Usefulness of Intravoxel Incoherent Motion DWI as Early Detection of Treatment Effect and Prognostic Factor in Patients with Head and Neck Cancer

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Purpose

Tumor diffusion and perfusion is important information for assessment of head and neck squamous cell carcinoma (HNSCC). Past reports have indicated clinical usefulness of diffusion and perfusion parameters as prognostic factor, monitoring tool for early treatment response (1, 2).

Intravoxel incoherent motion diffusion weighted imaging (IVIM-DWI) has been introduced to enable measurement of both fast and slow water molecular motion within single scanning by using multiple b-value acquisition (3). Fast water molecular motion reflects fast diffusion of volume flow mainly caused by microcirculation, called pseudo diffusion ($D^*$). On the other hands, slow water molecular motion reflects slow diffusion component which is mainly caused by tissue diffusion such as intracellular lesion, called true diffusion ($D$). In addition, perfusion fraction ($f$), percentage of area with fast diffusion component, can be measured simultaneously. IVIM-DWI can be useful tool for the non-invasive assessment of HNSCC by obtaining both diffusion and perfusion information.

The purpose of this study is to evaluate the usefulness of IVIM-DWI parameters ($D$, $D^*$, and $f$) for the assessment of patients with HNSCC as prognostic factor and monitoring tool for early treatment response.
Methods and Materials

subjects

From September 2011 to October 2012, 17 consecutive patients with HNSCC treated by super selective arterial infusion of Cisplatin with concomitant radiotherapy (SSAICR) were prospectively enrolled in this study. Patients included 14 males (mean age, 63 years; range, 47-77 years) and 3 females (mean age, 72 years; range, 59-83 years). The primary lesions of these 17 patients included maxillary sinus in 11 patients, tongue in 3 patients, and oropharynx in 3 patients (see table).

<table>
<thead>
<tr>
<th>Pt. No</th>
<th>Age</th>
<th>Gender</th>
<th>Primary lesion</th>
<th>TMN stage</th>
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<td>T4aN1M0</td>
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<td>Lt. oropharynx</td>
<td>T2N0M0</td>
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<td>T4aN2cM0</td>
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<tr>
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<td>77</td>
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<td>T2N0M0</td>
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<tr>
<td>13</td>
<td>59</td>
<td>female</td>
<td>Rt. Maxillary</td>
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</table>
MR scanning including IVIM-DWI and conventional anatomical imaging (Axial T1WI, T2WI) was performed pre-treatment and early treatment period (time point of 15-22Gy in total 65-70Gy, and time point between second and third of arterial infusion of cisplatin in total 4-5 times) in each patient.

**Imaging protocol**

Imaging protocol of IVIM-DWI was acquired with single-shot spin-echo EPI readout by using 12 point b-values (0, 10, 20, 30, 50, 80, 100, 200, 400, 800, 1000, 2000 (3 axis)). The parameters of IVIM-DWI was as follows; TR, 5000 ms; TE, 64 ms; FA, 90 degree; FOV, 230_230 mm; 64_64 matrix; slice thickness, 5 mm×25 slices; scanning time, 4’ 37.

Conventional anatomical imaging of T1WI and T2WI were also performed for tumor volume measurement. Imaging parameters were as follows; (a) T1WI: conventional spin echo; TR, 450 msec; TE, 10 msec; FOV, 240×240 mm; 512×512 matrix; slice thickness, 5 mm; inter slice gap, 30%; scanning time, 2’12”, (b) T2WI: Turbo spin echo; TR, 4500 msec; TE, 70 msec; TSE factor, 9; FOV, 240×240 mm; 512×512 matrix; slice thickness, 5 mm; inter-slice gap, 30%; scanning time, 2’06 “.

**Image analysis**

True diffusion coefficient (D), pseudo diffusion coefficient (D*), perfusion fraction (f) from IVIM-DWI, and tumor volume (TV) from conventional anatomical imaging (T1WI, T2WI) were calculated or measured respectively both pre-treatment and early treatment period.

In addition, change ratio in D, D*, f, and TV between pre-treatment and early treatment period was calculated in each tumor subsite.

**Tumor volume measurement:**

Each tumor was delineated with a polygonal region of interest (ROI) on all slice of T2WI which contain tumor site. T1WI was used for reference as additional information for delineation. After delineation, each tumor was divided into anatomical subsites.
tumor volume of each subsite was calculated as follows; (size of ROI) * (slice thickness). If tumors extended beyond two slices, the sum of the TV in all slices was calculated (Fig. 1 on page 6).

