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Chronic Diseases and Translational Medicine 3 (2017) 8–20

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Perspective

Quantitative magnetic resonance imaging biomarkers in oncological clinical trials: Current techniques and standardization challenges

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Received 1 December 2016
Available online 11 March 2017

Abstract

Radiological imaging plays an important role in oncological trials to provide imaging biomarkers for disease staging, stratifying patients, defining dose setting, and evaluating the safety and efficacy of new candidate drugs and innovative treatment. This paper reviews the techniques of most commonly used quantitative magnetic resonance imaging (qMRI) biomarkers (dynamic contrast enhanced, dynamic susceptibility contrast, and diffusion weighted imaging) and their applications in oncological trials. Challenges of incorporating qMRI biomarkers in oncological trials are discussed including understanding biological mechanisms revealed by MRI biomarkers, consideration of rigorous trial design and standardized implementation of qMRI protocols.

Keywords: Quantitative magnetic resonance imaging; Biomarkers; Oncological clinical trials

Introduction

Cancer is the leading cause of death worldwide and the global cancer burden is growing at a fast pace. The International Agency for Research on Cancer (IARC) estimated that in 2012 there were 14.1 million new cancer cases and 8.2 million cancer deaths worldwide, and the global burden is expected to grow to 21.7 million new cancer cases and 13 million cancer deaths by 2030.[1] In developing countries, cancer is the major public health problem with increasing incidence and mortality. A recent report of Cancer Statistics in China estimated 4,292,000 newly diagnosed invasive cancer cases in 2015. The leading cause of cancer death in China is lung cancer in men and breast cancer in women.[2]

Accelerated drug development is an important direction of endeavor in the battle of conquering cancer. Clinical trials of drug development involve five phases from phase 0 to phase IV. Phase 0 is exploratory study involving very limited human exposure to the drug, mostly including screening studies and micro-dose

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.cdtm.2017.02.002

studies. Phase I studies are usually conducted in healthy volunteers to determine the safety profile of the drug and how the drug is metabolized and excreted. Phase II studies gather preliminary data on effectiveness of the drug in patients, usually compared with a control group of patients who receive different treatment such as a placebo or a different drug. Phase II studies continue to evaluate safety and adverse events. Phase III studies gather more information about safety and effectiveness by studying a larger populations and different dosages. Phase III findings are submitted to Food and Drug Administration (FDA) for approval for marketing. Phase IV studies occur after FDA approval, which is usually investigator initiated studies and designed for acquiring additional information about a drug's safety, efficacy, or optimal use. Current anticancer drug development still struggles with high attrition rate partly due to lack of effective biomarkers and well-designed clinical trials for efficient go/no-go decision making process. Overall, cost-efficient accelerated drug development warrants the correct design and execution of clinical trials with accurate and precise biomarkers for evaluation of the effectiveness of the treatment.

Imaging biomarker

Radiographic characteristics, in parallel with molecular, histological or physiologic characteristics, are currently defined as one of the categories of biomarkers, by the FDA-National Institute of Health (NIH) Biomarker Working Group consensus statement.[3] Imaging biomarkers are non-invasive measurement of tissue properties derived from radiological images. Imaging biomarkers play an important role in oncology trials for disease staging, stratifying patients, defining dose setting, and evaluating the safety and efficacy of new candidate drug and/or innovative treatment. Imaging biomarkers facilitate the go or no-go decision-making process in early stages and form the basis of response and progression criteria in the late stages of clinical trials involving a large number of clinical trial subjects.

