

# Dynamic Contrast-Enhanced Magnetic Resonance Imaging As an Imaging Biomarker

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## ABSTRACT

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is being used in oncology as a noninvasive method for measuring properties of the tumor microvasculature. There is potential for DCE-MRI to be used as an imaging biomarker to measure antiangiogenic effects of cancer treatments. This article reviews the general methodology for performing DCE-MRI and discusses existing data and challenges to applying DCE-MRI for treatment response assessment in clinical trials.

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## INTRODUCTION

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a noninvasive imaging technique that can be used to measure properties of tissue microvasculature. DCE-MRI is sensitive to differences in blood volume and vascular permeability that can be associated with tumor angiogenesis, and thus DCE-MRI is a promising method and potential biomarker for characterizing tumor response to antiangiogenic treatment.<sup>1-3</sup>

DCE-MRI has been investigated for a range of clinical oncologic applications including cancer detection, diagnosis, staging, and assessment of treatment response. Tumor microvascular measurements by DCE-MRI have been found to correlate with prognostic factors (such as tumor grade, microvessel density [MVD], and vascular endothelial growth factor [VEGF] expression) and with recurrence and survival outcomes. DCE-MRI changes measured during treatment have been shown to correlate with outcome, suggesting a role for DCE-MRI as a predictive marker.

With the accelerating pace of drug development, there is a desire to identify biomarkers that can be used to assess tumor biology in vivo and to monitor the effects of treatment. The concept of an imaging biomarker is very appealing. An imaging biomarker can be measured noninvasively and repeatedly, and by evaluating the entire tumor in vivo, can capture the heterogeneity of both the tumor and its response to treatment. DCE-MRI is a particularly attractive method because of the intrinsic soft tissue contrast and anatomic detail provided by MRI in general, and the added ability of DCE-MRI techniques to measure properties of the microcirculation.

Pharmacokinetic modeling of the DCE-MRI signal is used to derive estimates of factors related to blood volume and permeability that are hallmarks of the angiogenic phenotype associated with most cancers. Tumor angiogenesis as measured immunohistochemically by MVD, has been shown to be an independent prognostic indicator, and angiogenesis is a direct or indirect target of many new anticancer agents.<sup>4</sup> Thus, there is great interest in developing DCE-MRI as a biomarker for angiogenic activity in tumors. Although data suggest that DCE-MRI has potential in this regard, there is a need to standardize techniques for both acquiring DCE-MRI data and defining how the imaging biomarker is quantified.

The accuracy of DCE-MRI relies on the ability to model the pharmacokinetics of an injected tracer, or contrast agent, using the signal intensity changes on sequential magnetic resonance images. Signal intensity changes can be rapid immediately after (small molecular weight) contrast injection, and thus the temporal sampling rate is important. However, increasing the temporal sampling rate of MRI has direct consequences on critical image characteristics such as spatial resolution, signal-to-noise ratio, and the volume of anatomy covered. The trade-offs between temporal resolution and spatial resolution for DCE-MRI are not clear, and are not easily tested. MVD measured histopathologically gives a partial picture of the tissue microvasculature, but does not reflect its functional properties, including permeability, that contribute to the DCE-MRI measurement. Thus, it is not surprising that studies reporting correlations between DCE-MRI parameters and MVD have found only moderate associations. MVD is also a heterogeneous property of tumors. MVD measurement methods are limited by histopathologic sampling and are generally hotspot values, which are, by definition, localized. Associations have

been reported between independent MVD and DCE-MRI hotspot measurements, although direct spatial correlation between the two has generally not been attempted. Most of the evidence in support of DCE-MRI is based on correlation of imaging parameters with histopathology and accepted prognostic factors such as tumor grade, metastatic status, and clinical outcome, arguably the more important end points on which to establish the value of DCE-MRI.

There are significant challenges to developing robust imaging biomarkers. It requires both establishing that one or more functional measurements sensitively capture the biology of interest, and defining a measurement method that can be applied in a reliable and standardized fashion. Specification of the measurement method can be complex, as in the case of MRI, where many experimental variables influence the signal. Thus, optimizing and subsequently standardizing functional imaging measurement methods presents a significant task.

