival was 1.3 years and overall survival 2.9 years.

Case 2

Clinical history

A 56-year-old man with AJCC/UICC stage III (T2aN2M0) non keratinizing undifferentiated nasopharyngeal carcinoma initially treated with chemotherapy and radiotherapy, re-presented 3 years later with bone, liver and abdominal lymph node metastases. There was no locoregional recurrence. He failed multiple lines of chemotherapy with progressive metastatic disease prior to commencement of nivolumab. His cancer progressed despite treatment with nivolumab.

Change in ADC and response

The liver tumour volume and ADC_{mean} measurements were taken from the largest left lobe liver metastasis. There was a relatively low baseline ADC_{mean} of $1.296 \times 10^{-3} \text{ mm}^2/\text{s}$. The intratreatment ΔADC and $\%\Delta\text{ADC}$ (Table 2, Figure 2), shows an early increase in the ADC_{mean} at 3 weeks, followed by a decrease in ADC_{mean} at 5 weeks. The overall objective response was progressive disease at 3 weeks and 5 weeks. The duration of progression free survival was 0.0 years and overall survival 0.9 years.

Table 2: Intratreatment tumour volume, ADC and clinical endpoints in case 2 (non-responder).

	Tumour volume (cm ³)	Tumour volume change (%)	ADC _{mean} (x10 ⁻³ mm ² /s)	ΔADC (x10 ⁻³ mm ² /s)	$\%\Delta\text{ADC}$	Overall ADC change*	Overall objective response	Progression free survival (years)	Overall survival
Baseline	28.90	N/A	1.29	N/A	N/A	N/A	N/A		
3 weeks	43.50	+50.50	1.73	0.44	34.18	Increase	PD	0.00	0.90
5 weeks	47.70	+9.70	1.26	-0.47	-27.49	Decrease	PD		

*Taking into account expected ADC variation; PD- progressive disease, N/A- not applicable

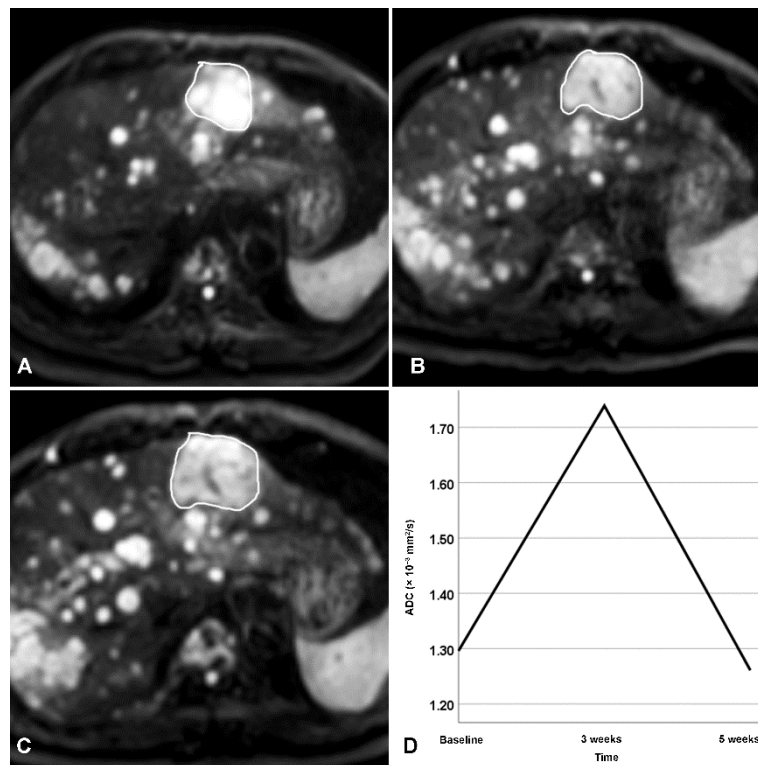


Figure 2: DWI images (b-value=600 sec/mm²) of the nasopharyngeal carcinoma liver metastases in case 2 obtained at (a) baseline, (b) 3 weeks, (c) 5 weeks after commencement of nivolumab and (d) tumour ADC changes during treatment, the ADC_{mean} increased at 3 weeks and decreased at 5 weeks.

DISCUSSION

The potential of DW-MRI to predict tumour response very early in the course of anticancer treatments has been

described in a number of studies.^{7,8} In patients with NPC as well as other solid tumours, changes in ADC values as early as 2 weeks after initiation of chemotherapy or chemoradiotherapy have correlated with clinical tumour

response.⁷ However, in the current two cases, no relationship between Δ ADC and tumour response could be seen with the very early DW-MRI performed at 3 weeks after commencement of nivolumab (following the 2nd dose). Specifically, a significant Δ ADC at 3 weeks was only observed in 1 patient (patient 2). Here, the tumour ADC_{mean} increased but progressive enlargement of the tumour was seen. In the other patient, no significant change in tumour ADC_{mean} was observed at 3 weeks despite reduction of tumour volume. These findings question the reliability of very early ADC changes at 3 weeks in predicting tumour response to immune checkpoint inhibitors compared to conventional treatments such as chemotherapy or radiotherapy.

We note that at 5 weeks (following the 3rd nivolumab dose), significant changes in ADC_{mean} in both patients appeared to more reliably correspond with tumour response as well as long term survival outcome. In Patient 2, a decrease in ADC_{mean} at 5 weeks was noted with an anatomical increase in tumour volume and overall disease progression. In the longer term, this patient showed a shorter overall survival. In patient 1, an increase in ADC_{mean} was observed with reduction in tumour volume. This patient demonstrated a longer progression free survival and overall survival.

Assessment of treatment related changes in ADC values requires consideration of ADC variability. Generally, ADC has demonstrated high repeatability in imaging across a wide range of tumour sites and patient populations. From the published literature, a study of head and neck squamous cell carcinoma reported a repeatability coefficient for ADC_{mean} values of 15%.⁹ In assessment of extracranial soft tissues, Winfield et al assessed the repeatability of ADC values across multiple extracranial body sites and reported a change in ADC of 20% as the upper 95% limit of agreement for ADC_{mean}.¹⁰ A further study in abdominal DW-MRI reported repeatability coefficients of 24.7% for the liver.¹¹ Taking a Δ ADC of less than 25% as within the range of ADC variability in this report, the Δ ADC values attributable to treatment related change for our cases (above the 25% limit) were -27.49 to 34.18% for the liver, and 57.09% for the nasopharynx, which is comparable to values quoted elsewhere in the literature. It is worthy to mention that recent developments in diffusion imaging techniques by using intravoxel incoherent motion has achieved smaller variance in the scan-rescan reproducibility in the liver.^{12,13} This may suggest that intravoxel incoherent motion may be an alternative to monitor treatment response for liver metastases in the future.

CONCLUSION

In summary, we provide a preliminary report of early treatment ADC changes in NPC patients undergoing treatment with immune check point inhibitors. There was no relationship between the very early intratreatment ADC at 3 weeks and clinical response, but ADC values

after 5 weeks were observed to potentially correspond with anatomical tumour response, as well as long term survival outcome. Dedicated studies in this area with larger sample sizes are needed to investigate the findings from this report, fully characterise patterns of treatment related ADC change to determine the best time point for assessment and the added value of DW-MRI to anatomical changes for predicting tumour response.

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Ethical approval: Not required

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