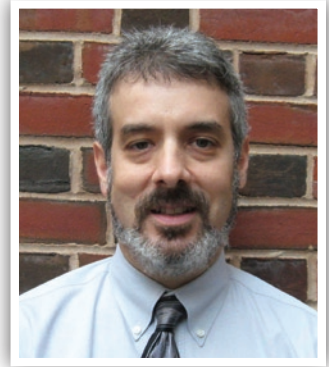


Key Imaging Technology

Dynamic Contrast Enhanced MRI (DCE-MRI) in Drug Development

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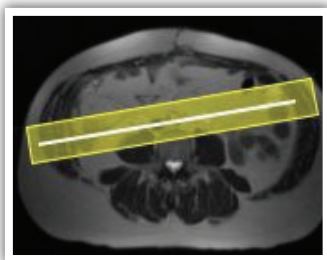
Background

It has long been understood that tumors must establish their own blood supply in order to grow, and that tumors elicit angiogenic factors to recruit new blood vessel growth. Anti-tumor therapies targeted specifically against tumor neo-vessels and angiogenic pathways are now in routine use in human oncology trials and in the clinic. Non-invasive means to determine the status of tumor neo-vessels would improve our ability to determine functional tumor responsiveness to these agents. Dynamic contrast enhanced MRI (DCE-MRI) is one such method that has been used successfully for these purposes.

Immature tumor blood vessels have poorly developed endothelial barriers, and are therefore highly permeable to small molecules, including gadolinium-based MRI contrast agents. By measuring the rate of gadolinium contrast accumulation into tumors (represented by the kinetic rate constant " K^{trans} "), we can probe the vascular status of the tumor microenvironment.

DCE-MRI

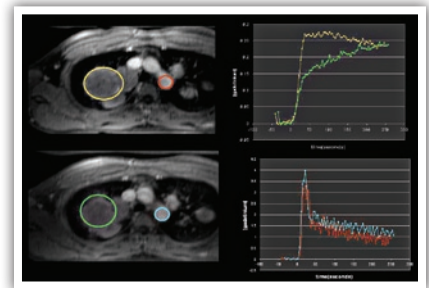
Routine contrast-enhanced MRI imaging is performed either in the steady-state after contrast administration (such as in brain MRI), or in a semi-dynamic manner after contrast administration (such as in breast MRI),



with temporal resolutions that vary between half a minute to several minutes. True DCE-MRI differs from these approaches, in that it seeks to determine the actual pharmacodynamics of tumor contrast enhancement,

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specifically the degree and rate of early tumor enhancement. In order to capture this pharmacodynamic information, imaging in DCE-MRI must occur at a much faster rate (on the order of 2-10 seconds) than that normally performed in clinical MRI. Imaging at these rates with existing MRI equipment places restrictions on image quality, image resolution, and volume of coverage.



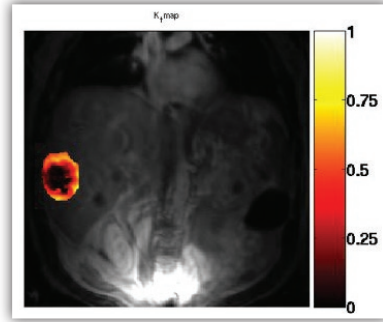
The nature of the trade-offs in prescribing a DCE-MRI exam therefore require careful interaction between the MRI physicist, radiologist, and technologist. The choice of tumor and imaging plane plays a large role in determining the quality of the DCE-MRI data. However, MR technologists and radiologists are not specifically trained in prescribing DCE-MRI, and careful site training is required in order to obtain high quality DCE-MRI image sets.

Quality Factors

Patient selection is another key component for improving DCE-MRI image quality. As the DCE-MRI study requires continuous observation of tumor enhancement for up to

10 minutes or more, respiratory motion can impede image analysis. Selection of patients with larger tumors, or those with tumors located in fixed areas of anatomy will ensure that the degree of respiratory motion is small relative to tumor size, thus simplifying the analysis of DCE-MRI data.

One additional pitfall regarding DCE-MRI is exam reproducibility. There are numerous factors that can influence the quality of the DCE-MRI examination, and thus the reliability of the tumor K^{trans} estimate. In most clinical protocols that employ DCE-MRI, test-retest procedures prior to commencing treatment are in order to provide estimates of tumor K^{trans} reproducibility.



Use in clinical trials

Despite the hurdles one must overcome in DCE-MRI, many clinical studies have demonstrated the efficacy of DCE-MRI for tumor vascular evaluation during vascular targeted therapy. DCE-MRI therefore can be a useful adjunctive

study in phase I or early phase II drug trials to identify in vivo tumor vascular responsiveness to the study drug. In phase I studies, DCE-MRI may be used to identify a dose-response curve, or to determine the longevity of anti-tumor effect. In phase II studies targeting a smaller number of tumor types, DCE-MRI response may be tracked and compared to downstream clinical markers of efficacy such as progression free survival.

The nature of DCE-MRI implementation in clinical trials will depend on the expectations of the physiologic effect. Therapies targeted toward VEGF pathways may take

several days or weeks to reach peak anti-angiogenic effect in tumors. Vascular disruptive agents often exert their effect more

quickly, sometimes reaching peak effect in a matter of hours after administration. Given the need for test-retest visits prior to therapy, and concerns for patient compliance, the ideal schedule of DCE-MRI in a study will vary for any given trial.

