

Minireview

Functional Magnetic Resonance Imaging in Oncology for Diagnosis and Therapy Monitoring

Michael V. Knopp,¹ Hendrik von Tengg-Koblighk, and Peter L. Choyke

The Ohio State University, Department of Radiology, Columbus, Ohio 43210-1228 [M. V. K., H. v. T.-K.], and NIH, Clinical Center, Diagnostic Radiology Department, Bethesda, Maryland 20892-1182 [M. V. K., P. L. C.]

Abstract

Functional magnetic resonance imaging is rapidly evolving as a capable noninvasive assessment tool for oncology to improve diagnosis and to monitor therapy. Current clinical techniques are based on microcirculation imaging using extracellular low molecular weight contrast agents such as gadopentetate dimeglumine and analogues. The temporal evolution of the enhancement visualizes the angiogenic properties of lesions with regard to vascular density and permeability, heterogeneity, and changes during therapy.

Introduction

Noninvasive imaging of therapy response and diagnosis in oncology has been focused on morphological assessment up to now. Despite its limitation and challenges, it is still the basis for ongoing diagnostic and therapeutic classifications (1). The limitation of morphological assessment is well documented, and it has already been shown that changes in metabolism and perfusion, for example, occur before morphological changes (2–4). MRI² has introduced many tools for oncology to improve morphological evaluation and recently added capabilities for functional characterization of lesions (5–14). Therapeutic options today are broadened to encompass multimodality and multidrug regimens as well as very targeted approaches such as antiangiogenic, cytostatic therapies. Therefore, early and reliable assessment of functional properties of lesions has become a necessity to correctly diagnose, differentiate, and guide therapy.

First of all, MRI enables a true three-dimensional delineation of lesions. Implementing distinctly different imaging sequences already allows a considerable tissue characterization regarding its proton/water or fatty tissue content. Whereas continuous improvements in image quality have

been achieved in MRI in the recent years, the major advance for oncologic applications is the clinical implementation of functional assessment techniques that provide additional information on top of morphology. The greatest clinical utility in MRI has been demonstrated for DCE-MRI. This technique allows the noninvasive assessment of microcirculatory characteristics of lesions.

The DCE-MRI methodology is based on the rapid diffusion of a small contrasting molecule such as a Gd-chelate complex (Gd-DTPA) to visualize neoangiogenic induced vascular changes. Correlative work has demonstrated that the signal intensity relates to the vascular density within the lesion and that the rate of enhancement characterizes the vascular fenestration and functional permeability (8, 15, 16). The interstitial environment further influences the diffusibility and temporary retention of the contrast agent.

Whereas this technique was initially used to characterize the angiogenic/microcirculatory properties of a lesion, it was shown to be a very robust technique to monitor changes during and after therapeutic interventions. Several studies have used DCE-MRI for monitoring chemotherapy as well as radiation therapy, and more recent applications are monitoring experimental immunogenic or antiangiogenic therapies.

Other imaging methodologies are available to assess angiogenesis such as positron emission tomography, radionuclide studies, contrast-enhanced and Doppler ultrasound, X-ray contrast-enhanced dynamic computed tomography, and optical imaging. The strength of MRI is the true three-dimensional imaging of large volumes in a highly standardized, readily available, and safe manner.

Technical and Pathophysiological Considerations

The technical requirements of this technique can be satisfied on current clinical 1.5 T MR systems if a highly standardized and integrated imaging/assessment approach is implemented. The essential components are as follows: (a) a dedicated, standardized imaging protocol encompassing optimized sequence and contrast delivery approaches; (b) rapid image transfer via picture archiving and communication system (PACS) network; (c) accessible post processing, preferably within a PC environment; (d) validated visualization and quantification methodology; and (e) well-trained, dedicated staff support. The technical details have been summarized recently (6).

DCE-MRI leads after post processing to a time-intensity plot that reflects the passage of the contrast agent within the target tissue. The contrast agent can be considered a “probe” that arrives via the vascular system, first mapping out its extent and then providing information about its leakiness as it diffuses into the extracellular space. By its interaction with the extracellular

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¹ To whom requests for reprints should be addressed, at Department of Radiology, The Ohio State University, University Hospitals, 163 Means Hall, 1654 Upham Drive, Columbus, OH 43210-1228. Phone: (614) 293-9227; Fax: (614) 866-9501; E-mail: Knopp-1@medctr.osu.edu.

² The abbreviations used are: MRI, magnetic resonance imaging; DCE, dynamic contrast-enhanced; Gd, gadolinium; Gd-DTPA, gadopentetate dimeglumine; MR, magnetic resonance; ROI, region of interest; IDC, invasive ductal carcinoma; VEGF, vascular endothelial growth factor.