Conventional imaging techniques provide anatomic tumor size measurement before and along the course of therapy, and the reduction of tumor size is used as a surrogate for effective treatments. Computer tomography (CT) is the most commonly used modality to measure targeted lesions. Magnetic resonance imaging (MRI) is also acceptable in certain situations except in lung. Many standard guidelines have been established for evaluating tumor morphology, such as World Health Organization (WHO) criteria, Response Evaluation Criteria in Solid Tumors (RECIST), Cheson, immune-related response criteria (irRC), and Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST). For example, RECIST[4] is well-standardized criteria that provide size measurements of solid tumors in clinical trials. The RECIST criteria were initially developed based on the mechanism of cytotoxic therapy that effective chemotherapeutic agents will cause tumor to shrink and disappear. However, reduction in tumor diameter usually occurs in the late course of treatment (typically 6–12 weeks), and thus relatively insensitive to early treatment effects.[5] Furthermore, with the discovery of innovative therapeutic agents and methods such as cytostatic, tyrosine kinase inhibitors, antiangiogenics, and immune-based therapies, the conventional RECIST criteria are not adequate for evaluation of the efficacy of these agents. These molecularly targeted agents inhibit tumor growth rather than induce tumor regression, therefore tumor size change may not accurately reflect the true tumor response and long-term outcomes secondary to these therapies. Tumor tissue micro-structural and micro-environment changes may occur earlier than the size reduction, or even initially increase with effective treatment. For example, in patients with glioblastoma, the effect of radiation (or chemoradiation) may cause increased contrast-enhanced signals or peritumoral edema on MRI scans, mimicking tumor progression (i.e. pseudoprogression). The phenomenon may result from transiently increased permeability of the tumor vasculature by irradiation.[6] Pseudoprogression usually subsides without further treatment over time, but in some cases may progress into radiation necrosis without true recurrent tumors.[6–8] Pseudoprogression has been reported in 10–48% of patients with glioblastoma patients undergoing post-therapy MRI scans following radiotherapy or chemoradiotherapy.[9–12] On the other hand, tumor pseudoresponse may present reduced contrast-enhanced signal enhancement and/or edema on MRI scans after treatments with antiangiogenic agents, due to reduced vascular permeability of contrast agents rather than true antitumor effect.[6–8] Moreover, the emerging immunotherapies bring new challenges in evaluating the efficacy of these novel drugs that stimulate host antitumor response by targeting the immune system. RECIST criteria are not reliable to determine the immune-related tumor response. Immune-related response patterns may present transient increased tumor size because of inflammatory cell infiltrates, necrosis, development of new lesions with edema and infiltrates of immune cells, yet followed by later tumor regression.[13,14]

A recent RECIST survey was conducted regarding the concerns of using RECIST criteria with

suggestions for future modifications.[15] This study demonstrated that the current RECIST criteria lack incorporation of early indicator of responses such as functional imaging, validation in rare tumor types and validation for targeted agents. It was suggested that advanced imaging techniques should be incorporated in tumor assessment.

Given the limitations of current anatomic tumor measurement criteria, there is significant interest in deriving quantitative imaging biomarkers for tumor tissue characterization and assessment of the efficacy of innovative targeted therapeutic methods. Quantitative imaging biomarkers may serve as early endpoints of response for adjusting treatment plan at an earlier stage to avoid unnecessary toxic effect in a patient who is a non-responder to a specific treatment.

Quantitative MRI biomarker

MRI has been increasingly used in clinical trials due to its non-ionizing radiation feature and various soft tissue contrast by manipulating imaging sequences and parameters. There are 955 open studies found in the ClinicalTrials.gov website with the search terms "MRI" and "oncology" till May 28th 2016. Among these studies, most (508 studies) are registered in the United States, and a total of 449 studies belong to phase 0, I–IV trials with more than half being phase II studies.

Quantitative MRI (qMRI) methods have been used in many clinical trials to provide biological and physiological information of tumor tissue property changes after treatment. The most commonly used qMRI techniques include dynamic contrast enhanced (DCE), dynamic susceptibility contrast (DSC), and diffusion weighted imaging (DWI). Other emerging investigational qMRI techniques include chemical exchange saturation transfer (CEST), elastography, and polarized MRI, etc.[16] Multi-parametric analysis provides multi-facet complementary insights of tissue properties. Most of these newly emerging qMRI techniques are still under technical development and have not been accepted in oncology trials. This paper will focus on the techniques and applications of three most commonly validated methods in clinical trials: DCE, DSC and DWI. Comparisons of DCE, DSC and DWI MRI techniques with respective clinical relevance are summarized in Table 1.

DCE-MRI

Introduced in 1990s, DCE-MRI underwent extensive technical development and has been widely used for non-invasive evaluation of tumor angiogenesis by measuring the blood volume and permeability of tumor tissues. Tumor growth requires new vessel formation (i.e. neoangiogenesis) and tumor vessels have a defective endothelial barriers resulting in increased transvascular leakage.

