Dynamic Contrast-Enhanced Magnetic Resonance Imaging for Assessing Tumor Vascularity and Vascular Effects of Targeted Therapies in Renal Cell Carcinoma
Mark A. Rosen and Mitchell D. Schnall

Abstract
Traditional cross-sectional tumor imaging focuses solely on tumor morphology. With the introduction of targeted biological therapies in human trials, morphologic change may lag behind other physiologic measures of response on clinical images. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a new imaging method for assessing the physiologic state of tumor vascularity in vivo. DCE-MRI, which uses available imaging techniques and contrast agents, assays the kinetics of tumor enhancement during bolus i.v. contrast administration. Modeling of the temporal enhancement pattern yields physiologic variables related to tumor blood flow and microvessel permeability. Changes in these variables after vascular-targeted therapy can then be quantified to evaluate the tumor vascular response. As these responses may precede morphologic tumor shrinkage, DCE-MRI might serve as a noninvasive means of monitoring early tumor response to vascular-targeted therapy. Renal cell carcinoma provides an excellent model for assessing the effect on DCE-MRI in clinical trials. The vascular richness of renal tumors provides a large dynamic scale of DCE-MRI measures. Patients with disseminated renal cell carcinoma frequently present with one or several large tumors, creating an easy imaging target for DCE-MRI evaluation. Finally, renal cell carcinoma is clearly susceptible to therapies that target tumor angiogenesis. DCE-MRI can be used to monitor the vascular changes induced by such therapies. Future efforts must be directed to standardizing image acquisition and analysis techniques to quantify tumor vascular responses.

Traditional Imaging of Renal Cell Carcinoma
Cross-sectional imaging, including ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), plays a dominant role in the imaging of renal cell carcinoma (RCC; refs. 1, 2). Much of the radiology literature regarding RCC imaging is devoted to two main topics: (a) differentiating RCC from benign renal lesions (e.g., cysts and angiomyelolipomas) and (b) local staging of suspected RCC for surgical management (3–7). With the explosion of the use of cross-sectional imaging throughout medicine, the diagnostic radiologist is frequently required to determine whether an incidental renal lesion is likely malignant. Criteria for these determinations are multifaceted, depending on the imaging modality. For example, CT imaging of the renal lesion before and after iodinated i.v. contrast allows for the delineation of solid (i.e., enhancing) lesions from non-enhancing cysts (8). When a primary renal lesion is shown to be solid, local staging by imaging is used to direct medical or surgical management. In the metastatic setting, cross-sectional imaging, usually CT, is again the preferred method for assessing disease progression and response to therapy. As is true for assessing metastatic response for other tumors, morphologic criteria (i.e., change in unidimensional or bidimensional diameters) are most commonly used (9).

Imaging “Phenotypes” in RCC
Given the vast experience in imaging of RCC, several observations have been made regarding the heterogeneity of the appearance of these tumors on cross-sectional studies. For example, the clear cell variant of RCC can often be determined through the demonstration of intracellular lipid by chemical shift–sensitive MRI (10–12). The pathologic extension of RCC has also been shown to be correlated with the presence or absence of a pseudocapsule on ultrasonography or MRI (13–17). Although such observations are not generally used clinically in lieu of pathologic examination of tissue, these studies show that the richness of imaging phenotypes of RCC can be shown through cross-sectional imaging.

One area of imaging-based tumor phenotyping that is coming into more prominence is that of tumor vascular...
assessment. There is a wide variation in the degree of tumor neovascularization in different RCC, and this variation is reflected by imaging as well. This variation is most prominent when comparing papillary to clear cell variants. Following i.v. contrast administration, clear cell variants of RCC will show greater overall enhancement on CT imaging compared with papillary RCCs (18–20). Furthermore, clear cell RCC will show more internal heterogeneity on post-contrast scanning compared with papillary RCCs (21). The nature of this heterogeneity is not certain, but possibly might reflect the inherent heterogeneity of the immature tumor neovasculature or areas of submacrogenic internal necrosis. Whatever the etiology, clear cell RCCs can exhibit a wide range of vascular “signals” on cross-sectional imaging.

**Need for Noninvasive Vascular Assessment in RCC**

The advent of molecular therapies targeted at angiogenic pathways and the preliminary efficacy that selected therapies show against RCC (22) create a unique opportunity for imaging as a means of assessing tumor vascularity for monitoring and possibly predicting clinical response to targeted agents. The traditional means of imaging-based assessment of tumor response to (cytotoxic) chemotherapy, that is, lesion shrinkage, may not be the optimal means of demonstrating in vivo activity and clinical efficacy of antiangiogenic therapies that are cytostatic rather than cytotoxic. Alternate imaging–based measures, such as time to tumor progression, may be a preferred method for assessing clinical responsiveness. However, these metrics may require longer follow-up and may be affected by the intrinsic heterogeneity of tumor growth rates in a given patient cohort.