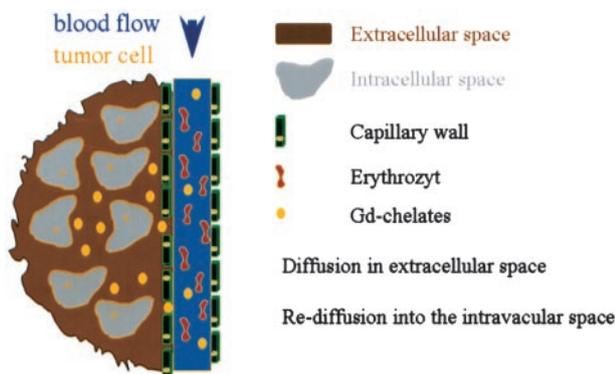


Fig. 1. Schematic pathway of i.v. injected extracellular contrast agent (e.g., Gd-GDTPA) of low molecular weight through malignant tissue. The altered capillary wall allows the contrast molecules to easily diffuse rapidly into the extracellular space (wash-in) during the first pass and subsequently re-diffuse back into the intravascular space (wash-out). The amount of temporary trapping of the contrast agent is dependent on endothelial changes and the interstitial environment.

environment, the probe can be temporarily trapped or will diffuse back into the vascular bed (Fig. 1).

We have implemented a well-established, pharmacokinetic, two-compartment model to derive quantitative information from the contrast passage. This quantitative information obtained from every voxel of the data set is encoded with a simple 16-color scheme to overlay this information on top of the morphological image. Whereas this approach allows a visual assessment and detection of suspicious regions, a detailed analysis requires placement of a ROI that enables the creation of time-intensity curves.

Several groups have demonstrated the clinical utility of this approach, but its implementation into clinical work has been hampered by lack of computing resources, standardization, and specially trained technologists to facilitate post processing. Dynamic acquisition leads to a large number of images (frequently more than 800) that cannot be reviewed using conventional approaches. The contrast enhancement within a cross-section can be viewed as a cinematic display of the sequential images and mapped as overview/summation images using quantification techniques.

A challenging aspect in quantification is the positioning of the ROI, for which a wide variety of approaches can be used. An overall placed ROI allows an estimation of the global

