QIBA DCE-MRI Technical Committee: DCE-MRI Profile v. 1.0

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EXECUTIVE SUMMARY

The RSNA QIBA Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) Technical Committee is composed of scientists representing the imaging device manufacturers, image analysis laboratories, biopharmaceutical industry, academia, government research organizations, and professional societies, among others. The goal of the DCE-MRI committee is to define basic standards for DCE-MRI measurements and quality control that enable consistent, reliable and fit-for-purpose quantitative transfer constant (K^{trans}) and blood normalized initial area under the gadolinium concentration curve ($IAUGC_{BN}$)[(2)] results across imaging platforms (at 1.5 tesla (1.5 T)), clinical sites, and time.

This effort is motivated by the emergence of DCE-MRI as a method with potential to provide predictive, prognostic and/or pharmacodynamic response biomarkers for cancer. Remarkably, the results demonstrating this potential have been obtained despite considerable variation in the methods used for acquisition and analysis of the DCE-MRI data. This suggests there are substantial physiological differences (i.e., benign vs. malignant or non-responsive vs. responsive tumors) underlying these observations. Thus, there appears to be a promising future for use of DCE-MRI for both clinical research and in routine clinical practice. However, in order to fulfill this promise it is essential that common quantitative endpoints are used and that results are independent of imaging platforms, clinical sites, and time.

For the application of DCE-MRI in the development of anti-angiogenic and anti-vascular therapies, the two most common quantitative endpoints are: K^{trans} and $IAUGC_{BN}$. Although there have been general recommendations on how to standardize DCE-MRI methodology[(1,2)], there are no guidelines sufficient to ensure consistent, reliable and fit-for-purpose quantitative DCE-MRI results across imaging platforms, clinical sites, and time. Hence, in this profile, basic standards for site and scanner qualification, subject preparation, contrast agent administration, imaging procedure, image post-processing, image analysis, image interpretation, data archival and quality control are defined to provide that guidance.

Summary of Clinical Trial Usage

This technique offers a robust, reproducible measure of microvascular parameters associated with human cancers based on kinetic modeling of dynamic MRI data sets.

CLINICAL CONTEXT AND CLAIMS

One application of DCE-MRI where considerable effort has been focused on quantitative endpoints is its use to provide pharmacodynamic biomarkers for the development of novel therapeutic (in particular, anti-angiogenic) agents targeting the tumor blood supply, which are presumed to act through altering tumor vasculature and reducing tumor blood flow and/or permeability. In this context, conventional endpoints, like tumor shrinkage as applied using Response Evaluation Criteria in Solid Tumors (RECIST), may not be the most effective means to measure therapeutic responses. DCE-MRI represents an MRI-based method to assess the tumor microvascular environment by tracking the kinetics of a low-molecular weight contrast agent intravenously administered to patients. In this context, K^{trans} and $IAUGC_{BN}$ can provide evidence of the desired physiologic impact of these agents in Phase 1 clinical trials.

Utilities and Endpoints for Clinical Trials

DCE-MRI is currently not the standard of care in many centers conducting clinical trials in oncology. Since these centers often do not have expertise in DCE-MRI and more than one center is typically involved, effort and precision are required to ensure consistent, reliable and fit-for-purpose quantitative DCE-MRI results. Hence, the guidelines provided in this profile will ensure that not only are the relative changes induced by treatment informative, but that absolute changes can be compared across these studies.

Claim:

Quantitative imaging biomarkers reflecting microvascular properties, specifically transfer constant (K^{trans}) and blood normalized initial area under the gadolinium concentration curve ($IAUGC_{BN}$), can be measured from DCE-MRI data obtained at 1.5T using low molecular weight extracellular gadolinium-based contrast agents with a 20% within-subject coefficient of variation for solid tumors at least 2 cm in diameter.*

Profile specified for use with: **patients with malignancy**, for the following indicated biology**: primary or metastatic**, and to serve the following purpose: **therapeutic response**.

*A 20% within-subject coefficient of variation is based on a conservative estimate from the peer-reviewed literature. In general, this suggests that a change of approximately 40% is required in a single subject to be considered significant .

PROFILE DETAILS

Imaging Procedure*:* Suitable localizer (scout) images must be collected at the start of exam and used to confirm correct coil placement as well as selection of appropriate region to image. This will be followed by routine non-contrast agent-enhanced sequences to delineate the number, location, and limits of tumor extension.

- ***Localizer***
- ***Anatomic sequences T_1, T_2 weighted imaging***
- ***Variable flip angle (VFA) T_1 weighted imaging (T_1 mapping)***
- ***3D fast spoiled gradient recalled echo volumetric imaging (dynamic imaging)***
- ***Anatomic, post-contrast T_1 weighted sequence***

Required Characteristics of Resulting Data

The DCE-MRI portion of the exam will consist of two components, both acquired using the same 3D fast spoiled gradient recalled echo sequence, or equivalent, and scan locations:

PROFILE DETAILS

For complete Profile see http://qibawiki.rsna.org/index.php?title=DCE-MRI_tech_ctte

Imaging Procedure (cont'd)

(a) Variable flip angle (VFA) series, for pre-contrast agent native tissue T_1 mapping.
- Ensure TR and TE values stay constant for all flip angles.
- Ensure that the machine gain settings are not reset automatically (by automated pre-scan features) between each flip angle acquisition so that system gain settings are identical for each flip angle acquisition.
- Pulse sequence and coils used for T_1 calculation should be the same used for the DCE-MRI Protocol.