In imaging acquisition, DCE-MRI acquires a time series of rapid T1-weighted gradient-echo magnetic resonance (MR) images (>5 minutes) with a steady-state phase of the passage of gadolinium (Gd)-based contrast agent as it traverses the tumor vasculature to the extravascular space. The acquisition time is long (>5 minutes *vs.* 2 minutes in DSC) to allow for the contrast agent to leak into the extravascular space and reach equilibrium over several passes of the contrast bolus through the tumor bed. The T1 shortening effect by Gd causes the increased signal intensity on T1-weighted images, and the degree and timing of signal enhancement reflect the perfusion and permeability properties of tumor tissues. The signal enhancement curve can be analyzed using semi-quantitative non-model based method or quantitative pharmacokinetic (PK) model-based method.

Non-model based DCE analysis

Semi-quantitative parameters can be directly extracted based on the shape characteristics of the signal intensity change curve overtime, such as wash-in rate, wash-out rate, peak, time-to-peak and area-under-the-curve (AUC) (Fig. 1).

Quantitative PK model-based DCE analysis

Quantitative PK parameters describe the exchange between the vessels and the interstitial area in terms of blood volume, interstitial volume and transvascular permeability. To calculate PK parameters, DCE signal intensity changes are first converted to the Gd concentration. The Tofts model[17] is the first PK model, which considers only the extravascular extracellular space (EES) compartment but neglects the plasmatic compartment. The extended Tofts model[18] is a two-compartment model, which considers that the concentration of the contrast agent in the plasma space and EES is at the diffusion equilibrium. Four principal parameters are derived from this model: transfer constant from plasma to EES across the capillary endothelium (k^{trans}), rate constant from EES to plasma (k_{ep}), fractional EES volume (V_e), and fractional blood volume (V_p). The generalized steps of quantitative PK model-based DCE analysis are illustrated in Fig. 2.

Other than the most commonly used extended Tofts model, several other existing PK model-based methods

Table 1
Summary of DCE, DSC and DWI MRI techniques.

qMRI Technique	Use of Gd-based contrast agent	MRI acquisition (acquisition time)	Major derived qMRI parameters	Clinical relevance
DCE	Yes Steady-state measurement of the passage of Gd-based contrast agent as it traverses the tumor vasculature to the extravascular space	T1-weighted gradient echo imaging (>5 minutes)	Wash-in rate, wash-out rate, time-to-peak, AUC, k^{trans}, k_{ep}, V_e, V_p, etc.	Evaluation of tumor angiogenesis by measuring blood volume and permeability of tumor tissues
DSC	Yes Measurement of first-pass of paramagnetic Gd-based contrast agent	T2*-weighted gradient echo imaging (~2 minutes)	MTT, CBF, CBV	Evaluation of perfusion of tumor tissues. Mostly used in neuro-oncology field
DWI	No Measurement of tissue water mobility using motion-probing gradients	Diffusion-weighted imaging (1–5 minutes dependent upon methods)	ADC, D_{fast}, V_{fast}, D_{slow}, V_{slow}, α, DDC, μ, β, etc	Evaluation of tissue water mobility that can be restricted by tissue microstructures

DCE: dynamic contrast enhanced; DSC: dynamic susceptibility contrast; DWI: diffusion weighted imaging; MRI: magnetic resonance imaging; qMRI: quantitative MRI; Gd: gadolinium; AUC: area-under-the-curve; k^{trans}: transfer constant from plasma to extravascular extracellular space across the capillary endothelium; k_{ep}: rate constant from extravascular extracellular space to plasma; V_e: fractional extravascular extracellular space volume; V_p: fractional blood volume; MTT: mean transit time; CBF: cerebral blood flow; CBV: cerebral blood volume; ADC: apparent diffusion coefficient; D_{fast}: fast diffusion coefficient; V_{fast}: fast diffusion volume; D_{slow}: slow diffusion coefficient; V_{slow}: slow diffusion volume; α: water molecular diffusion heterogeneity index; DDC: distributed diffusion coefficient; μ: space constant; β: structural complexity parameter.

implement different modelling for characterizing perfusion and permeability-related parameters such as bidirectional transfer constant (K_i) and permeability-surface area product (PS), etc.[19–24] The most preferred DCE imaging biomarkers used as clinical trial end-points are AUC and k^{trans}.[25,26]

There are several technical challenges in performing quantitative measurement of DCE-MRI. First, accurate and reliable arterial input function (AIF) measurement is critical for calculating PK models.[27] AIF estimated from averaged population-based method or fixed values is not reliable due to individual variations or differences between animal models and human studies. Difficulty in finding reliable tumor-feeding arteries, time delay between plasma and tissue contrast agent concentration change, and T2* induced signal decay may lead to inaccurate AIF measurement and erroneous PK parameters.[28] Second, accurate longitudinal T1 relaxation time measurement is required to convert signal intensity to contrast agent concentration. Various existing T1 measurement methods need to be calibrated and validated. For example, underestimation of T1 by 65% may result in overestimation of k^{trans} by 531%.[29]

