Clinical Oncology xxx (2014) 1–12

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Dynamic Contrast-enhanced Magnetic Resonance Imaging: Applications in Oncology

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Received 6 February 2014; received in revised form 22 April 2014; accepted 28 April 2014

Abstract

Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) allows functional characterisation of tissue perfusion characteristics and acts as a biomarker for tumour angiogenesis. It involves serial acquisition of MRI images before and after injection of contrast, as such, tissue perfusion and permeability can be assessed based on the signal enhancement kinetics. The ability to evaluate whole tumour volumes in a non-invasive manner makes DCE MRI especially attractive for potential oncological applications. Here we provide an overview of the current research involving DCE MRI as a biomarker for the diagnosis and characterisation of malignancies, prediction of the therapeutic response and survival outcomes, as well as radiation therapy planning.

Key words: Angiogenesis; dynamic contrast-enhanced imaging; functional imaging; magnetic resonance imaging; perfusion imaging

Statement of Search Strategies Used and Sources of Information

Pubmed was used for the literature search.

Introduction

Tumour Angiogenesis

Inducing angiogenesis is one of the hallmarks of cancer [1]. The ability to stimulate the formation of new blood vessels is a prerequisite for tumour expansion. In tumour cells, angiogenesis is modulated through a variety of signalling pathways targeting the ligand receptors of endothelial cells, for example, vascular endothelial growth factor (VEGF), angiopoietin-1 and placental growth factor, etc. [2].

The resultant tumour neovasculature is structurally and functionally aberrant. Tumours typically present with hypervascularity, excessive branching, irregularity and tortuosity [3]. Blood flows in a highly haphazard manner, ranging from near zero to several times that of the surrounding normal tissue. This is accompanied by increased permeability and leakiness, contributed by the lack of muscularis propia, widened inter-endothelial junctions, lack of basement membranes and presence of vesiculovascular organelles [4,5].

Functional characterisation of tumour microvasculature has been of great interest in the field of oncology imaging as there is evidence for tumours to exhibit a wide spectrum of anomalies in perfusion and these have been correlated with tumour characteristics and clinical outcome, and is a potential therapeutic target.

Basic Principles of Dynamic Contrast-enhanced Magnetic Resonance Imaging

As paramagnetic substances, gadolinium-based contrast agents shorten T1 and T2 relaxation times and enhance signal intensity on T1-weighted magnetic resonance imaging (MRI). It is administered intravenously, and then travels through the heart and arteries to the capillaries, where it extravasates into the interstitial space. The signal

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2014.05.014

enhancement represents the averaged concentration of the contrast agent within the vascular and interstitial spaces. The change in concentration of contrast with time is a function of the blood flow, permeability, density of vasculature and interstitial space. It is well known that most tumours display a characteristic rapid enhancement followed by an earlier contrast wash-out pattern. This may be attributed to the angiogenic process, in which the rapid proliferation of blood vessels results in increased blood flow, vascular space and capillary permeability. Therefore, contrasts allows for non-invasive evaluation of the perfusion and permeability of the tumour microvasculature.

Dynamic contrast-enhanced (DCE) MRI involves the acquisition of serial three-dimensional images at high temporal resolution after a rapid injection of contrast, so as to trace the first passage of contrast bolus through the tissue vasculature. Before that, a preliminary anatomical scan is carried out for slice localisation, such that each slice contains both the target lesion and an appropriate large blood vessel, which is used to obtain an arterial input function that allows the estimation of contrast concentration within the tumour blood vessels. In addition, baseline T1 mapping is carried out to calculate contrast concentration, which may not be linearly related to signal intensity due to the underlying native T1 of tissues [6].

Image Analysis

Interpretation of the contrast agent concentration–time curves can be carried out qualitatively, semi-qualitatively or quantitatively.

In the qualitative method, a radiologist visually inspects the shape of the curve with respect to its initial rise and delayed phases. The concentration–time curves may be described as having a 'rapid', 'medium' or 'slow' initial rise and a 'persistent', 'plateau' or 'wash-out' delayed phase. This method has been used for breast cancers as a complement to existing methods of diagnosis [7,8]. However, it is susceptible to both inter-observer and intra-observer variability, especially with respect to differentiating between the persistent and plateau or plateau and wash-out enhancement types [8].

The semi-quantitative analysis uses curve-derived measurements, such as time to onset, time to peak, initial and mean slope of signal enhancement curve, maximum signal intensity and wash-out gradient [9]. However, these methods are subject to variations in the baseline T1 of tissues, data acquisition method, scanner settings and patient factors such as cardiac output.

The quantitative analysis is carried out either through a model-free or model-based approach. The former takes an integration of the concentration–time curve over a period of time to give the initial area under curve (IAUC). Although the IAUC is presumed to be associated with blood flow and permeability, it does not differentiate the effects of each component. The model-based method describes tissue perfusion using tracer kinetic models that incorporate physiologically meaningful parameters such as blood flow, capillary permeability–surface area product, intravascular space, extravascular space and mean transit time [6]. These parameters are computed by fitting the tracer kinetic model to concentration–time curves derived from the DCE imaging data set. Several models have been developed, including conventional compartmental, generalised kinetic and distributed parameter models.

Applications in Oncology

To date, studies have investigated the feasibility of DCE MRI to improve methods of cancer detection, characterisation, response assessment, prognosis and radiation therapy planning (Table 1).

Diagnosis and Characterisation

Cancer Detection and Localisation

The ability to detect cancers at an early stage helps to reduce mortality. In some cancers, standard morphology-based imaging techniques are not able to discriminate between benign and malignant tumours, and functional characterisation of the tumours can aid in classifying these lesions. Multiparametric imaging is gaining popularity in the diagnosis of cancers and DCE imaging is one of the modalities that are commonly used.

Breast cancers are difficult to diagnose using mammograms in patients with dense breast tissues, yet MRI has poor specificity. On DCE imaging, malignant breast lesions may be distinguished by its rapid initial enhancement with subsequent wash-out pattern. Jansen *et al.* [10] showed that contrast uptake and signal enhancement ratios were able to identify malignant lesions with sensitivities and specificities in the ranges of 90% and 20–30%, respectively. Additionally, DCE MRI may aid the diagnosis of sonographically indeterminate adnexal masses, which make up almost 20% of adnexal masses [30]. For such cases, surveillance with repeat imaging is a common approach. However, this may cause a delay in treatment if there is a malignancy. Timely diagnosis is important, as treatment differs from simple resection in benign lesions, to radical surgical exploration in malignant lesions. Thomassin-Naggara *et al.* [11] showed the feasibility of characterising these masses by showing that malignant adnexal tumours had greater tissue blood flow and blood volume fraction and smaller interstitial volumes as compared with benign tumours.

Treatment-induced permeability changes result in non-specific contrast uptake that may resemble residual tumour or tumour recurrences, making it especially challenging to identify tumours by contrast-enhanced imaging alone. In glioblastoma surgery, where it is crucial to maximise tumour resection without causing additional neurological deficits, intraoperative DCE MRI may provide a quick assessment for residual tumours at the resection border. Based on a study by Özduman *et al.* [12], there were significant differences in the time-intensity curves, K^{trans} (permeability constant), K_{ep} (efflux constant), V_e (volume of extravascular–extracellular space) and IAUC, between remnant tumour and surgically induced enhancement. In

Please cite this article in press as: Teo QQ, et al., Dynamic Contrast-enhanced Magnetic Resonance Imaging: Applications in Oncology, Clinical Oncology (2014), http://dx.doi.org/10.1016/j.clon.2014.05.014