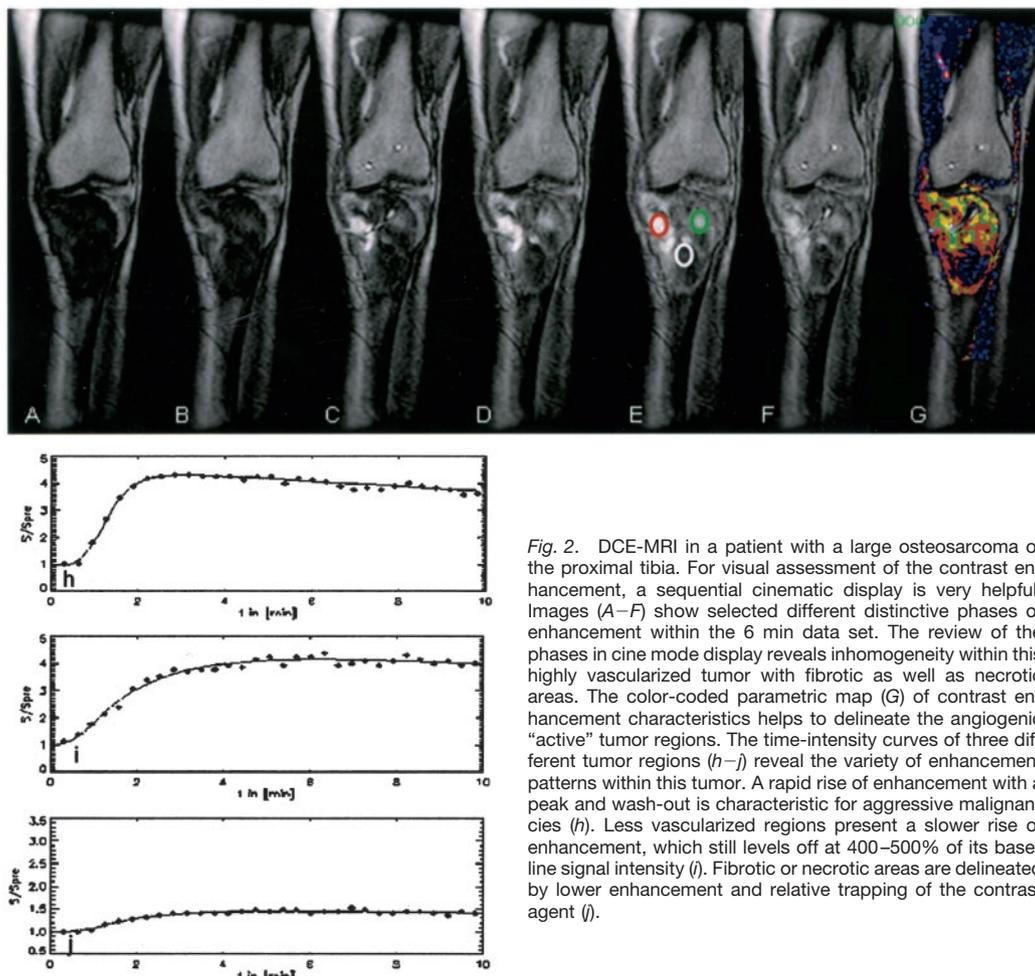


Fig. 2. DCE-MRI in a patient with a large osteosarcoma of the proximal tibia. For visual assessment of the contrast enhancement, a sequential cinematic display is very helpful. Images (A–F) show selected different distinctive phases of enhancement within the 6 min data set. The review of the phases in cine mode display reveals inhomogeneity within this highly vascularized tumor with fibrotic as well as necrotic areas. The color-coded parametric map (G) of contrast enhancement characteristics helps to delineate the angiogenic “active” tumor regions. The time-intensity curves of three different tumor regions (h–j) reveal the variety of enhancement patterns within this tumor. A rapid rise of enhancement with a peak and wash-out is characteristic for aggressive malignancies (h). Less vascularized regions present a slower rise of enhancement, which still levels off at 400–500% of its baseline signal intensity (i). Fibrotic or necrotic areas are delineated by lower enhancement and relative trapping of the contrast agent (j).

aspects of a lesion, but its characteristics can be disguised due to inhomogeneities within the lesion as well as the inclusion of larger vascular structures (Fig. 2) and tumor heterogeneity. Similar to the assessment of vessels within a histological cross-section, hot regions can be identified by the mapping technique to find the areas for analysis. Based on practical considerations, we have implemented the approach of using color-coded summation and projection images to detect the relevant areas of interest. We also use a cinematic movie display to verify distinct regions and differentiate those from larger vascular structures or artifacts. Statistical approaches that look at the percentile characteristics within regions are also frequently used.

Currently, nearly all clinical studies performed with DCE-MRI are using Gd-DTPA or analogue complexes. These substances reveal no substantial differences regarding their enhancement characteristics. However, MRI contrast agents are evolving into two different directions: (a) those agents with some tissue-specific uptake, for example, such as within the reticuloendothelial system; and (b) those agents with improved vascular enhancement characteristics due to increased relaxivity by protein interaction, higher molarity, or larger complexes either as macromolecules or (ultra) small particles of iron oxides (17). These agents reveal different

contrast enhancement characteristics due to their nature (metal ion), size, or interaction.

The current contrast agents are very safe and reveal no nephrotoxicity in the applied doses (18, 19). Current challenges in the development of new targeted oncological agents are safety considerations and the long regulatory approval process (20).

Future ongoing developments aim at designing targeted agents that are capable of visualizing distinct molecular pathways, but currently, radionuclide techniques offer a higher sensitivity for those more targeted agents.

Many different approaches can be proposed using new contrast agents and special imaging techniques (21), but the clinical basis of functional MRI in oncology today is the use of low molecular weight, diffusible, extracellular Gd-chelates (Gd-DTPA and derivatives) imaged using fast, high-resolution T1-weighted sequences covering large volumes of interest.

Functional MRI for Diagnosis

The additional information provided by functional MRI is the visualization of the angiogenic induced vascular properties of lesions. Angiogenesis by itself is not a malignant tumor-

