Magnetic Resonance Imaging as a Biomarker in Renal Cell Carcinoma*

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The ability to noninvasively discriminate the most common types of renal cell carcinoma (RCC) based on their magnetic resonance imaging (MRI) appearances or their magnetic resonance phenotypes is achievable. Intracellular lipids, a histologic characteristic of the clear cell RCC, can be identified on chemical shift MRI. Intratumoral hemosiderin deposition, as observed histologically with papillary RCC, correlates to the low signal intensity on T2-weighted images. In addition to morphologic imaging features, the different subtypes of RCC have distinct patterns of enhancement on dynamic contrast-enhanced MRI. Clear cell tumors demonstrate much greater enhancement than papillary and chromophobe RCCs during the corticomedullary and nephrographic phases. The MRI technique arterial spin labeling (ASL) uses magnetic fields to label the water protons in arterial blood and measures blood flow into tissue; quantitative images of blood flow can be generated without exogenous contrast media. Multiple measurements of tumor perfusion may be repeated before and after a physiologic or drug challenge (ie, antiangiogenic therapy). In RCC xenografts and in patients with metastatic RCC, ASL MRI assessments can be used to monitor blood flow changes in response to antiangiogenic therapies. High blood flow on ASL MRI in RCC xenografts correlates with viable tumor at histopathologic analysis, whereas zones of absent or diminished signal correspond to necrosis. ASL MRI has the potential to serve as a biomarker for patients with metastatic RCC by offering a noninvasive measure of tumor blood flow changes accompanying antiangiogenic therapy. Cancer 2009;115(10 suppl):2334–45. © 2009 American Cancer Society.

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Renal cell carcinoma (RCC) is a heterogeneous disease and includes multiple subtypes that differ in their histopathologic features, genetic expression pattern, and clinical behavior.1,2 During the last 2 decades, significant advances in the diagnosis, staging, and treatment of patients with RCC have resulted in improved survival in selected patients.3

Recent discoveries in the genetics of RCC have provided the opportunity for new molecularly targeted therapies in patients with metastatic RCC, including immunotherapy and antiangiogenic therapies.4,5 The success of such targeted therapies relies on an accurate histologic subtyping of the tumors. Percutaneous biopsy can provide a presurgical “tissue diagnosis” in selected patients, although inaccurate tumor subtyping rates can be as high as 26% in sampled primary renal tumors.6,7 Therefore, a method to accurately characterize the histologic
subtype of renal masses that is robust, noninvasive, and insensitive to sampling errors would have utility in clinical practice.

Traditional assessments of tumor response to anticancer therapies such as the Response Evaluation Criteria in Solid Tumors (RECIST) or the World Health Organization (WHO) criteria are based on size criteria. The limitations of these methods in detecting the activity of new cytostatic therapies, such as antiangiogenic and targeted therapies, has been documented in different metastatic tumors, including RCC.8-11 New imaging techniques that interrogate changes in tumor microenvironment and vascularity as biomarkers for response to these therapies of tumor cells are under intense evaluation. Preliminary results using some of these techniques are encouraging and support their incorporation into clinical practice as well as into clinical trials.12

In this article, we review the role of magnetic resonance imaging (MRI) as a biomarker, defined as a tool to noninvasively detect intratumoral anatomic, physiologic, biochemical, or molecular parameters,13 to characterize primary and metastatic RCC as well as its response to antitumor therapy. We present some of the MRI findings used for the determination of the histologic subtype in RCC, including imaging findings on conventional MRI and enhancement patterns on dynamic contrast-enhanced (DCE) MRI. Novel MRI techniques for assessment of tumor vascularization and response to anticancer therapy, including arterial spin labeling (ASL), breath-hold proton spectroscopy, blood oxygen level-dependent (BOLD) imaging, and diffusion-weighted imaging (DWI), are discussed.

