Assessment of tumor aggressiveness using intravoxel incoherent motion MRI in patients with papillary thyroid carcinoma

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Target audience: Researchers investigating imaging biomarkers in cancer.

Purpose: Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, representing about 80 percent of all thyroid cancer cases.[1] Thyroid surgery which includes partial thyroid lobectomy or total thyroidectomy is routinely recommended for all patients. However, recent studies have shown that even without any treatment, the vast majority of these still remain stable in size and confined to the thyroid gland when followed with active surveillance for up to 10 years.[2,3] There remains an urgent need to non-invasively differentiate between patients into two groups before treatment: one group harboring indolent disease that can be followed with active surveillance, and a second group with PTC that is likely to progress and therefore requires immediate surgery. Intravoxel incoherent motion imaging (IVIM) MRI allows for non-invasive measurement of water molecular diffusion and blood perfusion simultaneously, which may provide unique imaging biomarkers to assess tumor aggressiveness.[4] The purpose of this study was to assess tumor aggressiveness using IVIM-MRI in patients with PTC.

Methods: *IVIM-MRI data acquisition:* Our institutional review board approved this retrospective study and issued a waiver of informed consent. 15 patients (age: 28-66 years, M/F: 4/11, and tumor location (left/right/bilateral lobe) 4/6/5) were referred for IVIM-MRI study by physicians at our institution. All patients underwent pretreatment IVIM-MRI on a GE 3T Signa scanner with an 8-channel neurovascular phased-array coil prior to surgery. IVIM-MRI acquisitions were performed using a single-shot echo planar imaging (SS-EPI) spin echo sequence (TR = 4000 ms, TE = 98-104 ms, NEX = 4, ASSET is on, and shim FOV=14 mm) with 18 b values of b = 13, 17, 23, 30, 40, 53, 70, 92, 122, 161, 212, 280, 369, 488, 644, 850, 1121, and 1448 s/mm^2, respectively. The IVIM-MRI scans focused on the thyroid gland: with 4-8 slices of thickness 4-6 mm, FOV of 20~24 cm, and acquisition matrix of 128 × 128. *IVIM-MRI data analysis:* The regions of interest (ROIs) on the tumor and normal thyroid tissues were placed by an experienced neuro-radiologist. For both tissue types, the apparent diffusion coefficients (ADC) as well as f (vascular fraction), D (pure diffusion coefficient), D* (pseudo-diffusion coefficient) were calculated by using monoexponential and biexponential functions with a scheme of noise correction respectively.[5] *Histopathologic examination:* All patients underwent surgery after the MRI. The surgical specimen was reviewed by an experienced pathologist. Tumor aggressiveness was evaluated for each surgical specimen using following histopathologic features: presence or absence of tall cell variants, necrosis, vascular and/or capsular invasion, extrathyroidal thyroid extension, and regional or distant metastases. The tumor was termed aggressive if any one of the above features was present. *Statistical analysis:* The metrics of ADC, f, D, and D* among 4 different groups (i.e. normal thyroid tissue; tumor tissue; tumors without aggressive features; and tumors with aggressive features) were statistically analyzed to determine whether the groups were significantly different from each other by using non-parametric Mann-Whitney U test. P value <0.05 was considered significant.

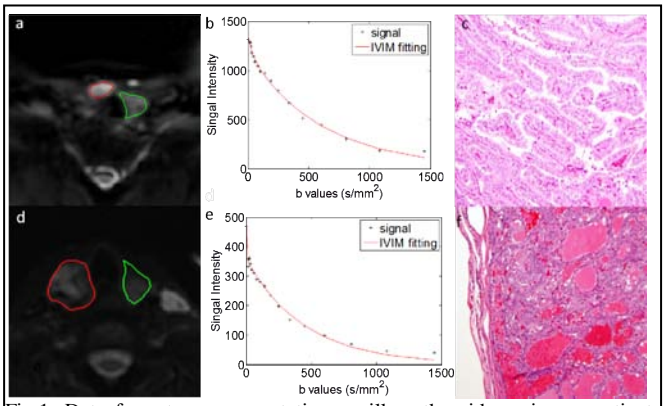

Fig.1. Data from two representative papillary thyroid carcinoma patients showing tumors with (top row) and without (bottom row) aggressive features. ROIs delineated with red coutours were for tumor tissues, and ROIs with green contours were for normal thyroid tissues. From left to right, IVIM MRI images, representative IVIM fittings for tumor tissues, and histopathology (at 10x resolution) of the tumors.

