Tumour response assessment using advanced MRI methods

Dr. Dow-Mu Koh
Royal Marsden Hospital, United Kingdom

Introduction

In oncological practice, the evaluation of treatment response is heavily reliant on imaging to provide non-invasive assessment. Using conventional imaging, the measurement of tumour size before and after treatment has remained the most widely used and accepted method for evaluating tumour response. However, reduction in tumour diameter often occurs late in the course of treatment (typically 6 – 12 weeks), and is thus relatively insensitive to early treatment effects. As each patient and tumour is unique, accurate response assessment at an early stage may allow modification of treatment by intensifying therapy in non-responders with the aim of improving clinical outcome, or early termination of ineffective treatment to avoid unnecessary drug toxicity.

Quantitative MR metrics such as the measurement of T1 and T2 relaxation times have also been applied for oncological assessment. However, there is now considerable interest in applying more advanced functional imaging techniques for tumour response assessment. Using these techniques enable the derivation of quantitative metrics, which reflects the pathophysiologic derangement in diseases. Such parameters are being investigated as response, predictive and prognostic imaging biomarkers in oncology.

In this talk, we will survey the different functional MR imaging (MRI) techniques currently in use for assessing tumour response to treatment. The focus of the discussion will be on two of the most frequently used techniques: dynamic contrast-enhanced MR imaging (DCE-MRI) and diffusion-weighted MR imaging (DW-MRI). Techniques such as MR spectroscopy (MRS), blood oxygenation level dependant (BOLD) imaging and dynamic susceptibility contrast-enhanced MR imaging (DSC-MRI) will be briefly mentioned. The potential for combining information from different MR functional or other imaging techniques will be highlighted in the context of future development. Challenges to widespread adoption of these quantitative MR techniques are also discussed.

Quantitative functional MR Imaging for assessing tumour response

There are a variety of functional MRI techniques that can now be applied to assess tumour response in oncology. These are summarised in ***Table 1.*** Each of these techniques inform on different aspects of the disease pathophysiology. They can be performed on most modern day MRI systems and combinations of these can be realistically incorporated into a study protocol of approximately 30 – 45 minutes' duration. As these techniques are increasingly utilised, there is a huge opportunity to compare and correlate such biologically relevant information, acquired in the spatially and temporarily resolved way, to improve our understanding of the biological aberrations associated with cancers. Serial measurements would also improve our understanding of the changes in tumour properties in response to treatment.

Table 1. Quantitative functional MR imaging techniques used in oncology
(Adapted from Koh DM & Padhani AR. MR Clinics of North America 2010)

Functional MR Imaging technique	Principles of MR measurement	Typical measurement time	Biological property on which measurement is based	Commonly derived quantitative imaging parameter	Pathophysiologic correlates
Dynamic contrast-enhanced MR imaging (DCE-MRI)	Gadolinium contrast - enhanced T1-weighted imaging at high temporal resolution (< 4s). Mathematical modeling of data.	Less than 10 minutes (including pre-contrast and post-contrast T1 measurements)	Rate of contrast uptake in tissues, which is influenced by blood flow, contrast transfer rates, extracellular volume and plasma volume fraction.	Initial area under the gadolinium curve (IAUGC), transfer and rate constants (K^{trans}, k_{ep}), leakage space fraction (V_e), fractional plasma volume (V_p)	Vessel density, Vascular permeability, Perfusion, Extravascular space, plasma volume
Diffusion-weighted MR imaging (DW-MRI)	Single-shot spin-echo echo-planar imaging. Contrast medium not required.	20 seconds to few minutes	Differences in water diffusivity between tissues	Apparent diffusion coefficient (ADC). Use of bi-exponential data fitting can be used to estimate fast diffusion component which may represent microcapillary perfusion.	Tissue architecture *[cell density, extracellular space tortuosity, cell membrane integrity],* Fluid viscosity, Microcapillary perfusion
^{1}H MR spectroscopy (^{1}H-MRS)	Single voxel or 3D chemical shift imaging. Metabolite assignment based on chemical shifts effects.	15 to 20 minutes	Cell membrane turnover/energetics, chemical composition of tissues	Quantified ratios of metabolites including choline, creatine, lipids, lactate and others depending on echo time.	Tumour grade, Tumour proliferation, Metabolic derangements
Dynamic susceptibility contrast MR imaging (DSC-MRI)	T2*weighted MR imaging at high temporal resolution to measure first pass of gadolinium contrast passage through the liver	1 to 2 minutes	Blood volume and blood flow	Relative blood volume (rBV/rBF), Mean transit time (MTT)	Vessels density, Blood flow, Tumor grade
Blood oxygenation level dependent (BOLD) or intrinsic susceptibility weighted MR imaging	T2*-weighted imaging performed using different echo-times to detect and quantify susceptibility effects	< 5 minutes	Deoxyhemoglobin shows higher relaxivity than oxyhemoglobin. Measurements also reflect blood volume, perfusion and intrinsic tissue composition	Intrinsic tissue relation rates (R2* = 1/T2*)	Ferromagnetic property of tissues, Level of tissue oxygenation