In light of these potential difficulties in applying imaging-based criteria for monitoring targeted antiangiogenic and antivascular therapies, there is increasing interest in evaluating alternate imaging measures—particularly imaging markers that may serve as surrogates for alterations in tumor perfusion—as a measure of in vivo drug effect and (potentially) as a marker of clinical responsiveness. Table 1 lists some of the imaging-based methods that have been used as a means of noninvasive assessment of tumor vascularity in humans. These range from variations of existing clinical imaging techniques to experimental imaging modalities that are not currently available outside academic or research settings. Dynamic contrast-enhanced MRI (DCE-MRI) represents the most widely used approach to vascular imaging.

**DCE-MRI for Evaluating Therapeutic Effects on Tumor Neovasculature**

DCE-MRI replicates traditional fast gradient echo T1-weighted imaging multiple times during i.v. bolus administration of gadolinium contrast agents. The resulting tumor enhancement over time reflects the delivery of the gadolinium contrast into the tumor interstitium. The rate of this contrast delivery and its subsequent washout from the tumor are related to several basic physiologic aspects of the tumor and its associated vasculature. These include the intratumoral intravascular volume fraction, the tumor blood flow, the vascular permeability-surface area product, and the accessible extravascular-extracellular space. Kinetic modeling of the tumor contrast concentration over time can then yield the appropriate physiologic variables.

DCE-MRI uses existing MRI scanner and software technology and small molecular weight contrast agents identical to those routinely used in daily clinical MRI practice. Thus, DCE-MRI can potentially be implemented at any institution or imaging center.

### Table 1. Imaging modalities used for vascular-based tumor assessment in humans

<table>
<thead>
<tr>
<th>Modality</th>
<th>Contrast mechanism</th>
<th>Contrast “agent”</th>
<th>Clinical availability</th>
<th>Ease of implementation</th>
<th>Anatomic limitations</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT perfusion</td>
<td>Extrinsic</td>
<td>Iodine</td>
<td>Widespread</td>
<td>Simple</td>
<td>None</td>
<td>Radiation iodine contraindications</td>
<td>(40, 41)</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Extrinsic</td>
<td>Gadolinium</td>
<td>Widespread</td>
<td>Moderate</td>
<td>None</td>
<td>Quantification difficult motion effects</td>
<td>(28–35)</td>
</tr>
<tr>
<td>ASL-MRI</td>
<td>Intrinsic</td>
<td>“Labeled” water</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Geometric</td>
<td>Not widely done outside of the brain</td>
<td>(42–44)</td>
</tr>
<tr>
<td>FDG positron emission tomography</td>
<td>Extrinsic</td>
<td>F18-deoxyglucose</td>
<td>Widespread</td>
<td>Simple</td>
<td>None</td>
<td>Bone lung deep tissue</td>
<td>(45)</td>
</tr>
<tr>
<td>$^{15}$O-H$_2$O positron emission tomography</td>
<td>Extrinsic</td>
<td>$^{15}$O water</td>
<td>Minimal</td>
<td>Moderate</td>
<td>None</td>
<td>$^{15}$O availability</td>
<td>(46–48)</td>
</tr>
<tr>
<td>Doppler ultrasonography</td>
<td>Intrinsic</td>
<td>RBC</td>
<td>Widespread</td>
<td>Simple</td>
<td>Bone lung deep tissue</td>
<td>Operator dependent</td>
<td>(49, 50)</td>
</tr>
<tr>
<td>Contrast ultrasonography</td>
<td>Extrinsic</td>
<td>Microbubbles</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Bone lung deep tissue</td>
<td>Quantification methods not fixed Limited availability</td>
<td>(51–54)</td>
</tr>
<tr>
<td>Optical imaging</td>
<td>Intrinsic</td>
<td>RBC, Hbg</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Superficial tissues only</td>
<td>(55, 56)</td>
<td></td>
</tr>
<tr>
<td>IGC optical imaging</td>
<td>Extrinsic</td>
<td>Indocyanine green</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Superficial tissues only</td>
<td>(57, 58)</td>
<td></td>
</tr>
</tbody>
</table>
center where modern MRI scanners are available. Nonstandard oblique planes of imaging facilitate the interrogation of all body parts where tumors may be found. The superior intrinsic tissue contrast of MRI, and the high anatomic resolution, aids in imaging vascular responses of small and heterogeneous tumors.