**MRI Phenotypes in RCC**

Clear cell (65%-70%), papillary (15%-20%), and chromophobe (6%-11%) RCCs represent the most common subtypes of RCC and differ in their prognosis and biologic behavior14 as well as in their response to available therapies.15 In addition to the ability of MRI to accurately characterize renal lesions as neoplasms,16-20 an ability to noninvasively discriminate the various types of RCC based on their MRI appearances or magnetic resonance phenotypes is achievable.21,22

The presence of intracytoplasmic vacuoles containing lipids, a histologic characteristic of the clear cell subtype, can be recognized with the use of chemical shift MRI techniques.23 The presence of intratumoral lipids results in a decrease in signal intensity on T1-weighted, opposed-phase images compared with the in-phase images in the non-necrotic “viable” tumor (Fig. 1). Areas of “viable” tumor containing lipids, as demonstrated on chemical shift images, enhance after administration of contrast. This allows for differentiation from areas of engulfed retroperitoneal fat within the tumor, which characteristically do not enhance. Reports on the value of this finding for the correct subtyping of a malignant renal mass as clear cell RCC indicate between 42% and 82% sensitivity and between 94% and 100% specificity.21,24

The presence of retroperitoneal collaterals, renal vein thrombosis, and intratumoral necrosis on MRI each predict high-grade clear cell subtype, whereas intratumoral necrosis directly relates to tumor size for clear cell carcinomas.21 A tumor capsule of low signal intensity on T1- and T2-weighted images may be observed, and its interruption is associated with locally advanced disease and higher nuclear grade.25,26

The majority (85%) of predominantly cystic neoplasms that contain “simple” fluid and small solid components and/or thickened or irregular septae represent low-grade clear cell RCCs.20,21 In contradistinction, cystic neoplasms with hemorrhagic contents and peripheral solid papillary projections are more commonly papillary neoplasms.21

Papillary carcinomas have other distinct MRI features that correlate with their unique histopathologic characteristics.27,28 These tend to be located in the surface of the kidney, they are small in size, and they have homogeneous and lower signal intensity compared with the cortex on T2-weighted images.21,27,28 The latter characteristic has been correlated with cytoplasmic or interstitial histiocytic hemosiderin deposition22 and provides an accurate distinction from clear cell RCC, which typically exhibits heterogeneously increased signal intensity on T2-weighted images.21,27 The histologic characteristics of cystic papillary RCC may be evident on diffusion tensor MRI because of restriction of the motion of water molecules along the well developed fibrous capsule and the fibrovascular core in the papillary projections.29 The overall sensitivity and specificity of MRI to predict the histologic subtype using a feature analysis is 92% and 83% for clear cell RCC, and 80% and 94% for papillary RCC, respectively.21
MRI Assessment of Tumor Vascularity in RCC

Capitalizing on the unique attributes of tumor microvasculature and the dependency of tumor growth on vascular recruitment, contemporary cross-sectional imaging techniques that assess tumor vascularity are of increased interest and relevance. Such techniques are particularly attractive in the era of targeted antiangiogenic therapies applicable to a variety of cancers.

Traditional assessments of tumor progression based on size criteria (ie, RECIST, WHO criteria) often are inadequate to assess tumor response to cytostatic therapies. These new systemic therapies induce changes in tumor vascularity that precede those in size. Thus, there is a need for imaging tools that robustly and reproducibly can monitor alterations in tumor vascularity with a potential to serve as a surrogate for tumor response. MRI is uniquely suited to this task because it provides a variety of ways to assess changes in tumor vascularity either with or without exogenous contrast media.

DCE-MRI

DCE-MRI allows for interrogation of tumor signal intensity before, during, and after the intravenous administration of a bolus of contrast. The accumulation of the contrast agent in the tumor over time can be used to extract quantitative information regarding the functional integrity of tumor microvasculature. Compared with DCE-computed tomography (CT), the lack of associated ionizing radiation and the excellent sensitivity of MRI to detect small amounts of intravenous contrast are potential advantages for its use in DCE imaging protocols. Most DCE-MRI protocols use the standard gadolinium-based extracellular contrast agents that are common to clinical practice. These are small-molecular-weight contrast agents that diffuse variably between the intravascular and intracellular compartments.

FIGURE 1. Intracellular lipids demonstrated by chemical shift magnetic resonance imaging in clear cell carcinoma. Axial (A) in-phase and (B) opposed-phase, T1-weighted gradient echo images demonstrated a large mass arising from the right kidney. The tumor contained areas of high signal intensity on the in-phase image (A, arrow) that were hyperintense to the renal cortex (A, arrowhead). Note the decrease in signal intensity in the same areas on the opposed-phase images (B, arrow) compared with the signal intensity of the renal cortex (B, arrowhead); this finding is highly specific for the presence of the intratumoral lipids, and it is characteristic of the clear cell subtype.
extravascular spaces based on vascular permeability in the tumor bed.

