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REVIEW ARTICLE

Magnetic Resonance As a Cancer Imaging Biomarker

A. Gregory Sorensen

From the Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, and the Division of Health Sciences and Technology, Harvard Medical School and the Massachusetts Institute of Technology, Boston, MA.

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Address reprint requests to A. Gregory Sorensen, MD, Building 149, Room 2301, 13th St, Charlestown, MA 02129; e-mail: sorensen@nmr.mgh.harvard.edu.

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ABSTRACT

Cancer is a diverse disease with many manifestations. Magnetic resonance (MR) has a wide range of sensitivities, and therefore has often been used to study cancer in humans in numerous different ways, most typically with MR spectroscopy and MR imaging. This article is not an exhaustive catalog of the use of MR in cancer, but will briefly highlight some of the many promising MR methods that have been developed, proposed, or used to focus on the problem of detecting and characterizing cancer, its treatments, and adverse effects.

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INTRODUCTION

The possible application of nuclear magnetic resonance (NMR, or now, MR) or magnetic resonance imaging (MRI) to cancer has been long standing: Some 35 years ago, MR was reported to characterize the difference between the magnetic relaxation properties of cancer and noncancer tissues.[1] However, although MRI can clearly detect presence of certain cancers once they are macroscopic mass lesions, the specificity of MRI, MR spectroscopy (MRS), or other MR-based techniques have repeatedly fallen short of initial speculation or claims, including some spectacular failures.[2,3] Therefore, although the remainder of this review will describe many promising techniques, it is important to keep this historical perspective. Although the role of MR in cancer care will undoubtedly continue to expand, the very complexity that gives MR its power can also highlight the even greater complexity of biology, and careful clinical studies are still required in almost all areas of MR cancer research.

MR provides information about the resonance of populations of nuclei. (For overviews, see standard MRI textbooks such as Edelman et al[4] and Stark and Bradley.[5]) These resonances are influenced by many environmental factors, and depending on the encoding scheme, an MR measurement can be sensitive to a wide variety of physical and biologic properties of interest. These properties range from local tissue chemical content to temperature to water diffusion to blood flow to tissue elasticity to the presence of extrinsic contrast agents. This range of sensitivity is one of the great strengths of MRI, but its implication is that measurement conditions must be carefully controlled before conclusions can be drawn. When thinking about MR as an imaging biomarker for cancer, therefore, it may be useful to first review what precisely is required.

ESTABLISHING THE UTILITY OF AN IMAGING BIOMARKER

For the purposes of this review, an imaging biomarker can be defined as anatomic, physiologic, biochemical, or molecular parameters detectable with imaging methods used to establish the presence or severity of disease.[6] By this definition, much of imaging can be thought of as a biomarker, and certainly MR methods fall in to this definition. However, the utility of an imaging biomarker, especially in decision making about cancer and its treatment, requires more than detection; it requires understanding of the method's strengths and weaknesses. One formalism introduced to describe imaging biomarkers from a regulatory and drug development perspective[7] describes four stages of utility, outlined in Table 1.

Many of the new MRI techniques that will be discussed in this review fall somewhere between the pre-biomarker and the biomarker stage. For example, the US Department of Health and Human Services has indicated that MRS has not yet fully established its reproducibility across centers,[9] whereas others point to "successful" multicenter clinical trials carried out with this technique,[10] suggesting that some accept MRS as a biomarker while others would put it in the pre-biomarker stage. In practice, this probably represents the give and take between the desire for ideal, evidence-based medical decision making and the realities of the practice of medicine. During the following survey of MR techniques, it will be clear that most are in the first two stages. Nevertheless, it is useful to consider this

Table 1. Stages of Biomarker Development

Term or Stage	Meaning	Example
Pre-biomarker	Proof of concept establishing technical performance	A new MR technique such as carbon-13 MRS
Biomarker	Safety and reproducibility established, but utility not yet clear	Most conventional MRI techniques
Surrogate	Qualified for use in drug development	Disease-free survival in testing adjuvant colon cancer therapies[8]
Licensed	Used in therapeutic decision making	Iodine-131 tositumomab

NOTE. Adapted with permission.[7]
Abbreviations: MR, magnetic resonance; MRS, MR spectroscopy; MRI, MR imaging.

formalism of stages, at least because such a formalism can serve as a reminder of the standard of evidence that rational observers require.

This review will serve as only a brief introduction to the various techniques that groups are using or have proposed using as cancer imaging biomarkers; more exhaustive reviews of these and other topics are available.