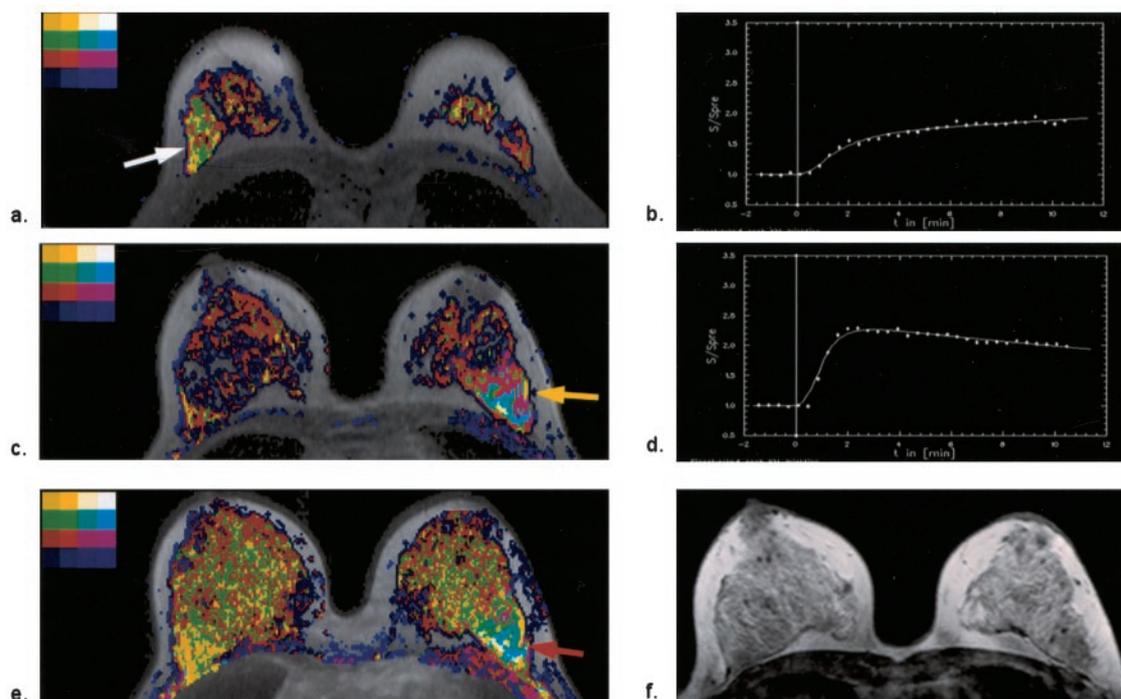


Fig. 3. Clinical presentation of a functional MR mammography study using DCE-MRI to differentiate lesions. Color-coded maps analyzed with a pharmacokinetic two-compartment model have been overlaid on top of the morphological images showing strong enhancement within the whole breast tissue, but with different characteristics demarcating a highly angiogenic lesion. The time-intensity curve of the right lesion (a, white arrow) demonstrates a slow and (b) moderate-intense enhancement with no peak and a continuous wash-in. This is characteristic for benign angiogenic processes such as fibrocystic disease, which was histologically confirmed as proliferative mastopathy. The left breast lesion (c, yellow arrow) reveals a time-intensity curve with a rapid enhancement (d), an early peak and wash-out (d), which is typical for highly angiogenic tumor and was confirmed to be IDC. The cranial-caudal summation image reveals the extent of the carcinoma (red arrow) in the outer left quadrant (e). This could not be differentiated in a static contrast enhanced image (f).

