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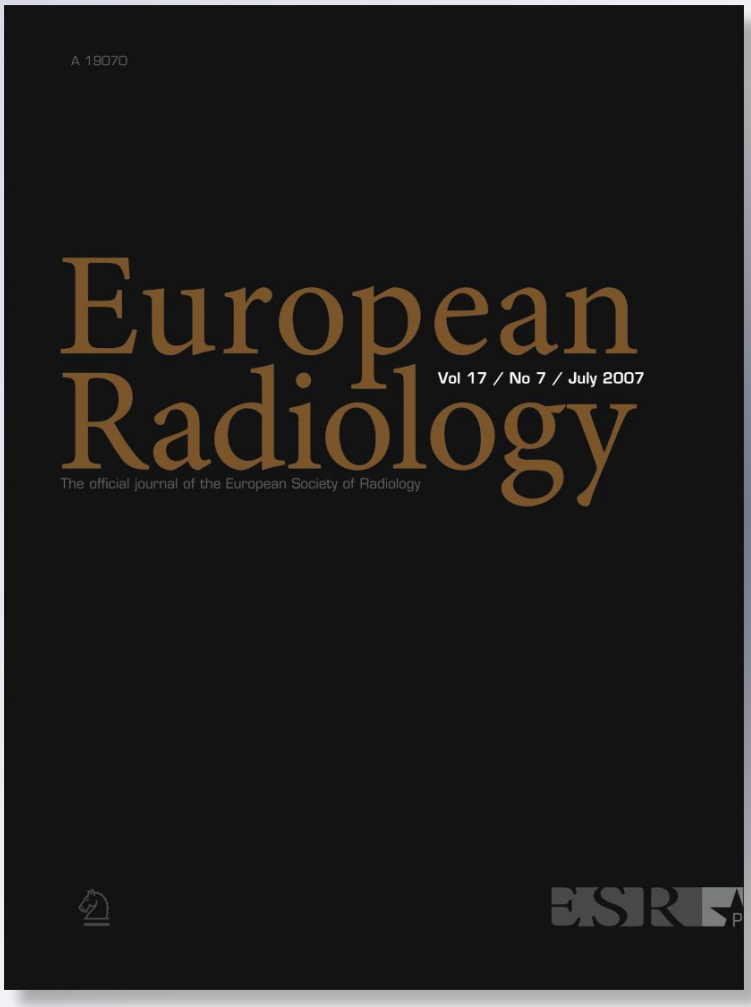

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MAGNETIC RESONANCE

Imaging vascular function for early stage clinical trials using dynamic contrast-enhanced magnetic resonance imaging

M. O. Leach · B. Morgan · P. S. Tofts · D. L. Buckley · W. Huang · M. A. Horsfield · T. L. Chenevert · D. J. Collins · A. Jackson · D. Lomas · B. Whitcher · L. Clarke · R. Plummer · I. Judson · R. Jones · R. Alonzi · T. Brunner · D. M. Koh · P. Murphy · J. C. Waterton · G. Parker · M. J. Graves · T. W. J. Scheenen · T. W. Redpath · M. Orton · G. Karczmar · H. Huisman · J. Barentsz · A. Padhani · on behalf of the Experimental Cancer Medicine Centres Imaging Network Steering Committee

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Abstract Many therapeutic approaches to cancer affect the tumour vasculature, either indirectly or as a direct target. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has become an important means of investigating this action, both pre-clinically and in early stage clinical trials. For such trials, it is essential that the measurement process (i.e. image acquisition and analysis) can be performed effectively and with

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consistency among contributing centres. As the technique continues to develop in order to provide potential improvements in sensitivity and physiological relevance, there is considerable scope for between-centre variation in techniques. A workshop was convened by the Imaging Committee of the Experimental Cancer Medicine Centres (ECMC) to review the current status of DCE-MRI and to provide recommendations on how the technique can best be used for early stage trials. This review and the consequent recommendations are summarised here.

Key Points

- *Tumour vascular function is key to tumour development and treatment*
- *Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can assess tumour vascular function*
- *Thus DCE-MRI with pharmacokinetic models can assess novel treatments*
- *Many recent developments are advancing the accuracy of and information from DCE-MRI*
- *Establishing common methodology across multiple centres is challenging and requires accepted guidelines*

Keywords Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) · Tumour vasculature · Angiogenesis · Cancer · Early phase trials

Introduction

Magnetic resonance imaging can probe vascular physiology, most commonly using contrast agents that distribute in the

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vascular space, leak into the extravascular extracellular space (EES), and then are eliminated by the kidneys. Uptake rates are highly variable in tumours depending on vascular phenotype, but neoangiogenesis is a feature of many cancers and a target for new treatments. The contrast agent alters the MR relaxation times according to the concentration in tissue, changing the signal intensity in the images. T_1 relaxation enhancement is in proportion to the local contrast agent concentration (DCE-MRI). Standardisation of measurements is of international interest [1, 2]. Enhanced T_2* relaxation causes loss of signal, which can also give information reflecting microvascular structure and functional blood volume (dynamic susceptibility contrast MRI, DSC-MRI). Although DSC-MRI is widely used in studies in brain tumours, there are challenges to quantification and the confounding effects of T_1 signal changes make analysis of leakage effects problematic. It has been little used outside of the brain. There are other flow- (perfusion-) related MR imaging methods but the focus of this report is DCE-MRI.