MRS

Brief Introduction to MRS Terminology

Inside every clinical MRI machine is an MR spectrometer; this is the radiofrequency receiver system that detects the MR signal. For the most part, MRI ignores the spectrum of resonances that might come out of a given voxel of tissue and lumps together all the various peaks and valleys in a spectrum in to a single signal that then is white, black, or somewhere in between on a given image. However, with the proper hardware and software modifications, MRI machines can provide the full information contained within a region (ie, the full spectrum). However, resolving the peaks and valleys of the spectrum requires more signal than simply averaging the whole spectrum together. Obtaining this additional signal usually is done by making the sample size, or voxel size, larger. Thus, MRS is usually either shown as a spectrum from a single voxel (so called single-voxel spectroscopy), or else a grid of voxels that is lower resolution than a standard MR image, typically a single slice of a 8 × 8 grid or the like, as shown in Figure 1. Spectra are collected from each voxel in the grid, and then images from peaks in the spectra can be generated.

Spectra are collected from spinning nuclei (spins), and the spectra shown in Figure 1 are from hydrogen nuclei (protons, typically surrounding water). Because water is so abundant in humans, and so visible to an MRI measurment, the majority of MRS studies have been carried out with proton spectroscopy. Fortunately, spectra can be obtained of other nuclei, and in the cancer realm those of interest include phosphorus (^{31}P), carbon (^{13}C), and fluorine (^{19}F) among others. However, these nuclei are typically at much lower concentration in vivo than water/protons, so imaging of these nuclei is difficult, and specialized hardware and software is required.

As described earlier, despite decades of searching, there is no one cancer signature on MRS or MRI. However, there are MRS findings that are more common in cancer. Elevated choline levels have been described in brain,[11] breast,[12] prostate,[13] colon,[14] and cervical cancers[15] as well as metastases.[16] Reduction of normal metabolites as normal tissue is displaced by malignant tissue is also a feature; for example, *N*-acetyl aspartate (NAA) is the most abundant amino acid in the brain, and so tumor has been associated with an elevated choline in the presence of decreased NAA (when compared with healthy brain tissue).

Examples of MRS Use in Cancer

Much of the enthusiasm for MRS comes from the broad utility of NMR. (Some five individuals have been awarded Nobel prizes for MR-related work.) NMR on ex vivo tissue can often identify clear abnormalities and separate tissue samples from malignancies from normal control. However, in vivo can be substantially more challenging, and experience varies by location and tumor type.

Brain. The brain has been the focus of most MRS research; its near-spherical shape and relative lack of motion confer technical advantages. As a result, brain cancer has been extensively studied with MRS, with most manuscripts documenting technical feasibility. More recently, single-center studies have shown that MRS can retrospectively distinguish high-grade gliomas (grade 3/4) from low-grade lesions (grade 1/2),[17] whereas other studies have investigated the value of MRS in pediatric tumors,[18] in distinguishing primary versus metastatic lesions,[19,20] MRS as a predictor of survival or progression,[21] or use of MRS to identify radiation necrosis after treatment.[22] At least one study has directly examined the diagnostic benefit of adding MRS to a standard MRI.[23] However, there is not yet a published large multicenter study demonstrating any added benefit of MRS over MRI in diagnosis or monitoring of brain cancer.

Breast. A number of single-center studies have documented that elevated choline is correlated with malignant breast cancer. The level of phosphocholine in breast cancer cells is at least an order of magnitude above that of healthy breast epithelial cells,[12] and the phosphocholine peak in the spectra of breast tissue is relatively easy to identify reliably. MRS-based measurement of water T2 has also been correlated response to neoadjuvant chemotherapy.

Prostate. Single-center studies have documented a correlation between prostate cancer grade and MRS findings.[24] Both choline elevation and more recently elevation of citrate have been identified as correlated with lesion grade.

Other. Abnormalities in MRS have also been identified in cervical, pancreatic,[25] and colon cancers,[14] as well as metastatic lymph nodes.[16]

MRS for Tracking Delivery of Drugs

Fluorine is a visible nucleus on MR, with a per nucleus sensitivity of approximately 83% compared with protons. Because fluorouracil and other chemotherapeutic agents containing fluorine are therefore visible, some investigators have sought to use MR detection of fluorine as a method to study the pharmacokinetics of chemotherapeutic agents.[26] This is technically feasible but challenging, but it can open up possibilities for noninvasive testing of certain important hypotheses. For example, the antiangiogenic agent bevacizumab combined with fluorouracil has shown efficacy in treating metastatic colon cancer, but bevacizumab alone has not shown substantial efficacy.[27] The combined efficacy therefore might be a result of synergistic killing by both