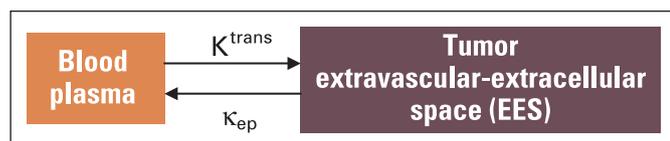
## DCE-MRI MEASUREMENT METHODS

### Basic Principles and General Methodology

DCE-MRI is performed by obtaining sequential magnetic resonance images before, during, and following the injection of a contrast agent. For human studies, the contrast agent is generally a small molecular weight gadolinium-containing compound such as gadopentetate dimeglumine. T2\* or susceptibility-weighted MRI can be used early after contrast injection (in the first few seconds) to observe the transient first-pass effects of contrast agent, which provides information about perfusion. The T2\* effect is measured as a rapid drop and subsequent recovery of signal intensity after bolus injection. Measurement of first-pass T2\* effects necessitates a rapid imaging method that is generally performed over a single slice through the target tissue and is thus of limited value in assessing disease morphology or extent. Dynamic T2\* methods are less commonly used than dynamic T1-weighted methods, outside of the brain.

Dynamic T1-weighted imaging is used over a longer time course (in the first several minutes) to observe the extravasation of contrast agent from the vascular space to the interstitial space, providing information about blood volume and microvascular permeability. The accumulation of contrast agent in the interstitium results in a signal increase on T1-weighted MRI. A subsequent wash-out effect can be observed if the vascular permeability is high and there is reflux of contrast agent back to the vascular space.

Signal intensity will change in proportion to the contrast agent concentration in the volume element of measurement, or voxel. The principles of tracer pharmacokinetics can be applied to DCE-MRI images if the dependence of signal intensity on contrast agent concentration is known (Fig 1).<sup>5</sup> To accurately relate the change in signal



**Fig 1.** A generalized tracer kinetic model applied to dynamic gadolinium-enhanced magnetic resonance imaging (MRI) is used to estimate three physiologic parameters: (a) volume transfer constant ( $K^{\text{trans}}$ ) between the blood plasma and EES, (b) volume of EES per unit volume of tissue ( $v_e$ ), and (c) flux rate constant between the EES and plasma,  $\kappa_{ep}$  ( $\kappa_{ep} = K^{\text{trans}}/v_e$ ).

intensity ( $\Delta S$ ) to contrast agent concentration in the tissue ( $C_t$ ), the precontrast tissue T<sub>1</sub> value is needed. The tissue contrast as a function of time  $C_t(t)$  also depends on the arterial blood plasma concentration as a function of time [ $C_p(t)$ ], which varies depending on the mode of injection (short v long bolus) and is affected by differences in cardiac output among subjects. Variability in  $C_p(t)$ , also called the arterial input function (AIF), can have a sizable effect on pharmacokinetic parameters. To properly account for these effects,  $C_p(t)$  should be measured for each patient, generally by including a large vessel in the imaging field of view.  $C_t(t)$  and  $C_p(t)$  can be related through a generalized kinetic model<sup>6</sup>:

$$dC_t/dt = K^{\text{trans}}(C_p - C_t/v_e) = K^{\text{trans}}C_p - \kappa_{ep}C_t$$

where  $K^{\text{trans}}$  is the volume transfer constant between the blood plasma and extravascular extracellular space (EES) per unit volume of tissue ( $\text{min}^{-1}$ ),  $\kappa_{ep}$  is the rate constant between the EES and blood plasma ( $\text{min}^{-1}$ ), and  $v_e$  is the volume of extravascular extracellular space per unit volume of tissue. In a 1999 consensus publication,<sup>6</sup> this set of terms was recommended by an international group of investigators developing DCE-MRI methodologies. The authors related the three parameters,  $K^{\text{trans}}$ ,  $\kappa_{ep}$  and  $v_e$ , to previously published terms and symbols and proposed that this set of kinetic parameters and symbols be used universally to describe the uptake of low molecular weight gadolinium-based contrast agents that are in clinical use today.

