Imaging Of Brain Tumour Microstructure

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Our understanding of the biology and treatment of brain tumours, particularly glioma has changed radically over the past 5-10 years and the expectations of imaging techniques are changing in parallel. Conventional MR imaging forms the mainstay of diagnosis, staging, surgical planning and follow-up in glioma. However, since, the 1990s we have seen the development of qualitative imaging-based biomarkers, used in many cases to generate parametric maps of biologically important parameters such as blood volume, blood flow and vessel wall permeability. These imaging biomarkers were originally used, in most studies, to estimate whole tumour values and applied to the differential diagnosis of lesions and to study prognostic or predictive power and therapeutic response.

Most tumors demonstrate biological heterogeneity with regional variations in genomic subtypes, rates of proliferation and cell death, variations in the expression of growth factors and pro and anti-angiogenic factors and metabolic activity all of which interact with the angiogenic process to produce significant heterogeneity in vascular structure, oxygenation and nutrient supply.

In-growth and invasion of tumour cells at the tumour/tissue boundary also represents a form of regional heterogeneity, which is of considerable importance. Accurate identification of tumour extent is highly desirable in order to guide radiotherapy and invasive procedures. Increasingly, targeted novel therapies can be expected to reduce or negate invasive potential and there is a need for imaging-based biomarkers to quantify these responses. Increasingly there is also recognition that that relapse results to a large extent from cancer stem cells which exist in distinct micro-environmental niches (11-14).
The use of imaging biomarkers in drug discovery and development is growing rapidly as a direct consequence of our increased understanding of tumour biology, increased sophistication in therapeutic intervention and the development of novel targeted molecular agents. Once again it is increasingly clear that therapeutic responses can produce limited regional changes in functional parameters rather than overall gross tumour shrinkage. Similarly, response and relapse to novel therapeutic agents can produce patterns of tumour behaviour, which vary considerably from those of the primary tumour.

Both clinical and early phase drug trials are therefore making increasing demands for imaging biomarkers which provide information concerning spatial variations in the tumour microenvironment and in treatment induced changes.

In this presentation I will review the reasons for the increased interest in the development of MR biomarkers of tumour heterogeneity and microstructure. I will also summarise the commonest techniques for quantification of micro-environmental structure with a particular focus on the method used to characterise the vascular microenvironment (DCE-MRI) and the cellular structure both within the tumour and that the tumour edge (DWI). I will give an overview of the generic technical problems associated with the production of heterogeneity and microstructural biomarkers from MR data and provide illustrative examples of the clinical application of heterogeneity and microstructural biomarkers and their potential benefits.

**Teaching points:**

At the end of the lecture the attendees should be able to:

- Understand the biological basis of tumour heterogeneity.
- Understand the potential benefits associated with quantification of tumour heterogeneity and microstructure.
- Understand the generic technical problems associated with quantification of microstructure and the calculation and generation of heterogeneity metrics.
• Have a general understanding of the most commonly used heterogeneity metrics and how they have been applied to DCE-MRI and DWI.