Microstructural Assessment of Oral Squamous Cell Carcinoma Using Time-Dependent Diffusion MRI

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Introduction: Although diffusion-weighted (DW) MRI and its derived metric, the apparent diffusion coefficient (ADC), are widely used for tumour assessment[1], ADC provides limited insight into specific microstructural features such as cell density (CD)[2]. Time-dependent diffusion contrast (TDDC) was previously introduced to characterise tumour microstructure[3]. This study tested the hypothesis that TDDC is a more specific measure of CD than ADC in oral squamous cell carcinoma (OSCC).

Methods: *Ex vivo* DW-MRI was performed on ten fresh OSCC specimens using a 3 T MRI (Ingenia 3 T, Philips HealthCare, The Netherlands) with three diffusion sequences: two pulsed gradient waveforms (pWF_{short}, pWF_{long}) and one oscillating (oWF) waveform, with effective diffusion times of 26, 46, and 16 ms. Two TDDC maps were generated by subtracting normalised DW-MRI signals with the same b-value: $TDDC_o$ (pWF_{long} – oWF) and $TDDC_p$ (pWF_{long} – pWF_{short}). After MRI, specimens were formalin-fixed, sectioned parallel to MRI slices, paraffin-embedded, and stained with haematoxylin and eosin (HE). Tumours were manually delineated on the HE-stained slices, and a cell detection algorithm generated CD maps. Within the tumour delineation, voxel-wise and ROI-based correlation analyses were conducted on TDDC, ADC, and CD maps (Figure 1).

Results and Discussion: In the voxel-wise analysis, $TDDC_o$ demonstrated a stronger correlation with CD than $TDDC_p$ ($TDDC_o$: ρ_s= 0.23 [-0.03, 0.42], $TDDC_p$: ρ_s= 0.06 [-0.08, 0.31], ADC: ρ_s= -0.04 [-0.57, 0.27]), likely due to higher SNR in $TDDC_o$. Stronger correlations between CD and both TDDC maps were observed in the ROI-based analysis ($TDDC_o$: ρ_s= 0.58, $TDDC_p$: ρ_s= 0.79), while ADC showed a weaker inverse correlation with CD (ρ_s= -0.47), further highlighting the potential advantage of TDDC for characterising tumour microstructure. Future studies should focus on a larger sample size and quantify histological features such as stromal content and tumour-infiltrating lymphocytes to refine our understanding of TDDC's relationship with tumour microstructure.

Conclusion: The findings support the hypothesis that TDDC is a more specific measure of CD than ADC and show promise for improved characterisation of tumour microstructure in OSCC.

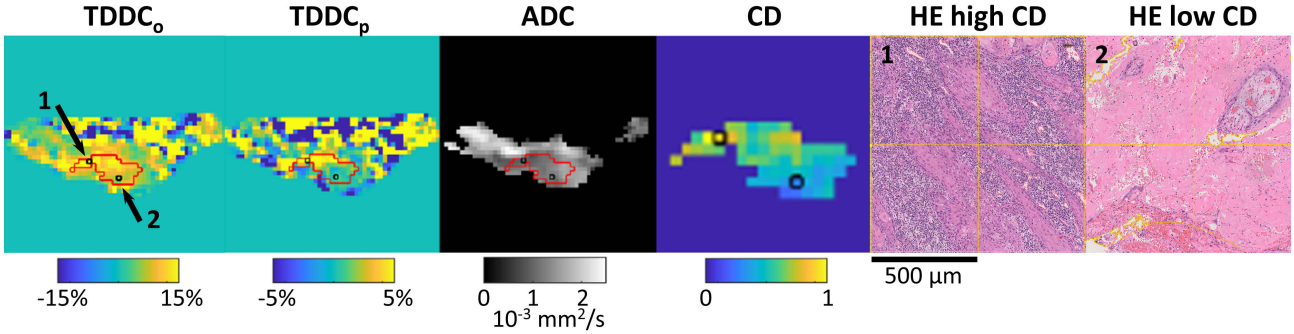

Fig. 1: Visualisation of the TDDC maps, ADC map, zoomed-in CD map and two magnified sections of the HE-slice from voxel 1 and 2 (black arrows). A positive percentage in the TDDC maps corresponds to more restricted diffusion. The tumour delineation is visualised in red on the TDDC and ADC maps. Voxel 1 (high TDDC, high CD) showed tumour cells with lymphocyte infiltration, while voxel 2 (low TDDC, low CD) contained mainly keratin structures.

References: [1] Koh, AJR Am J Roentgenol (2007). [2] Bourne, Diagnostics (2016). [3] Jokivuolle, Med Phys (2025).