Dynamic Contrast-Enhanced MR Imaging (DCE-MRI)

Biological Basis for MR Measurements

Perfusion imaging by DCE-MRI tracks the passage of contrast medium through tissues after intravenous injection. The temporal evolution of signal intensity change in tissue or tumour is used to extract quantitative kinetic parameters which reflect the vascular component within each imaging voxel. Because of the often limited spatial resolution of the acquired data, it is not possible to directly image microvessel blood flow. Hence, the signal measured at DCE-MRI represents changes that occur on the global level as a consequence of microcirculatory changes within the tissue.

Technical considerations

After intravenous contrast administration, repeated T1-weighted imaging is performed over the tissue of interest using a high temporal resolution technique (usually ≤ 4 seconds) to track the passage of contrast. Typically, a 3D gradient echo sequence is employed. The passage of contrast through tissue is observed as an increase in the tissue T1 signal intensity. In areas that are prone to respiratory motion, motion correction can be performed prospectively using navigator techniques that track diaphragmatic movement and /or retrospectively by registration software. The plane of data acquisitions depends on local anatomy, with coronal data acquisition being particularly advantageous for evaluation of the kidneys and the liver.

In order to extract quantitative parameters from DCE-MRI data, mathematical kinetic modelling is usually applied to describe the rate of contrast change in tissue with time. Key to this process is the identification of the arterial input function (AIF), which simplistically translates to the contrast-induced signal intensity change in an artery supplying the tissue of interest. Where this cannot be directly measured, an AIF derived from population studies can be applied. In the liver, a dual vascular input in the form of hepatic artery and portal vein exists, and a dual input model can thus be used.

Typically, using a two-compartment model, quantitative indices such as the inflow transfer constant (K^{trans}), extracellular volume (v_e) and outflow rate constant (k_{ep}) can be derived. The inflow transfer constant reflects both flow and vascular permeability. Depending on the mathematical model applied, the quantitative parameters obtained may differ between kinetic models. More simplistic non-model based approaches have also been successfully utilised. These include the hepatic perfusion index (HPI) in the liver and the initial area under the gadolinium concentration curve (IAUGC), which represents the integrated area under the gadolinium-enhanced curve, usually in the first 60 or 120 seconds of enhancement.

Perfusion DCE-MRI for treatment response assessment

Alterations in the vascular kinetics of tumours have been used as the basis for assessing therapeutic response to both conventional and novel therapeutics. To date, there have been more than 50 published studies validating the use of DCE-MRI technique for tumour response assessment. Not surprisingly, the majority of these have evaluated the efficacy of drugs that target tumour vasculature (e.g. antiangiogenic or antivascular therapies). These studies have shown that treatment using such drugs that modulate tumour vascularity result in a reduction in quantitative parameters such as K^{trans} or IAUGC.

Diffusion-weighted MR Imaging (DW-MRI)

Biological basis for MR measurements

The mechanism of contrast of DW-MRI is based on differences in the mobility of water protons between tissues. Water diffusion in tissues reflects the tortuosity of the extracellular space, tissue cellularity, integrity of cell membranes and fluid viscosity. Cellular tissues show a lesser degree of signal attenuation with increasing diffusion-weighting (b-values), and thereby appear relatively conspicuous on DW-MRI, thus facilitating their detection. By quantitative evaluation, cellular tissues usually return lower apparent diffusion coefficients (ADC), indicating impeded water diffusivity. However, as DW-MRI discriminates tissue on the basis of water diffusion, the technique is not specific for malignancy.

Technical considerations

High quality DW-MR images can be obtained by free breathing image acquisition using single shot echo planar technique. As an extension, respiratory triggering may be used in addition to further overcome the effects of respiratory motion at the expense of longer acquisition times. There is increased interest in using DW-MRI to probe the fast component of tissue diffusion, which reflects microcapillary perfusion at low b-values. To do this effectively, there has to be sufficient confidence in the signal-to-noise ratio of images acquired at low b-values, and the accuracy of low b-values delivered on individual scanners.