The rate of delivery and washout of contrast media into the tumor vascular bed depends on several physiologic characteristics of the tumor vascular microenvironment. With DCE-MRI, these characteristics are reflected in the determination of the intratumoral vascular volume fraction, the tumor blood flow, the vascular permeability-surface area product, and the accessible extravascular-extracellular space. These values, although considered quantitative, are derived from a series of assumptions regarding compartmental tracer kinetics. DCE-MRI has been used to evaluate the response to antiangiogenic therapies in a variety of cancers both in patients and in animal models.

MRI sequences used for DCE examinations are 2-dimensional (2D) or 3-dimensional (3D), T1-weighted gradient echo sequences, most of which are similar to or derived from those used in routine clinical practice. The 3D sequences have the advantage of covering larger anatomic areas and provide a volumetric assessment of tumor vascularity. In contrast, 3D acquisitions are vulnerable to breathing artifacts compared with the relatively motion-insensitive 2D acquisitions. In an effort to determine the tumor perfusion, most DCE-MRI research protocols are tailored to demonstrate tumor vascularity during the initial portion of the bolus and, thus, use a high temporal resolution/low spatial resolution approach. However, the spatial resolution and/or the anatomic coverage required to evaluate a specific tumor affects the achievable temporal resolution. Ultimately, a particular DCE-MRI protocol represents a compromise between the temporal and spatial resolution (including anatomic coverage) based on the nature and location of the tumor.

For example, an assessment of a highly vascularized tumor in the upper abdomen (eg, clear cell RCC) would require a DCE-MRI protocol with high temporal resolution that is relatively insensitive to respiratory motion; a sacrifice in the anatomic coverage and/or spatial resolution is inherent to achieving these simultaneous goals. In contrast, DCE-MRI protocols for relatively hypovascular tumors located in organs with a limited range of motion (eg, breast, prostate) can use a lower temporal/higher spatial resolution volumetric (3D) acquisition.

The dynamic contrast enhancement features of the different histologic subtypes of RCC may assist in the imaging diagnosis. By using DCE-CT, it has been demonstrated that clear cell RCCs enhance more avidly and heterogeneously than papillary tumors. Furthermore, quantitative kinetic parameters of tumor vascularity on DCE-CT correlate with microvascular density in RCC. The 3 most common subtypes of RCC, clear cell, papillary, and chromophobe tumors, can be distinguished based on their enhancement patterns using a simple 3D DCE-MRI protocol with a precontrast dataset and 2 postcontrast datasets. Clear cell tumors exhibit a greater percentage enhancement during the corticomedullary and nephrographic phases than papillary tumors, whereas chromophobe RCCs exhibit an intermediate percentage enhancement at both phases.

Some of the limitations of DCE-MRI in clinical trials include the poor standardization of the imaging technique across different vendors and the quantification of tumor perfusion. The latter is particularly challenging when using extracellular contrast agents because these undergo different degrees of transendothelial diffusion, depending on the permeability of the tumor blood vessels. The relative contribution of vessel leakiness (ie, permeability) and tumor blood flow to the overall signal intensity changes observed on DCE-MRI frequently is unknown. Often and erroneously, those 2 terms are used interchangeably, which can be confusing when interpreting data. Different tumor compartment modeling approaches have been proposed to correct for this variability and may be applicable to specific tumors. However, accurate determination of tumor perfusion using these models may not be possible for all tumors.

Recently, intravascular contrast agents that do not diffuse into the extravascular space have been developed and have the potential to offer additional information regarding the tumor aggressiveness and its response to antiangiogenic therapy. At the time of this writing, few are available worldwide and none are approved by the Food and Drug Administration.

**ASL MRI**

ASL is an MRI technique for the measurement of blood flow into tissue that uses magnetic fields to label the nuclear spins of the endogenous water in arterial blood. Quantitative images of blood flow can be generated that can be used as quantitative markers for response to therapy. ASL has been used widely in animal studies and in
humans, and different versions of the technique have been validated in animals using microspheres and in the normal human brain using H2O15 positron emission tomography. Initial clinical applications of ASL have been focused on benign neurologic disorders. The history of the development of the ASL MRI technique is summarized in Table 1.

