

The Role of DCE-MRI in Clinical Trials

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Medical imaging holds the potential to significantly increase the quality of care able to be provided to injured or ill patients. It is now proving to be a valuable tool in the fight against cancer as well. Dynamic contrast-enhanced magnetic resonance imaging is aiding oncologists in drug development during clinical trials, enabling the assessment of blood flow to the cancerous tumors.

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Medical imaging as a means of diagnosing and staging tumors has become an integral part of oncologic practice. Imaging endpoints have also become one of the primary biomarkers for all phases of new drug development. The driving force for such a rapid integration of imaging biomarkers in drug discovery has been the development of the new generation of functional imaging techniques. While traditional imaging methods provide detailed structural information, novel functional imaging techniques quantifies real-time physiologic and metabolic processes at the cellular or molecular level. Functional imaging's ability to detect and stage tumors, select and monitor treatment, gauge prognosis, and measure outcomes has spawned valuable biomarkers that are, and will be, indispensable in drug discovery.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a functional imaging technique that provides valuable insight into the tumor's blood supply. Tumors need to be near a blood supply to metastasize. Capillaries are the tumor's lifeline, delivering oxygen to and removing waste from it. Vascular disrupting agents are a new class of anti-cancer drugs that are designed to prevent nutrient supply to the tumor, thereby leading to the necrosis of solid tumors.

DCE-MRI differs from standard MRI in its ability to assess blood flow, specifically the degree and rate of early tumor contrast enhancement as an indication of tumor vascularity.

DCE-MRI tracks the diffusion of an intravascularly administered paramagnetic contrast agent (i.e., gadolinium) into the extravascular tissue over time. It estimates blood flow by the rate of contrast accumulation (K^{trans}). As the mean contrast agent concentration within a volume of tissue (i.e., a voxel) increases, its signal intensity increases. Using mathematical algorithms and compartmental modeling, this relative signal increase is converted into a quantitative measure of contrast agent

entering tissue over time. The primary determinants of K^{trans} are the volume of blood vessels in the voxel, the rate of flow, and the rate of diffusion. The rapidity of these processes necessitates faster image acquisition for DCE-MRI than for conventional MRI (i.e., every 2-10 seconds vs. every 30 seconds to several minutes). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.

Revealing much about tumor microcirculation, DCE-MRI is used to assess drugs targeting angiogenic pathways. The immature blood vessels found in tumors are highly permeable to gadolinium-based contrast agents (i.e., MRI dye). Because tumors elicit angiogenic factors to spur blood vessel growth, vascular destructive (or anti-angiogenic) agents can be effective anti-tumor therapies, particularly in combination with other drugs. Demonstrating vascular changes before anatomical images reveal tumor shrinkage, DCE-MRI allows earlier assessment of drug efficacy. This saves time and money in the drug development process.

Indeed, DCE-MRI has been (and continues to be) used extensively in all phases of oncology drug trials for a wide array of cancers. In Phase I studies, DCE-MRI can help determine the dose-response curve and measure the longevity of anti-tumor effect. In late Phase I or Phase II drug trials, it can be an adjunctive study to identify *in vivo* tumor vascular responsiveness to the study drug. In Phase II studies targeting fewer tumor types, serial DCE-MRI results can be compared to clinical outcomes, such as progression-free survival.

Many studies have evaluated DCE-MRI results as predictors of clinical outcomes, including treatment response to chemotherapy. DCE-MRI results have also been compared to conventional diagnostics as predictive biomarkers. Some studies have shown vascular changes on serial DCE-MRI to be predictive of disease progression and/or malignant transformation of tumors.

Successful integration of functional imaging techniques such as DCE-MRI in a clinical trial requires thoughtful orchestration and rigorous standardization to reduce variability. Functional acquisition techniques that might be employed in trials, variability in technology across sites, and the nature of image-derived information require a different approach to quality assurance than is generally employed in therapeutic trials. For example, most DCE-MRI protocols include test-retest procedures to ensure similar levels of contrast accumulation and exam reproducibility. Precise site training is essential to obtain high quality images. Patient selection, region of interest, and imaging plane all affect image quality.

Despite challenges to employing DCE-MRI, this imaging method appears to have a promising future in drug development trials. As the number of vascular destructive agents involved in various phases of clinical oncology trials is rapidly growing, DCE-MRI will be increasingly employed. Over time, its role will become better established. Ultimately, DCE-MRI may prove to be a widely recognized and reliable predictive biomarker for clinical oncology outcomes.

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