A Pharmacokinetic and Pharmacodynamic Technologies Committee (PTAC) workshop on MRI methods in early stage trials was held in 2002 [3, 4]. This and other reports [5–9] made a number of recommendations, which have been adopted in subsequent studies of agents affecting vascular function [10–15]. Since 2002, the use of these approaches has increased in a variety of ways. For detection and diagnosis, evaluation of the data often relies on qualitative assessment of enhancement along with morphological features, for example in targeted screening for breast cancer [16]. Objective assessment of response to treatment requires more quantitative techniques, and DCE-MRI methods have been used as biomarkers in many early phase clinical trials to aid in selecting an optimal drug dose and making go/no-go decisions with regard to continuing a drug development programme. To generate the necessary tissue vascular parameters, reliable calculation of contrast agent concentrations (quantifying delivery and accumulation) is required; physiological models are then fitted to these concentration–time curves to derive physiologically relevant parameters such as blood volume, leakage space volume, and the contrast agent transfer coefficient. Figure 1 shows an example of a model fit and calculated parameter maps before and after treatment in a patient with a neuroendocrine tumour [17].

Over the last 8 years there have been considerable advances in instrumentation, image analysis, and contrast agents. Wider use of DCE-MRI, particularly in late-stage trials or within the healthcare system, demands well-validated, robust, and reproducible measurements, consistently available across a range of imaging platforms at multiple sites. Key aspects of image signal acquisition, analysis, and reporting are considered below, with recommendations to aid standardised and robust DCE-MRI evaluation that build on the previous PTAC recommendations [4].

Aspects of instrumentation affecting quantitative DCE-MRI

Recent advances include greater static magnetic field strength and improved coil technology to increase the MR signal-to-noise ratio (SNR); parallel imaging techniques enable rapid acquisition of 3D volumes, allowing good tumour and organ coverage. Shorter magnet bore lengths and larger patient apertures both increase patient acceptance. Increased automation of setup, acquisition, and processing simplifies operation and increases patient throughput. These advances have generally been optimised by the manufacturer to improve consistency of the MR imaging process and to improve the quality of clinical MRI investigations. However, in simplifying these complex tasks, automatic adjustments may be performed that adversely affect the reliable quantification of image data.

B_0 and B_1non-uniformity and field strength

Non-uniformity in the main static (B_0) magnetic field causes distortion and mis-registration between individual sequences and across visits, worsening reproducibility, particularly in large field of view (FOV) imaging.

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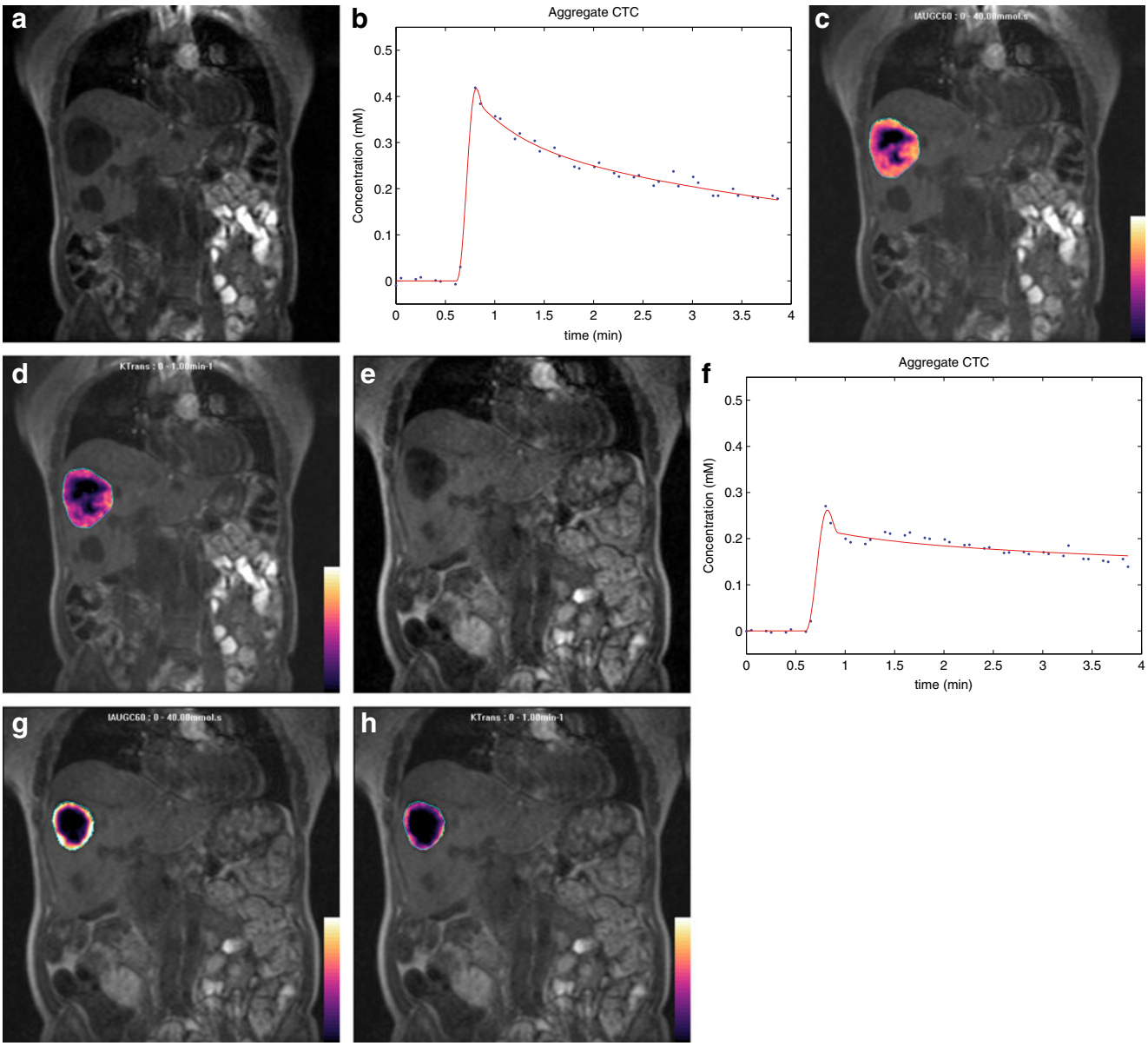

