Using MR to Assess Therapeutic Response – An Investigators perspective

Johannes T. Heverhagen, PhD, MD

Philips University
Department of Diagnostic Radiology
Marburg, Germany

Traditionally, therapy trials, for chemotherapy or radiation therapy, have been focused on morphological assessment like the RECIST [1] or WHO [2] criteria as non-invasive, surrogate markers for treatment response [3]. Despite its limitation and challenges, it is still the basis for ongoing diagnostic and therapeutic classifications [1]. However, the use of size criteria for assessment of tumor response to treatment is controversial since size changes usually progress slowly. Therefore, the distinction between responders and non-responders to therapy, and an adjustment in therapy can be delayed. Moreover, the different criteria for size changes vary significantly, so that investigators are unsure which criteria to use. Therasse and co-authors reported the outcome of a tumor therapy trial would have changed if RECIST instead of WHO criteria would have been used [4].

Therefore, many investigators search for alternative, non-invasive surrogate criteria to evaluate tumor response. MRI has introduced many tools for oncology to improve morphological evaluation and recently added capabilities for functional characterization of lesions [5,6,7]. The major advance for oncologic applications is the clinical implementation of functional assessment techniques that provide additional information on top of morphology. The greatest clinical utility in MRI has been demonstrated for DCE-MRI. This technique allows the noninvasive assessment of microcirculatory characteristics of lesions. Whereas this technique was initially used to characterize the angiogenic/microcirculatory properties of a lesion, it was shown to be a very robust technique to monitor changes during and after therapeutic interventions. Several studies have used DCE-MRI for monitoring chemotherapy as well as radiation therapy, and more recent applications are monitoring experimental immunogenic or antiangiogenic therapies. Other imaging methodologies are available to assess angiogenesis such as positron emission tomography, radionuclide studies, contrast-enhanced and Doppler ultrasound, X-ray contrast-enhanced dynamic computed tomography, and optical imaging. The strength of MRI is the true three-dimensional imaging of large volumes in a highly standardized, readily available, and safe manner.

However, these methods need considerable experience by the investigators, a standardized imaging and evaluation approach, as well as a general

understanding which methodology can be used for which tumor-treatment combination.

Therapeutic options today are broadened to encompass multimodality and multidrug regiments as well as targeted approaches such as antiangiogenic, cytostatic therapies. As we are implementing more and more of these targeted therapies (Figure 1), non-invasive imaging enables us with capable insights into the tumor micro-environment and heterogeneity. Many of today's targeted therapies do not exhibit the initial or overall biologic response by uni-dimensional size changes (RECIST) and can only be appropriately, non-invasively assessed by imaging methodologies. Therefore, early and reliable assessment of functional properties of lesions has become a necessity to correctly diagnose, differentiate, and guide therapy.

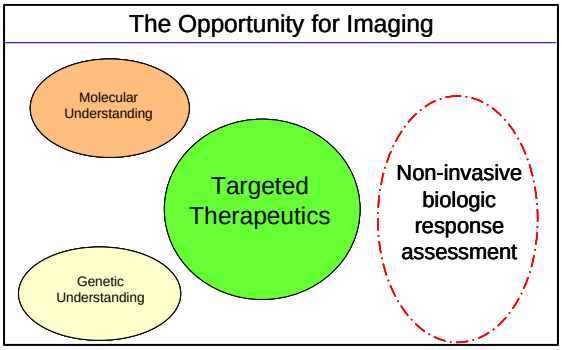

Figure 1: Opportunity for non-invasive biologic response assessment
(Presented at the NCI Workshop on translational Reseach in Cancer – Tumor Response 11/2004)

Possible problems in MRI as an assessment tool for therapeutic response in clinical trials

General Assessment Challenges

Motion and Registration

Imaging of moving organs such as the lung, liver, and kidney can be burdened by motion-induced artifacts. Advanced image processing techniques can correct for motion and distortion artifacts and will enable quantitative assessment within moving organs. Most developments and initial clinical experiences have been demonstrated by expert groups, and broad multicenter evaluations have been still fairly limited.

However, coregistration is not a trivial task. And besides the difficulties of registering 1000 and more images, other problems can arise during the registration process. Since registration always involves averaging and redistribution of image pixels, it is mandatory, but not trivial that the signal intensity in these pixels is preserved.

Figure 2 illustrates that coregistration can lead to substantial signal intensity changes in a ROI. This is undesirable since DCE-MRI is thought to be quantitative, and uncontrolled changes in the signal intensities in parts of the image will influence the evaluation process of the dynamic curve.

