A Potential Biomarker from Diffusion Weighted Imaging and Parametric Response Map Analysis for Treatment Response Prediction in Nasopharyngeal Cancer

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Abstract. Diffusion-weighted imaging (DWI) is an MRI technique which provides functional information of tissue by detecting microscopic motion of water molecules. The change of apparent diffusion coefficient (ADC) derived from DWI was used as an imaging biomarker for treatment response prediction in cancers [1]. However, it was based on whole-tumor analysis which did not reflect heterogeneity within the tumor. To overcome this limitation, a new method called parametric response map (PRM) analysis was proposed to evaluate response by quantifying voxel-wise changes in ADC [2]. Here we investigated the use of PRM analysis on ADC from DWI as an imaging biomarker for treatment response prediction in nasopharyngeal cancer (NPC) patients. We collected thirteen patient datasets including ten complete response (CR) patients and three partial response (PR) patients at King Chulalongkorn Memorial Hospital where one patient dataset consisted of DWI and ADC data acquired before (i.e. pre-treatment) and at five weeks after (i.e. mid-treatment) initiation of chemoradiation therapy. For each dataset, we compared pre-treatment ADC image with co-registered mid-treatment ADC image, and calculated the percentage of voxels with increased ADC values with respect to total voxels within the tumor ROI, defined as PRM+ . To validate the feasibility of the PRM biomarker, we computed the mean and standard deviation (SD) of percentage change in tumor volume (%ΔVol) and in ADC (%ΔADC) and PRM+, across CR and PR patients, where tumor response was from 6-month follow-up data using RECIST1.1 guideline. The results showed that %ΔVol as well as %ΔADC between both groups was not significantly different. In contrast, PRM+ was significantly different between both groups (p < 0.05, 82.7±7.8% in CR vs 66.7±6.5% in PR). Our results implied that the proposed PRM+ biomarker could be a potential biomarker for early treatment response prediction in NPC patients.
1. Introduction

Nasopharyngeal cancer (NPC) is the sixth most common cancer in men living in Southeast Asia [3]. Most patients diagnosed with NPC have already reached the advanced stage. In such cases, standard concurrent chemoradiation therapy (CCRT) in locally advanced NPC is routinely used to manage the disease and gives satisfactory results with high overall survival. Assessing tumor response to CCRT is crucial to patient management. Currently, this is achieved by monitoring changes in tumor size by using computed tomography (CT) and/or magnetic resonance imaging (MRI). Unfortunately, this assessment monitors a relatively late event because functional changes occur prior to alterations in size [4] and tumor size assessments are usually undertaken halfway through a course of treatment. Biomarkers that can provide an earlier indication of response are essentially required.

Diffusion-weighted imaging (DWI) is a powerful MRI technique which probes abnormalities of tissue structure by detecting microscopic changes in water molecules due to thermal Brownian motion within a voxel of tissue. Conventionally, the change of apparent diffusion coefficient (ADC) derived from DWI was used as an imaging biomarker for treatment response prediction in cancers [5]. Cui et al. [6] investigated the use of ΔADC as an imaging biomarker for predicting the outcome of chemotherapy in 23 patients with colorectal and gastric hepatic metastases with a total of 87 lesions. The results indicated that ΔADC after treatment in days 3 and 7 showed great promise in predicting and monitoring the early response to chemotherapy of hepatic metastases from colorectal and gastric carcinoma. Harry et al. [1] studied in 20 patients with advanced cervical cancer and chemoradiation treatment. Imaging and clinical examinations were performed before chemotherapy started, at 2 weeks after the start and at the end of therapy. From the results, ADC values after 2 weeks of therapy showed a significant correlation with eventual MRI response and clinical response. They further concluded that DWI had the potential to provide a biomarker of treatment response in advanced cervical cancers. It follows from the above studies that early increase of ADC may be a predictor of response to treatment.

However, the change of apparent diffusion coefficient (ADC) was based on whole-tumor analysis which did not reflect heterogeneity within the tumor. To overcome this limitation, a new method called parametric response map (PRM) analysis was proposed to evaluate response by quantifying voxel-wise changes in ADC [7]. Individual voxels were stratified into three categories based on the change in ADC between pre-treatment and mid-treatment. The PRM derived from ADC was reported to be useful as an imaging biomarker for prediction treatment response to chemotherapy and/or radiation therapy in various diseases such as head and neck cancer, lung cancer and brain tumor [2, 8, 9].

The present study aimed to use PRM analysis on ADC as an imaging biomarker to predict treatment response in NPC patients.