Challenges exist that have thus far limited the use of DCE-MRI in clinical trials. The wealth of imaging options available to the magnetic resonance radiologist, creates the potential for imaging variations that may affect the subsequent quantification of image intensity for DCE-MRI analysis. This is further complicated when DCE-MRI protocols are implemented. Differences in vendor models of magnetic resonance scanners, and in software versions for pulse sequence implementation, may further complicate the use of DCE-MRI in the multisite setting.

The accuracy of DCE-MRI quantification is related, in part, to the temporal resolution of the DCE-MRI series. The radiologist performing DCE-MRI must make choices regarding volumetric coverage, image quality, and speed of imaging, choices which may affect the types of analyses which may subsequently be done. Thus, DCE-MRI protocols optimized for evaluation of one tumor type and/or anatomic location may be suboptimal when applied to a patient with a different tumor type and/or anatomic tumor burden. DCE-MRI interpretation is further complicated by the fact that the small molecular weight gadolinium compounds generally available for clinical use are partially diffusible and therefore cannot be used explicitly to derive either tumor perfusion (as freely diffusible agents would) or tumor blood volume (as nondiffusible blood pool agents would). Newer contrast agents emerging clinically may play a role in the future development of DCE-MRI in tumor vascular evaluation (23, 24). These aspects of image quantification and subsequent tumor compartment modeling are reviewed further elsewhere (25–27).

Fig. 1. Intratumoral heterogeneity of antivasculareffects of CA4P. Patient with large thyroid cancer metastasis to the sacrum (between arrows) underwent five daily i. v. infusions of CA4P. A, early postgadolinium image from the baseline DCE-MRI study. B, the same tumor after gadolinium 4 h after the day 5 dose of CA4P. Note the large area of tumor devascularization in the inferior portion (asterisk). Representative tumor enhancement curves before and after therapy for the anterior (C) and posterior (D) portions of the tumor, respectively.
Despite the hurdles, the ubiquity of MRI scanner availability and the contrast and resolution advantages of MRI have drawn researchers to investigate the potential of DCE-MRI to monitor tumor vascularity and vascular-based changes induced by targeted and nontargeted therapies. Many of these studies have focused on one tumor type and/or one anatomic location, simplifying the implementation of a DCE-MRI algorithm (28–32). Other human DCE-MRI studies have examined the effect of a single agent or single combination of agents, regardless of tumor type and location (33–35). Interpreting the results of these latter studies is complex because tumors of different cellular origin may exhibit vastly different degrees of responsiveness to the agent in question. Imaging reproducibility and the sensitivity of the DCE-MRI examination to tumor vascular changes may also vary for imaging in various anatomic compartments.

**Current Clinical Results of DCE-MRI for Monitoring Vascular Targeted Therapy in Humans**

Several studies of DCE-MRI assessment of antivascular therapies in humans have been reported. Three phase 1 evaluations of combretastatin A4 phosphate (CA4P) were reported, all using DCE-MRI as an adjunct to evaluate antivascular response (33–35). In all, 35 patients who received various dose levels and administration schedules of CA4P were evaluated before and during or immediately after the first course of therapy. These results showed...
variability in the DCE-MRI–measured tumor response to CA4P. However, a threshold effect of CA4P at a dose level of 52 mg/m² was suggested, with no imaging responses seen below this level. Another important aspect of these studies was the demonstration of intratumoral heterogeneity of vascular response (Fig. 1). These findings highlight the value of high-resolution imaging for probing tumor vascular responses because tumors may contain regions of varying neovascular maturation (36).

A more directed study (28) of the effect of dose escalation of PTK787 on metastatic colorectal cancer was done at two sites, with a total of 26 patients studied before, on day 2, and at the end of the first 28-day treatment cycle. From these results, the authors were able to generate a dose-response curve comparing the drug area under the curve exposure to the vascular inhibitory effect. The ability to use DCE-MRI to monitor physiologic responses for dose findings in early trials is a potentially important attribute when evaluating agents with minimal systemic toxicity.

DCE-MRI of Vascularly Targeted Therapy in RCC

To date, the published results of DCE-MRI vascular response of RCC to targeted therapy has been mostly anecdotal. In the recently completed phase 2 trial of single-agent sorafenib (37), patients from one of the participating institutions underwent DCE-MRI evaluation before and after initiation of therapy (38). In this group, large reductions in the first-order rate constant for gadolinium serum-tumor transfer ($K^{\text{trans}}$) were identified (Fig. 2), and an association was noted between initial tumor $K^{\text{trans}}$ and time to tumor progression. These results have spurred the incorporation of DCE-MRI into larger-scale clinical trials. As part of the National Cancer Institute initiative to develop translational research in oncologic imaging applications (39), a multi-institutional study of DCE-MRI monitoring of targeted multidrug therapy in RCC has been launched. These studies should help further determine the feasibility of large-scale DCE-MRI implementation in clinical oncology trials and define whether imaging-based end points such as DCE-MRI may be usefully incorporated in the evaluation of targeted therapies in RCC.