Fig. 1 Images from a clinical study of 90Y DOTATOC treatment in neuroendocrine tumours within 12 h pre-treatment (**a**–**d**) and 3 months post-treatment [17]. (**a**, **e**) T1-weighted pre-contrast-enhanced images, (**b**, **f**) calculated contrast agent concentration time curve from the indicated region of interest, (**c**, **g**) integrated area under the concentration time curve over 60 s (IAUGC60), (**d**, **h**) calculated K^{trans} map

Non-uniformity of the radio frequency (RF) field (B_1) is probably the largest source of systematic error for measurement of T_1, and therefore of contrast agent concentration. This arises from the RF transmit coil and from the subject. RF uniformity is optimal using a body transmit coil (instead of a smaller transmit/receive coil). Although imaging at higher field strength offers better SNR, RF non-uniformity is increased. Parallel transmission (incorporating B_1 shimming) is now becoming available to improve this and is helpful for large FOV imaging. B_1 mapping allows field uniformity to be assessed and a number of methods have been reported [18–20].

Pulse sequences using a train of readout pulses (e.g. variable flip angle spoiled gradient echo) are particularly prone to errors in B_1 field and flip angle calibration [21]. Small flip angle errors can lead to large errors in calculated vascular parameters [22, 23]. If uncorrected, such errors may make comparison of these parameters from different studies or centres difficult. Magnetisation prepared (MP) sequences (e.g. saturation recovery), if available, are less affected by B_1 non-uniformity.

Different equipment, RF coils and image archiving

A multi-centre trial will typically require the use of different MRI platforms and software levels. Although these may have similar clinical function, uniform quantification may

not be easy to achieve. Selecting centres that only use a particular manufacturer may compromise study recruitment and timelines. Follow-up studies on the same patient should use the same equipment and acquisition methods. Quality assurance (QA) procedures should be applied across centres to ensure that consistent parameters can be calculated.

Phased array 'receive' systems provide improved SNR and now allow parallel imaging algorithms such as SENSE or GRAPPA [24] to improve temporal resolution; however the more complex acquisition and processing required may affect quantification.

DICOM is a standardised image format that has embedded (header) information regarding image acquisition, signal scaling and grey scale display. Ideally, the DICOM header could contain all details required for quantitative analysis including image signal intensity scaling, i.e. receiver gain, transmitter gain, absolute timing of the start of acquisition, and timing of the centre of the k-space for each image, especially if gating is used. Manufacturers should be encouraged to ensure that image data include embedded data in well-defined public fields, to allow robust and reliable image scaling. The DICOM standard should be revised to include the information necessary for image quantification.

Recommendations on instrumentation

- Defined quality assurance standards should be established for all equipment, sequences, and reconstructions used in a study to demonstrate that derived quantitative values are equivalent. This is particularly important if absolute values are to be used in between-patient comparisons
- At or above 3 T, B_1 mapping or shimming is recommended. If unavailable, B_1 insensitive sequences should be used
- Ideally use a single MRI model. If this cannot be guaranteed, then ideally equipment-neutral protocols should be used for multi-centre studies
- Defined QA processes should be established for quantification. Less stringent requirements may be appropriate if inter-patient comparisons are not required
- Parallel imaging reconstruction should only be used if QA procedures show that accurate parameter calculation is possible in all centres
- Follow-up studies on the same patient should use the same equipment
- DICOM image headers should include all information necessary for quantification in the study

Phantoms, calibration, and quality assurance

Phantoms (test objects) are required to provide objective assessment of fundamental system performance metrics [1, 25–28]. Here, we concentrate on physical phantoms to characterise acquisition performance of MR systems, with emphasis on available existing phantoms. The Eurospin phantom has been widely used and provides calibrated gels reflecting tissue relaxation time values [27, 29]. Calibration sample containers are preferably cylinders of at least 2 cm in length to avoid partial volume in the slice select direction. In principle, phantoms can be designed to approximate aspects of anatomy, such as subcutaneous fat and air containing structures, and/or dynamic tissue function, but add substantial complexity [1, 30].

Current international initiatives to develop phantoms

- Reference Image Database to Evaluate Response (RIDER) [1, 2]
- Image Response Assessment Team (IRAT)
- Quantitative Imaging Network (QIN)
- AAPM: Working group for standards for quantitative MR measures
- RSNA: Quantitative Imaging Biomarker Alliance (QIBA) [1]. MRI/DCE subcommittee
- ISMRM: Ad hoc committee on standards for quantitative MRI

http://wiki.ismrm.org/twiki/bin/view/QuantitativeMR/MRPhantomDatabase

Measurement of T_1

Phantoms allow assessment of T_1 mapping for proposed sequences [31–34]. A T_1 phantom must include an array of solutions (or gels) having constant accurately measured values reflecting the range anticipated in clinical trials with a T_1 of 50–2,000 ms (in order to cover peak values of contrast agent concentration during bolus passage [35]) and a T_2 of 20–100 ms at 1.5 T. Values should be calibrated and be appropriate for the B_0 field used.