2. Materials and Methods

2.1. Patients

This study was approved by the Ethics Committee of the Faculty of Medicine, in Chulalongkorn University. Thirteen patient dataset were collected at King Chulalongkorn Memorial Hospital (KCMH) (2 female and 11 male patients with mean age of 45 years). All patients had nasopharyngeal cancer without any prior radiation therapy and chemotherapy, evaluated with MRI simulation for radiation treatment planning before treatment verification and treatment with concurrent chemoradiation therapy (CCRT).

Response was determined by CT and/or MRI 4-6 months after initiation of treatment. Treatment response was stratified by clinical outcome at 6 months from the start of treatment using the Response Evaluation Criteria in solid tumors (RESIST) guideline version 1.1 by evaluating change in the maximum diameter of the primary tumor in the largest axial slice. Thereby, the patient’s response was classified as either showing complete response (Disappearance of all target lesions, n = 10) or partial response (< 30% decrease in the sum of diameters of target lesions, n = 3) [10].
2.2. Magnetic Resonance Imaging
An MRI study was performed before treatment and at 5 weeks after initiation of chemoradiation therapy. All MRI data were acquired on MRI Simulator 1.5 T MRI scanner (Signa HDxt, GE Medical systems, Chicago, United States) using eight-channel head and neck phased array coil with routine MRI simulation protocol except for diffusion-weighted sequence. DWI was acquired at slice thickness of 5 mm including two b-values (0 and 1000 s/mm\(^2\)) in pre-treatment and 5 weeks after treatment in DICOM format files. To quantify the diffusion motion, ADC was calculated form the DWI as follows:

\[
ADC = -\frac{1}{b} \ln \frac{S_b}{S_0},
\]

where \(S_0\) and \(S_b\) are the DWI values at b-value 0 and 1000 sec/mm\(^2\), respectively.

2.3. Data analysis

2.3.1. Region of interest analysis. Regions of interest (ROIs) were manually drawn over each tumor-bearing slice on ADC image by information from MRI at pre-treatment and mid-treatment by one experienced radiologist. A reduction in size for each tumor was calculated by percentage change of volume at mid-treatment from pre-treatment as follows

\[
\%\Delta Vol = 100 \times \frac{(V_P - V_M)}{V_P},
\]

where \(V_P\) is lesion volume at pre-treatment and \(V_M\) is lesion volume at 5 weeks after the initiation of therapy.

2.3.2. ADC analysis. Percentage change of whole tumor ADC in lesion at mid-treatment were calculated relative to the pre-treatment value

\[
\%\Delta ADC = 100 \times \frac{(ADC_P - ADC_M)}{ADC_P},
\]

where \(ADC_P\) is lesion ADC value at pre-treatment and \(ADC_M\) is lesion ADC value at 5 weeks after the initiation of therapy.

2.3.3. PRM analysis. PRM analysis is based on voxel-wise subtraction, which requires that pre-treatment and mid-treatment images are aligned. Image registration were performed in serial MR images co-registered from pre-treatment and mid-treatment using affine registration of mono-modal image registration using mutual information algorithm on MATLAB.

The PRM of ADC was calculated the difference between the ADC in mid-treatment and pre-treatment for each voxel (\(\Delta ADC = \text{mid-treatment ADC in lesion} - \text{pre-treatment ADC in lesion}\)).

Each voxel will be classified according its corresponding \(\Delta ADC\) and a threshold that designates a significant change in ADC. In this work, we will use the threshold of 100 \(\times 10^{-5}\) mm\(^2\)/sec. Specifically, the PRM analysis will classify voxels within tumor into three categories based on \(\Delta ADC\). A voxel with ADC increasing by more than a pre-defined threshold will be classified as significantly increased and displayed in red (\(\Delta ADC > 100 \times 10^{-5}\) mm\(^2\)/sec). A voxel with ADC decreasing by more than the threshold will be classified as significantly decreased and displayed in blue (\(\Delta ADC < -100 \times 10^{-5}\) mm\(^2\)/sec). Any voxel whose absolute value of ADC change less than the threshold will be classified as no significant change in ADC and will be displayed in green (-100 \(\times 10^{-5}\) \(\leq \Delta ADC \leq 100 \times 10^{-5}\) mm\(^2\)/sec). The percentage PRM in each category can be obtained by PRM\(_i\) (increased ADC), PRM\(_d\) (decreased ADC), PRM\(_0\) (unchanged ADC) as follow:

\[
PRM_i = \frac{\text{Number of voxels with } Y \text{ value}}{\text{Total number of voxels}} \times 100,
\]
where PRM is the number of voxel with increased ADC value in the tumor volume. The scatter plots illustrate the distribution of changes in PRM throughout the entire volumes of interest. For PRM analysis, we will focus on only the percentage of voxel with significant increase ADC (PRM) [11].