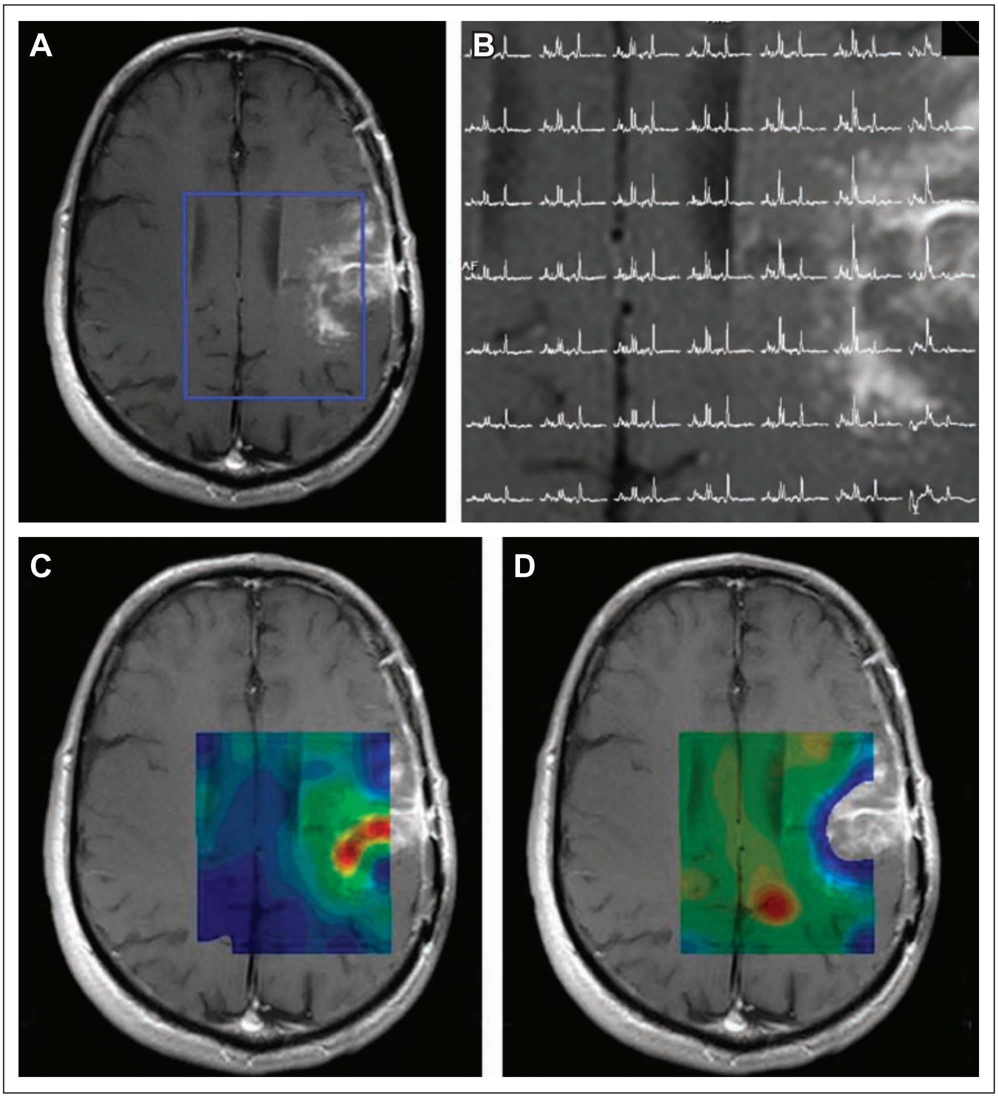

Fig 1. Magnetic resonance spectroscopy (MRS) in a 45 year-old-male with recurrent glioblastoma. (A) Box outlines the volume of tissue to be sampled. (B) A portion of the 8 × 8 grid showing individual spectra overlaying tissue. Each is representative of an approximately 1 cm × 1 cm × 1 cm cube of tissue. (C) Synthesis of the data in Figure 1B, highlighting levels of the combined creatine and choline resonances. Note that the enhancing tumor has high creatine/choline (red) compared to the remainder of the brain (blue). (D) Synthesis of the data in Figure 1B, highlighting levels of the N[r]-acetyl aspartate (NAA) resonance. The tumor has very little NAA. This pattern of low NAA in the tumor with high choline/creatine has been frequently described as associated with malignant glioma. Acquisition details: 3 Tesla MRI (Trio, Siemens Medical Solutions), 12-channel head coil, courtesy of Weiting Zhang, MGH-HST A.A. Martinos Center for Biomedical Imaging, Boston, MA.

bevacizumab (through reduction of vessels) and fluorouracil, or perhaps bevacizumab causes so-called vascular normalization[28] and is delivering its efficacy by means of improvement in the tissue delivery of fluorouracil, without any direct killing effect on its own. This mechanistic question could be sorted out in patients by measuring the delivery of fluorouracil before and after bevacizumab.