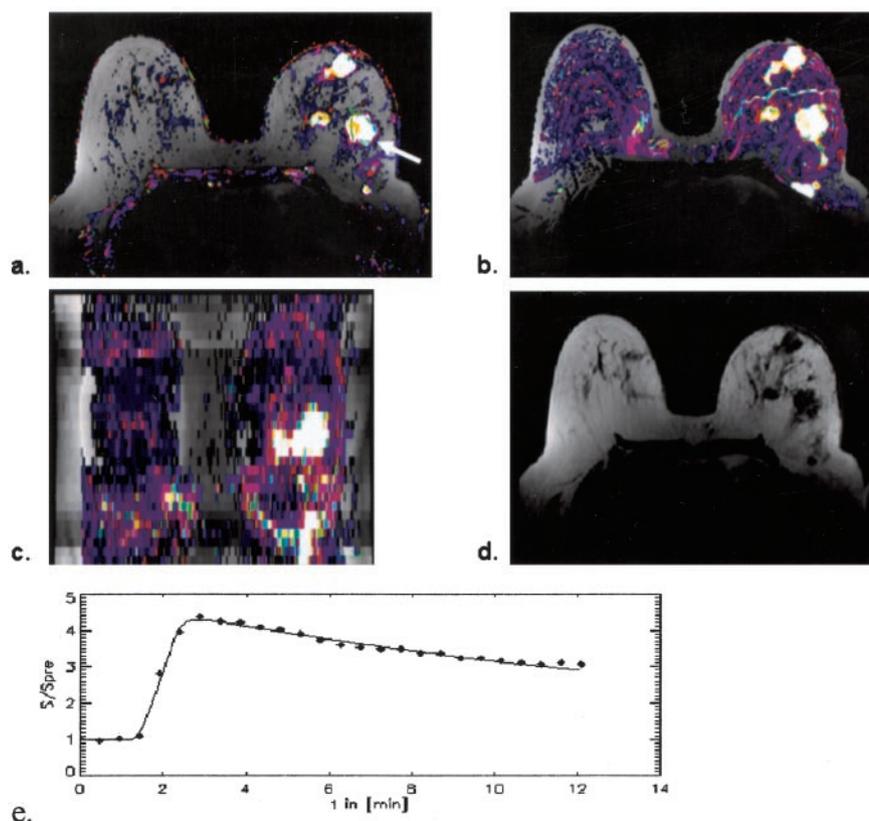


Fig. 4. Color-coded pharmacokinetic mapping of the enhancement characteristics after DCE-MRI in a patient with multifocal IDC. The contrast media were administered using a slow infusion rate of a constant 60-s duration with a dosage of 0.1 mmol/kg body weight. The multiple lesions are clearly identified on the color-coded summation image (a). Maximum intensity projection images in the cranial-caudal (b) and in the frontal view (c) demonstrate the extensive invasion and multifocality of the tumor in the left breast as well as adenopathy. The cine mode display enables a dynamic evaluation of the contrast enhancement characteristics (d). The time-intensity curve is obtained from the main lesion (white arrow) and presents a rapid signal increase to a high peak followed by a typical wash-out (e).

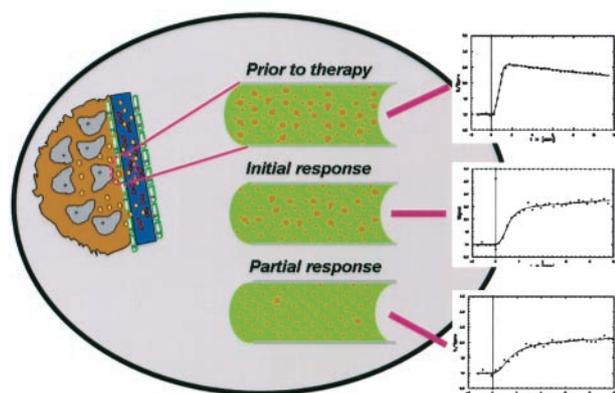


Fig. 5. Schematic of the angiogenic effects of therapy response relevant for functional imaging with low molecular weight Gd-chelate contrast agents. During successful therapy, the number of fast, leaky components of the vascular wall decreases, which leads to a slower rise of contrast enhancement. Continued successful treatment leads to a decreased maximum signal intensity (SI) within the up slope of contrast enhancement, indicating a regression of the tumor angiogenic properties. Simultaneously, the re-diffusion is slower, and due to fibrosis and other therapeutic effects, a temporary trapping (wash-in) can be noted.

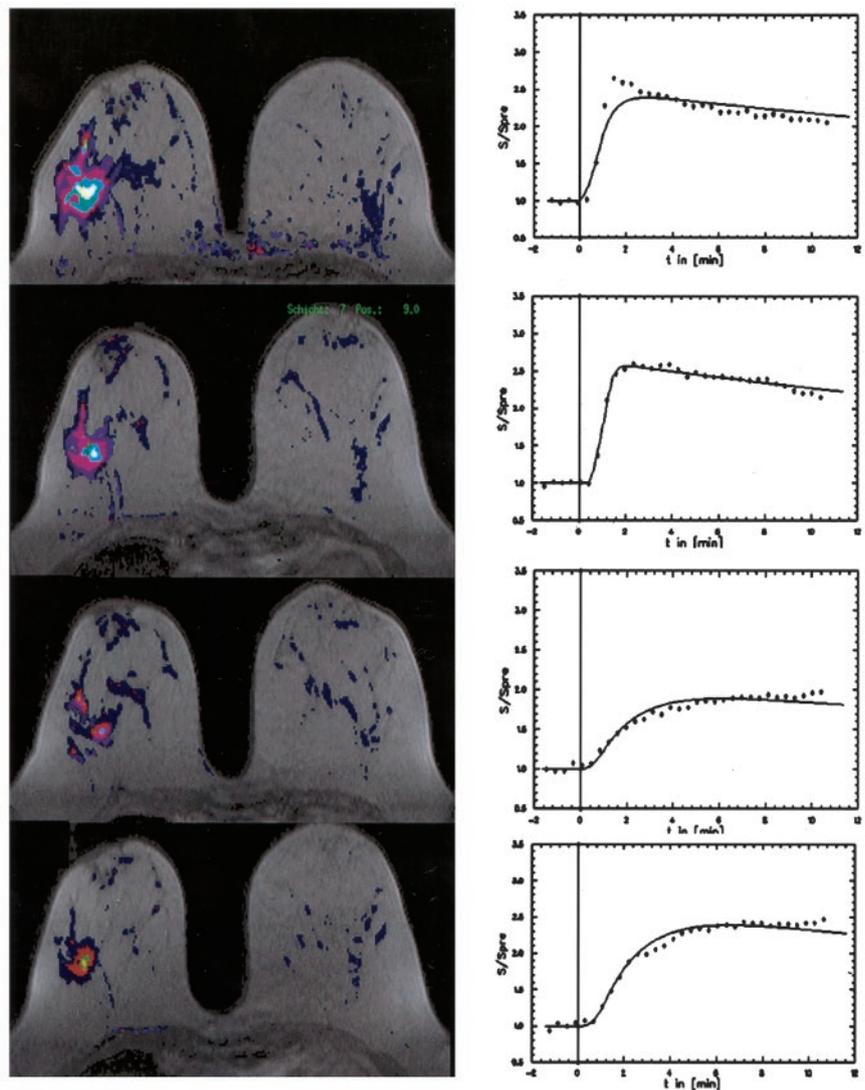
specific process (4), but malignancies have quite distinct angiogenic features that can be detected by the passage of the contrast agent. One of the early applications of DCE-MR was MR mammography (22–24), which, after initial, very encouraging observations with excellent sensitivity (>95%) and specificity (>90%), was found to lead to low specificities