Conclusions

There is great potential value for noninvasive imaging-based assessment of tumor vascular responses to targeted antiangiogenic therapy. However, clinical implementation of such studies has been hampered by the limited availability of novel imaging modalities and the lack of standardization of imaging techniques and quantitative modeling. Small-scale studies have shown the ability of DCE-MRI to monitor therapy-induced changes in the tumor neovasculature. The wide availability of MRI makes the implementation of DCE-MRI assessment an attractive target for further trial development. However, few large-scale human studies have been done to test whether such imaging-based functional end points can serve as markers of clinical efficacy. Continued studies are required to examine how DCE-MRI may best be incorporated into therapeutic monitoring in trial design, and eventually, routine clinical practice.

Open Discussion

Dr. Atkins: Is there any way to distinguish, before therapy, the particular tumors that might be appropriate to treat with a particular therapy?

Dr. Rosen: We don’t have any firm data, but the more vascular tumors seemed to have more durable clinical responses.

Dr. Atkins: It would be interesting to try to link imaging data to pathology and molecular biology so we could have a better sense of what we are looking at with different imaging techniques.

Dr. Rosen: In terms of biology, we know that clear cell RCCs and papillary RCCs behave differently. They also look very different on conventional CT or MRI, even though both are solid renal neoplasms. It would be interesting to see whether more physiologic imaging, such as DCE-MRI differentiate between clear cell RCCs with the von Hippel-Lindau mutation from those not driven by von Hippel-Lindau mutations. Evaluating patients in the neoadjuvant setting would be one scenario, where we could theoretically obtain tissue before therapy, and then subsequently at the time of debulking nephrectomy.

Dr. Atkins: One of the problems with trying to do predictive models is that we have pathology on the primary tumors but we are treating the metastases. It would be nice if we had a procedure other than a biopsy that could tell us what is happening in the metastatic lesion. Imaging has this potential.

Dr. Rosen: A question I ask oncologists is, “Is the metastatic cell selected from the primary for its ability to metastasize, and do all metastases look the same?” In melanoma, there will be spontaneous hemorrhagic necrosis in some but not all metastases, a phenomenon not necessarily driven by size. This has implications for how we measure tumors, but it may also tell us something about interlesional biologic variability. Can we use our experience with the predictive value of molecular biomarkers, and attempt to create image-based metrics that will provide us with a set of imaging biomarkers?

Dr. Sukhatme: What are the technologies for looking at the oxygenation status of tumors?

Dr. Atkins: There is a large experience using blood oxygen level–dependent MRI in kidneys, measuring hypoxia in the renal medulla, and we could certainly do that in tumors. There are other noninvasive ways to assess for tumor oxygenation, including near-IR optical techniques and positron emission tomography with hypoxia-sensitive agents. MRI provides more resolution to look at tumor heterogeneity. Positron emission tomography provides a means to evaluate the whole body tumor burden more efficiently. Which method will provide more reproducible data? I do not know. Ideally, one should use multiple imaging modalities in serial studies, although patients may opt out of trials if too many imaging modalities are introduced. We therefore have to be selective and consider what we are trying to measure and in whom.

Dr. Ernstoff: Is there an ability to predict for the rare toxicity in the brain or bleeding complications by measuring response and vascularity in normal tissue?

Dr. Rosen: We have not looked at normal tissues except as an internal control during DCE-MRI tumor studies; it’s not clear what one would look for to predict hemorrhagic
complications in normal tissues. For tissues such as kidney or liver, there are numerous physiologic factors to control for, as perfusion in these organs is highly regulated.

**Dr. George:** You have looked serially with DCE-MRI target lesions. What is the optimal time to look with this? Is there any indication of when somebody is going to progress?

**Dr. Rosen:** Time to onset of antiangiogenic activity will depend on biologic and pharmacologic factors, so there is unlikely to be a single imaging window that is optimal across all studies. In the sorafenib trial, we have not done serial DCE-MRI systematically. Anecdotally, we have examined long-term responders with residual masses, and found them largely devoid of any flow.

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**References**

8. Israel GM, Hindman N, Bosniak MA. The current radiological approach for, as perfusion in these organs is highly regulated.

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**DCE-MRI for Tumor Vascular Assessment**

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