To adequately apply a two-compartment pharmacokinetic model to the MRI enhancement time course, measurement of the intrinsic T<sub>1</sub> value and AIF are needed. The need to measure T<sub>1</sub> increases total scan time and may not be feasible in clinical practice. In the absence of a baseline T<sub>1</sub> measurement, an assumption of linearity between signal intensity and gadolinium concentration can be made (removing the need for baseline T<sub>1</sub>), or the signal-intensity time curve can be quantified using empirical quantitative measures such as the initial area under the curve, peak enhancement, time to peak enhancement, or signal enhancement ratio (SER). It may also be infeasible to include a large vessel in the field of view appropriate for measuring the AIF. Expanding the field of view to accommodate a large artery may compromise image resolution. The AIF requirement is often addressed using average values measured in healthy control subjects from blood samples, which have been reported in the literature. The relative merit of alternative approaches and the impact of using global estimates of AIF, or of ignoring T<sub>1</sub> effects, have not been established clinically.

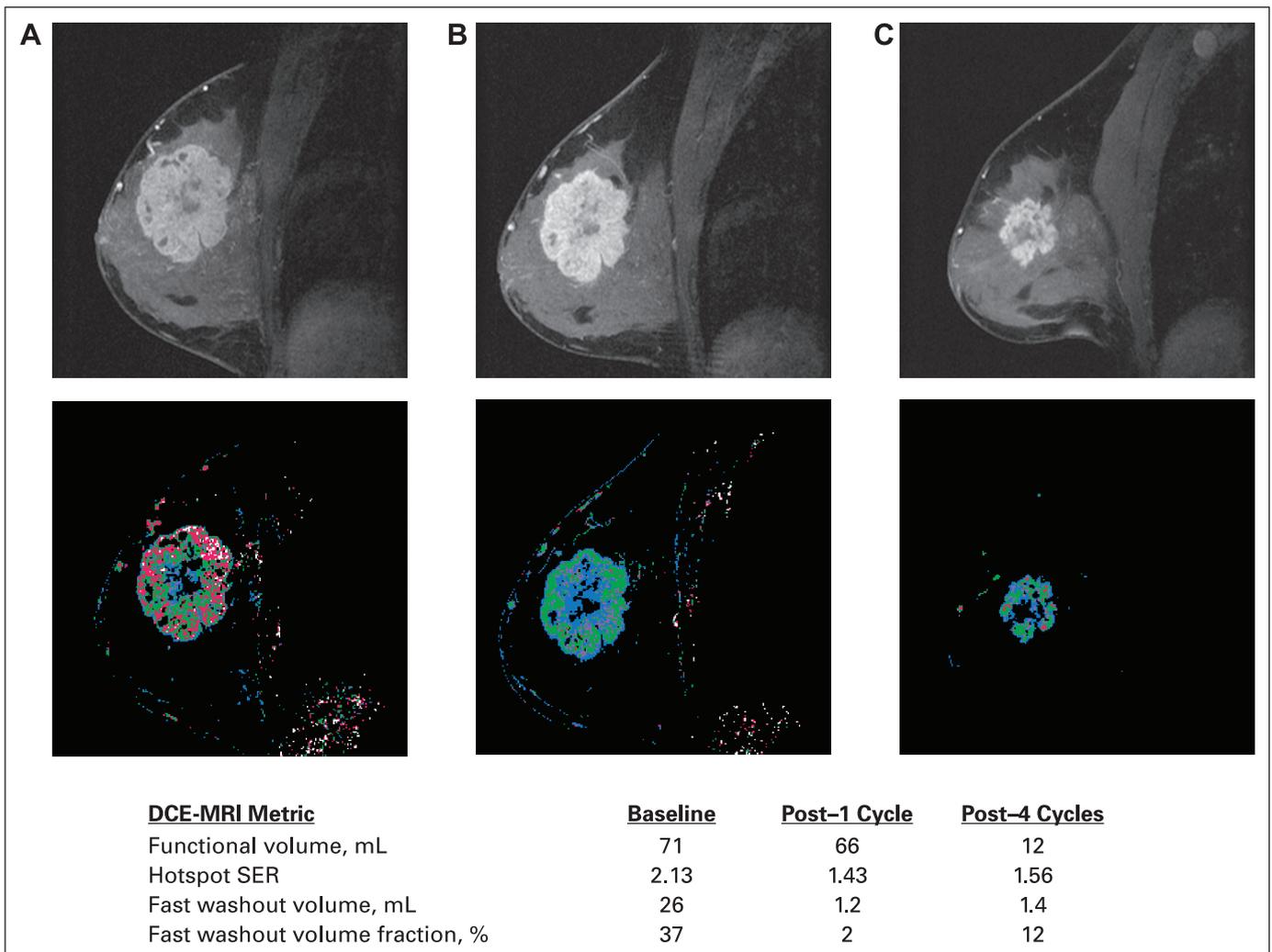
Although DCE-MRI methods are based on well-described principles of pharmacokinetics, the application to MRI imposes unique considerations, including the indirect dependence of signal intensity on contrast agent concentration, and the limitations imposed by the combination of fast leakage of standard gadolinium contrast agents and constraints on temporal resolution to obtain an adequate signal-to-noise ratio. These considerations typically require that trade-offs be made between temporal and spatial resolution, and these in turn affect the estimates of quantitative parameters derived from the images. Although theoretical models predict more accurate estimates using high-temporal sampling, it is difficult to assess the negative impact of increased volume averaging that occurs with the concurrent reduction in spatial resolution.