(>50%) in larger patient populations. This discrepancy was due to the underlying pathophysiology. Whereas the contrast enhancement by itself is nonspecific because it reflects the “uptake” and distribution of a diffusible tracer, differences in vascular properties can only be detected if appropriate imaging and post processing approaches are used. Fig. 3 shows the time-intensity curves of two different enhancing lesions within the breast tissue that have similar overall signal intensities of enhancement. This would be the only criteria using static imaging techniques, but by the temporal resolved functional assessment, distinct differences in the enhancement patterns are revealed that reflect the true pathophysiological angiogenic differences between both lesions. The IDC is characterized by a rapid enhancement toward a maximum peak level followed by a subsequent “wash-out,” whereas the benign, fibrocystic (mastopathic) area reveals a slower rate of enhancement with a continuous “wash-in.” This comparison exemplifies that no difference would have been detected by a purely static analysis.

The same approach is used in monitoring therapy by assessing the changes in the time-intensity curves as well as its regional distribution within a lesion.

Current applications have been demonstrated in a wide variety of clinical areas. Stationery organ systems can be imaged more readily such as the central nervous system (25), bone marrow (26), the musculoskeletal system (27, 28), the breast (8, 29), and pelvic regions (7, 9, 30, 31). Imaging of moving organs such as the lung, liver, and kidney can be burdened by motion-induced artifacts. Advanced image

Fig. 6. Therapy monitoring of neoadjuvant chemotherapy in a patient with an IDC that was classified as a partial response. Although there was substantial tumor volume reduction, strong contrast enhancement remained, indicating that the therapeutic regimen was not yet successful in completely destroying the malignancy. After the first cycle, only moderate effects were observed with a nearly unchanged time-intensity curve. After the second cycle, a substantial decrease in the rate of enhancement is noted, which remained fairly unchanged to the final follow-up. In histology, residual tumor clusters were found surrounded by reactive tissue changes and fibrosis.



processing techniques can correct for motion and distortion artifacts and will enable quantitative assessment within moving organs. Most developments and initial clinical experiences have been demonstrated by expert groups, and broad multicenter evaluations have been still fairly limited. Although overwhelming evidence can be found on the utility of DCE-MRI in the literature, the lack of standardized methodology has been a tremendous hindrance for implementation in nonexpert sides.

One of the strong indications for DCE-MRI in the breast is the assessment of multifocal malignancy (Fig. 4). DCE-MRI can provide the diagnostic radiologist with functional information that facilitates evaluation of the total extent of the disease, improving diagnostic accuracy and confidence.

One of the very powerful aspects of this technique is the visualization of the heterogeneity in angiogenic properties within an individual tumor (Fig. 2). Our knowledge regarding the relevance of lesion heterogeneity is continuously increasing,

and it becomes obvious that noninvasive *in vivo* assessment is preferential. Lesion heterogeneity is also of crucial importance in the assessment of therapy response. Whereas therapy might be able to reduce the bulk of the tumor burden, small regions of the tumor might not respond to ongoing therapy, and the assessment using morphological criteria would be misguided. This is currently found in many clinical examples within therapy monitoring trials, and it becomes evident that this information will have substantial impact on patient management in individualized therapies.