The repeatability and accuracy of T_1 measurements should be assessed in various positions within the MRI aperture, between visits and between MRIs in the study, under conditions approaching the likely trial measurement conditions, including temperature [28]. Static phantom measurements do not allow for physiological motion, region of interest (ROI) placement, and flip angle (FA) errors; however there is currently no accepted dynamic phantom available.

Signal and contrast-to-noise ratio

In general, SNR should be maximised within the limits of the temporal and spatial resolution required. Large differences in SNR between systems may bias data analysis, and this should be considered in the design and analysis of a study. The SNR of each MR system should be determined, particularly under DCE-MRI conditions.

Spatial uniformity of the transmit B_1 field and receive coil sensitivity

The flip angle (FA) may vary over the imaged volume, which may result in spatial variation in the accuracy of contrast agent

concentration measurement. This can be minimised by choice of imaging sequence (for example 3D acquisitions), as well as RF pulse shape. Calculating quantitative T_1 values to derive contrast agent concentrations will lessen this effect. A suggested standard for the flip angle (FA) and calculated T_1 is that they should be accurate to within 5 % in DCE-MRI phantom studies over all samples within a defined field of view. For phantom studies, the spatial uniformity of the transmitted B_1 field should be measured. Complex assessments across the whole field of view may be impracticable and it may be prudent to restrict the volume of interest (VOI) to the centre of the FOV.

Recommendations for quality assurance

A QA process should be in place using phantoms. This should be based on the study requirements and should demonstrate:

- That the effects of regional variations in B_1 homogeneity are small compared with the minimum change to be measured in patients
- That the effects of any automated image enhancement processes do not affect quantification
- That flip angles are calibrated correctly and the T_1-weighted signal is stable over the acquisition period
- Equivalence for different field strengths (if used)

Contrast agents (dose, delivery, compounds, safety)

Introduction

Many low molecular weight (LMW) gadolinium-based contrast agents have been approved for use in humans [36]. DCE-MRI use is technically "off-label" but similar in dose and delivery rate to clinical protocols. Some gadolinium-based contrast agents have significant liver uptake or protein binding that would need special protocols if used. It is unclear whether ionic and non-ionic agents produce different values of DCE-MRI parameters. Iron- and manganese-based agents are not recommended for DCE-MRI.

Safety

The frequency of acute adverse events after administration of gadolinium chelate ranges from 0.07 % to 2.4 %. Most of these are mild, including coldness at the injection site, nausea, headache, paraesthesia, dizziness, and itching. Idiosynchratic responses vary in frequency from 0.004 % to 0.07 %. A rash or urticaria are the most frequent, and bronchospasm may occur. Severe, life-threatening anaphylactic reactions are exceedingly rare (0.001 % to 0.01 %). However, gadolinium-based contrast media are associated with the rare severe and potentially fatal condition nephrogenic systemic fibrosis (NSF), which occurs in patients with severely impaired renal function. The ionic macrocyclic agents are considered the safest in this regard [37]. Although patients with malignancy may have impaired renal function, those with significant renal failure would usually be excluded from multi-centre trials. If a trial intentionally involves patients with renal impairment then the selection of contrast agents should take into account the risk of NSF [38–41].

Dose

Most agents are available in 0.5 M concentration. A single dose is typically 0.1 mmol/kg body mass leading to 10–20 ml injection volume. Once the contrast agent and dose are set, they should remain fixed for the same patient throughout the trial.

Delivery

A bolus injection approach is preferred to infusion, since meaningful physiological data are obtained from the early enhancement phase. An injection rate of at least 3 ml s^{-1}, unless limited by access or cannula size, with a consistent 20–40 ml chasing saline bolus, is recommended. Adequate intravenous access at the ante-cubital fossa and a constant rate infusion pump are recommended to optimise bolus delivery, maintaining this throughout the study. Central lines are not always suitable for use with a pump injector.

Recommendations for contrast agents (dose, delivery, compounds, safety)

- Use the same contrast agent within the same patient. At a minimum the same class of LMW agent should be used within a study and, preferably, the same agent
- A single dose of 0.1 mmol/kg is typically used. Once set, the dose and delivery rate should remain the same for all patient visits
- Bolus injection using a power injector should be used
- Agent, dose, and injection protocol should be clearly recorded
- In renal failure the risk of NSF should be considered

Measurement protocols, lesion selection, and study design

Sequence specification

For DCE-MRI, a 3D T_1-weighted spoiled gradient recalled echo (GRE) is widely available and ideally should be used if adequate temporal resolution for the physiological model can be achieved. The sequence should be optimised for SNR over the range of T_1 values anticipated for the study, including the baseline T_1 value, and throughout the dynamic T_1-weighted acquisition. Using parallel imaging, a volume data set can be obtained in around 3 s. Volume coverage should be defined in the protocol and maintained throughout the study.