| Year       | Milestone                                                                 | Reference                                      |
|------------|---------------------------------------------------------------------------|-----------------------------------------------|
| 1986       | Arterial spin labeling angiography proposed and demonstrated              | Dixon 198655                                  |
| 1992       | Arterial spin labeling perfusion proposed and demonstrated in rat brain  | Detre 199256; Ruppert-Kohlmayr 200443          |
| 1994       | Validation in rat brain                                                   | Wang 200654                                   |
| 1994-1995  | Initial images in human brain                                            | Edelman 199457; Roberts 199458; Kim 199559; Kwong 199550 |
| 1995       | First images of human kidney perfusion                                    | Roberts 199553                                |
| 1994-1995  | Quantification strategies developed for longer transit delays in human brain | Alsop & Detre 199662; Buxton 199863; Wong 199864 |
| 1998-1999  | Multislice techniques developed                                           | Alsop & Detre 199865; Edelman & Chen 199866; Yongblut 199867; Zaharchuck 199968 |
| 2000       | Background suppression introduced to reduce variability                  | Ye 200059                                     |
| 2000       | Validation in humans                                                      | Ye 200070                                     |
| 2005-2008  | Application to renal cancer                                               | Williams 199249; Walsh 199450                 |
| 2005       | Correlation of brain tumors with grade/vascular density                   | Wolf 200571; Noguchi 200872                  |

There are several potential advantages of using ASL techniques for the evaluation of tumor perfusion. First, because no intravenous contrast is administered, multiple measurements may be performed without accumulating tracer materials. Thus, assessment of tumor perfusion at multiple time points and before and after physiologic or drug challenges (ie, antiangiogenic therapy) is readily achievable. Second, compared with DCE-MRI, there is no ambiguity regarding the contribution of permeability and blood flow to signal intensity; signal intensity on ASL is directly proportional to blood flow.

Some of the limitations of the current implementations of ASL techniques include the lack of widespread commercial availability, its better suitability for higher flow tumors, and the limited anatomic coverage provided by the 2D acquisitions. Future implementations of the technique using 3D acquisitions will further improve the evaluation of tumor response by providing a volumetric assessment of tumor perfusion.

de Bazelaire et al demonstrated the feasibility of this technique to monitor response to antiangiogenic therapy in RCC metastases. In a recent trial, ASL and DCE-MRI were used to assess the response of patients with metastatic RCC to an antiangiogenic therapy with PTK787/ZK 222584 (Vatalinib; Novartis Pharmaceuticals, East Hanover, NJ; Schering AG, Berlin, Germany). Early changes at 1 month in blood flow and tumor size were compared with tumor size changes at 4 months. ASL blood flow changes were correlated significantly with time to progression, whereas tumor size and DCE-MRI blood flow changes at 1 month were not. No correlation was observed between blood flow changes and tumor size changes at 1 month. If validated, the sensitivity of ASL to detect early changes in tumor vascularity shortly after the initiation of therapy may play an important role in determining the effectiveness of new antiangiogenic drugs in these patients (Fig. 2).

ASL can be used to detect early changes in therapeutic response to antiangiogenic therapy in animal tumor models. Schor-Bardach et al recently studied the response rate to sorafenib therapy of 3 different human RCC xenografts implanted in nude mice. Caki-1 (sorafenib resistant), A498 (sorafenib sensitive), and 786-0 (early response followed by rapid development of resistance by Day 5) tumors exhibited different levels of blood flow on ASL MRI at baseline. Specifically, Caki-1 tumors demonstrated minimal blood flow at baseline (10.2 mL ± 9.0 mL/100 mg/minute) relative to 786-0 tumors (75.1 mL ± 28.6 mL/100 mg/minute) and A498 tumors (80.1 mL ± 23.3 mL/100 mg/minute). These findings correlated with the lack of response of Caki-1 tumors to sorafenib therapy, possibly suggesting that low levels of perfusion on ASL may be a useful biomarker for predicting poor response to therapy.
responsiveness to certain types of antiangiogenic therapy.\textsuperscript{75}

Although blood flow changes on ASL after antiangiogenic therapy varied in these animal models, its regional distribution within the tumors corresponded tightly to their histopathologic appearance. Regions with high signal intensity on ASL correlated to viable tumor, with zones of absent or diminished signal (ie, $<2 \text{mL/100 mg/minute}$) representing necrosis. In those lines that responded to sorafenib, ASL provided important information regarding tumor viability with a tight radiologic-pathologic correlation to induced intratumoral necrosis.\textsuperscript{75}

Thus, the potential to use ASL as a means to base therapeutic decisions for patients with well perfused tumors also can be appreciated.