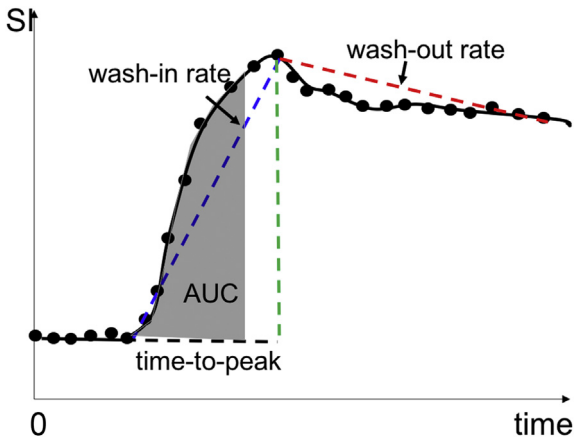

Fig. 1. Diagram showing the extraction of non-model based semi-quantitative dynamic contrast enhanced (DCE) parameters based on the shape characteristics of the signal intensity (SI) change curve over time: wash-in rate, wash-out rate, time-to-peak and area-under-the-curve (AUC).

DCE-MRI has been used as a vascular-specific imaging biomarker in early phase clinical trials and investigator initiated studies for monitoring the treatment response, predicting the treatment outcomes, and optimizing drug dose and schedule. There are considerable evidence showing significant reduction of k^{trans}, AUC and other related DCE parameters following the anti-vascular and vascular-targeting treatment in breast cancer, hepatic metastasis, colorectal cancer, glioblastoma, cervical cancer and several other advanced cancers.[30–45] However, some recent studies showed none or weak correlation between DCE parameters and clinical outcomes in various tumor types, mainly due to the low reproducibility and high measurement variability of DCE-MRI.[46–58] In terms of the predictability of baseline DCE measurements, several studies

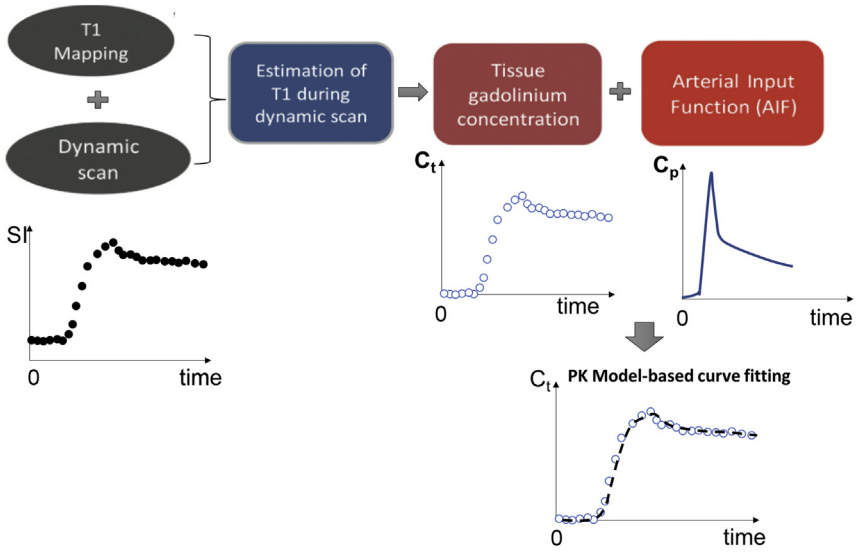

Fig. 2. Diagram showing the steps of quantitative pharmacokinetic (PK) model-based dynamic contrast enhanced (DCE) analysis. After contrast-enhanced dynamic scan and tissue T1 estimation, DCE signal intensity (SI) changes over time are converted to tissue gadolinium concentration (C_t) changes. With measured arterial input function (AIF) (C_p) in the blood vessels, quantitative PK model-based parameters can be calculated through a Laplace transformation.