### Image Acquisition and Quantification Methods

After image acquisition, analysis of the time series of images is performed to extract the appropriate pharmacokinetic or empirical parameters. The quantitative parameter can be measured for a region-of-interest defined manually by a reader in an anatomic region of interest. Alternatively, the quantitative parameter can be solved at every pixel in the image, creating a parametric map. The maps can be further analyzed by measuring mean values over regions of interest, extracting hotspot values, or applying volumetric techniques such as histogram analysis.

For DCE-MRI to be used as a biomarker, the method for quantifying the assay has to be defined. There are several goals to be weighed in optimizing the biomarker definition. The biomarker needs to (1) maximize the sensitivity to biologic changes caused by treatment; (2) capture tumor heterogeneity, which is an important and unique aspect of imaging as a biomarker; and (3) be reproducibly measured and not adversely affected by reader subjectivity. Figure 2 is an illustration of parametric analysis of DCE-MRI images using an empirical parameter, the SER, for a patient with locally-advanced breast cancer treated

preoperatively with doxorubicin-cyclophosphamide (AC) chemotherapy. MRI was performed before chemotherapy, 2 weeks after the first cycle of chemotherapy, and at the end of AC treatment, before surgery, using a three-time point DCE-MRI method. Pharmacokinetic properties of the tumor were quantified by computing SER at each pixel, defined as  $SER = (S_1 - S_0) / (S_2 - S_0)$ , where  $S_0$ ,  $S_1$  and  $S_2$  are the precontrast (baseline), early postcontrast (2.5 minutes after injection) and late postcontrast (7.5 minutes after injection) signal intensities. The  $S_1$  images acquired at the pretreatment, post-first cycle AC and post-treatment time points are shown in the top row of Figure 2 and the corresponding SER parametric maps are shown below. SER markers were quantified according to several different metrics using an automated computer method. A functional tumor volume was defined as the sum of all voxels with SER more than 0.9. A hotspot SER value was defined as the highest 8-connected voxel average over the tumor volume. A fast wash-out volume was defined as the volume of tumor with SER more than 1.3; this was also expressed as a percentage of total tumor volume. The values for these four metrics are listed below the images for each treatment time point and capture different