Using the interactive capabilities of workstations and the extensive information available within the data set, a “virtual biopsy” can be envisioned by identifying areas to be characterized based on their enhancement characteristics and can even be combined with methods of artificial intelligence.

The diagnostic validity of functional MRI depends strongly on the methodological implementation and the specific tumor entity or population studied. Overall, this methodology

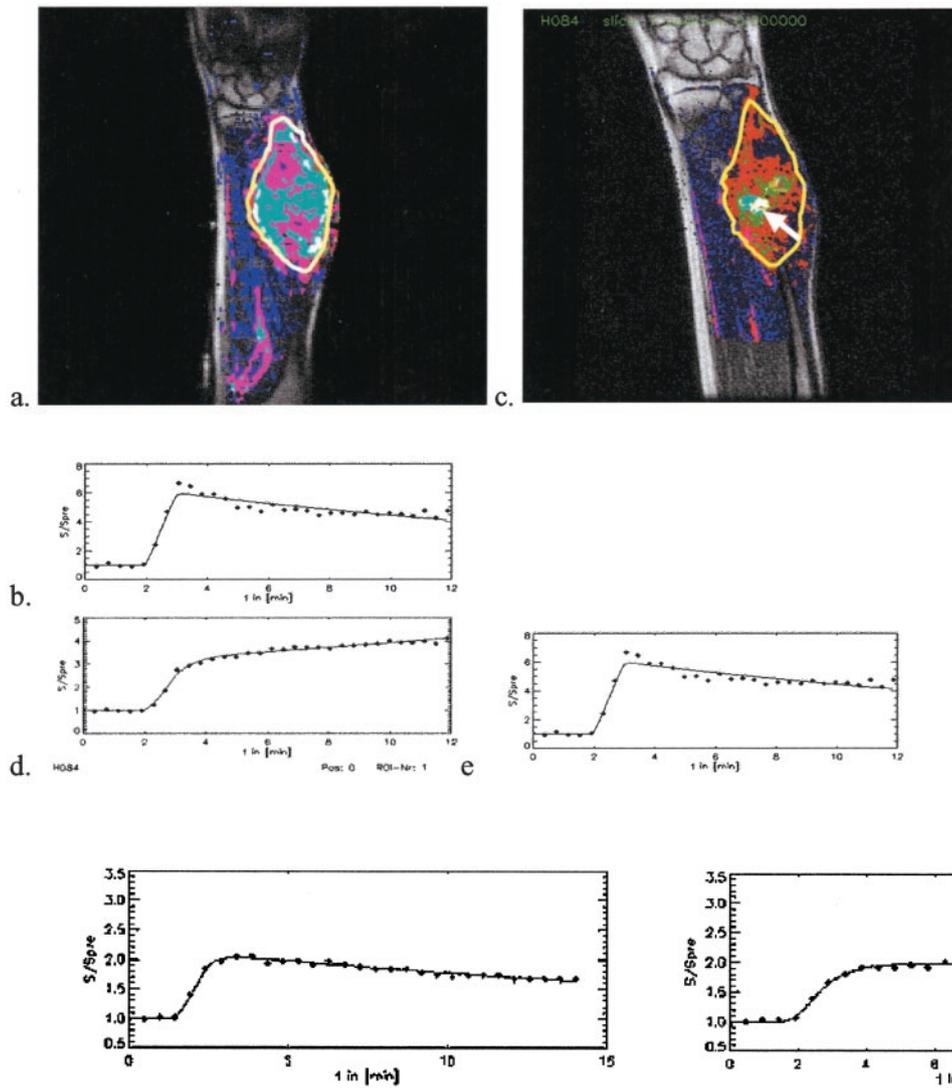


Fig. 7. Monitoring neoadjuvant chemotherapy with functional MRI in a young patient with an osteosarcoma of the lower arm. After a color-coded mapping of the entire tumor region and placement of a ROI over the total tumor area, the time-intensity curve shows a fast wash-in followed by a peak signal intensity with a subsequent rapid wash-out that is characteristic for malignant, highly permeable tumor vessels (a and b). After chemotherapy, the color-coded map presents a heterogeneous appearance of contrast enhancement with hot spots (c, white and green areas). The overall contrast enhancement pattern of the tumor shows a slower uptake and a subsequent trapping of contrast agent within the tumor tissue (d). Further detailed functional analysis of different tumor areas confirms the existence of vascularized active tumor areas (white arrow) with an enhancement pattern similar to that seen for the total tumor area before chemotherapy (e).