(b) DCE-MRI Protocol: Pulse Sequence:
- ***Pulse Sequence:*** 3D fast spoiled gradient recalled echo or equivalent.
- ***Coils:*** Transmit: Body coil; Receive: Dependent on which body part is being studied). ***Parallel imaging options are not recommended due to vendor-specific implementations of such techniques and the fact that the effects of such techniques on within-patient coefficients of variation in K^{trans} and $IAUGC_{BN}$ have not been evaluated***.
- ***Imaging plane:*** Should include the lesion of interest and a **feeding vessel with in-plane flow** in order to capture a **vascular input function (VIF)** and should try to mitigate the effects of lesion motion.
- ***Frequency encoding direction*****:** Should be adjusted so as to minimize motion artifact.
- ***Temporal resolution*****:** The temporal resolution should be less than 10 sec.
- ***Flip angles*****:** A flip angles in the 25-35 degree range is recommended in order to minimize saturation effects in the signal intensity vs. contrast agent concentration response curve, particularly in vessels.
- ***Receiver Bandwidth***: Greater or equal to ±31.25 kHz (or ~250 Hz/pixel).
- **Field of View (FOV) and Partial Fourier ("fractional echo" and/or reduced phase-encoding FOV) as needed to meet temporal resolution requirements.**
- ***Number of Slices*****:** Acceptable: ≥10 prior to zero fill. Ideal: as many as possible while maintaining ideal temporal resolution.
- ***Slice thickness***: *Ideal*: <5 mm, *Target*: 5.1-6 mm, *Acceptable*: 6.1-8 mm
- ***Matrix*****:** 256 x 160 (before applying rectangular FOV) – in order to meet 1-2mm in-plane spatial resolution
- ***Number of acquisitions (phases)*****:** Sufficient to allow acquisition of at least 5 minutes of post injection data plus at least 5 phases acquired before contrast agent injection (baseline images).
- ***Digitized bit depth*****:** The maximum dynamic range should be utilized.

Imaging Data Acquisition:

Patient and coil positioning:
- If tumor location known – coil positioning will be per clinical standard of practice.
- When the subject under investigation may have uncertain tumor location(s), the most suitable lesion will depend on size, location relative to areas of pulsatile or respiratory motion artifacts, and presence or absence of necrosis or cystic areas.
- The claims of this profile are only applicable to lesions greater than or equal to 2cm.
- Tumors that are predominantly solid without significant necrosis or cystic characteristics would be considered the ideal choice of tumor for analysis. Tumors < 2cm with extensive hemorrhage, or completely cystic or necrotic lesions are considered non-ideal and should be excluded from consideration.
- Tumor locations should be chosen to minimize the effects of excessive respiratory or pulsatile motion.

Patient instructions: In patients with target lesions in the abdomen or thorax, patients will be instructed to relax and perform slow, steady breathing. No triggering is recommended.

Image Post-processing:

There are no specific image post-processing requirements, user-selected post-processing filters or image normalization methods recommended as part of this profile. If phased-array receiver coils are used, image combination and reconstruction should be according to standard manufacturer algorithms

Parametric image formation: Analysis of DCE-MRI data is carried out in a series of distinct steps:
- Generate a native tissue T_1 map using the VFA data.
- When required, apply time-series motion correction to the dynamic data.
- Convert DCE-MRI signal intensity data, $SI(t)$, to gadolinium concentration ($[Gd](t)$).
- Calculate a vascular input function (VIF).
- Identify the region or regions of interest in the dynamic data.
- Calculate the DCE-MRI imaging biomarker parameters, K^{trans} and $IAUGC_{BN}$.
- Please see details of these steps in: http://qibawiki.rsna.org/index.php?title=DCE-MRI_subctte

Parametric image analysis:

Derivation of quantitative parameters characterizing the response associated with a lesion of interest from parameter maps is a multistep process for which most, if not all, steps are being studied by on-going research. When multi-institutional trials are undertaken, a central site for analysis is highly recommended in order to reduce variability in analysis.

Input data to be used

The input data that will be utilized will be in the form of parametric maps of K^{trans} and $IAUGC_{BN}$ from which ROI analysis can be performed.

Tumor ROI Definition

The first step in the extraction of quantitative parameters (K^{trans} or $IAUGC_{BN}$) associated with a particular lesion is to segment this lesion from adjacent tissues. The segmentation techniques used must be tailored to the particular organ system being studied with DCE-MRI.

Registration of segmentations and parameter maps

Unless the segmentations are derived from relatively motion-free or motion-corrected dynamic, image registration techniques may be needed to register the parameter maps into a single anatomic framework.