Evaluation: MRS As a Biomarker

MRS has been around for many decades, and has prima facie evidence of sensitivity to the microenvironment inside tissue. Nevertheless, as mentioned herein, the technique still is considered a prebiomarker by most investigators (ie, at the stage where agreement on technique, reproducibility, and comparability across centers is still a challenge). There are substantial challenges to performing a multicenter trial with MRS because the tremendous sensitivity that MRS possesses can be contaminated by any number of events ranging from machine imperfections to minor motion by the patient. This can quickly lead to artifacts and increased variance in the results, and this has lessened enthusiasm for MRS as a reliable cancer imaging biomarker. This is not necessarily because of any flaw in MRS; rather, it is perhaps precisely because of the tremendous flexibility and range of possibilities that has led to a lack of standardization: Each new study decides that advances in technology dictate a new approach. Fortunately, there has been a trend in recent years by equipment manufacturers and investigators alike to identify some common elements that can be part of clinical trials (while not precluding the flexibility that MRS virtuosos demand). As with any biomarker at this stage (pre-biomarker/biomarker), additional multicenter studies are needed not only to identify the precise technique to be used but to define the utility of that specific technique in a prospectively defined clinical setting.

PERFUSION MAGNETIC RESONANCE

Blood Flow and Blood Volume Measurements

Blood flow in cancer has been of interest for many years: Radiographic studies of in vivo cancer angiogenesis were published as early as 1939.[29] Increased tumor blood flow has been seen so frequently in lesions that it was only logical that MRI methods to measure tumor tissue blood flow would be sought. MRI perfusion imaging of the brain was developed in the late 1980s,[30] on the basis of the first-pass imaging of a gadolinium contrast agent and its resultant magnetic susceptibility effects on T2 and T2* as it passed through the compartmentalized brain vessels with their blood-brain barrier.

This technique, termed dynamic susceptibility contrast (DSC), demonstrated the ability to measure blood volume in brain tumors. Although its initial spread was limited by the need for high performance instruments, it is now widely available, and some 10 years ago DSC was extended to provide blood flow as well as blood volume measurements.[31,32] Numerous single center studies have documented the correlation between tumor blood volume and lesion grade in the brain.[33] A typical example is shown in Figure 2A and 2B. DSC is more difficult in other organs lacking the equivalent of a blood-brain barrier because the contrast agent is not compartmentalized to the same degree, and therefore the susceptibility effect is diminished. Dynamic imaging can still be performed, of course, as dynamic contrast-enhanced (DCE) MRI, covered elsewhere in this issue. But the liver can still show a first-pass susceptibility effect;[34] and blood pool agents could enable DSC in a wider range of organs. It appears that angiogenic vessels are often inefficient, with many blind-ending, irregular vessels, and therefore blood volume is often increased in tumors in which blood flow is not (perhaps somewhat like a slow-moving stream or swamp, rather than a fast-moving river). The full relationship between tumor blood flow and tumor blood volume (and their quotients, perfusion efficiency and mean transit time) is still an active area of research, but very well may be a sensitive way of determining the effect of antiangiogenic agents.

Vessel Size

A unique feature of DSC MRI is sensitivity to the size of the vessel containing the contrast agent, with spin-echo imaging and gradient-echo imaging showing sensitivity to capillary-sized vessels versus all vessels, respectively. This can be exploited to potentially map the size of vessels in a voxel, as shown in Figure 2D, and

