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Diffusion-weighted magnetic resonance imaging for early response assessment of chemoradiotherapy in patients with nasopharyngeal carcinoma

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ABSTRACT

Purpose: To prospectively evaluate the feasibility of diffusion-weighted magnetic resonance imaging (DWI) for monitoring early treatment response to chemoradiotherapy (CRT) of nasopharyngeal carcinoma (NPC).
Materials and methods: Thirty-one patients with stage III and IV NPC were enrolled in this study from February 2012 to November 2012 T2-weighted and DWI sequences with diffusion factor of 0 and 800mm²/s were performed using a 3.0 T Philips Achieva TX scanner at baseline and 3 days, 20 days (after the first cycle of chemotherapy), 50 days (6 days after radiotherapy initiation) after neoadjuvant chemotherapy (NAC) initiation. The diameter of each primary lesion and target metastatic lymph node before and after the first cycle of NAC was measured and classified into stable disease (SD), partial response (PR) or completed response (CR) based on RECIST 1.1. The apparent diffusion coefficient (ADC) values and changes compared to baseline at each time point were compared between responders (CR and PR) and non-responders (SD). The rates of residual at the end of CRT were compared between these two groups.
Results: A significant increase in ADC was observed at each stage of therapy (P=.001) in lesions of primary and metastatic. The ADC values (ADC), ADC changes (ΔADC) and percentage ADC changes (Δ%ADC) of day 20 in responders were significantly higher than in non-responders for both primary lesions (p=.005, p=.006, p=.008, respectively) and metastatic lymph nodes (p=.002, p=.002, p=.003). Non-responders showed a higher rate of residual for both primary lesions (p=.008) and metastatic lymph nodes (p=.024) than responders.
Conclusions: DW MR imaging allows for detecting early treatment response of NPC. Patients with high ADC values and large ADC increase early after NAC initiation tended to respond better to CRT. Thus, accessing the curative effect of NAC in advanced NPC provides the opportunity to adjust following CRT regimen.

1. Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common malignancies in China and South Asia. Unlike most other squamous cell carcinomas of the head and neck, NPC has a distinct epidemiology, etiology, and histological features. Most patients diagnosed with NPC tend to present with stage III or IV disease as a result of its deep location and vague symptoms. Although radiotherapy is the primary treatment modality for all locally and regionally confined stages and the control of early-stage NPC is usually successful, the prognosis of locally advanced NPC treated with radiotherapy alone remains poor because of local relapse and distant metastasis [1–4]. The curative effect of neoadjuvant chemotherapy (NAC) in advanced NPC has been tested and investigated over the past decade. The results of these clinical trials have varied while most studies have reported that neoadjuvant chemotherapy is a relatively safe and effective method of treating locally advanced NPC and significantly improve its survival by reducing distant metastases [5–9]. Combined chemotherapy and radiation therapy has become the current standard treatment of advanced NPC.

Early detection of treatment response of tumor could help to detect potential persistent or recurrent lesion at an early stage [10–12]. There are various imaging modalities or techniques that can be used to evaluate the early response of the tumor to treatment. 18 F-Fluoro-deoxy-glucose positron emission tomography (18 F-FDG-PET) can provide additional value for the prediction of treatment outcome and tumor recurrence. However, treatment-induced inflammation and low spatial resolution may decrease its accuracy [13–15]. Magnetic resonance imaging (MRI) is available for detecting the response to chemoradiotherapy (CRT) of NPC by monitoring the tumor size and functional metrics changes such as the apparent diffusion coefficient

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(ADC), which can be used to detect alterations in water mobility which reflect changes in tissue structure at the cellular level [16]. Diffusion-weighted imaging (DWI) has been a valuable tool for monitoring treatment response with detectable changes in ADC produced by tumor cell density, proliferation and apoptosis [17,18].

There were some clinical studies reported that DWI was available for evaluating the tumor response using ADC value before the morphological changes[19,20]. Previous studies have also shown that DWI can be used in prediction of treatment response and survival in squamous cell carcinomas of the head and neck [21,22]. Golden et al.[23] revealed that a complete response to induction chemotherapy is a significant predictor of overall survival. However, to our knowledge, there are no studies focusing on patients with NPC undergoing NAC and track early treatment induced changes in MRI derived parameters. Accurate and timely detection of presence of responsive or non-responsive tumor can be critical in malignancy treatment management. The application of conventional imaging plus DWI is potentially useful in the evaluation of the optimal time window for alternative treatment regimens. Therefore we conducted this preliminary study to assess the feasibility and reliability of ADC measurements of treatment response and prediction of treatment outcome early after CRT for NPC in correlation with alterations in tumor size in both primary tumors and metastatic lymph nodes.