**Fig 2.** Contrast-enhanced magnetic resonance images (top row) and signal enhancement ratio (SER) parametric maps (bottom row), acquired before treatment (A), 2 weeks after the first cycle of doxorubicin-cyclophosphamide (B), and at the end of chemotherapy, before surgery (C), for a patient with locally advanced breast cancer. Blue, green, and red color coding corresponds to low ( $SER < 0.9$ ), moderate ( $0.9 \leq SER \leq 1.1$ ), and high ( $SER > 1.1$ ) values, respectively. Dynamic contrast-enhanced magnetic resonance imaging metrics are listed in the table below the images.

aspects of tumor change over treatment. These metrics are being tested prospectively in an ongoing multicenter trial (American College of Radiology Imaging Network [ACRIN] trial 6657) for their ability to measure objective tumor response and to predict 3-year recurrence-free survival.

At this time, there is a great deal of variability in the approaches used to quantify the DCE-MRI assay. Systematic testing of various quantification approaches has not yet been done and requires a prospectively collected database with clinical outcomes. The method of quantification adds another degree of variability to DCE-MRI methodology; however, since it is a post-imaging processing step, multiple analysis methods can be applied to the same data set and compared retrospectively to the relevant clinical outcome.

### DCE-MRI MARKER STUDIES

DCE-MRI has been proposed as a method to improve the diagnostic specificity of MRI over conventional (enhanced or unenhanced) imaging alone, or to be used as a noninvasive prognostic factor or predictive marker of treatment efficacy. Since no gold standard is available to directly verify the pharmacodynamic measurements by DCE-MRI, and because the value of DCE-MRI will be determined ultimately by its clinical utility, most DCE-MRI studies test against clinical outcome or by comparison to existing prognostic and predictive markers. For example, histopathology is used as the end point in diagnostic applications, association with tumor grade, tumor size, metastatic status, MVD, or VEGF expression in correlative studies of prognostic factors, or objective tumor response and survival in predictive studies of therapeutic response.

DCE-MRI has been used in many oncologic applications to study cancers of the breast, prostate, cervix, liver, lung, and rectum.<sup>7-24</sup> DCE-MRI measurements have included quantitative descriptors of the time-intensity curves such as the maximal enhancement, time to peak enhancement, enhancement gradient or SER,<sup>11,13,18,21-26</sup> or pharmacokinetic modeling parameters.<sup>10,12,16,20,21,27</sup> Many studies have correlated DCE-MRI parameters with known prognostic factors including histologic grade, lymph node status, or presence of metastatic disease.<sup>10,16,18,20,23,26,28</sup> The majority of these correlative studies have found associations between DCE-MRI parameters and other angiogenesis markers, most commonly MVD and VEGF expression.<sup>7,9,11,14-16,21,22,24,25,29</sup> Most have been single institution studies with small sample sizes and most have found statistically significant correlations between DCE-MRI measurements and one or more of the histopathologic factors, immunohistochemistry assays or clinical outcomes. Because of differences in technique and populations studied, it is difficult to compare these results.

### DCE-MRI IN PHASE I TRIALS OF ANTIANGIOGENIC THERAPY

DCE-MRI has also been investigated for its ability to measure the effects of antiangiogenic therapy. Because of its sensitivity to properties of the microvasculature, DCE-MRI is seen as a promising biomarker candidate for assessing tumor angiogenesis and the effects of antiangiogenic therapy.<sup>1-3</sup> Several recent phase I trials of antiangiogenic agents have included correlative studies of DCE-MRI to investi-