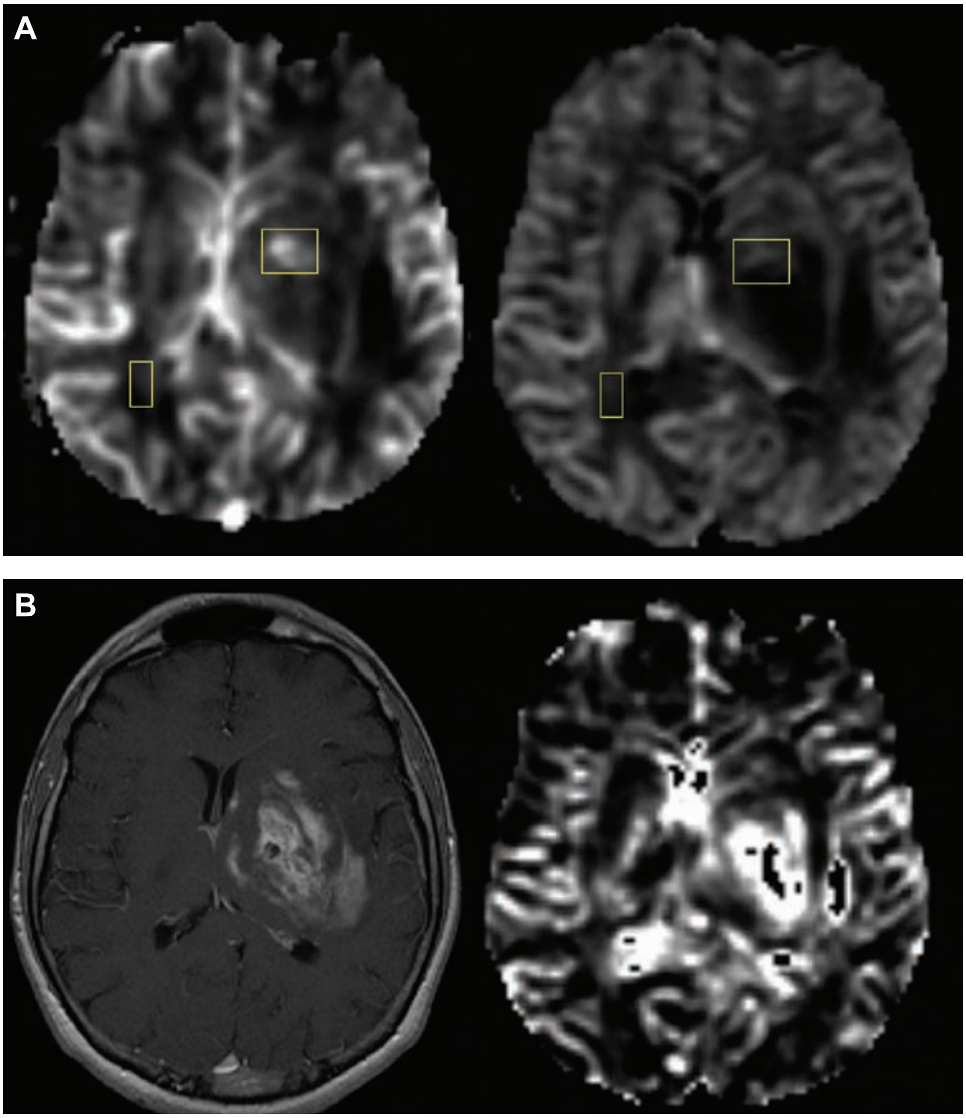

Fig 2. (A, B) Dynamic susceptibility contrast (DSC) of a patient with pilocytic astrocytoma. (A) Gradient echo-planar-imaging (EPI)–based cerebral blood volume (CBV) map; (B) spin echo EPI-based CBV map; (C) postcontrast T1-weighted image; (D) average vessel sizes based on the simultaneously acquired GE and SE EPI DSC data. Figure 2 courtesy of Melina Pescitides, MGH-HST A.A. Martinos Center for Biomedical Imaging, Boston, MA.

preliminary data in animals[35,36] and humans[37] suggest that this may represent a further opportunity for characterization of changing vessel size with antiangiogenic therapy.

Permeability Measurements

The same injection of contrast can be used to measure not just blood flow and volume, but also breakdown of the blood-brain barrier. The intact blood-brain barrier is not usually permeable to gadolinium contrast agents, and so as the contrast leaks across, this causes an increase in signal, which can be quantified. The signal change is typically mathematically described as the product of permeability and capillary surface area. Although this technique has the advantage of being provided at the same time (in the brain, at least) as DSC MRI, it has not been nearly as widely studied as DCE MRI. Like DCE, DSC-based permeability may change with effects on the vasculature such as from antiangiogenic agents, and as with DCE,[38] one might consider using this effect for dose finding. However, given the inconsistent results with DCE as a biomarker for antiangiogenic drug efficacy (eg, where the dose selected for a drug using DCE did not show a progression-free survival advantage per central review in phase III[39]), permeability with DSC may also be limited in its utility to dose-ranging.

Evaluation of Perfusion MR As a Biomarker

Because brain tumors are relatively uncommon, perfusion with DSC remains an off-label use of gadolinium contrast agents in the United States (although not in Europe). No multicenter trials have been published, although some are in planning or execution stages. On the other hand, there is much more uniformity in acquisition of DSC compared with MRS (or DCE) approaches, and therefore, while DSC MRI is firmly in the pre-biomarker stage, this may be more easily rectifiable.

DIFFUSION MAGNETIC RESONANCE

Apparent Diffusion Coefficient Measurement

The diffusion or microscopic movement of water (on the range of 10 to 50 μ) can now be routinely quantitatively measured with MRI.[40] The has become a mainstay in the imaging of acute ischemic stroke because it is highly sensitive to early tissue damage, before most other imaging approaches show abnormalities.[41] The diffusion coefficient (called the apparent diffusion coefficient [ADC] in recognition that forces other than random diffusion may influence water mobility) reported by most MRI systems is an average of the water mobility in all directions. Tumors pretreatment do not show much water restriction compared with normal tissue, and single-center studies of brain tumor grade and ADC have shown only weak correlations.[42] More recently, some investigators have proposed using whole-body diffusion imaging to identify the somewhat lower diffusion coefficient that some cancers (especially lymphomas) have than other tissues, in a type of image reminiscent of positron emission tomography (PET) images.