Table 1. Statistical analysis between different thyroid tissue types

Metrics	Normal tissues (N=15)	Tumor tissues (N=15)	Tumor tissues without aggressive features (N=5)	Tumor tissues with aggressive features (N=10)
ADC (10^{-3}mm^2/s)	1.62±0.41	1.65±0.47	2.12±0.38	1.41±0.20*
f	0.40±0.14	0.36±0.12	0.39±0.16	0.35±0.10
D (10^{-3}mm^2/s)	1.04±0.61	1.18±0.53	1.61±0.56	0.97±0.36**
D* (10^{-3}mm^2/s)	58.06±46.38	30.7±38.7	16.26±15.58	37.2±40.8

Note: *ADC (p<0.01) and **D (p<0.04) were significantly different between tumor with and without aggressive features.

Results: Of 15 patients, 10 patients were found to have aggressive tumors, and 5 patients were found to have non-aggressive tumors, based on the histopathologic features. Figure 1 shows studies from two representative PTC patients with (female; 47y; max. tumor diameter, 2.4cm) and without aggressive tumor features (female; 34y; max. tumor diameter, 2.6 cm). Pathology results show a more aggressive phenotype, as demonstrated by the columnar and tall cell nature of the tumor without associated colloid and of the tumor with extrathyroidal invasion in surrounding fibroadipose tissue in Fig. 1(c), clearly showing an aggressive tumor [ADC=1.36×10^{-3}mm^2/s, and D=1.53×10^{-3}mm^2/s]. Pathology results for tumors that are without aggressive features show that the papillae are lined up by neoplastic cells, showing classical nuclear features, such as open and clear chromatin and the presence of colloid in Fig. 1(f) [ADC=2.13 ×10^{-3}mm^2/s, and D=2.20×10^{-3}mm^2/s]. The Mann-Whitney U test was performed on all 15 patients for comparing the parametric difference in the 4 different groups (see Table 1). The results showed that tumor group with aggressive features had significantly lower ADC values than that of tumor group without tumor aggressive features (1.41±0.20 vs 2.21±0.38 ×10^{-3}mm^2/s, p<0.01) (Table 1), and this difference is mainly due to the difference of D (0.97±0.36 vs 1.61±0.56 ×10^{-3}mm^2/s, p=0.04). No other parametric significance was found between any other pair of groups (Table1).

Discussion: ADC is a composite metric that combines the effects of water diffusion and blood perfusion in tumor tissues. By using the technique of IVIM MRI, these two effects can be separated and quantified. In our study, we found that ADC and D were significantly different between tumors with and without aggressive features, clearly showing D not perfusion related metrics were the main contributors of ADC in thyroid tumor tissues. The study also found that there was no significant parametric difference between normal and tumor tissues, but tumor tissues with aggressive features had significantly lower ADC and D than tumor tissues without aggressive features. No perfusion related metrics were found significantly different. The presence of colloids in non-aggressive tumors could be one of the factors for higher diffusion coefficients in this group. While the loss of colloids and presence of tall cells and increased compactness would lead to lower water diffusivity in tumors with aggressive features. Similar trends in ADC were observed in prostate cancer and a recent study reported that tumor ADC values were inversely associated with tumor Gleason scores i.e. highly aggressive tumors had lower ADCs than less aggressive tumors.[6]

Conclusion: The study revealed that water molecular diffusion coefficient is a surrogate biomarker for tumor aggressiveness in patients with PTC.

References: [1] Enewold L et al., Cancer Epidemiol Biomarkers Prev. 2009; 18(3):784-91. [2] Ito Y et al., World J Surg 2010;34:2333-233.; [3] Sugitani I et al., World J Surg. 2010; 34(6):1222-31. [4] Le Bihan D et al., Radiology 1988;168(2):497-505. [5] Lu Y et al., JMRI 2012;36(5):1088-96. [6] Jung SI et al., Radiology. 2013;269(2):493-503.