demonstrated that a lower level of pretreatment k^{trans} may indicate weak treatment response,[59] whereas a high level of pretreatment k^{trans} may suggest significant vascular suppression after treatment.[60–62] However, some other studies did not report pretreatment baseline DCE parameters can predict the treatment responses.[63,64] In addition, some studies demonstrated that the greater immediate decreases of DCE parameters after treatment may predict better clinical outcomes.[63–65] The controversial DCE-MRI findings of treatment response attributed to complicated mechanism of different anti-vascular and vascular-targeting agents. With anti-vascular agent targeting vascular endothelial growth factor (VEGF) ligand and VEGF receptor 2, it is believed that vascular permeability is reduced that can be measured by reduced k^{trans}. However, imaging changes in response to other factors such as blocking platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), or c-Kit are not well understood.[66] The antitumor efficacy of some agents may result in blood flow reduction and induce central necrosis, but not alter vascular permeability substantially.[67] The vascular response measurement by DCE-MRI has also been used in phase I trials to define the biologically active dose of a drug, and to assist dose selection and drug scheduling in phase II trials.[68] Overall, the role of DCE-MRI for decision making in drug development remains controversial and there is no generally accepted consensus yet, although there have been general recommendations on how to standardize DCE-MRI methodology.[69,70]

DSC-MRI

DSC-MRI tracks the first-pass of paramagnetic Gd-based contrast agent by acquiring a series of rapid echo-planar MR images (~2 minutes). The susceptibility effect of Gd causes a transient T2* weighted signal decrease, which dominates the T1 shortening effect due to the direct interaction of intravascular protons with the gadolinium chelate.[71] DSC-MRI provides hemodynamic features of tissue vascular network. Semi-quantitative perfusion parameters, also called summary parameters, can be obtained by analysis of DSC signal intensity curve during the passage of the contrast bolus, such as time-to-peak (reflecting blood flow) and negative enhancement integral (reflecting blood volume). PK models can be applied to the time course of DSC-MRI signal changes to measure quantitative perfusion parameters including mean transit time (MTT), relative cerebral blood flow (CBF) and relative cerebral blood volume (CBV).

It is assumed in basic DSC kinetic models that contrast agent remains in the intravascular space during the bolus pass; however, contrast leakage may lead to miscalculated DSC parameters in tumors (especially high grade tumors) with brain-blood-barrier (BBB) breakdown unless corrected.[72] Leakage correction can

be performed by using a contrast agent preload or by using a post-processing correction algorithm.[73] Alternatively, blood pool agent ferumoxytol, an iron oxide nanoparticle, is not prone to BBB leakage, providing more robust DSC measurements for reliable diagnosis of pseudo-progression.[74] Furthermore, a newly described method Bayesian post-processing outperforms singular value decomposition (SVD)-based deconvolution by implementing a rigorous probabilistic estimation of hemodynamic parameters that is fully adaptive and insensitive to arterial-tissue delay. In addition, the Bayesian method is more robust against noise and truncation when the signal-to-noise ratio is low.[75]

DSC-MRI has been mostly used in neuro-oncology field to determine brain tumor grade,[76–80] distinguish between recurrent tumor and radiation necrosis,[81–84] and identify pseudo-progression.[74,85] DSC-MRI has also been used for monitoring or predicting anti-angiogenic treatment response. Lower baseline CBV may predict better patient outcome.[86] Malignant tumor transformation can be detected by increased CBV at earlier stage than by conventional contrast enhanced imaging.[87] A recent multi-center, randomized phase II trial reported that early decreases in CBV are predictive of improved survival in patients with recurrent glioblastoma treated with bevacizumab.[88,89] Another study showed increased tumor CBF associated with improved overall survival of patients treated with cediranib, a VEGF receptor tyrosine kinase inhibitor.[90] However, fluctuated CBV changes at different time points[89] and increased CBF[90] after treatment were not fully understood, which may be explained by the vascular normalization theory. In vascular normalization theory, an effective anti-angiogenic treatment will decrease inefficient blood vessels resulting in decreased blood volume and enable a more efficient blood flow possibly resulting in an increased blood flow.[91]

DWI

DWI uses the mobility of water molecules as an endogenous probe to measure changes of tissue properties at a cellular level.[92,93] This technique does not require administration of exogenous contrast medium. DWI utilizes motion-probing gradients to detect the signal decreases arising from intravoxel incoherent motion of water molecules. Water molecules exhibit random Brownian motion that is restricted by tissue microstructures including the cell membrane, cytoskeleton, subcellular proteins, organelles, and extracellular barriers of the tortuous interstitium. Conventional apparent diffusion coefficient (ADC) derived from an intermediate range of diffusion weighting b-values (b) up to 1000 s/mm^2 using a simplified mono-exponential model has been widely used in clinical practice. ADC decreases with high cellularity that is usually associated the tumor malignancy, whereas ADC increases with tumor necrosis or reduced cellularity that is reflective of effective treatment response.