A practical clinical application of ASL imaging is to characterize renal lesions into those with and without measurable blood flow, a distinction critical for
identifying neoplasms, when the administration of contrast media is not desirable (eg, in patients with substantial renal insufficiency). The use of ASL in this manner is in the early stages of validation.\textsuperscript{76}

**Spectroscopy**

Magnetic resonance spectroscopy (MRS) techniques have been applied for years to the characterization of brain lesions and the differentiation of neoplastic versus non-neoplastic tissues. MRS separates different molecular contributors to the total MRI signal by using the changes in signal frequency induced by the molecular environment. These frequency changes are so small that they are measured in parts per million (ppm) and require special magnetic resonance techniques for their measurement. Recent implementation of the techniques for performing proton MRS in the abdomen and thorax at higher field strengths (ie, 3 T), including breath-held acquisitions,\textsuperscript{77} may facilitate the detection of unique metabolic surrogates in specific tumors. For example, MRS applied to patients with metastatic RCC demonstrates a significantly lower ratio of signal at a 5.4-ppm frequency shift to that at 1.3 ppm (the latter may be correlated with the lipid content in the voxel) in metastatic RCC compared with that in healthy tissue, suggesting that this ratio may be a useful marker for renal malignancy and potentially may aid in monitoring treatment.\textsuperscript{78} If such findings can be confirmed in patients with earlier stage disease and, ideally, can be correlated with the underlying histologic and molecular features, then MRS could provide a useful metabolic signature of the disease. Some of the limitations of MRS as a biomarker include its relatively low spatial resolution and the difficulty with which it can be used to assess large tumors and, thus, to detect heterogeneity within tumors because of the attendant time and signal-to-noise constraints.

**BOLD Imaging**

The paramagnetic properties of deoxyhemoglobin, compared with the diamagnetic characteristics of oxyhemoglobin, can be exploited to image tumor hypoxia. Differences in concentrations of deoxyhemoglobin modulate microscopic field gradients in the vicinity of blood cells and vessels.\textsuperscript{79} These intravoxel alterations in the magnetic field cause loss of phase coherence, which leads to signal loss on gradient echo T2-weighted images, the so-called BOLD contrast.

A direct correlation between oxygen levels measured by BOLD MRI and tumor hypoxia in a variety of animal tumor models establishes a useful tool for investigating interventions (such as drugs) that affect tumor vasculature.\textsuperscript{80-82} BOLD studies in humans have focused primarily on gliomas, suggesting utility in monitoring vascular reactivity.\textsuperscript{83,84} The mechanistic elements of RCC, its hypervascular nature, and its oxygen deregulation provide a rationale for the pursuit of BOLD imaging. To the best of our knowledge, the ability of BOLD imaging to detect tumor changes in patients with RCC who are undergoing chemotherapy has not been reported.

**Diffusion-weighted Imaging**

Diffusion-weighted imaging (DWI) is an MRI technique that allows for detection of the direction and magnitude of the random motion of water. Random (Brownian) motion of water molecules within tissues results in signal attenuation during the application of 2 balanced gradients applied symmetrically around a 180-degree refocusing pulse (ie, diffusion-weighting gradients). In contrast, water molecules with restricted motion acquire phase shifts during the application of the first gradient that are cancelled out by the second gradient, thus without incurring signal loss. The degree of water diffusion within tissues, or the apparent diffusion coefficient (ADC), can be calculated by acquiring multiple images with different amplitudes or durations for the diffusion-weighting gradients (b values). Increased cellularity and decreased interstitial space result in restriction of water motion and decreased ADC values within tumors compared with most non-neoplastic tissues.\textsuperscript{85}

An ability of DWI to function as a biomarker to predict and monitor tumor response to targeted and/or antiangiogenic therapy has been described.\textsuperscript{85,86} Preclinical and clinical studies have demonstrated some correlation between ADC values and tumor cellularity and grade.\textsuperscript{87} Baseline ADC values may predict the likelihood that a patient will respond to therapy.\textsuperscript{88,89} For example, a significantly higher ADC value at baseline has been reported for nonresponding patients with rectal adenocarcinomas compared with the value for patients who responded to chemotherapy and chemoradiation.\textsuperscript{89} However, the prognostic implications of the pretreatment ADC values
require further validation. Differences in the geographic distribution of high ADC values may account for tumor necrosis and, thus, may indicate a poor response to therapy.

