Therapy Monitoring with Functional and Molecular MR Imaging

Roberto García-Figueiras, MD, PhD[a,*], Anwar R. Padhani, MBBS, FRCP, FRCR[b], Sandra Baleato-González, MD, PhD[a]

KEYWORDS

• Oncology • Anticancer treatments • Tumor response • Functional imaging • MR imaging • Diffusion MR imaging • Perfusion imaging/methods • Multiparametric imaging

KEY POINTS

- MR imaging offers an attractive combination of anatomic, physiologic, and molecular information of tumor phenotype.
- MR imaging findings of tumor response depend on tumor type, on anatomic locations, on the mechanism of action of therapy given, and on the imaging techniques.
- Multiparametric MR imaging has demonstrated to be a useful tool for tumor response evaluation in multiple tumor types.

INTRODUCTION

Historically, cancer therapy has been based on different combinations of surgery, radiotherapy (RTP), and chemotherapy (CTP). These therapies have proven value but have also shown obvious limitations (eg, RTP and CTP do not kill cancer cells specifically) with treatment-related side effects commonly encountered. Recently, there has been a continuous effort in order to develop oncologic therapies (OTs) designed to target and disrupt specific tumor hallmarks (angiogenesis, metabolism, proliferation, and invasiveness) and genetic-related tumor changes (eg, epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] mutations).[1,2] Many advances in our understanding of key biological processes that are altered in tumors have been translated into the development of these OTs, including antiangiogenic/antivascular drugs, drugs interfering with tumor growth signaling (EGFR, ALK, tyrosine-protein kinase Kit [c-KIT], and pathways mediating their downstream effects), hormonal therapy (HT), immunotherapy (IT), and interventional techniques (eg, embolization or ablation).[1–4] In this scenario, the effectiveness of these approaches needs to be evaluated, in particular the onset, duration, and heterogeneity of benefits requires assessment.

Intrinsically magnetic resonance (MR) offers a combination of anatomic, physiologic, and molecular information, which makes MR an ideal tool for evaluating different aspects of the cancer phenotype in vivo.[5] Many functional and molecular imaging (FMI) techniques that are available on MR imaging systems include dynamic contrast-enhanced MR imaging (DCE-MR imaging),

Disclosure statement: Dr A.R. Padhani serves on the advisory board for Siemens Healthcare Speakers Bureau, Siemens Healthcare, Johnson & Johnson. He is also a researcher for Siemens Healthcare. Drs R. García-Figueiras and S. Baleato-González have nothing to disclose.

[a] Department of Radiology, Complexo Hospitalario de Santiago de Compostela (CHUS), Choupana s/n, Santiago de Compostela 15706, Spain; [b] Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, Northwood, Middlesex HA6 2RN, UK

* Corresponding author.

E-mail address: roberto.garcia.figueiras@sergas.es

Magn Reson Imaging Clin N Am 24 (2016) 261–288

http://dx.doi.org/10.1016/j.mric.2015.08.003

dynamic susceptibility contrast-enhanced MR imaging (DSC-MR imaging), diffusion-weighted MR imaging (DW-MR imaging), and Magnetic resonance spectroscopy and spectroscopic imaging (MRS/I).[5–13] These noninvasive FMI techniques can demonstrate the spatial and temporal distribution of important tumor characteristics. They also provide quantitative biomarkers for the objective assessment of physiologic and molecular processes and, thus, enable assessment of changes in response to therapy. Understanding the relationship between tumor hallmarks, therapy effects, and MR imaging findings is essential for an adequate evaluation of OTs. In this article, the authors describe the role of functional MR imaging in oncology for therapy monitoring.

MR IMAGING TECHNIQUES FOR THE EVALUATION OF TUMOR PHENOTYPE

When considering therapy effects on tumors, imaging observations are sometimes difficult to interpret. Imaging findings seem to depend on anatomic locations, on interactions between specific tissue characteristics and the mechanism of action of therapy given, and on the imaging techniques making the observations. Different FM–MR imaging techniques are available in modern scanners (**Table 1**).[5–13] MR-based FMI techniques are increasingly being used to monitor the tumor response to therapies in daily clinical practice. MR imaging is able to predict the success of therapy before size changes become evident, and FM–MR imaging methods are increasingly being used as biomarkers of response in early phase drug development.

TUMOR RESPONSE ASSESSMENT USING MR IMAGING

Tumor and normal tissue response evaluations are critical roles of imaging in oncology. In this setting, imaging findings depend highly on the type and method of therapy delivery, the timing of treatment, and the imaging technique being used to observe the effects (**Table 2**). Additionally, combined therapies are increasingly being used in many tumor types, which may sometimes make it difficult to separate the net effect on imaging findings of every type of therapy.

Conventional Oncologic Therapies: Chemotherapy and Radiotherapy

CTP causes cellular lysis often via dominant necrosis or apoptotic mechanisms. On DW-MR imaging, cellular lysis results in increased water diffusion, which increases the apparent diffusion coefficient (ADC) values.[8–10] Elevations of ADC depend on the degree of cell kill and reactive inflammatory changes if any. Early increases in ADC often precede any change in the tumor size and may be used in the early assessment of response. The use of histogram analysis of ADC values has been shown to be more sensitive to detect effective treatment response than average tumor ADC change or shrinkage of tumor. In patients with successful treatment, the ADC histogram shifts to higher values, in contrast to nonresponders whereby no shift or shift to lower values is observed[14] (**Fig. 1**). In the case of bone metastatic involvement, whole-body MR imaging (WB-MR imaging) is increasingly being used to evaluate metastatic bone disease and to monitor its therapeutic response.[11,15,16] Effective tumor response results in greater water diffusivity manifested as lower signal intensity on high b-value images, reductions in the extent of bone disease usually accompanied by higher ADC values.[8–10] However, the extent of ADC increases with therapy (including CTP) is very variable and depends on the mechanism of cell kill and the complexity of bone marrow (BM) composition (hematologic cells, bone cells, fat, tumor involvement, and so forth), which can be independently altered by accompanying therapies and their effects. So granulocyte colony-stimulating factor (G-CSF) when used to support CTP can increase background high b-value image intensity due to normal BM hyperplasia, and HT can cause increased BM fat so lowering high b-value signal intensity. In the latter setting, a particular difficulty is the presence of fat intermixed with tumor infiltration as seen in myeloma or return of marrow fat infiltration that usually accompanies response and can counteract expected increases in ADC. This feature may explain the smaller ADC increases associated with bone disease responding to therapy.[15,16] Conventional mono-exponential diffusion MR imaging evaluation assumes a Gaussian behavior of diffusion process (ie, free and unrestricted diffusion of water). However, in many biological tissues, the water diffusion process is no longer Gaussian, a feature noticeable on ultrahigh b-value images (>1500 s/mm^2). Diffusional kurtosis imaging (DKI) quantifies the deviation of tissue diffusion from a Gaussian pattern.[12] Recently, the clinical value of DKI for tumor response evaluation has been undertaken. Chen and colleagues[17] report that DKI might be superior to mono-exponentially derived ADC values for predicting early response to neoadjuvant CTP in patients with nasopharyngeal carcinoma; the latter is probably related to changes in intracellular complexity. Tumor cell kill also causes a