Feasibility of performing weekly intravoxel incoherent motion DW-MRI and monitoring anatomical and functional changes in nasopharynx tumors during chemoradiation therapy

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Target audience: Researchers who investigate imaging biomarkers to assess radiation therapy response in cancers.

Purpose: Although standard cisplatin chemotherapy in combination with 70Gy of radiation has resulted in locoregional control of approximately 90% while 10% of the nasopharyngeal cancer (NPC) patients fail treatment. Furthermore, many patients suffer from severe toxicities requiring nutritional support by using percutaneous gastrostomy tube in order to complete the standard treatment. We sought to find imaging biomarkers predictive of treatment response to select which tumors may achieve tumor control without the need to receive 70Gy of radiation with the goal of toxicity reduction and also identify the non-responders so that an additional "boost" of radiation can be given [1]. This is important given that surgery is ineffective and highly morbid and not part of the treatment paradigm. IntraVoxel Incoherent Motion (IVIM) diffusion weighted magnetic resonance imaging (DW-MRI) is a non-invasive imaging method that enables simultaneous monitoring of perfusion and diffusion without the use of a contrast agent injection [2]. In this study, a weekly IVIM DW-MRI study was designed to monitor early treatment response to chemoradiation therapy in patients with NPC.

Methods: *Patients*: Our institutional review board approved this prospective study. Five patients with histologically proven NPC were enrolled under an approved IRB protocol. Patients were treated with chemoradiation therapy that included standard radiotherapy (70Gy) and Cisplatin with/without adjuvant carboplatin/5FU. *MRI data acquisition:* The timeline of the study design is shown in Figure 1. A total of 37 MRI studies (8/7/7/8/7) including pretreatment MRIs were conducted for these patients. The MRI studies were performed on a 3T MRI scanner (Philips, Netherlands) with a neurovascular phased-array coil. The MRI images were acquired using standard MRI protocols with multi-planar T1/T2 weighted anatomic scans followed by IVIM DW-MRI scans with multi b-values. The IVIM DWI-MRI images were acquired with a single shot spin echo echo planar imaging sequence using: FOV=18-22 cm, slice thickness=6mm, NEX=4, imaging matrix=128×128, and b=0,20,50,80,200,300, 500,800,1500,2000s/mm^2. *Advanced processing:* Mono- and bi-exponential functions were used to calculate diffusion and perfusion based metrics such as ADC (Apparent Diffusion Coefficient, mm^2/s), f (perfusion fraction), D (pure diffusion coefficient, mm^2/s) and D* (pseudo-diffusion coefficient, mm^2/s) from the IVIM-DWI images [3]. For all metrics, the mean, standard deviation and range were calculated. The relative change (%) of metrics was calculated as $(x_i-x_0)/x_0$ where 'x' denotes the mean of calculated metrics and 'i' denotes the ith week. *Clinical response assessment:* All patients were assessed for early clinical response with a median follow-up time of 3-4 months. Loco-regional control (LC) was determined by clinical and radiographic examination using established criteria [4]. Patients with residual morphologic abnormalities on follow-up imaging were not classified as Loco-regional Failure (LF) unless recurrence was proven by biopsy or the abnormality progressed in imaging.

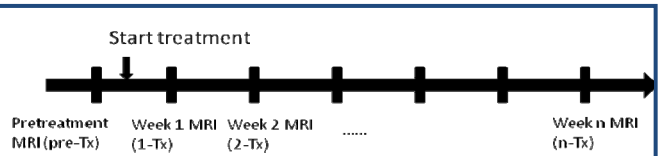

Figure 1. Timeline of the study design

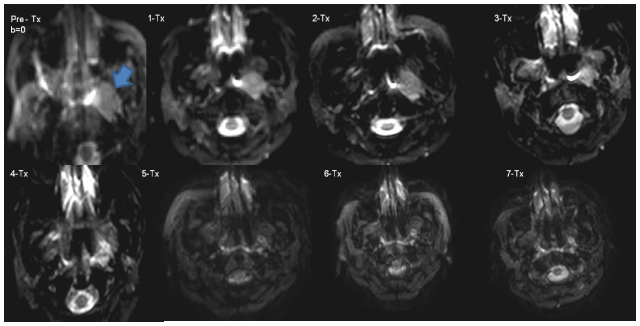

Figure 2. Weekly IVIM DW-MRI data (b=0) from a nasopharyngeal cancer patient (Patient #1 in Table 1) undergoing chemoradiation therapy (The blue arrow delineates the location of the tumor).