ADC primarily represents extracellular tissue diffusion. There is quite a debate, however, whether cellular density alone is responsible for the ADC value, or whether other factors such as inflammation, fibrosis, extra-cellular space configuration, and micro-organizational structure play a role.[94,95] Prior studies have investigated the role of ADC in tumor grading, and found that while it does show promise, there is an overlap in ADC between tumor grades and types, limiting its use as a reliable diagnostic tool.[96–98]

More complex diffusion models are being investigated in hopes of exploiting the tumor microstructural architecture. Extended DWI-MRI methods utilize additional calculations at higher b values (e.g. up to 4000 s/mm^2) to infer tissue microstructural properties on the basis of the separate tissue compartment model or anomalous diffusion model.[99–102] With a broader range of b-values, the DWI signal decay deviating from mono-exponential decay is not negligible, and the extended signal decay characteristics may reveal tissue diffusion in separate extracellular and intracellular space and tissue complexity and tortuosity as well.

The bi-exponential two-compartment model[99] assumes a high-mobility (fast) water population of extracellular water molecules, as well as a low-mobility (slow) water population of intracellular and/or bound water molecules. Fast diffusion coefficient (D_{fast}) and volume (V_{fast}), and slow diffusion coefficient (D_{slow}) and volume (V_{slow}) can be derived.

The stretched exponential model[103] describes the heterogeneity of intravoxel diffusion rates and the distributed diffusion effect. By using a stretched exponential model, the water molecular diffusion heterogeneity index (α) and the distributed diffusion coefficient (DDC) are calculated.

The anomalous diffusion model evaluates the heterogeneous tissue environment through fractional order calculus.[100] Anomalous diffusion parameters space constant μ, structural complexity parameter β ($0< \beta < 1$) and a generalized diffusion coefficient D can be derived.

Numerous studies have used DWI techniques for tumor detection, tumor tissue characterization and treatment response evaluation for a variety of tumor types in different body parts. DWI with conventional ADC calculation has been widely accepted as part of standard clinical protocols. Many studies have shown that ADC increases after a variety of treatments including chemotherapy, radiotherapy, radiofrequency ablation, cryoablation, embolization and other targeted novel therapies. Treatment-induced cellular damage will lead to tumor lysis, loss of cell membrane integrity and apoptosis, resulting in increased tissue water mobility that can be measured by DWI. It is important to monitor DWI changes along the time course after treatment, which is usually feasible because DWI does not require the administration of contrast agent and can be acquired within 1−5 minutes. The time-dependent ADC change pattern after effective treatment can be summarized as (1) rise to peak and then decrease to normal tissue range; (2) sustained rise over a long period; (3) initial increase but then decrease under the normal range, which may be due to fibrosis, inflammation, vasogenic oedema and/or haemorrhage; and (4) initial transient decrease due to acute cell swelling. In non-responders, there is no change or sustained decrease of ADC after treatment.[5] These various patterns can be related to different tumor types and treatment methods. Pre-treatment ADC values have also been used to predict treatment responses. Tumors with lower pre-treatment ADC values had better responses to chemotherapy and radiotherapy in rectal carcinoma,[104−106] cerebral gliomas,[107,108] colorectal and gastric hepatic metastases.[109,110] However, the pre-treatment ADC predictability was not reported in other type of tumors such as breast[111,112] and cervical cancer.[113] Controversial findings were reported in head and neck cancer.[114,115]

In 2008, a National Cancer Institute (NCI) sponsored conference reached a consensus that DWI should be tested as an imaging biomarker in the context of well-defined clinical trials and recommended that DWI should be added to existing NCI-sponsored trials, particularly those with tissue sampling or survival indicators. The report suggested that there is an extraordinary opportunity of DWI to evolve into a potentially important imaging tool for drug development.[116] In addition, there is considerable interest in applying sophisticated mathematical DWI models to derive more quantitative parameters describing more complex tissue microenvironment and micro-structural properties.

