

Recommendations for MR measurement methods at 1.5-Tesla and endpoints for use in Phase 1/2a trials of anti-cancer therapeutics affecting tumor vascular function

Type of measurement

- Study design should incorporate quality assurance of the MR system, sequences, set-up procedures and radiological processes (e.g., T1 accuracy, system stability, B1 homogeneity)
- Pharmacodynamic assessment should use T1 weighted studies of low molecular weight gadolinium chelates
- When available, preclinical tumor data should be used to determine timing of DCE-MRI measurements for drugs with novel mechanisms of action
- Adjust orientation so that motion is in-plane when motion effects cannot be avoided (e.g., liver, lungs)

Pre-injection

- Acquire high quality clinical images of entire anatomic region (preferably in two orthogonal planes)
- Acquire T1- and T2-weighted images registered in the same planes as the dynamic data
- If possible, measure T1 (using same resolution and field of view for dynamic data)

Contrast agent injection

- Use power injector to minimize variation
- Injection dose should be standardized by weight
- 15-30 sec for total injection, at least 20 cc saline flush
- Document injection site, use same site for subsequent studies in same subject
- Minimum of 24 h between studies

Dynamic study

- For first 150 sec after bolus injection, use fastest sampling possible consistent with spatial resolution/anatomic coverage requirements, but not slower than 20 sec temporal resolution (note: the arterial input function cannot be sampled and K^{trans} will be artificially lowered with 20 sec temporal resolution unless the contrast injection is slowed)
- Acquire data out to at least 8 min (continual sampling is optional)

- If possible, include in imaging volume a normalization function (e.g., arterial or other tissue)
- For serial studies, imaging volume of interest should be adjusted to sample same region of tumor

Primary endpoints

- The primary endpoint should be the transfer constant (K^{trans} , min^{-1}) and/or initial area under the gadolinium concentration time curve (IAUGC, $\text{mMGd}\cdot\text{min}$; over first 1.5 min after contrast arrival)
- Measurements of K^{trans} or IAUGC should be made voxelwise
- In tissues with substantial motion ROI average measurements may be appropriate
- A minimum of 3 slices are preferred as single slice measurements (in theory) may be prone to bias
- Tumor dimensions (three orthogonal axes) for total tumor and region analyzed should be reported
- Vascularised tumor volume can be obtained by summing voxels with values above a predetermined threshold (report threshold definition).
- All data including ROI definition and analysis should be recorded and traceable to support external review

Measurement requirements to assess K^{trans} and IAUGC

- Both K^{trans} and IAUGC require calculation of instantaneous tumor gadolinium concentration, based on the change in relaxation time due to contrast uptake $\Delta R1$. This requires:
 - An estimate of contrast agent relaxivity
 - Measurement of tumor T1 immediately prior to contrast uptake
 - An accurate T1 measurement method verified for all spatial locations, coils and scanners used
 - Cardiac output (or normalization function)
 - Reproducible injection

Secondary endpoints

- Other endpoints derived from compartmental models and DCEMRI such as V_b , V_e , K_{ep} may be of value
- Simplified methods based on signal intensity changes may be less sensitive than K^{trans} or IAUGC and are harder to compare between centers

- More elaborate pharmacokinetic models may improve evaluation of dynamic data but are not yet supported by sufficient evidence to warrant use as primary endpoints

Trial design

- Entry criteria should consider tumor size in relation to pharmacological mechanisms, MRI resolution, sensitivity to motion and potential confounding factors from previous treatment (e.g., radiation) or rapid tumor growth rates
- Tumors in a fixed superficial location should be at least 2 cm in diameter; other tumors should be at 3 cm in diameter

Nomenclature

- Standardised terms should be employed as defined in Tofts et al (1999)

Analysis

- Model analysis should be based on the well-accepted Tofts or equivalent models, but with inclusion of arterial input normalization (or equivalent normalization function), blood volume, and classification of fit failures
- Estimates of uncertainty should monitor model fitting and chi-squared error, mapping this factor and including it in error analysis
- Fit failures should be categorised as model fit failure (possibly multiple classes), no enhancement, or noise
- ROI analysis, based on whole tumor mean values, may not evaluate tumor heterogeneity; although it may be robust to motion, it may not reflect small areas of rapid change and so may be insensitive
- Voxel mapping allows all data to be evaluated, allowing description and evaluation of regional change; individual voxels will have relatively poor signal to noise
- Analysis techniques, such as histogram and principal components analysis, may yield sensitive assessment of change.

ROI

- ROI placement needs to be supported by method of definition, and recorded to permit re-evaluation.
- Before placement of an ROI, individual images should be examined for the presence of patient motion, best seen on subtraction images
- Ideally dynamic image datasets should be spatially registered before analysis

- Both early (60-120sec after contrast) and late (more than 5 min after contrast) subtraction images should be generated
- Ideally the early subtraction images may guide the position for ROI placement (may not apply in some region; e.g., liver), which should also take account of non-enhanced images (i.e., include non-enhancing tumor)
- If early enhancement is low, the late subtraction dataset should be used
- If no enhancement is seen, the baseline data (non-enhanced) aided by conventional images should be used for ROI placement
- The outer limit of the lesion should act as a boundary of the ROI to minimise partial volume effects.
- Adjacent blood vessels or regions with other sources of artefact should be excluded
- The ROI should be constant in position and size for each image in the series under analysis; in the event of significant motion, it may be necessary to adjust the ROI position on each image, measuring only a mean value
- The position of the ROIs, corresponding graphs and table of enhancement values should be recorded, ideally in digital and hard copy form for future reference
- Analysis should take account of potential partial volume and ROI shape
- Definition of ROI should be stated explicitly in all reports of DCE-MRI data

Recommendations for future research in DCE-MRI

- Explore 3-Tesla – compare with 1.5-Tesla results
- Explore new macromolecular contrast agents as they become available
- Make available public domain analysis software or standard capabilities built into MR systems
- Compare DCE-MRI with other contrast mechanisms, functional/molecular imaging techniques, and other bioassays
- Implement parallel imaging
- Implement motion robustness (e.g., navigator echoes)
- Implement robust registration algorithms
- Implement sequences providing greater coverage
- Implement quantitative sequences
- Address normalization function
- Evaluate relationship to clinical response (both pre-treatment and early after treatment) which would ultimately lead to CPT code
 - Colorectal CA
 - Renal cell CA
- Evaluate impact of prior/concurrent treatment on ability of DCE-MRI to detect vascular response
- Explore potential for DCE-MRI to detect normal tissue effects and/or predict normal tissue toxicity
- Automate appropriate data acquisition and image analysis
- Address intra- and inter-tumor heterogeneity questions
- Evaluate impact of ROI definition on variability of results
- Reach consensus on acceptable statistical measures of reproducibility
- Evaluate information content of alternate (both simple and complex) analysis approaches
- Use ‘standard’ tissue (e.g., benign prostatic hyperplasia, meningioma) to evaluate method variability independent of biological variability
- Data sets with known outcome for evaluation of analysis methods available in public data base
- Further refine patient selection criteria
- Develop improved T1 phantom