Although ADC does not appear to have high diagnostic discriminatory power, some investigators have begun to investigate diffusion as a marker for treatment effect. This has been proposed for acquisition in the days after chemotherapy, with the idea that changes in water mobility may represent early tissue damage.[43] In early ischemia, water is restricted, and then with necrosis, the water becomes more mobile, typically 3 to 7 days after ictus.[44] It is this more mobile phase that investigators have sought to use as a marker for early cytotoxic effects.

Diffusion Tensor Imaging

Diffusion is not the same in all directions, and more complex sampling and measurement approaches can be taken, such as diffusion tensor imaging (DTI)[45] or diffusion spectrum imaging (DSI).[46] These can show tissue microarchitecture, and a number of groups have demonstrated the utility of tissue visualization before cancer surgery,[47] or in treatment planning, such as shown in Figure 3. DTI or DSI may be useful in probing treatment effects in such architecture, such as the changes in white matter after whole-brain radiation.[48] These techniques are still in their early stages of development.

None of these uses of ADC as a cancer imaging biomarker have been tested in any formal setting, and therefore ADC is a pre-biomarker. Fortunately, there is widespread agreement about how to

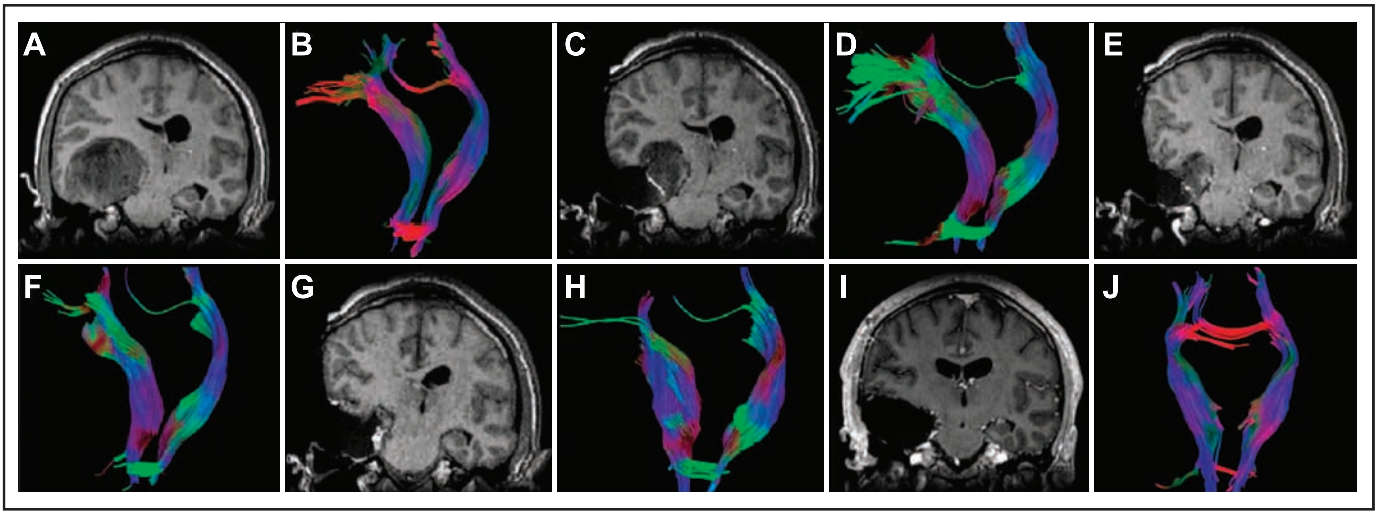

Fig 3. Diffusion tensor imaging highlighting the displacement of white matter fibers away from a mass obtained intraoperatively in a right temporal oligoastrocytoma WHO grade 3 in a 29 year old male patient. (A, C, E, G, I) T1-weigthed coronal MRI scans obtained intraoperatively; (B, D, F, J) tractography of the pyramidal tracts. (A, B) preoperative; (C, D-H) during tumor research with G and H after completed tumor removal; (I, J) 3 months after surgery. Red, right/left direction of fibers; green, anterior/posterior; blue, superior-inferior. The color code for the intraoperatively obtained tractograms (D, F, H) has right/left and anterior-posterior switched because of the horizontal placement of the head for surgery. Adapted with permission.[47]

acquire ADC data and even fairly wide agreement about how to acquire diffusion tensor imaging, and so this is a tool that may well soon be in biomarker status and perhaps move beyond.