Table 1 Proposed nomenclature for quantities determined by DCE-MRI (NB numbers refer to references)

Symbol	Name	Units
E	Extraction fraction (a, b)	None; 0<E<1
F_b	Blood perfusion (c, d)	ml min^{-1} (100 ml tissue)$^{-1}$
F_p	Plasma perfusion (e)	ml min^{-1} (100 ml tissue)$^{-1}$
Hct	Haematocrit (a, l)	None; 0<Hct<100 %
IAUGC	Initial area under the Gd concentration time curve (f)	mM s
k_{ep}	Rate constant (a, f, g)	min^{-1}
K^{trans}	Transfer constant (a, f, h)	min^{-1}
PS	Vessel permeability surface area product per unit volume of tissue (a, f, i)	min^{-1}
r_1	T_1 relaxivity (a)	s^{-1} mM^{-1}
T_{10}	Pre-contrast T_1 of tumour (a, j)	s
v_b	Blood volume fraction (a, f)	None; 0<v_b<100 %
v_e	EES volume fraction (a, f, k)	None; 0<v_e<100 %
v_p	Plasma volume fraction (a, f)	None; 0<v_p<100 %

(a) Already proposed in [9]

(b) Also called initial extraction ratio [9]; in simple models $E = K_{trans}/F_p$

(c) Initially called simply perfusion F [4], or blood flow per unit volume of tissue. Sometimes F refers to blood flow per unit *mass* of tissue (ml min^{-1} (100 g tissue)$^{-1}$ [9]; however imaging cannot give this without knowledge of tissue density

(d) The CT group called this regional blood flow

(e) $F_p=F_b(1\text{-Hct})$

(f) Already proposed in [4]

(g) $k_{ep} = K^{trans}/v_e$ (v_e given as a fraction, i.e. o<v_e<1)

(h) Formally the volume transfer constant from *plasma* to the EES; CT measurements sometimes derive the transfer constant from *blood*. PET nomenclature for K^{trans} and k_{ep} differs from MRI

(i) PS can also be per unit *mass* of tissue [9]

(j) Native T_1, i.e. without any Gd

(k) EES = extravascular extracellular space

(l) Hct may be reduced in small vessels [97]

A DCE acquisition time of 8–10 min is recommended: although K^{trans} (see below for modelling parameters and Table 1 for definitions) may be measured in 2–3 min, if it is low post-treatment or if measurement of v_e is required, images acquired beyond peak amplitude are helpful [42, 43]. A minimum of three pre-injection time points is recommended to measure pre-bolus signal intensity accurately. Baseline T_1 (T_{10}) can be measured most accurately by using a set of variable flip angle images (including proton density weighted) before the DCE acquisition.

Where possible, all parameters should be harmonised across imaging platforms to achieve acquisition equivalence. These would include standard sequence parameters including bandwidth, k-space trajectory, and transmit coil (body coil recommended). Certain options, such as parallel imaging, optional (user-selectable) data processing, or filtering settings and fat suppression may need to be excluded if harmonisation is to be achieved across the study. Highly specialised or vendor-specific techniques such as dynamic k-space techniques are not recommended for clinical trials.

Lesion selection

Reproducibility studies suggest that the target lesion should be at least 2 cm, preferably >3 cm in diameter [44, 45]. Ideally, target lesions should be in areas away from respiratory, peristaltic, or pulsatile motion unless the acquisition and analysis are designed to be robust to movement. Predominantly cystic lesions (identified from standard T_2-weighted images) should be avoided, as these may show poor enhancement.

Study design

Pre-treatment baseline measurements are essential when evaluating post-treatment changes. Selection of study examination intervals should be based on the biological processes to be measured and depend on treatment regime, findings from preclinical studies, the information required for decision making, regulatory issues, ethical considerations, and patient acceptability. It is desirable to assess the repeatability of the measurements by performing two baseline studies, first to measure the repeatability of the technique if not previously

established and second, at least for initial cases, for QA at each individual centre [30, 46]. This is even more important if analysis is expected to concentrate on individual responses rather than to detect an overall cohort response.

Recommendations on measurement protocols

- 3D spoiled GRE is widely available and recommended if adequate temporal resolution for the physiological model can be achieved
- Sequences should be optimised for SNR and the range of T_1 anticipated in the clinical study
- Two pre-treatment examinations are desirable if repeatability of the method is not known or as centre QA for initial cases
- Recommended imaging protocols for various tumour types and locations should be developed
- DCE-MRI acquisition time of 8–10 min is recommended
- Avoid lesions <3 cm in diameter or predominately cystic in nature
- Where possible, key imaging parameters should be harmonised across sites or complex acquisition parameters should not be used
- DICOM image information should confirm harmonised sequence parameters and scaling information to allow QA for central analysis of data
- Highly specialised or vendor specific methods are not recommended for multicentre clinical trials

Motion and registration

Problems can be avoided by selecting tumours that are not affected by involuntary (cardiac, respiratory, or peristaltic) motion. However, trial design may demand the study of tumours that do undergo motion, especially because more than 50 % of metastatic cancer occurs in the liver and lung. Effective protocols that address tissue motion are therefore required. Motion causes two problems: first, motion during image acquisition causes ghosting and blurring; second, movement between image acquisitions will affect registration of sequential images, making analysis of the contrast time-intensity curve of a pixel problematic.

Where possible, it is preferable to minimise motion when acquiring image data. Breath-holding is one approach to achieving this [47], but prohibits temporal sampling between breath holds, potentially limiting data analysis methods [48]. Breath-holding at full expiration gives the most reproducible position but demands patient cooperation and operator input.

Alternative approaches include fast image acquisition (in less than 1 s), effectively freezing motion during gentle breathing, but reducing volume coverage. Since respiratory movement is normally in the head–foot direction, for coronal/sagittal acquisition tumours will stay approximately in the image slice despite in-plane movement, particularly in a supine, arms-raised position [44]. However, ROIs will need to be defined for each time point and pixel-wise analysis may be compromised.

