Validation of in vivo VERDICT fIC against matched histology from whole-mount prostatectomy

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Synopsis

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Motivation: Intracellular volume fraction (fIC) maps from VERDICT-MRI have shown potential to improve prostate cancer (PCa) stratification, but the microstructural origin of the signal has not yet been investigated in in vivo settings.

Goal(s): Investigate the accuracy of fIC from in vivo VERDICT-MRI as a measurement of cell density using matched prostatectomy specimens.

Approach: Using personalised moulds from multiparametric (mp)MRI and deep learning image registration, we align whole prostatectomy histology images with corresponding VERDICT MR images. We compare fIC maps against cell density maps derived from histology.

Results: fIC maps show very strong agreement with histology-derived cell density maps of epithelial cells (r=0.8303).

Impact: Our study shows that VERDICT fIC maps are accurate descriptors of epithelial cell density in the prostate. The biological interpretability of these maps will facilitate translation into clinical practice, improving PCa stratification from MRI.

Introduction

Histological analysis is the most accurate way to diagnose prostate cancer (PCa). Multi-parametric MRI (mpMRI) provides a non-invasive alternative, but mpMRI PCa diagnosis shows significant variation across radiologists[1] due to the heterogeneous morphology of PCa on MRI and confounding conditions such as benign prostatic hyperplasia (BPH)[2], leading to diagnostic errors[3,4]. Most mpMRI DWI studies use the Apparent Diffusion Coefficient (ADC), which is useful for tumour detection[5] but confounds several histological changes like cell density, size, and vascular perfusion effects that can occur in tumours.

The Vascular Extracellular and Restricted Diffusion for Cytometry (VERDICT)-MRI framework has a specific DWI protocol with a biophysical tumour model for the diffusion signal[6]. The intra-cellular volume fraction (fIC) from VERDICT-MRI provides better discrimination of clinically significant (cs) PCa than ADC maps from mpMRI[7–9] and better identifies false positive lesions[10]. Ex vivo validation of VERDICT fIC shows that high fIC zones correspond to high histological cell density[11], but in vivo VERDICT validation with accurate registration is lacking.

This study uses personalised 3D-printed prostate moulds and a deep learning registration pipeline to obtain accurate matching of whole-mount prostatectomy slices and in vivo VERDICT-MRI. We aim to validate the fIC maps against cell density maps from prostatectomy histology images.

Methods

Patient data. The study cohort is from the Histo-MRI clinical trial (NCT04792138), which performs mpMRI and VERDICT-MRI on men with clinical PCa suspicion[12]. MR images are acquired on a 3T scanner (Achieva, Ingenia; Philips Healthcare; Best; The Netherlands). Pre-operative MRI is used to print personalised 3D moulds of the prostate for prostatectomy candidates. The prostate is scanned in the mould (ex vivo MRI) and sectioned following the mould's guides[13], resulting in histology slices with the same spacing and orientation as the MRI.

The sample presented corresponds to a 68-year-old White British with lesions graded Likert Score 3 from mpMRI and Gleason Score 3+4 from prostatectomy. Annotations on MRI (T2-weighted from mpMRI and VERDICT fIC) and histology are drawn by experienced radiologists and histopathologists.

Registration. We extend ProsRegNet[14], a deep learning multi-modal registration network, to register histology to DWI. We compare performance of histology to fIC registrations against the default histology to T2-weighted (T2W) registrations using the DICE coefficient and Hausdorff distance of the prostate masks.

fIC validation. We compare fIC to cell density maps derived from whole-mount histology using a custom pipeline on QuPath[15], validated by an expert histopathologist, where each outputted pixel corresponds to a 512-pixel-wide patch from the histology with an area of 0.216μm^2. Epithelial and basal cell sizes are calculated from manual segmentations on histology.

Results

Figure 1 shows the ProsRegNet registration performance. There is no significant difference when using fIC maps as target than when using T2W images from mpMRI.