CONTRAST AGENTS

A comprehensive review of MR contrast agents in cancer is beyond the scope of this article, and there are other excellent reviews of this topic.[49,50] From the human perspective, however, this can be quickly summarized: There are no MR contrast agents specifically on the market for cancer in the United States. In brief, this area is challenging; because these agents are typically administered intravenously, they are regulated as drugs, with the same challenging regulatory environment and costly path and investor demands. As a result, although there are a number of MR contrast agents in development both commercially and at academic centers, only a few of these are seeking direct approval for cancer imaging, and none yet have been successful. The new exploratory investigational new drug (IND) may be useful for testing new contrast agents,[51] but the later costs and final regulatory hurdles facing imaging drug developers are still substantial.[52] As an example, one agent that has been the subject of a recent US Food and Drug Administration Advisory Committee meeting[53] is ferumoxtran-10, an iron-based T2 agent that is collected in normal lymph nodes but excluded from metastatic nodes, as shown in Figure 4. Although a single-center study showed evidence of efficacy, the overall application was not considered robust enough for the Advisory Committee to recommend approval.

Nevertheless, enthusiasm for these agents remains high given how widely available MRI is. In thinking about the possible types of contrast agent, one might begin by considering what signal changes the reporter molecules can cause. There are two broad types of signal modification that MR contrast agents typically can exert: shortening of T2, typically causing signal dropout, so-called dark contrast, or shortening of T1, causing increased signal, or bright contrast. Prototypically, iron chelates cause darker signal, whereas gadolinium-based agents cause brightening (though there are exceptions to this rule). A new class of agents, so-called chemical exchange saturation transfer (CEST) agents,[54] use neither and have been designed to have the capacity to be turned off and on inside the MR scanner, and may provide even further flexibility in using MRI to probe events in vivo.

Another productive way to think about contrast agents is by the type of event they should signal. Agents have been designed with a variety of properties. Properties that might be favorable to cancer imaging range from receptor-specific agents to blood-pool agents (agents that remain solely in the blood) to apoptosis-imaging agents. Developers have been surprisingly innovative in finding ways to overcome the basic sensitivity challenges of MRI (gadolinium contrast agents typically must be present at about 100