Registration of images is possible both during and after image acquisition. Diaphragmatic navigators are available on many MRIs, as are sequences that correct for rotational motion of the head, but these result in variable timing of acquisitions and may be affected by changing image contrast during the DCE-MRI sequence. Use of these methods also adds complexity to the study and causes difficulties in harmonisation across sites. A further range of non-rigid and rigid body registration methods has been developed, and applied with varying degrees of success to DCE data [49, 50]. Tracer model-based registration methods [51] assume the same model holds for all pixels, which will often not be the case. Current approaches are still largely in the research and validation phases, so are not available on equipment as standard tools. Hence, for multi-centre studies, minimisation of motion and post-acquisition registration methods are recommended, but if used must undergo QA for accuracy of registration.

Recommendations on motion and registration

- Target fixed lesions, if possible, for the purposes of the study
- Optimise selection of planes to facilitate tracking and registration of residual motion, e.g. oblique coronal/sagittal plane
- Minimise motion by acquiring in supine, arms-up position during gentle breathing or perform sequential breath-holds in expiration
- If free breathing is to be used, robust registration methods need to be demonstrated and registration applied consistently across all subjects
- Perform registration as required

Measuring the arterial input function

Pharmacokinetic (PK) modelling relies on knowledge of the blood and tissue contrast agent concentrations. To measure the blood concentration [i.e. the arterial input function (AIF)] accurately after bolus injection, high temporal resolution (2–3 s) is required. The sequence must deal with high arterial contrast agent concentration (0.5 mM in whole blood), in-flow effects, and the need to optimise for vessel orientation as well as tumour position [22, 35, 52, 53].

Measuring the AIF from a pre-bolus is possible [54], although it increases the length of the imaging session by some 8–10 min and adds complexity. It involves injecting a small dose of contrast agent (typically one-tenth of the standard dose), accompanied by an imaging protocol optimised to measure the AIF with subsequent scaling of calculated concentrations [55–58]. The tissue of interest is loaded with a small amount of contrast agent before the main dynamic study, which may affect signal intensity changes.

An alternative approach derives the AIF from a reference region (RR) of normal tissue such as muscle,

which is presumed to have known PK properties allowing reverse calculation of the AIF [59–65]. However, perfusion in the RR may be altered by the studied treatment, and errors due to inadequacies of the PK model may be magnified.

If measuring the AIF accurately is not possible, an empirical [66], or population-derived input function described by a simple bi-exponential form, can be used [35, 67]. Recently published model forms more fully capture the complexity of the AIF following a bolus of Gd contrast [35, 68, 69]. Use of these forms may substantially improve measurement repeatability [35]. However, use of an assumed AIF may confound the interpretation of the study if the pharmacological agent employed affects cardiac output or systemic or local vascular resistance.

Recommendations on measuring the arterial input function

- Measurement of the arterial input function (AIF) needs to be considered in trial design and interpretation
- Direct measurement of the AIF or a pre-bolus measurement are acceptable approaches
- Unless the AIF can be measured reliably and with adequate temporal resolution then a population average may give better repeatability
- If the AIF cannot be measured, the model used to analyse the data must be appropriate

Analysis

Measuring the concentration–time data may be performed for an ROI, VOI (ROIs from several slices covering the whole tumour), or for each voxel in the image (requiring good SNR). The ROI or VOI approach can make model fitting more robust, at the expense of lost detail in heterogeneous tumours. Analysis will usually be performed on data from the whole tumour or from a representative subset of the tumour volume. Global tumour parameters may be a fit of the average signal from an ROI/VOI or ideally a median or mean of the result of all fitted voxels. Using the mean or the median can mask or bias important biological changes, however, and histogram analysis (listing numbers of pixels within data value ranges) can aid evaluation of heterogeneity and changes resulting from treatment. On the other hand, it is difficult to analyse histograms statistically and therefore for clinical trials, the data will generally need to be collapsed to a single scalar, although methods to capture spatial heterogeneity have been proposed [70]. Histograms should be generated according to standard methods to aid inter-centre comparisons [71].

Significant errors can arise from the definition of ROIs, particularly if there are tissues that enhance differently bordering the tumour. Setting the ROI on defined criteria should be done on all patient time points at the same time by appropriately trained operators, ideally overseen by a radiologist. Assessing agreement between different operators for ROI definition may provide useful quality control (QC) data. This process should be blinded to the study time point and treatment group.

The analysis software and procedure should be defined in detail, with a full audit trail to allow transparency. This will ideally include analysis software name, source and version number and date, details of how VOIs are defined, details of the parameters supplied to the analysis software, a date record of the source images, VOI definition, entered parameters for each analysed data set, together with any other variable parameters, such that an identical analysis could be repeated and would provide the same results. In particular, the model-fitting procedure must be defined, with convergence criteria and precautions to avoid local false minima in the sum of squares. All fixed parameter values (e.g. Hct) should be stated. Clear criteria should be defined for the identification and documentation of fitting failures, and the reason for failure, which can include excessive noise, insignificant enhancement, and lack of convergence or non-physiological values. Reporting confidence intervals on parameter estimates is recommended if possible [58, 72, 73].

In multi-centre studies, central analysis is favoured to ensure uniformity of approach. This also allows quality control of the data from each site.

