Speciality area: Diffusion-weighted MRI Applications in Cancer
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Highlights:

- Standard diffusion techniques have limited value in cancer applications.
- Biophysical modelling can potentially offer insight into microstructure and resolve ambiguities associated with standard techniques.
- Advanced diffusion acquisition methods allow greater sensitivity, which may be required by the complex nature of cancer pathology.

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Target Audience: Researchers and clinicians who are familiar with the basic diffusion MRI methodology and are interested in an overview of the available diffusion MRI techniques in oncology.
Outcome: Following this lecture, the audience should be able to understand the basic concept of the different diffusion MRI methods in cancer applications, their strengths but also limitations in describing the diffusion process in cancerous tissue.
Purpose: Currently diagnosis and therapy treatment depends on histological tumour evaluation via biopsies, which are invasive, limited to very small samples and blind to the exact location of the tumour. Consequently, the need for multiple biopsies and the possibility of missed metastases is increased. Medical imaging has major potential advantages: i) it can be performed in vivo, ii) it can be non-invasive, and iii) allows a non- localised view of the whole organ or region of interest. In particular diffusion-weighted MRI (DW-MRI) provides imaging contrast driven by the displacement of water molecules in the body. Although this technique provides unique insight into microstructural tissue composition, standard DW-MRI techniques have shown limited value in cancer-imaging applications. In this lecture we will discuss the standard and new diffusion methods for examining cancerous tissue.
Methods: This lecture will provide an overview of the following DW-MRI methods for various cancer applications:

- *Apparent Diffusion Coefficient (ADC)* Most DW-MRI studies have used the technique in its simplest form by calculating the apparent diffusion coefficient (ADC) to identify clinically significant tumour foci more clearly [5, 6]. In general,

ADC values are lower in tumours compared to healthy tissue and are believed to reflect the highly cellular environment of neoplastic tissue, which constrains water mobility. However, this simplified model of water diffusion remains a blunt tool, which fails to discriminate the variety of histological changes (cell density, size, shape, permeability, subcellular architecture, and vascular perfusion effects) that occur within cancers.

- *Intravoxel Incoherent Motion (IVIM)* Le Bihan et al[3] proposed the intravoxel incoherent motion (IVIM) model to separate "pure" water diffusion effects in the tissue from pseudo-diffusion of water in the blood capillary network. IVIM characterises water dispersion as a combination of a slow component associated with Brownian motion and a fast component associated with the bulk motion of molecules inside microcapillaries. However, its description of diffusion in the cellular component of the tissue remains simplistic, as it does not account for cellular geometry and compartmentalisation.

- *Diffusion Kurtosis Imaging* (DKI) Diffusion kurtosis imaging (DKI) is a generalisation of ADC estimation[4] that quantifies the Gaussian and non-Gaussian components of the diffusion behaviour in tissue. Several studies have demonstrated greater discriminatory sensitivity of DKI for benign and cancer tissue than standard ADC[5]. Yet, as for ADC, DKI lacks specificity to the underlying microstructural features that cause the changes.

- *Compartment models for cancer (VERDICT)* The recent VERDICT framework [6] uses a three compartment tissue model designed to capture the main histological features that influence the DWI signal from in-vivo cancer tumours. The three compartments account explicitly for i) water trapped in cells, ii) water in the vascular network, and iii) interstitial water. Thus, VERDICT provides estimates of specific tissue properties such as the size and packing density of the cells, the vascular and extracellular-extravascular space (EES) volume fractions. Experiments so far show excellent recovery of microscopic parameters and changes preclinically in colorectal tumours [6] and feasibility of discriminating benign and cancerous tissue in a clinical prostate study[7].

- *Restriction Spectrum Imaging (RSI)* The RSI model[8] is an extension of the linear spherical deconvolution model used to probe tissue structures over a broad range of length scales. The diffusion signal is a mixture of components, where each component describes the signal dependence on specific tissue properties (e.g., cell size, density, orientation, etc.) as a function of imaging parameters. The total signal becomes the weighted sum of these components, and the goal is to determine the individual weights. Recently the method has been used for investigating tumours [9.] Results in brain tumours and prostate patients identify the lesions using the restricted component, which represents a cellularity measure.

- *Beyond Pulse Gradient Spin Echo sequences* Other useful tumour histological features may also be accessible from other kinds of DW-MRI measurement,

for example, it maybe possible to estimate permeability or exchange time parameters via double pulsed-field gradient (dPFG) measurements[10], or access smaller subcellular structures with oscillating gradient DW-MRI that provides measurements for shorter diffusion times[11, 12].

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