Extraction of values for statistical comparison

To derive values for statistical comparison from K^{trans} or $IAUGC_{BN}$ parameter maps, median, mean and standard deviation of the pixel values should be calculated, and the median is considered the primary figure of merit. In a patient with multiple lesions due to metastatic disease, each lesion should be reported and tracked separately.

QUALITY CONTROL

The following section deals with all aspects of quality control in DCE-MRI studies. This includes selecting and qualifying an MRI imaging center, MRI personnel, and specific MRI scanners.

Selection of appropriate imaging centers for DCE-MRI studies

Typically, sites are selected for DCE-MRI due to their competence in clinical oncology and access to a sufficiently large patient population under consideration. Sites must also be highly competent in clinical MRI techniques appropriate to the area(s) of anatomy to be imaged during the DCE-MRI study. In order to ensure high quality DCE-MRI results, it is essential to implement procedures that ensure quality assurance of the scanning equipment and reliable image acquisition methodology. These processes must be set-up at the outset, and followed throughout the duration of the study. A site "imaging capability assessment" prior to site selection is therefore a requirement for any DCE-MRI study. This will include assessment of:
- appropriate imaging equipment and quality control processes
- appropriate injector equipment and contrast media
- experienced MR technologists
- experienced MR radiologists
- experienced MR physicists or MR imaging scientists
- procedures to assure imaging protocol compliance during the trial

Site qualification process

Site readiness for DCE-MRI should be documented prior to the initiation of the DCE-MRI trial. In single-site studies initiated by in-house investigators, imaging procedures should be reviewed with the DCE-MRI team prior to study initiation. In multi-site studies, site readiness assessment can begin with a simple questionnaire completed as a pre-qualification step. A subsequent site visit prior to DCE-MRI study initiation is recommended. During the site visit, study related imaging procedures and protocols are discussed. Ideally, all DCE-MRI scan parameters are reviewed and entered at the MR scanner at the time of the study visit. In some cases, initial phantom scanning can be performed during the site visit to familiarize local MR personnel with proper phantom handling, set-up, and scanning. The following steps are required for qualification:
- Scanner qualification
- Phantom imaging
- Phantom imaging data analysis
- Signal stability
- Signal response characteristic assessment
- T_1 measurement precision
- Ongoing MRI scanner quality control
- Use of human test subjects

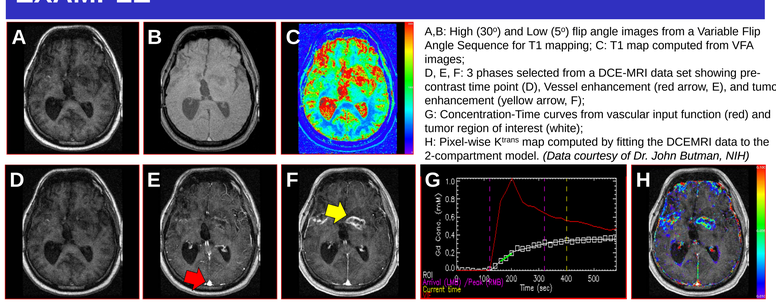
Quality control of DCE-MRI studies

Each DCE-MRI study will undergo its own quality control measures in order to ensure that the data obtained will be of sufficient quality to meet the standards stated in the claim. QC of the data will be within the following categories:
- Selection of target lesion
- Determination of subjects unsuitable for DCE-MRI analysis
- Determination of DCE-MRI exams unsuitable for DCE-MRI analysis
- Editing of DCE-MRI exams prior to DCE-MRI analysis

COMPLIANCE

Compliance is an important facet to be adhered by all parties including protocol developers, equipment venders and clinical sites utilizing DCE-MRI technology. Typically, clinical sites are selected due to their competence in oncology and access to a sufficiently large patient population under consideration. To obtain reproducible quantitative DCE-MRI imaging biomarker measures, however, the following issues, in addition to those specifically outlined above, must be addressed prior to final site selection for a specific trial:
- appropriate imaging equipment and quality control processes
- appropriate injector equipment and contrast media
- experienced MR personnel for the imaging procedure

EXAMPLE



A,B: High (30º) and Low (5º) flip angle images from a Variable Flip Angle Sequence for T1 mapping; C: T1 map computed from VFA images;
D, E, F: 3 phases selected from a DCE-MRI data set showing pre-contrast time point (D), Vessel enhancement (red arrow, E), and tumor enhancement (yellow arrow, F);
G: Concentration-Time curves from vascular input function (red) and tumor region of interest (white);
H: Pixel-wise K^{trans} map computed by fitting the DCEMRI data to the 2-compartment model. *(Data courtesy of Dr. John Butman, NIH)*

References

1. Leach MO, Brindle KM, Evelhoch JL et al. Assessment of antiangiogenic and antivascular therapeutics using MRI: recommendations for appropriate methodology for clinical trials. Br J Radiol 2003; 76 Spec No 1, S87-91.
2. NCI. 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. Dynamic contrast MRI (DCE-MRI) guidelines resulted from the NCI CIP MR Workshop on Translational Research in Cancer. MR Workshop on Translational Research 2004