Figure 2 illustrates the correspondence between fIC maps and histology cell density maps. High fIC values in cancerous regions correspond to high cell density areas in histology. There is an area with high fIC and medium histology cell density due to an intra-prostatic portion of the ejaculatory duct (on histology). Figure 3 quantifies the correlation between the maps using 15 ROIs throughout the prostate (r=0.8303). Areas of BPH do not show high fIC values.

Figure 4 presents the VERDICT fIC map alongside two benign and two PCa histology ROIs, showing high epithelial cell density in areas of high fIC. Basal cells surrounding epithelial cells in benign tissue do not appear in PCa patches, while there is characteristic proliferation of epithelial cells in PCa regions[16].

The VERDICT radius (R) map (Figure 5) shows little spatial variation (11-14μm). This matches the histological cell size analysis (boxplot), where we find no significant difference in epithelial cell size in benign and PCa regions. Epithelial cells are significantly larger than basal cells.

Discussion and Conclusion

This work presents an in vivo validation of VERDICT-MRI fIC maps, showing excellent agreement with histological analysis of whole-mount prostatectomy.

We adapt ProsRegNet to accurately align histology with fIC maps and demonstrate comparable performance to registrations against T2W images. Histological analysis shows that epithelial cell size does not change with PCa and that only epithelial cells proliferate in areas of high fIC, confirming that high fIC values are due to high epithelial cell density. In our results, pathologies that mimic cancer, like BPH, do not have high fIC, suggesting the ability of fIC maps to further improve tissue characterization.

This validation of VERDICT fIC maps can accelerate the incorporation of VERDICT-MRI into clinical practice, potentially reducing unnecessary biopsies[8]. Future work will analyse more samples for statistical analysis.

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Figures

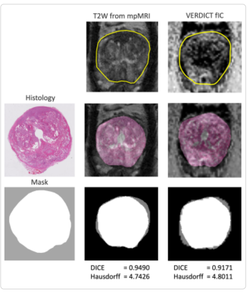

FIGURE 1. Top: Target images (T2W from mpMRI and fIC from VERDICT-MRI). Middle: Source image (histology) and overlap of warped histology on target images. Bottom: Source mask (histology) and overlap of warped source mask and target masks. DICE coefficient and Hausdorff distance are calculated from prostate masks.

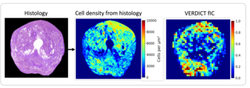

FIGURE 2. Comparison of fIC map against cell density map from histology (after histology to DWI registration). There is strong visual correspondence between the maps. A region of disagreement in the posterior peripheral zone corresponds to an intra-prostatic portion of the ejaculatory duct, which the VERDICT model does not account for.

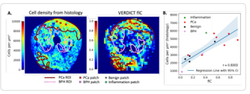

FIGURE 3. A: Cell density from histology and VERDICT fIC maps. PCa and BPH ROIs are outlined in red and pink, respectively. Patches are chosen throughout the prostate (crosses). B: We plot the average value of the patches alongside the linear regression line and the 95% confidence interval (CI). r: Pearson's correlation coefficient.

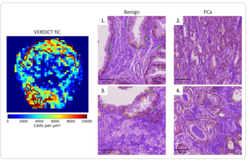

FIGURE 4. PCa lesions (from histology) are contoured on the VERDICT fIC map in black and red. Some epithelial (yellow) and basal (green) cells are contoured in benign (1 & 3) and PCa (2 & 4) patches. PCa patches show epithelial cell proliferation. Basal cells are only present in benign patches.

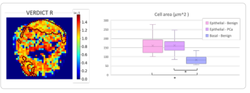

FIGURE 5. The VERDICT R map shows cell radius estimates and has little variation between benign and PCa (contoured in black and red) areas. The box plot illustrates the area of epithelial and basal cells from six different patches (three benign, three PCa). Asterisks indicate statistical significance ($p<0.001$). Epithelial cells show no significant difference in size between benign and PCa regions.