Recommendations on analysis

- The analysis plan should be prospectively defined
- ROIs for all sequential studies should be defined at the same time, blinded to the date of the imaging and treatment arm but not to patient identifier
- All steps in data analysis should be saved and be auditable
- Central analysis process promotes consistency and ensures blinding for study time point and treatment assignment
- Recommendations to address the histogram or other voxel-based analyses need to be developed

Modelling

Dynamic contrast-enhanced MRI used in previous early phase trials has largely focused on measuring change, where a decrease in enhancement parameters is normally viewed as beneficial. The simplest approach to data analysis is to use descriptive measures of curve shape, with evaluation of the 'initial area under the enhancement curve' after contrast agent injection providing a non-model-based quantitative assessment [6]. This metric has no direct physiological meaning but is easy to obtain. Previous recommendations [4, 9, 74] suggested that analysis should be based on the well-accepted Tofts or equivalent models, including, where supported by data, a term for plasma volume. This provides K^{trans}, v_e, and v_p (defined in Table 1). Model choice may be partly dictated by temporal resolution. K^{trans} and v_e may be determinable at low

temporal resolution and with an assumed AIF, but estimation of v_p is unlikely to be accurate. If a one-compartment model fits the data well there may be no case for using a more complex model; however, in vascular tumours measured at high temporal resolution a poor fit is likely as a one-compartment model may not model the vascular component [75]. More elaborate PK models may improve evaluation of dynamic data and better characterise physiological parameters and biological effects [76–84], but are not yet supported by sufficient evidence to warrant use as primary endpoints.

Formulae and terms for common compartmental models

These models describe the transfer of a contrast agent from the plasma compartment to the tissue extra-cellular extra-vascular space. Terminology and further information on models may be found in [4, 9, 75, 98]. Variables are detailed in the tables

The Tofts Model (one-compartment, two parameter model) assuming that the plasma contribution of contrast derived signal to the tissue signal is negligible

$$C_t(t) = C_p(t)^{*}K^{trans}\exp(-K^{trans}t/v_e)$$

* Represents a convolution

$C_t(t)$ is the tissue concentration of the contrast agent

$C_p(t)$ is the plasma concentration of the contrast agent obtained from an arterial input function and may be measured or estimated from a population or published model

v_e is the fractional volume of the tissue extra-cellular extra-vascular space

K^{trans} describes the transfer constant of contrast from the plasma to the tissue extra-cellular extra-vascular space. This term contains both the perfusion to the tissue (F_p) and the permeability-surface area product (PS) describing transfer across the vascular endothelium

k_{ep} is the rate constant between the plasma and the extra-cellular extra-vascular space ($k_{ep} = K^{trans}/v_e$)

The Modified Tofts Model (two-compartment, three parameter model) assumes that there is a significant contribution from plasma contrast derived signal to the tissue signal

$$C_t(t) = v_pC_p(t) + C_p(t)^{*}K^{trans}\exp(-K^{trans}t/v_e)$$

v_p is the plasma volume fraction

The Two Compartment Exchange Model (two-compartment, four parameter model) enables PS to be measured separately from tissue perfusion, provided that there is adequate data support

$$C_t(t) = C_p(t)^{*}F_p[A\cdot\exp(-\alpha t) + (1-A)\cdot\exp(-\beta t)]$$

PK parameters can be calculated from the fit parameters (F_p, A, α, and β) using the following expressions:

$$v_p = F_p/(A(\alpha-\beta)+\beta)$$
$$PS = v_p(\alpha+\beta-v_p\alpha\beta/F_p) - F_p$$
$$v_e = PS\cdot F_p/(v_p\alpha\beta)$$

F_p is the plasma flow or perfusion

Models should be chosen objectively, and complex models should only be used if justified by the requirements of the trial end points and statistical arguments related to fit quality [72, 85–87]. Increasing the model complexity typically requires the measurement of an AIF. If data are not adequate, the fit may become ill-conditioned, with increasing uncertainty in the fitted parameter sets, and individual parameters that are not physiologically meaningful [85–89]. Statistical tests to assess whether extra parameters are warranted include the F-test (for nested models) [85] and those based on information theory, such as the Akaike Information Criterion [86, 90].

Previous guidelines [4, 74] recommended that estimates of uncertainty should be given for model parameters and included in the error analysis. This is particularly relevant in pixel-by-pixel analysis where many thousands of fits may be performed and data quality is poor with extreme variations across pixels in many tumours. Fit failures should be categorised, since some, for example those due to lack of enhancement, can provide information on treatment response [91–93]. Confidence intervals on parameter estimates are rarely reported, but would be helpful in assessing data quality and comparing models.

It is currently unclear which models best suit data from various tumour types, tumour sites, and treatment methods. Processes to support sharing of data and open access data repositories would allow assessment and validation of different and novel models.

Recommendations on models

- Report K^{trans} and v_e whichever model is used
- Expanding the model to include further variables requires higher quality data and higher temporal resolution (and normally a measured AIF)
- Use of complex models should be reserved for additional exploratory endpoints
- Reporting should evaluate uniqueness of fit and ideally the standard error of parameters
- Sharing of data would allow assessment and validation of standard and novel models

Nomenclature (definition of parameters, what should be used)

A consensus was reached within the MRI community on standard terminology [4, 9]. The resulting agreement to use K^{trans}, v_p, v_e, k_{ep}, and initial area under the gadolinium curve (IAUGC; amongst other parameters) has had a large influence, and virtually all publications now use this convention. Here we extend this nomenclature to more physiological quantities [extraction fraction (E), perfusion by blood (F_b) and by plasma (F_p); Table 1]. Perfusion refers to total blood volume flow rate per unit volume of tissue, including any flow passing through (large-vessel) shunts. Since multiple modalities are employed in different studies, it is desirable that the terminology should be comparable across imaging modalities (MR, CT, PET, and ultrasound).

