Assessment of Tumor Angiogenesis

Dynamic Contrast-enhanced MR Imaging and Beyond

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KEYWORDS

• Angiogenesis • Biomarker • Clinical trials • DCE-MR imaging • Diagnosis • Quantitative imaging

KEY POINTS

- Dynamic contrast-enhanced (DCE) MR imaging methods track the passage of a contrast agent bolus through tumor microvessels, thus enabling estimation of blood flow, blood volume, and permeability.
- DCE-MR imaging has some limited practical applications in clinical medicine that include screening for disease, lesion localization and characterization, and monitoring response to therapy.
- DCE-MR imaging has a well-established role in go/no-go decision-making tools in early-phase trials of angiogenesis inhibitors.
- Further prospective studies with adequate power are required to determine whether DCE-MR imaging and other imaging techniques have a role as prognostic biomarkers or predictive indicators to specific antiangiogenic therapies.
- Imaging techniques such as DCE-MR imaging have been hampered by a lack of validation and addressing this shortfall is an area of intense current research.

INTRODUCTION

Over the last 30 years there has been much interest in using imaging to identify, quantify, and monitor change in the vascular architecture and function of tumors, particularly in tracking response to antiangiogenic therapy. Although the term angiogenesis dates back to 1971 with the seminal publication by Folkman,[1] initial computed tomography (CT), MR imaging, or PET studies evaluating angiogenesis in preclinical models of cancer and in patients were not published until the late 1980s.[2,3] Following a steady increase in publications to around 200 per year, interest in imaging angiogenesis pathways and therapeutic inhibition was further fueled in the early 2000s, when the modest survival advantage of vascular endothelial growth factor (VEGF) inhibition became clear in renal,[4] colorectal,[5] non–small cell lung,[6] hepatocellular,[7] ovarian,[8] and other cancers. From 2004 until the present date, more than 400 journal articles covering imaging and angiogenesis in cancer have been published yearly and this trend continues to increase.

Imaging studies can probe tumor angiogenesis in various different ways. PET tracers can show

Disclosure: The authors have nothing to disclose.
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Magn Reson Imaging Clin N Am 24 (2016) 45–56
http://dx.doi.org/10.1016/j.mric.2015.08.010
1064-9689/16/$ – see front matter

proof of mechanism by mapping and quantifying the in vivo distribution of drug targets, including VEGF receptors[9] and α_v integrins.[10] Clinical studies have mapped and quantified drug-target interaction for VEGF inhibitors[11] and α_v integrin–targeted agents.[12] This research not only shows proof of mechanism but also helps to map the variation in drug target expression. For example, the uptake of ^{18}F-galacto-RGD peptide ($\alpha_v\beta_3$-selective PET tracer) showed substantial spatial variation between individual patients with breast cancer and also between primary and metastatic lesions in the same individuals.[13] These molecular imaging studies are expensive and limited to specialist centers, but provide clear mechanistic data to facilitate drug development.

In contrast, most studies that image angiogenesis quantify and map aspects of the microenvironment at the phenotypic level, rather than the molecular level.[14,15] These methods are also expensive and require investment of time from both patients and scientists. This article focuses on the role of T_1-weighted dynamic contrast-enhanced (DCE) MR imaging as a method of evaluating tumor angiogenic signatures and response to therapy in the clinic and in research applications. It summarizes the major strengths and limitations and provides examples, with particular focus on how DCE-MR imaging has altered decision making. The benefits of DCE-MR imaging are then contextualized with other competitor methods (imaging and nonimaging) and the unmet needs and future directions of angiogenesis imaging are discussed.

KEY METHODOLOGICAL DECISIONS

The term DCE-MR imaging represents a family of related methods, all of which image the passage of low-molecular-weight gadolinium-based contrast agents as they traverse the tumor vasculature. All methods require a T_1-weighted sequence to be performed and serial images are collected so that the differences in contrast agent concentration within the tumor can be visually interpreted (qualitative assessment by radiologist) or measured (semiquantitative or truly quantitative assessment by imaging scientists)[15,16] (**Fig. 1**). In general, scan quality (determined by spatial resolution) is sacrificed for

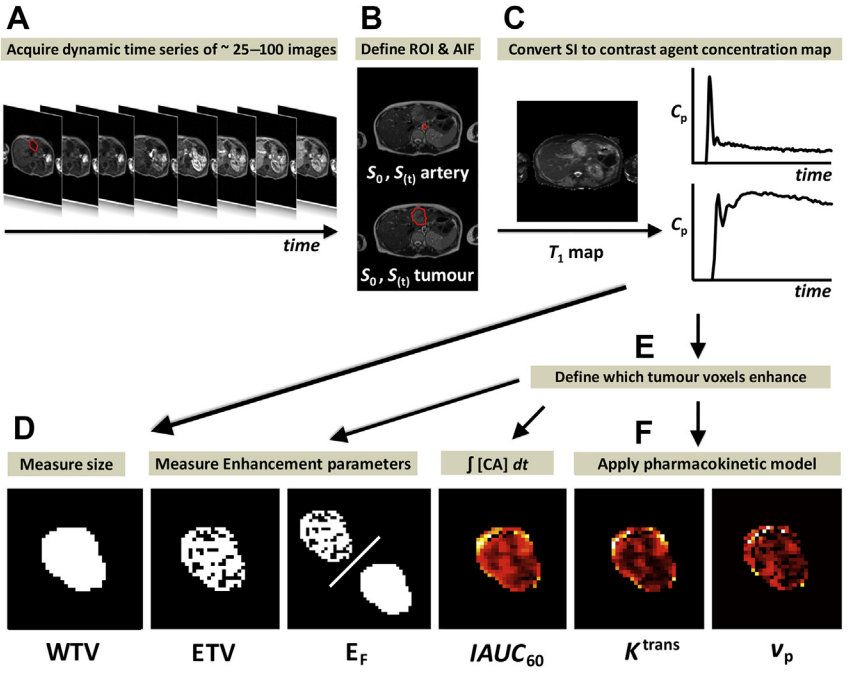

Fig. 1. Overview of DCE-MR imaging data acquisition and analysis. (*A*) Multiple images (approximately 25–100) are acquired before and then after a bolus of gadolinium-based contrast agent (CA) passes through tissue capillaries. (*B*) The region of interest (ROI) for a tumor and the feeding vessel arterial input function (AIF) are defined. (*C*) Signal intensity (SI) values for each voxel are converted into CA concentration by calculating the longitudinal relaxation (T_1) values, to allow plots of contrast agent concentration in plasma (C_p). These steps allow calculation of (*D*) whole-tumor volume (WTV). (*E*) Next, the voxels that enhance are used to calculate enhancing fraction (E_F), from which the $IAUC_{60}$ can be defined. In addition, in (*F*) tracer kinetic models may be applied to derive parameters such as K^{trans} and plasma volume (v_p). ETV, Enhancing tumor volume. (*From* O'Connor JP, Jackson A, Parker GJ, et al. Dynamic contrast-enhanced MRI in clinical trials of antivascular therapies. Nat Rev Clin Oncol 2012;9:169, with permission.)