An increase in ADC values as a result of therapy-induced tumor cell lysis and necrosis has been demonstrated in both preclinical and clinical studies. Changes in ADC values may precede those in tumor volume, making DWI a potential biomarker for early response to therapy. Furthermore, several studies have demonstrated a positive association between therapy-induced elevation in ADC values and better clinical outcomes to a variety of antitumor therapies.

However, the mechanisms that lead to the changes in ADC values after therapy are not completely understood. Early cellular swelling and decreased vascularity induced by therapy may lead to a transient decrease in ADC value in tumors that respond effectively to treatment.

Conclusions

An array of MRI techniques can offer the capacity to noninvasively characterize renal masses and evaluate response to therapy in primary and metastatic disease. More widely available imaging techniques, including T2- and T1-weighted imaging, fat and water separation, and contrast enhancement, have high sensitivity and specificity for identifying renal mass malignancy and subtype. Several newer techniques that are under development and evaluation offer the potential for improved characterization of vascularity and cellularity and for monitoring therapeutic efficacy. Although ASL imaging needs further validation, it is particularly attractive as a quantitative method for accurately monitoring tumor response to antiangiogenic therapy in patients with metastatic RCC. The potential for imaging and, in particular, for MR techniques to serve as biomarkers needs to be carefully considered.

OPEN DISCUSSION

The questions and discussion below follow from the oral presentation given at the Third Cambridge Conference on Innovations and Challenges in Renal Cancer and do not correspond directly to the written article, which is a more general review.

Dr. Bernard Escudier: How long does it take to do 1 ASL MRI?

Dr. Ivan Pedrosa: It takes about 3 minutes to obtain an ASL acquisition in 1 anatomic location. We start with some standard anatomic imaging to localize the tumor. Then, we typically acquire at least 2 orthogonal planes through the tumor. In the current format, the exam duration may vary between 20 and 45 minutes.

Dr. W. Marston Linehan: With ASL, can you tell if a tumor is solid?

Dr. Pedrosa: The ASL technique provides information about tumor vascularity. Similar to the experience with contrast-enhanced techniques, one could assume that a renal mass that demonstrates vascularity throughout is solid.

Dr. Linehan: If you are trying to follow a renal mass, what is your best approach?

Dr. Pedrosa: We like to follow renal masses with contrast-enhanced MRI using a high-resolution 3-dimensional technique that allows us to subtract the precontrast dataset from the postcontrast datasets. In our experience, this is the best tool to determine whether there is enhancement or not, particularly in a cystic lesion. We are confident that we can detect very small enhancing components within cysts.

Dr. Linehan: If you are doing a clinical trial with a lot of imaging, however, that is going to be a fair amount of contrast.

Dr. Pedrosa: Yes, but unless there is severe renal failure, we believe that gadolinium MR is safer than contrast-enhanced CT.

Dr. Gary Hudes: How much experience is there in terms of ASL baseline flow with response to any antiangiogenic treatment?

Dr. Pedrosa: As far as I know, our experience in the human xenografts implanted in mice is the only evidence that we have that the differences in baseline flow are predictive of response.

Dr. Michael Atkins: In addition, this type of approach could help one choose both the right time and the right part of the tumor to biopsy.

Dr. Hudes: Is there any experience right now with DC MRI in terms of response in patients?

Dr. Pedrosa: There are very limited data. Our initial trial included both ASL and DCE MRI. In contradistinction to the ASL technique, we did not find a definitive
correlation between early changes on DCE MRI and changes in tumor size at 4 months. However, I know other groups are working on this approach, and they may show different results.

**Dr. Jeffrey Sosman:** How early do you think you could look? Have you taken this back even closer to the initiation of therapy?

**Dr. Pedrosa:** The earliest changes in perfusion we have seen were within 7 days, with complete disappearance of the perfusion in some cases; but, again, we have not performed ASL imaging earlier than that.

**Dr. Sosman:** What does normalization of blood flow mean for the ASL?

**Dr. Pedrosa:** ASL MRI uses arterial blood as an endogenous contrast agent, so the quantification of tumor perfusion is not affected by increased tumor permeability. This technique has been validated, and there is a tight correlation between signal intensity on ASL and blood flow measured with other techniques. However, we have not investigated the potential advantage of ASL MR in determining “normalization” of tumor blood flow.

**Conflict of Interest Disclosures**

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