Fig. 8. Monitoring of an experimental antiangiogenic (anti-VEGF) therapy in a patient with inflammatory breast cancer in an ongoing trial. This is a follow-up after an initial cycle. The time-intensity curve on the left shows the contrast enhancement pattern within the tumor before therapy, and on the time-intensity curve on the right shows the contrast enhancement pattern within the tumor after one anti-VEGF cycle. The therapeutic concept is that it should lead to a decrease in the vascular leakiness as a therapeutic effect. As explained above, the rate of enhancement reflects the leakiness for the Gd-chelate contrast agent. We observed in this case a substantial decrease in the permeability (exchange) rate k_{ep} from 2.6 to 1.2 min^{-1} , whereas the intensity (amplitude) of enhancement remained nearly unchanged with 1.1 to 1.0 arbitrary units. We interpret this finding that antiangiogenic therapy led to a substantial reduction in leakiness, whereas the extent of vasculature remained unchanged during the first treatment cycle. The decrease in wash-out is also consistent with a reversal of the tumor angiogenesis factors induced increased permeability.

has a very high sensitivity in detecting invasive malignant tumors that have up-regulated angiogenic properties.

Functional MRI for Monitoring Therapy

Cytotoxic therapy leads to many different ongoing effects that coincide with direct or indirect angiogenic changes (32–34). As therapy interacts with tumor tissue, it leads to a reduction of interstitial pressure, expression of angiogenic factors, and change in metabolism. Initial clinical studies monitoring neoadjuvant chemotherapy in breast cancer revealed that changes in the time-intensity curve occur even before morphological changes (14). It was recognized that successful therapy resembles a reversal of the angiogenic

characteristics of contrast enhancement toward more benign patterns (8).

The current understanding of therapy effects on the contrast enhancement kinetics can be summarized as shown below.

Response to therapy leads to a decrease in vascular permeability of the neoangiogenic vessels that is reflected by a decrease in the rate of enhancement. Subsequently, a reduction of the vascular density within the region can lead to a decrease of the overall signal intensity. Due to the ongoing repair mechanisms within the treated tissue, changed contrast agent interaction within the interstitial space can be noted with reduced diffusibility that in turn results in a wash-in or accumulation pattern of enhancement. This con-

cept is demonstrated in Fig. 5, where the functional changes in the vascular fenestration lead to changes in the time-intensity curve from a rapid rise and wash-out to a slow rise and wash-in.

Two case studies have been selected (Figs. 6 and 7) to demonstrate the characteristics of this approach in a breast cancer patient receiving neoadjuvant chemotherapy and a juvenile patient with an osteosarcoma.

Radiation therapy causes different biological effects that initially induce angiogenic response during the early phase of therapy followed by a regression in the later stages of radiation therapy (31, 35–38).

Noninvasive imaging is also an essential tool for assessing *in vivo* effects of antiangiogenic therapy. Recent and ongoing clinical trials are using imaging methodologies to demonstrate the capabilities of imaging-based assessment, provided that appropriate imaging methodology was used. The capabilities can be nicely demonstrated in a case within an ongoing trial where a single therapy cycle of an anti-VEGF agent led to a distinct decrease in the permeability rate while showing no effects on the overall contrast enhancement (Fig. 8).

The capabilities of DCE-MRI for diagnosis and monitoring therapy can be identified as follows: noninvasive, true three-dimensional visualization of the extent of a lesion and its angiogenic properties; visualization of lesion heterogeneity and inhomogeneity; improved detectability of lesions; improved discrimination of benign to malignant tumors; detectability of changes in angiogenic properties before morphological alterations; potentially predictive indicator for overall response during therapy; and a robust, readily available methodology that can be integrated within standard imaging protocols.

Outlook

MRI is currently a strong evolving methodology for oncologic applications. Today, standardization and multicenter validation of implemented methodologies are necessary to facilitate wide applications outside of expert institutions within the clinical environment. A distinct strength of this methodology is that it can be readily implemented within standard clinical MRI systems currently performed only to assess morphology.

Advanced contrast agents have the potential to improve diagnostic accuracy as well as imaging of distinctive therapeutic effects.

Current efforts to improve and standardize quantification as well as visualization are readily available on PC platforms and will enable a broader accessibility to this methodology. Without any question, DCE-MRI is already a capable tool to improve diagnosis and monitor diagnostic changes during oncologic therapy.

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Molecular Cancer Therapeutics

Functional Magnetic Resonance Imaging in Oncology for Diagnosis and Therapy Monitoring

Michael V. Knopp, Hendrik von Tengg-Kobligk and Peter L. Choyke

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