gate its potential as a predictive marker.<sup>30-34</sup> In a pilot study of patients with inflammatory and locally advanced breast cancer treated with the anti-VEGF agent bevacizumab alone for one cycle and subsequently in combination with chemotherapy, DCE-MRI was performed at baseline and after cycles 1, 4 and 7. A dynamic, T1-weighted technique was used with a two-compartment pharmacokinetic analysis to measure  $k^{\text{trans}}$ ,  $k_{\text{ep}}$ , and  $v_e$ . All three of these parameters showed significant decreases after cycle 1 after treatment with bevacizumab alone, with continued decrease after the addition of chemotherapy. However, no significant differences in any of these parameters were found between clinical responders and nonresponders.<sup>30</sup> In correlative studies of DCE-MRI performed as part of two phase I studies of a VEGF receptor tyrosine kinase inhibitor, PT787/ZK 222584, DCE-MRI of the liver was explored as a potential biomarker for PTK/ZK treatment of patients with colorectal cancer and metastatic liver lesions. Twenty-six patients were evaluated by DCE-MRI at baseline and one or more time points during treatment (day 2 and end of each 28-day cycle). A significant negative correlation between the DCE-MRI pharmacokinetic parameter  $K_i$  (related to  $K^{\text{trans}}$ ) and both the oral dose and plasma levels of PTK/ZK were found. Significantly greater reductions in  $K_i$  were found for nonprogressors (defined as Response Evaluation Criteria in Solid Tumors [RECIST] categories complete response, partial response, or stable disease) than progressors.<sup>33</sup>

Liu et al<sup>31</sup> incorporated DCE-MRI in a phase I study of the tyrosine kinase inhibitor AG-013736. Twenty-six of the patients enrolled with solid tumors in the lung, liver, chest wall, and other sites were evaluated with DCE-MRI at baseline and approximately 3 hours after the first dose of AG-013736. In the 17 patients with assessable MRI data, a linear inverse correlation was measured between two DCE-MRI parameters  $K^{\text{trans}}$  and initial area under the curve, and AG-013736 plasma exposure.

O'Donnell et al<sup>32</sup> used DCE-MRI to evaluate the effects of a VEGFR2 inhibitor, SU5416, in a phase I study of patients with a variety of treatment refractory solid tumors, including soft tissue sarcoma; cancers of the ovary, cervix and endometrium; melanoma; renal cancers; and head and neck cancers. DCE-MRI was performed using a five-slice T1-weighted saturation recovery method through the center of the target lesion and acquiring dynamic images every 9 seconds for 6.3 minutes. Of the 24 patients studied, many were not assessable at one or more time points. No changes were seen in  $K^{\text{trans}}$  or  $v_e$  in response to treatment in this trial. The lack of measurable response by DCE-MRI may have reflected insufficient potency of the agent at the doses studied for detection with DCE-MRI, or other factors, including physiologic variability among the wide range of tumor sites evaluated, small sample sizes, and image analysis methods.

In 2002, ACRIN and Cancer and Leukemia Group B (CALGB) jointly opened a multicenter clinical trial testing imaging and molecular biomarkers for assessing tumor response to neoadjuvant chemotherapy for patients with stage III breast cancer. Companion trials ACRIN 6657 and CALGB 150007 are performed as correlative science observational trials, enrolling patients receiving standard neoadjuvant regimens. MRI and core biopsies are performed before the start of an AC regimen, after one cycle of AC, between the end of AC and start of a taxane, and again at the end of taxane regimen and before surgery. DCE-MRI is performed using a high-spatial resolution imaging method and acquiring images at baseline and two postcontrast time points, without measurement of an AIF or baseline T1. An empirical method is used to quantify the signal-intensity time curve using the

SER, which is the ratio of early to late signal enhancement. The imaging aims will test whether groups with statistically different 3-year disease-free survival can be identified among the group of clinical partial responders on the basis of tumor volume and SER changes with treatment. The trial accrual completed in March 2006, and 3 years of follow-up data are being collected to record recurrence or death events.

These studies and others indicate a potential for DCE-MRI to be used as a noninvasive method to assess the effects of antitumor treatments. The studies to date have been performed primarily as correlative studies to phase I or II multicenter clinical trials of antiangiogenic agents. DCE-MRI results were evaluated against response end points such as clinical response and by comparison to other biomarkers. Most studies explored the predictive value of DCE-MRI measured at an early time point in treatment, with varying results.