Nomenclature for MR imaging sequences and measurements should also be harmonised (Table 2). The term AIF

Table 2 Proposed nomenclature for other concepts

Short name	Full name	Other acceptable names	Discouraged names
AIF	Arterial input function	Blood concentration (a), vascular input function	
VIF	Vascular input function		
Blood signal	Blood signal curve		AIF (b)
C_p	Plasma concentration curve (c)		AIF
DCE-MRI	T_1-weighted dynamic-contrast-enhanced MRI (d)	K^{trans}-imaging	Permeability-MRI, relaxivity MRI
DSC-MRI	T_2/T_2*-weighted dynamic-susceptibility-contrast-enhanced MRI	Bolus tracking (g)	Perfusion MRI, PWI(e)
2CXM	Two-compartment exchange model (f)	(Open) two compartment model	

(a) Blood concentration can be derived from blood signal using T_{10}, FA, TR, r_1, and a model of the MR sequence

(b) AIF has also been loosely used in MRI to refer to the blood signal

(c) Derived from blood concentration using Hct

(d) In CT this is DCE-CT or perfusion-CT

(e) The American College of Radiology (ACR) uses perfusion-weighted imaging (PWI) to mean dynamic susceptibility contrast (DSC) imaging

(f) See [52, 75]

(g) Although bolus-tracking can also be done with T_1-weighted techniques

has been variously used in MRI to refer to the blood signal curve, the whole blood concentration curve [35, 66], and the plasma concentration curve (which is the input for the PK modelling [42, 67]). We propose that 'AIF' should only be used to describe the arterial whole blood concentration, since this convention is already established [35, 66]. It is recognised that in some tumours or tissues, the blood supply may not be from an artery and using the term vascular input function (VIF) would recognise this.

New recommendations on nomenclature

- AIF refers to whole blood concentration (not blood signal or plasma concentration)
- Blood perfusion is termed F_b; plasma perfusion is F_p

Transparency of reporting approach (ability to track and report measurement and analysis variables, provide data in formats for further analysis)

Guidelines for reporting a DCE-MRI study

Clinical studies would benefit from a set of guidelines for reporting DCE-MRI. This would be similar to an already published set of guidelines for functional MRI [74, 94].

Two levels of reporting are proposed:

(1) For peer review of the paper and for meta-analysis.
(2) So that the analysis can be completely reproduced, by storing all data and image analysis as 'electronic supplements'. It was agreed that this level is very complex and difficult to achieve without dedicated funding.

The MR imaging protocol needs to be relayed in sufficient detail so that the sequence can be reproduced exactly.

Examples of raw data, allowing assessment of quality of data and of model fit, should be provided. Publications should provide statistics to determine the quality of fit, e.g. goodness of fit and analysis of uncertainty (or confidence limits) on parameters. Clinical studies should be reported in the manner of CONSORT 2010 guidelines [95, 96]. Similar guidelines are given in Neuroimage fMRI reporting guidelines [94].

In addition, understanding and evaluation of analysis approaches is to be encouraged through data sharing (see modelling section). It is recommended that ethical approval for studies should include permission for further analysis and publication of anonymised data.

Categories for reporting results

- Inclusion criteria
- Acquisition methods: *enough detail to repeat sequence and injection*
- Data: *blinding, exclusions from data set*
- Presentation of data: *Demonstrate range of quality of data, provide representative curve fits and uncertainty of estimates*
- Algorithms/software: *Provide enough detail to reproduce the analysis, ROI selection, movement compensation, ROI modification in series, models, and AIFs employed*
- Statistical tests: *taking into account multiple variables, uniqueness of fits*
- Additional documentation (e.g. audit trail)

Conclusions

Dynamic contrast-enhanced MRI provides an effective tool for evaluating changes in tumour vascular support resulting

from anti-cancer therapies. Current approaches using the Tofts model have provided sensitive measurements of anti-angiogenic and antivascular directed therapies. Recent advances in technology permit increased volume coverage with good temporal resolution, allowing more complex models to be employed that may better inform physiology. However, the advances in both equipment and modelling result in many more potential variables in the measurements, leading to an increasing need for careful quality assurance and standardisation of methods within trials. These recommendations provide a basis for standardising approaches within a trial, facilitating the development of more detailed quality assurance standards.

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Conflict of Interest M.O. Leach and D.J. Collins: Software developed at the Institute of Cancer Research and using some of the approaches referred to in this paper may be commercialised by the Institute of Cancer Research and commercialised or licensed to users. In those cases employees may receive some income under the Institute's rewards to inventors scheme.
B. Whitcher: Employed by GlaxoSmithKline (pharmaceutical industry) at the time of the ECMC workshop and until 6 May 2011. Now employed by Mango Solutions (software industry) and provides medical image analysis services to the pharmaceutical industry.
G. Parker: Received research grant income and consultancy income from pharmaceutical companies for work in DCE-MRI associated with clinical trials. Specifically, within the last year received research grant income from AstraZeneca, Pfiizer, GSK, Roche, Genentech, Bayer, and Merck-Serono. Received consultancy income from Bayer. Also a shareholder and director of Bioxydyn limited, a specialist imaging company with an interest in DCE-MRI.
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