Multi-parametric analysis

Multi-parametric analysis of qMRI methods offers greater insight into the tissue properties and changes after treatment than a single method or single parameter. Since the mechanisms of many therapeutic agents are complicated and the biological rationales of treatment response are not fully understood, multi-parametric MRI data analysis may provide additional and complementary information.[117] The complementary biomarkers can be derived either from a single method or from combination of different methods. For example, various parameters derived from DCE-MRI have been combined to evaluate for antivascular and vascular-targeting treatment response[35,38,118]; DWI parameters derived from different diffusion models have been used in differentiation of tumor grading of gliomas.[119,120] More recently, multi-parametric MRI has been increasingly utilized in diagnosis, staging, characterization and treatment planning of prostate cancer, where the combination of conventional MRI images and at least two qMRI techniques such as DWI and DCE-MRI has shown the promise to characterize prostate lesions and reduce the incidence of prostate biopsy.[121]

Challenges of quantitative MRI biomarkers in oncology trials

Quantitative MRI, when used as endpoints in oncological clinical trials, has encountered challenges due to the complexity of these techniques. Rigorous qualification, validation and standardization processes are required before they can be used as a decision-making tool in clinical trials. A better understanding of whether the qMRI biomarkers measure biological mechanisms or relate to clinical outcomes, rigorous trial design and implementation regarding how and when to perform qMRI is essential for performing successful clinical trials with qMRI measurements as endpoints. Validation of a quantitative biomarker starts with an interdisciplinary expert collaboration with a thorough literature review of present imaging methods and biological mechanism. Appropriate qMRI techniques need to be selected based on the nature of the underlying clinical condition, the relationship between the image-based endpoint and proposed treatment benefit, the precedent for use of an imaging-based primary endpoint in the specific therapeutic area, specific trial design and logistical and feasibility issues, etc.[122] Reproducibility (i.e. variability across different venders) and repeatability (i.e. variability within the

same vendor and same patient) need to be established to determine the reliability of using an imaging endpoint to detect the real treatment responses. The imaging equipment should be accredited and calibrated throughout the whole trial period. Quality control (QC)/quality assurance (QA) procedures using specially designed objects (phantoms) or testing patients need to be performed to ensure the accuracy, precision and reproducibility. In addition, test and retest on the same patient are sometimes acquired to set up the baseline variation of the techniques. Imaging biomarkers with poor reproducibility and availability limit their qualification in multicenter trials.

Standardization is the key to the success of clinical trials especially that integrate qMRI biomarkers as primary endpoints. Standardized guidelines including imaging platform, data acquisition protocols, imaging post-processing and analysis, data transfer, reporting system, QC/QA processes and other related safety factors need to be established. Imaging process variability may result in increased variability in measurements that will limit the ability of the trial to achieve its objectives. These trials should involve highly standardized imaging protocol as well as trial-specific endpoint measures performed by qualified imaging centers with continuous accreditation process.

Technical standardization by consortia efforts

The Quantitative Imaging Network (QIN) (http://imaging.cancer.gov/informatics/qin), is designed to promote research and development of quantitative imaging methods for the measurement of tumor response to therapies in clinical trial settings, with the overall goal of facilitating clinical decision-making. The QIN covers a broad range of imaging modalities including MRI, DCE-MRI and DWI. Its current efforts are focused on phantom studies and QA, longitudinal studies and database development and sharing. The QIN is organized with four Working Groups: Data Acquisition Working Group, Image Analysis, and Performance Metrics Working Group, Bioinformatics/IT and Data Sharing Working Group, and Clinical Trial Design and Development Working Group.

The Quantitative Imaging Biomarker Alliance (QIBA) (http://www.rsna.org/qiba/) was organized in 2007 by the Radiological Society of North America (RSNA). QIBA's mission is to seek to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time. The QIBA is working on identifying needs, barriers, and solutions to develop and test consistent, reliable, valid, and achievable quantitative imaging results across imaging platforms, clinical sites, and time. The QIBA develops "Profiles", which are documents that describe one or more "Claims" that tell a user what can be accomplished by following the Profile and "Details" that tell a vendor what must be implemented in their products and tell a user what procedures are necessary. The Profile establishes a written standard procedure for obtaining an accurate and reproducible measurement that reflects an imaging biomarker of clinical interest. DCE-MRI profile was released in 2012, which defines basic standards for DCE-MRI measurements and quality control that enable consistent, reliable and fit-for-purpose quantitative k^{trans} and blood-normalized initial area under the gadolinium curve (IAUGC) results across imaging platforms, clinical sites and time.[123]

The American College of Radiology Imaging Network (ACRIN) is designed to provide resources for conducting clinical trials of imaging techniques that apply to cancer screening, diagnosis, staging, imaging as a biomarker and image-guided treatment. The protocols and concepts are reviewed and approved by the Cancer Imaging Program, NCI Steering Committees and the Protocol Review Committee of the Clinical Trials Evaluation Program. The ACRIN was recently merged with Eastern Cooperative Oncology Group (ECOG) to form the ECOG-ACRIN in 2011 with the broader mission to improve patient outcomes through earlier cancer detection and more successful therapeutic interventions.