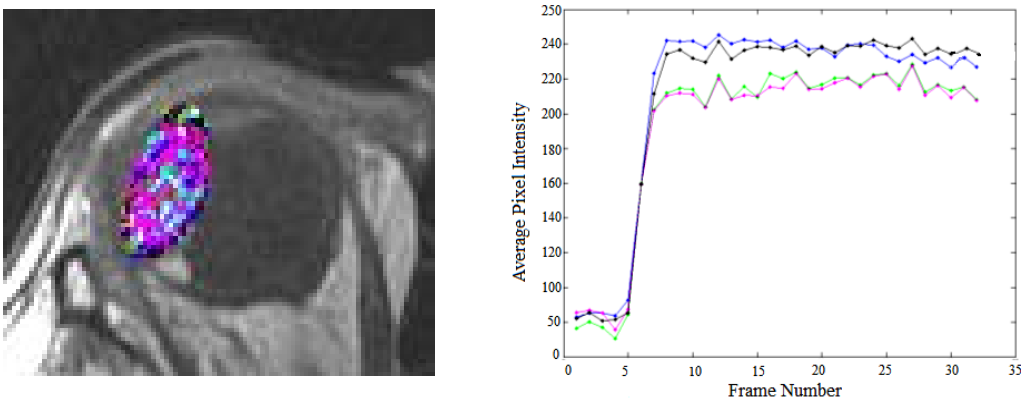

Figure 2: (a) shows a color-coded pixel map of a DCE-MRI data-set projected on anatomical map of a melanoma in right eye. (b) demonstrates the average pixel intensity of the selected color coded ROI at the 32 time-points; Blue-Original data; Black/green/ red–deformed datasets with progressively better registration.

Heterogeneity of Disease

Another unaddressed challenge is the appropriate assessment of the microenvironment, the lesion heterogeneity and the heterogeneity in response within a lesion or lesions. We currently do not yet have robust quantitative parameters to describe changes in lesion heterogeneity or heterogenic response to therapy. Figure 3 shows an example of a possible approach to assess lesion

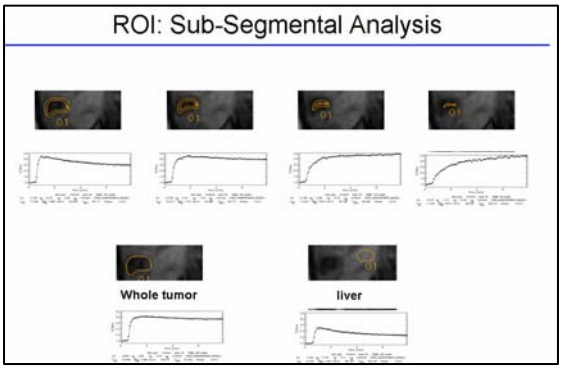

Figure 3: Example of advanced lesion heterogeneity assessment using an onion peeling approach to assess the DCE-MRI contrast enhancement signatures within a lesion. A sub-segmental analysis is essential for biologic response assessment in case of heterogeneity of disease and heterogeneity of response to therapy

Clinical Single Center vs Multicenter Trials

Many problems that occur when using MRI within therapy trials are similar for single center and multicenter trials. The main problem in these trials is coordination and communication between the different people on the Oncology and Imaging team. In addition, in a multi center trial the communication between possible Core Labs, the sponsor and the sites has to be coordinated.

One very important tool in order to keep the entire team informed about the imaging part of the study is to provide a dedicated site manual. This manual should provide detailed information exceeding that provided in the study protocol. It should not duplicate the protocol but rather provide the additional information necessary to conduct the imaging part of the trial. It should be specific for the site with information about the MRI scanner and coils to be used as well as the specific imaging sequences and parameters. The manual should provide detailed information not only about the imaging procedures involved, but also about scheduling, timing of the imaging studies with the trial, patient registration with the appropriate study numbers, data anonymization/deidentification, data archiving and data transfer to the core labs. It also should contain the contacts of the all key personnel involved in the trial from the site as well as the core labs and the sponsor.

For single center trials, a ‘light’ version of a site manual can be extremely helpful in order to keep the entire team informed about trial specific procedures. Even in a single center a variety of different people from different specialties are involved and a central document, e.g. a site manual, will provide valuable information to all of them. Such a document will prevent misunderstandings and miscommunication within the trial team.

Learning Objectives

During the course, the audience should learn about the specific problems that can occur in the planning, execution, assessment and evaluation of MRI studies to monitor therapy response. The following objectives will addressed specifically:

General Assessment Challenges
- Motion and Registration
- Heterogeneity of Disease
- Reproducibility of Studies

Planning and Execution of Clinical Trials
- Sense and non-Sense of a Site Manual
- Institutional Review Board Approval
- Informed Consent
- Trial Budget and Reimbursement

References

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