Measurement of IVIM-DWI parameters:

ROI of each subsite in the tumor used for TV measurement was copied and placed on IVIM DWI of each b-value. Mean value of each ROI was measured and used for the calculation of D, D*, and f (Fig. 2 on page 6). Past reported equation was used for the calculation of IVIM-DWI parameters (Fig. 3 on page 7). Mathematical software (MATLAB, version 2012a) was used for the calculation of each parameter by least square fitting.

Post treatment assessment

Clinical judgment of complete remission (CR) or non-CR; After the treatment of full course of SSAICR, short-term result whether CR or non-CR was determined in all tumor subsites by multi-modality assessment and follow-up. Multi modality assessment was performed using PET-CT, and MRI. If clearly presence of residual tumor was observed by PET-CT (like focal uptake lesion) or MRI (like large mass lesion), this lesion was determined local control failure (= non-CR). Multimodality assessment was determined consensus reading of PET-CT and MRI by two neuroradiologist and one head and neck surgeon. After the treatment, if no residual tumor was observed by multimodality assessment, follow-up (3-13 months, median 7 months) was conducted, during which the presence or absence of a residual / recurrence tumor was clinically determined by periodically evaluating the presence of enlargement of post-treatment granulation by CT, MRI, and endoscopy.

Statistical analysis

The value of pre-treatment TV, D, D*, and f in each tumor subsite was compared between CRs and non-CRs using non-paired t-test. In addition, change ratio of TV, D, D*, and f in early treatment period was also compared between CRs and non-CRs using non-paired t-test. A p-value of 0.0125 was considered to indicate a significant difference (after Bonferroni adjustment from p-value of 0.05)
Fig. 1: Each tumor was delineated and divided into anatomical subsites with a polygonal region of interest (ROI) on T2WI. This figure shows divided tumor of tongue and tonsile (arrow).

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Fig. 2: ROI of each subsite used for TV measurement was copied and placed on IVIM DWI of each b-value (arrow). IVIM parameters of each subsites was calculated using mean pixel value of each ROI.

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\[ S_b = S_0 \times (1-f) \times \exp(-bD) + S_0 \times f \times \exp(-b(D+D^*)) \]

Fig. 3: The equation for the calculation of IVIM-DWI parameters. Where \( S_b \) was signal intensity in each b-value, \( S_0 \) was signal intensity of b0 image, \( b \) was b-value (12 points, 0-2000).

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Results

In 17 patients, 39 subsites in 17 primary tumors were evaluated. Six sites of non-CRs and 33 sites of CRs were determined by multimodality assessment and short-term follow up after treatment.

Pre-treatment f was significantly lower in non-CRs (10.1±1.9) compared to CR (6.6±0.7). On the other hands, there were no significant difference in pre-treatment D, D*, and TV (Fig. 4 on page 9 Fig. 5 on page 9, Fig. 6 on page 10, Fig. 7 on page 11).

Change ratio of D in early treatment period was significantly lower in non-CRs (1.0±0.09) than CRs (1.7±0.4). However, significant difference was not observed in change ratio of D*, f, TV in early treatment period between CRs and non-CRs (Fig. 8 on page 12, Fig. 9 on page 13, Fig. 10 on page 14, Fig. 11 on page 15).
Fig. 4: There was no significant difference in pre-treatment D between CRs and non-CRs (p=0.28).

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Fig. 5: There was no significant difference in pre-treatment D* between CRs and non-CRs (p=0.72).

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**Fig. 6:** Pre-treatment $f$ was significantly lower in non-CRs (6.6±0.7) compared to CRs (10.1±1.9) ($p>0.001$).

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Fig. 7: There was no significant difference in pre-treatment TV between CRs and non-CRs (p=0.38).

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**Fig. 8:** Change ratio of D in early treatment period was significantly lower in non-CRs (1.0±0.09) than CRs (1.7±0.4) (p>0.001).

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Fig. 9: There was no significant difference in change ratio of D* between CRs and non-CRs (p=0.14).

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**Fig. 10:** There was no significant difference in change ratio of f between CRs and non-CRs (p=0.41).
**Fig. 11:** There was no significant difference in change ratio of TV between CRs and non-CRs (p=0.19).

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Conclusion

Pre-treatment value of f in CRs was significantly higher compared to that of non-CRs. This indicates pre-treatment perfusion fraction will be one of prognostic factor in determining the treatment effect of HNSCC. Change ratio of D of CRs in early treatment period was significantly higher than that of non-CRs. This also indicates true diffusion coefficient will be one of monitoring tool for early treatment response. In addition, TV percent change in early treatment period didn't differ significantly between CRs and non-CRs; this means true diffusion coefficient will be more detectable for early treatment response compared to TV which is considered clinically standard like a RECIST measurement.

In conclusion, IVIM-DWI can be useful tool for the non-invasive assessment of HNSCC as prognostic factor and monitoring tool for early treatment response.
References


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