DW-MRI for assessing tumour response to treatment

Changes in tumour ADC measurements often precede any measurable change in tumour size or volume. Hence, determination of ADC response may influence clinical practice by allowing much earlier adjustments in therapy. Temporal evolution of ADC within tumour tissue to therapy has been shown to vary to some extent according to tumour type and the nature of treatment administered.

In theory, tumour ADC increases after initiating treatment because of cellular damage leading to tumour lysis, loss of cell membrane integrity and apoptosis; thus increasing the mobility of water in the tissue microenvironment. However, acute cellular swelling due to treatment can lead to transient decrease in ADC value. The post-treatment increase in ADC value should normalize and decrease with time towards that of normal tissue as cancer cells are destroyed. Tumour re-growth could lead to further reduction in ADC value. However, deviation from this simplified schema can result from specific therapies, and also from tissue responses such as inflammation, fibrosis and fat infiltration, which can modify the ADC evolution.

What has been consistently shown in the published literature is that ADC increase can be observed in response to a range of anticancer therapies within 30 days of initiating treatment in many cancers. In cervical, rectal, liver metastases and head and neck cancers, increase in ADC has been reported within the first two weeks post chemotherapy or radiotherapy. However, in some studies, ADC increases were investigated and reported at later imaging time points (e.g. at 3 months or beyond). Despite the considerable variability in the timing of ADC investigations in relation to therapy reported in the literature, ADC still appears to be a useful response indicator in cancer treatment.

Other functional MR imaging techniques

The use of MRS is still not widespread because of the considerable technical expertise required for its implementation and data analysis. When placed within a magnetic field, nuclei contained in human tissues will demonstrate characteristic resonance frequencies. Depending on the local micro-environment, protons associated with different molecules resonate at slightly different frequencies which are expressed as chemical shifts. By observing chemical shifts, the metabolic profiles of the tissue can be obtained, characterised and quantified. Effective anti-tumour treatment can lead to metabolic atrophy of the tumour signature.

The principal basis for utilizing contrast in BOLD imaging is the difference in the relaxivity of oxygenated and deoxygenated haemoglobin. Deoxygenated haemoglobin shows increased susceptibility effects and higher longitudinal relaxation rate, R2* (reciprocal of the longitudinal relaxation time T2*). Thus, the measured tissue R2* indirectly reflects tissue oxygenation/ hypoxia and tissue blood volume.

DSC-MRI is underpinned by observing the first pass passage of contrast through tissues, and is observed as transient signal loss on T2*-weighted MR imaging. From this imaging data, mathematical modeling using a γ-variate fit can be used to derive tissue blood volume, tissue blood flow and mean transit time. Although the technique has been used widely and successfully in the brain, its application in the body has been more limited.

Multi parametric quantitative imaging

Given that each functional MR imaging technique provides unique insight into a particular aspect of altered pathophysiology in disease, there is now the opportunity to compare and correlate parametric maps derived using more than one functional MR technique. Such correlative imaging comparison is not confined to MR derived information, but can be also extended to CT or PET/CT imaging. By combining the information derived from a number of imaging techniques, it is possible to gain a multifaceted insight into the phenotypic expression of diseases before and after anti-tumour treatment.

Future developments and challenges

One of the key challenges in the development of multi-parametric imaging and quantitative MR imaging as a whole, is a lack of standardisation in image acquisition and data analysis. To some extent, the lack of standardisation has resulted from MR vendors driven innovations which have aimed to emphasize and create differences between imaging platforms rather than to encourage harmonisation between systems. However, there is now recognition within the industry and research organisations on the need to move our work towards more standardised functional MR imaging methods. More work is needed to ensure systematic validation of these techniques in well designed prospective studies, particularly in those where there is tissue collection or sampling, and in those where important clinical endpoints are assessed.

Suggested Reading

1. O'Connor JP, Jackson A, Parker GJ, Jayson GC. DCE-MRI biomarkers in the clinical evaluation of antiangiogenic and vascular disrupting agents. Br J Cancer. 2007 Jan 29;96(2):189-95.
2. Padhani AR, Miles KA. Multiparametric imaging of tumor response to therapy. Radiology. 2010 Aug;256(2):348-64.
3. Thng CH, Koh TS, Collins DJ, Koh DM. Perfusion magnetic resonance imaging of the liver. World J Gastroenterol. 2010 Apr 7;16(13):1598-609.
4. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol. 2007 Jun;188(6):1622-35.