2.4. Statistical analysis
From the data of DWI in each of the CR and PR groups, we were obtained the mean and the standard deviation (SD) of %ΔVol, %ΔADC and PRM. An unpaired two tailed t-test was used to compare differences of three biomarkers between both group of patients. Statistical computations were performed using SPSS (IBM SPSS Statistics for Windows, Version 22), p value of less than 0.05 was considered statistically significant. Moreover, for each biomarker, we also computed signal-to-noise ratio (SNR) for classification between CR and PR groups [12] which is given by

\[
SNR_{class} = \frac{|m_{CR} - m_{PR}|}{\sqrt{SD_{CR}^2 + SD_{PR}^2}}
\]  

where \(m_{CR}\) and \(m_{PR}\) (SD\(_{CR}\) and SD\(_{PR}\)) denote the mean values (the standard deviation) of the biomarker for CR and PR groups, respectively. SNR\(_{class}\) represents the separability of biomarker values from CR and PR groups.

3. Results
The representative cases of PRM analysis of CR and PR patients are displayed in Figure 1. It shows tumor overlaid on unregistered ADC image at pre-treatment as well as the corresponding scatter plots of pre-treatment ADC vs mid-treatment ADC value for the entire tumor volume. Color coding is as follows; red: voxels with significant increase in ADC; green: unchanged in ADC or blue: voxels with significant decreased in ADC values. In the CR patient 91.5% of the tumor volume was found to have a significant increase in ADC (shown as red voxels), the PR patient had only 64.6% of the tumor volume producing a significant increase in ADC. Results from PRM of the two patients showed that the PR patient had PRM value less than the CR patient.

A total of 13 patients were analyzed to determine the differences in percentage change in tumor volume (%ΔVol), the percentage change in ADC (%ΔADC) and PRM between pre- and mid-treatment. The box plot in Figure 2 showed no significant difference between both groups in %ΔVol (\(p = 0.450, 86.88\pm8.9\%\) in CR vs 91.1±2.2% in PR) and %ΔADC (\(p = 0.068, 70.43\pm26.94\%\) in CR vs 37.3±11.69% in PR). In contrast, PRM was significantly different between CR and PR groups (\(p < 0.05, 82.7\pm7.8\%\) in CR vs 66.7±6.5% in PR). Table 1 presents SNR\(_{class}\) for the three biomarkers. As can be seen, PRM-
Figure 2. displays the box plot of treatment response: the percentage change of volume, the percentage change of ADC and the percentage of voxel with significant increase ADC (PRM+). Significant different between both groups of patients was as assessed by t-test with p < 0.05.

Table 1. SNR for classification between CR and PR groups of %ΔVolume, %ΔADC, and PRM+.

|               | %ΔVolume | %ΔADC | PRM+ |
|---------------|----------|-------|------|
| SNR_class     | 0.64     | 1.59  | 2.23 |

has higher SNR_class than %ΔADC and %ΔVol (2.23, 1.59, 0.64 for PRM+, %ΔADC and %ΔVol, respectively).

4. Discussion and Conclusion
Recently, PRM analysis has been reported to be an effective biomarker for early cancer treatment response prediction. Our results indicated that PRM analysis on ADC from DWI had the potential for early treatment response prediction in NPC patients. Comparing between %ΔADC and %ΔVol, the SNR for classification between CR and PR groups when using %ΔADC as biomarker was higher than using %ΔVol. This may be because effect of treatment is pronounced in tissue functional processes earlier than in anatomical structures. Moreover, PRM+ had higher SNR_class than %ΔADC, which was resulted from the fact that PRM+ is a voxel-based technique accounting for heterogeneity in the tumor and is more sensitive than a whole-tumor technique, such as %ΔADC. In addition, only PRM+ showed significant difference (p < 0.05) between CR and PR groups.

However, our study had limitations. First, our study was a preliminary result which was based on small-size. Second, NPC is the cancer that has complex pattern. Possible mismatch between pre-treatment and mid-treatment may occur due to poor registra
tion.

In conclusion, the proposed PRM biomarker to quantify the ratio of voxels with significantly increased ADC values as assessed by PRM+, which was based on voxel-based analysis which accounted for intratumoral heterogeneity, could be a potential biomarker for early chemoradiation treatment response prediction in NPC.
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