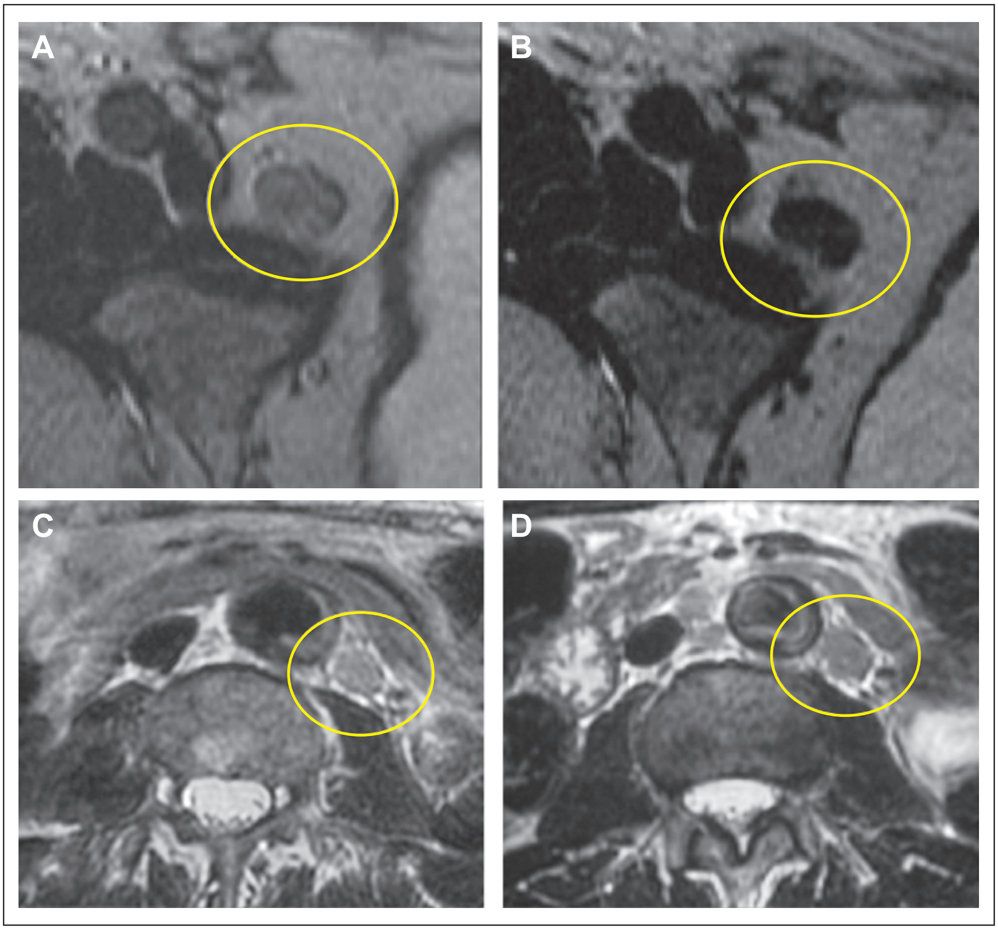

Fig 4. Ferumoxtran-10 imaging of benign lymph node (top) and malignant lymph node (bottom). On each row, the image on the left is the precontrast image, and the image on the right is the postcontrast image 24 to 36 hours later. In the top row, note that the lymph node (circled) becomes much darker as the iron-containing agent is accumulated. On the bottom row, the node does not collect any iron, indicating replacement of normal parenchymal by metastatic tumor. Courtesy of Mukesh Harisinghani, MGH.

μM concentration to be visible, much higher than with nuclear medicine techniques).

Although this is an extremely rich area, with many opportunities, no MR contrast agent is specifically approved for cancer imaging, and therefore all of these agents are pre-biomarkers.

OTHER TECHNIQUES

MRI is a rich and innovative modality, and new approaches for cancer imaging with MR are being proposed and evaluated constantly. A few that are so early as to definitely be pre-biomarkers are discussed now, not out of any attempt to be complete but rather to further illustrate the diversity of techniques.

Vessel Tortuosity Measured With MR Angiography

Some investigators have noticed that the arteries feeding a tumor are often abnormal in appearance, and have begun to quantify this tortuosity.[55] They have identified highly torruous vessels as belonging to more malignant lesions, and have proposed that some part of the angiogenic process leads to macroscopically as well as microscopically abnormal vessels. Although such changes typically would be noticed only well after a mass was present as well, it might be feasible to use these tortuosity measures as a biomarker for treatment effect if they do in fact change after effective therapy.

Elastography With Magnetic Resonance

More than a decade ago, investigators found a way to use MRI to visualize how elastic or stiff tissue is.[56] Physicians have known for millennia that tumors are often hard on palpation; this MR approach is an attempt to quantify this sense of firmness. This has been most actively applied in breast cancer, where palpation has long been a mainstay of diagnosis, not in an attempt to replace palpation but rather to serve as an aid to characterization of lesions. The basic approach is to generate acoustic waves in the organ of interest and to use MR to image the propagation of these waves, and then to analyze tissue stiffness on the basis of how these waves interfere with local tissue.

Combined MR and PET

The striking success of combining computed tomography (CT) and PET together into PET-CT scanners has surprised most observers: It has been estimated that more than 90% of new PET systems installed are now PET-CT systems. At least one manufacturer has announced plans to integrate a PET detector system directly inside the bore of an MR system and allow for true simultaneous imaging.[57] The clinical demands for this are varied, but oncology applications are likely to be strongest in the pelvis, where CT has difficulty distinguishing among tissues and PET can show high glucose utilization in a number of normal structures such as bowel or ovary. These systems are still not yet on the market. The ability to combine the functional capability and sensitivity of PET with the anatomic and functional imaging abilities of MR will need careful evaluation to identify true diagnostic benefit rather than just convenience.

Hyperpolarized ^{13}C MR

Although formally this innovation might best fall under the contrast agent topic above, it is unusual enough to deserve separate mention. While ^{13}C is in theory easily seen, in practice it is so rare that imaging of ^{13}C in vivo is essentially impossible unless special measures are taken. One such measure is called hyperpolarization. In this approach, rather than using the large magnetic field of the primary magnet in the MRI system (eg, at 1.5 or 3.0 Tesla) to polarize nuclei, the nucleus of interest is treated with special tools (such as a laser-based system or a system kept at near absolute zero) to hyperpolarize a substantial number of spins.[58] With the regular MRI system, perhaps one spin in a million is polarized, whereas with the hyperpolarization approach, half or more are polarized by the specific special tools—improving signal by some five to six orders of magnitude, and making some moieties visible that would have been impossible to detect in vivo otherwise. With further effort, this hyperpolarization can be transferred to carbon-based compounds of biologic interest, such as lactate, and imaged although only for a few seconds before the signal decays away. This is still some years away from human use, but the ability to image specific carbon-based molecules that are chemically identical to those in the body except for containing ^{13}C instead of carbon-12 could be extremely useful in cancer imaging.

SUMMARY

MR is a wide-ranging modality. Although its anatomic depictions are widely used for traditional cancer imaging needs such as volumetric assessment, its true power as a cancer imaging biomarker may come from the more physiologic and functional abilities it contains. Further effort is needed to advance the most promising of the techniques from the pre-biomarker stage into later stages with more clearly established utility. If this is done, these imaging tools could more fully realize their potential to reduce morbidity and mortality from cancer.

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Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.