2. Materials and methods

2.1. Patients' population and treatment

The study protocol was approved by the Regional Committee for Medical and Health Research Ethics, and all patients signed written informed consent. Thirty-five newly diagnosed NPC patients with no prior treatment and referred to chemoradiotherapy were enrolled from February 2012 to November 2012. Four patients were later were excluded because of distant metastases before treatment, and two had inadequate DW-MR image quality due to serious motion on MRI examinations. Hence, the final study population consisted of 31 patients (26 males and 5 females, age 45 ± 10.1 years).

All patients' TNM status were determined by radiologists with reference to the latest 7th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system after department discussion and consensus based on MR examination of head and neck and radiograph or computed tomography examination of the chest, ultrasound or nuclear medicine examination results on the other part of the body. Individual patients' data were shown in Table 1. Patients were candidates for two cycles ($n = 25$) or three to four cycles ($n = 6$) of neoadjuvant chemotherapy (all patients were repeated in 21 ± 3.2 days per cycle). Twenty-nine patients were given a dose of 100 mg/m^2 cisplatin (Qilu Pharmaceutical Co, Ltd, Shandong, China) on days 1, 2, 3 accompanied with 135 mg/m^2 Taxol (Hainan Chuntch Pharmaceutinal Co, Ltd. Hainan, China) on day 1 while another 3 patients were given a dose of 100 mg/m^2 cisplatin on days 1, 2, 3 accompanied with 1,000 mg/m^2 Gemcitabine (Jiangsu Hansoh Pharmaceutinal Co, Ltd, Jiangsu, China) on day 1. Two patients gave up further radiotherapy after NAC. Radiotherapy was delivered to a total dose of 70 Gy by means of a hybrid fractionation schedule in 29 patients over a total of 44 to 63 days (35 daily fractions of 220 cGy; n = 26, 32 daily fractions of 200 cGy; n = 3), with concurrent chemotherapy (100 mg/m^2 cisplatin on days 1 and 22 of radiation treatment; n = 21) and/or immunotherapy (two patients completed one cycle DC-CIK immunotherapy and one patient with Cetuximab (Merck KGaA, Darmstadt, Germany) according to the instructions).

Table 1
Individual patients' data.

Patient	Age	Gender	Staging
1	18	M	T4N2
2	43	F	T4N3
3	49	M	T2N2
4	66	M	T4N1
5	46	M	T2N3
6	47	M	T3N2
7	44	M	T4N2
8	43	M	T2N2
9	42	M	T3N2
10	34	M	T2N2
11	45	M	T3N2
12	46	M	T1N2
13	39	M	T2N3
14	46	M	T3N1
15	49	M	T4N3
16	45	F	T3N2
17	37	M	T4N2
18	48	M	T4N3
19	68	F	T2N2
20	54	M	T4N2
21	50	M	T4N1
22	57	M	T4N2
23	34	F	T3N3
24	36	M	T3N1
25	51	M	T4N2
26	58	M	T4N2
27	48	M	T4N1
28	29	M	T2N2
29	41	M	T2N2
30	35	M	T2N1
31	50	F	T2N3

Abbreviation: M = Male, F = Female.

2.2. Pre-treatment and follow-up evaluation

Following-up was done to review treatment response and lesion relapse. The current study focused on assessing local control of the primary disease and metastatic lymph nodes. Additional therapeutic strategies were done at the end of chemoradiotherapy for potential partial responders/non-responders including boost dose radiotherapy, adjuvant chemotherapy or cytokine-induced killer therapy that made it difficult to assess the role of induction chemotherapy. Thus, the status at the end of CRT was used as the clinical endpoint in this study. All stable disease (SD), partial response (PR) or completed response (CR) lesions were confirmed by MRI examination based on RECIST 1.1 criteria [24]. After the first cycle of NAC, PR lesions were categorized into responders, and non-responders referred to SD lesions based on MR examination. At the end of CRT, we categorized lesions as residual lesion and CR [24]. Patients diagnosed with residual primary lesions as MRI examination suggested residual soft tissues or thickening of the mucous membrane of the nasopharynx with local bulges.

All subjects were scheduled for receiving five MRI studies during the courses of treatment prospectively, including exams at pre-treatment (Pre), 3rd day (Day3), 20th day (Day20, one cycle of NAC) after neoadjuvant chemotherapy initiation, 6th days after radiotherapy initiation (Day50) and at the terminal of CRT (Post) respectively. Although it was difficult to keep the exact timing of serial MRI scans for all patients, all efforts were made to minimize this variability. The pre-treatment examinations were conducted at 4 ± 1.77 days (range, 1–7 days) before chemotherapy, 3.42 ± 0.62 days (range, 3–5 days) for day 3 examinations and 21 ± 1.13 days (range, 19–24 days) for day 20 examinations after initiation of chemotherapy, and 48.22 ± 5.05 days (range, 39–55 days) after initiation of chemotherapy for day 50 examinations. Post-treatment scans were done at 2.3 ± 1.9 days before or after completion of treatment. Variances at every scan time-point were mainly due to the