Results: Early clinical follow up showed that all 5 patients had LCs. Representative IVIM DW-MRI images of pretreatment and 7 week MRIs from patient #1 (female, 49 years old), are shown in Fig. 2. In this patient, tumor was visible only till the sixth week during treatment, and on the seventh week, no tumor was seen on MRI images. Quantitatively, the tumor volume decreased with time, from 19.48 cm^3 (pretreatment) to 0.49 cm^3 (week 6 during treatment) while ADC increased from 0.74 to 1.67×10^{3}mm^2/s, f changed from 0.25 to 0.58 and pure diffusion D from 0.53 to 1.03×10^{-3}mm^2/s (as shown in Fig. 3). The ith week when tumor was not seen on MRI for the 4 patients (#1,2,4,5) was 6/5/5/3 weeks during treatment respectively. Patient #3 had tumor infiltration of the prevertebral muscle before treatment. The tumor outside the muscle was not seen at week 3 but tumor infiltration of muscle was still observed at week 6 of treatment. The volumetric and IVIM DWI analysis of the tumor in Patient #3 was outlined conservatively to avoid contamination with muscle. For patients #1, 2, 4 and 5, tumor volumes (V) decreased, and ADC and f increased. However, for patient #3, ADC values remained relatively unchanged and tumor was visible in the muscle at pretreatment and during treatment, although total tumor volume was reduced.

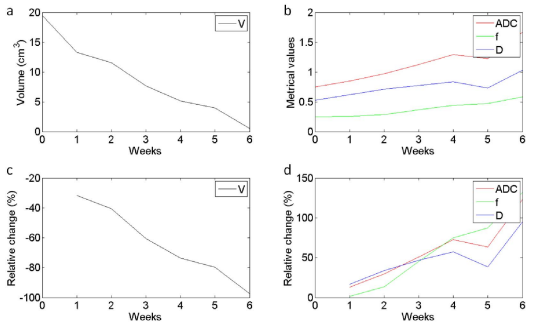

Figure 3. Metric values measured at pretreatment (week 0) and during treatment (week 1-6) for nasopharyngeal cancer patient #1: (a) absolute tumor volume changes; (b) absolute IVIM-DWI metrics ADC, f and D value changes; (c) depicts the relative change in volume; (d) represents the relative changes in IVIM DW-MRI metric values during treatment.

Discussion: The preliminary findings show that tumor behavior in Patient #3 is biologically distinct compared to the other four NPCs as the ADC remained unchanged during the course of treatment. The follow-up observations on this patient are expected to reveal additional tumor characteristics. All patients in the study will be followed clinically for progression free survival and distant metastases for a minimum of 2 years. Currently we are enrolling more NPC patients in the study and the data will be presented subsequently. These results will be verified in a larger cohort of NPC patients using the quantitative imaging biomarker to predict treatment response during radiotherapy with the goal of personalizing radiotherapy, i.e, dose de-escalation for early responders and dose escalation for non-responders.

Conclusion: This pilot study used weekly IVIM DW-MRI data collected for NPC patients and revealed that chemoradiation, in many cases, led to a decrease in tumor volume with an increase in perfusion and diffusion metric values during the course of treatment.

References: [1] Okunieff P, et al., Int. J. of Rad. Onc., 1995; 32(4):1227-37. [2] Le Bihan D et al., Radiol. 1988;168(2):497-505. [3] Lu Y et al., JMRI 2012;36(5):1088-96. [4] Robert MW, et al., Radiat. Oncol., 2013;8(1), 173-177.

Table 1. The change in metrics from 5 patients based on IVIM DW-MRI data from pretreatment to the last week tumor was visible on MRI during treatment.

Patient No.	Volume (cm^3)	ADC (10^{-3}mm^2/s)	f	D (10^{-3}mm^2/s)	D* (10^{-3}mm^2/s)
1	19.48 - 0.49	0.74 - 1.67	0.25- 0.58	0.53 - 1.03	3.11-11.38
2	9.03 - 0.22	0.61 - 1.17	0.18 - 0.38	0.44 - 0.81	12.71 - 12.50
3	2.22 - 0.42	0.97 - 0.96	0.26 - 0.43	0.73 - 0.61	6.87 - 9.05
4	3.67 - 0.25	0.47 - 0.68	0.10 - 0.33	0.38 - 0.35	12.48 - 10.18
5	12.20 - 0.06	0.71 - 1.44	0.19 - 0.39	0.53 - 1.07	11.17- 4.39