The Quantitative Imaging in Cancer: Connecting Cellular Processes to Therapy (QuIC-ConCePT) (http://www.quic-concept.eu/) consortium was created under Innovative Medicines Initiative (IMI) to qualify imaging biomarkers of tumor cell proliferation, apoptosis, and necrosis. The QuIC-ConCePT evaluates imaging biomarkers, assesses their reproducibility, effects of intervention, timing, dose-response, and imaging-histopathology correlation in animals and patients. Platforms for data acquisition, analysis, and dissemination will be standardized and integrated across the consortium in order to support this project.

Procedure standardization for using imaging biomarkers in clinical trials

When designing the clinical trial, an interdisciplinary team is formed with early engagement with imaging experts to select appropriate imaging biomarkers based on the understanding of biological mechanism, and discuss on the feasibility and cost-

effectiveness. Imaging charter is developed with specific imaging guidelines. Statistical power calculation is performed to decide the requisite sample size.

Before activation of the trial, evidence of scanners calibration and/or accreditation and test scans on phantom or human subjects needs to be submitted to investigators/sponsors. Standard operation procedures (SOP) and QA/QC program need to be established followed by proper site staff training (e.g. investigator, imaging technologist, and research coordinator, etc.). Independent central review may be used to avoid bias and to reduce measurement variability. Imaging central review procedures need to be defined including review panel, description of imaging criteria, and turn-around time, etc. Independent reviewers need to receive adequate training.

During the trial, imaging data protection, QA/QC, data transfer, data management and tracking, and imaging analysis and interpretation should strictly follow the SOP and criteria set out in the imaging charter.

After accrual, database is locked down and results are summarized and prepared for submission to the regulatory agency. It is essential to have a well-documented pathway from acquisition to the final disclosure of results.

Other factors related to MRI biomarkers

Last but not least, MRI safety for patients enrolled in clinical trials needs to be considered when designing the protocol. The toxicity risk of gadolinium-based contrast agent (GBCA) used in DCE- and DSC-MRI must be taken into consideration. It is associated with increased risk of nephrogenic systemic fibrosis (NSF), particularly in patient with renal insufficiency, or with glomerular filtration rate (GFR) less than 30 mL/(min · 1.73 m^2).[124] In July 2015, FDA issued a drug safety communication regarding the risk of brain deposits with repeated use of GBCA for MRI, even in individuals with normal kidney function. It is unknown whether these gadolinium deposits are harmful or can lead to adverse health effects. FDA, including its National Center for Toxicological Research (NCTR), will study this possible safety risk further. FDA states: “To reduce the potential for gadolinium accumulation, health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols”. It is suggested that transition from linear non-ionic GBCA to more stable types of macrocyclic ionic GBCA may reduce the risk of the retained gadolinium. However, the use of new types of GBCA brings new challenges that require revalidation of the qMRI techniques due to the different relaxivity of these new contrast agents. In addition, the MRI accreditation program by American College of Radiology (ACR) expanded its requirements in 2012 and created the ACR Guidance Document for Safe MR Practices 2013 that addresses numerous MR safety related topics.

Conclusions

To accelerate the research on drug development, detection of drug effects is essential to understand the mechanistic actions of the drug, and help the dose optimization and decision making for subsequent late-stage or large-scale trials. To incorporate quantitative imaging biomarkers in oncological clinical trials, it is required that the measured changes in imaging biomarkers be faithfully reflective of underlying tumor biological changes, and that the imaging biomarkers should be applicable, reliable and robust to be deployed at multi-centers in a consistent way. The qMRI techniques in clinical trials as primary endpoints need further validation with histopathological analyses to fully understand the relationship between the imaging measurements and tumor biology. Highly standardized imaging protocols and organized infrastructure need to be established across clinical trial organizations, cancer centers and imaging facilities.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Edited by Pei-Fang Wei