### PROSPECTIVE CLINICAL EVALUATION OF DCE-MRI AS AN IMAGING BIOMARKER

The data from correlative studies of DCE-MRI from single and multicenter therapeutic clinical trials suggest that a prospectively designed clinical evaluation of DCE-MRI, using standardized methods, is warranted. Because the pharmacokinetics, imaging approaches, and clinical outcomes differ by disease site, evaluation of DCE-MRI as a biomarker needs to be undertaken for a particular disease site and therapeutic strategy. The lack of findings in the phase I study of SU5416 may have been attributable to the mixture of tumor types evaluated.<sup>32</sup> The techniques for DCE-MRI also varied considerably from study to study. Standardized methods will be required for a prospective clinical evaluation of DCE-MRI. There is likely to be reasonable consensus regarding the image acquisition methods, given the state of the art in MRI technology and the practical constraints involved in implementing a multicenter clinical evaluation of DCE-MRI. There is greater variability among the quantification methods used to analyze DCE-MR images. The relative merit of alternative approaches to estimating pharmacokinetic parameters from DCE-MRI data is difficult to assess because there is no gold standard that can be used to verify accuracy. DCE-MRI techniques are usually measured against clinical variables, existing prognostic factors, or treatment response outcomes such as objective response, pathologic response, or disease-free or overall survival. The availability of well-defined and prospectively collected DCE-MRI data with clinical outcomes would be extremely useful, and in fact requisite, for a meaningful evaluation and comparison of the many analysis approaches based on the relevant clinical outcomes.

There are several practical limitations that have to be considered in the design of a clinical trial to prospectively assess DCE-MRI as a biomarker of therapeutic response. The need to use the images for clinical assessment of tumor morphology, extent of disease and to

evaluate invasion or local metastatic spread (in addition to their use for functional measurements) may place requirements for signal-to-noise ratio, resolution, and anatomic coverage that limit the temporal resolution. This is the case with breast MRI, in which the assessment of tumor morphology is critical to the diagnostic assessment. There are also challenges involved in acquiring standardized data at multiple sites with different equipment capabilities and levels of expertise. The need to establish a common standard may dictate that, although state-of-the-art techniques are used, cutting edge technology is not feasible.

For a clinical evaluation of DCE-MRI, a recommended minimum set of requirements would include measurement of an arterial input function and baseline T1, and temporal resolution of 1 minute or less dependent on disease site and clinical considerations with respect to signal-to-noise ratio, resolution, and anatomic coverage. The resulting data set, annotated with both technical parameters and clinical outcomes, would be a valuable test set for evaluating different analytic approaches and comparing the relative value of pharmacokinetic parameters for predicting clinical outcomes. The general availability of large image data archive for secondary analyses will be extremely useful for retrospectively optimizing how individual imaging biomarkers are defined and quantified (eg, which cutoff values are used to define a positive biomarker) and whether hotspot values or a volumetric approach such as histogram analysis best differentiates response categories.

### SUMMARY

DCE-MRI is a promising biomarker candidate for assessing antiangiogenic treatment. Correlative studies performed in combination with therapeutic trials have demonstrated proof of concept for DCE-MRI as a biomarker; however they have not been powered to adequately evaluate biomarker performance. Prospective clinical trials are needed with primary aims designed to test standardized DCE-MRI methods for both data acquisition and marker quantification. A prospective evaluation of DCE-MRI will require a change in the way imaging is performed as part of clinical trials. Like those for tissue and serum based biomarkers, the assay methods used to measure the imaging biomarker are critical. The technical specification for measuring an imaging biomarker must be well defined, and adherence to these specifications must be monitored. Changes will be required to the clinical practice culture to emphasize the importance of maintaining technical standards for quantitative imaging. It is common in today's clinical practice to make adjustments to MRI parameters at the time of the scan to accommodate individual patients. Changes in resolution or slice coverage can affect timing parameters, which will impact pharmacokinetic modeling. Consistent methodologies for contrast administration are also needed to assure the reproducibility of DCE-MRI measurements.

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**Author's Disclosures of Potential Conflicts of Interest**

The author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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