Review Article

Role of Quantitative Magnetic Resonance Imaging Parameters in the Evaluation of Treatment Response in Malignant Tumors

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Abstract

Objective: To elaborate the role of quantitative magnetic resonance imaging (MRI) parameters in the evaluation of treatment response in malignant tumors.

Data Sources: Data cited in this review were obtained mainly from PubMed in English from 1999 to 2014, with keywords "dynamic contrast-enhanced (DCE)-MRI," "diffusion-weighted imaging (DWI)," "microcirculation," "apparent diffusion coefficient (ADC)," "treatment response" and "oncology."

Study Selection: Articles regarding principles of DCE-MRI, principles of DWI, clinical applications as well as opportunity and aspiration were identified, retrieved and reviewed.

Results: A significant correlation between ADC values and treatment response was reported in most DWI studies. Most quantitative DCE-MRI studies showed a significant correlation between K^{trans} values and treatment response. However, in different tumors and studies, both high and low pretreatment ADC or K^{trans} values were found to be associated with response rate. Both DCE-MRI and DWI demonstrated changes in their parameters hours to days after treatment, showing a decrease in K^{trans} or an increase in ADC associated with response in most cases.

Conclusions: Combinations of quantitative MRI play an important role in the evaluation of treatment response of malignant tumors and hold promise for use as a cancer treatment response biomarker. However, validation is hampered by the lack of reproducibility and standardization. MRI acquisition protocols and quantitative image analysis approaches should be properly addressed prior to further testing the clinical use of quantitative MRI parameters in the assessment of treatments.

Key words: Apparent Diffusion Coefficient; Diffusion-weighted Imaging; Dynamic Contrast-enhanced Magnetic Resonance Imaging; Microcirculation; Oncology; Treatment Response

Introduction

Incidences of malignant tumors continue to increase due to a combination of factors, including smoking, aging population and carcinogenic substances in the environment. Attempts with therapeutic options include radiotherapy, various chemotherapeutic regimens and individualized molecularly targeted drugs have highlighted the limitations of the evaluation of treatment response based on tumor size reduction only, which may not always typically occur until days or weeks after fractionated regimens. Another considerable problem is that the functional changes acted by any effective therapy in the tumor microenvironment are not directly evaluated on anatomic imaging.

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The identification of factors that enable evaluation of treatment response is important with regard to the selection of the optimal following therapy. Tumors identified to be less responsive can be subjected to alternative treatment strategies or investigational therapies. Unfortunately, the histologic treatment response information acquired by morphologic imaging is limited. Therefore, there is a need for clinically significant noninvasive evaluation of treatment response.

In view of the diversity of magnetic resonance imaging (MRI) sequences available, an ever-increasing body of research indicates that quantitative MRI parameters may play an important role on this respect of research.[1-9] In this review, we will focus on the recent development in this field, especially dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted imaging (DWI).

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Principles of dynamic contrast-enhanced magnetic resonance imaging

Dynamic contrast-enhanced-MRI is a promising imaging technique that can enable noninvasive quantitative assessment of tissue microvasculature, such as tissue perfusion, capillary permeability, and integrity.[10,11] The information acquired from data can be applied to a study of angiogenesis, hypoxia, and evaluation of various biomarkers. Regions of necrosis, muscle, vessel, and viable information inside the tumor display distinct signal enhancement in dynamic images. DCE-MRI in combination with tumor morphologic imaging could provide a possible prognostic response to antiangiogenic treatment.[7] Quantitative measures generated from DCE-MRI data involve evaluation of some combination of principal kinetic parameters: The influx volume transfer constant (K^{trans}), the efflux rate constant (k_{ep}), the relative extravascular extracellular space (EES) fractional volume (v_e), and the relative vascular plasma space (v_p) from a two-compartment pharmacokinetic model proposed by Tofts *et al*.,[10] and the corresponding differences (ΔK^{trans}, Δk_{ep}, Δv_e, and Δv_p) between outer and inner tumor.[6,8,12-14] The K^{trans} (min^{-1}) is transendothelial transport of contrast medium from the vascular compartment to the tumor interstitium. The k_{ep} (min^{-1}) reflects the reverse transport of contrast medium back into the vascular space. K^{trans} and v_e relate to the tissue's basic physiology, whereas the rate constant (k_{ep}) is the ratio of the transfer constant to the EES:[10]

$$k_{ep} = \frac{K^{trans}}{v_e}$$

k_{ep} can be derived from the shape of the gadolinium concentration versus time results, whereas K^{trans} and v_e require knowledge of the absolute values of gadolinium concentration. K^{trans} has several physiologic interpretations, depending on the tissue's vascular permeability and perfusion.

Compared with the complex quantitative parameters, a qualitative assessment of perfusion based on the shape of the signal intensity versus time curve may also be useful clinically for assessing response to treatment. Tissues are described using a number of descriptors including onset of enhancement, maximum signal intensity, and the washout gradient and so on.[15] These semi-quantitative parameters have the advantage of being relatively straightforward to calculate and can be used when quantitative techniques fail.

Principles of diffusion-weighted imaging

Diffusion-weighted-MRI is a technique that is acquired to make the MR signal sensitive to the molecular motion of water by applying strong magnetic field gradients. Movement including directed perfusion and passive thermally-induced diffusion can be measured, which is constrained by the cell size, structure, membrane, and organelles form physical boundaries. The rate of diffusion of water molecules in cellular tissues is usually described by means of an apparent diffusion coefficient (ADC), which is always lower than that of free water. Many treatments, such as radiation and/or chemotherapy, can result in the loss of the cell membrane integrity that may affect water diffusion and perfusion. Thus, DW-MRI can provide microstructural information on the cellular level in a detectable way long before tumor size reductions are seen. This ability aids in determining prognosis as well as planning treatment strategies.

Diffusion-weighted images acquired at a minimum of two sensitivity levels defined by the sequence b-value provide an estimate of ADC, which represents the magnitude of random motion of water molecules. ADC value is impeded by cellular packing, cell membrane and macromolecules presented in the various tissues, and displays lower especially in tumors. On the other hand, ADC values are often increased in the necrotic regions and tissues with damaged or permeable cell membranes. Therefore, variation in ADC values reflects the alteration and redistribution of water molecules between intracellular and extracellular compartments of tissue.[16]

The b-value determines the extent of DW in a scan. The proper selection of b-value is an important technical consideration, and dependent on the given body DWI application and objective. Observed signal attenuation differs in different tissues, which may follow the two types of decay models: Bi-exponential behavior and a single exponential behavior. In most clinical DWI studies, the bi-exponential behavior of signal attenuation is not observed due to the low b-values used. Therefore, it is common practice to fit the DWI data to a single exponential decay model.

Clinical Applications

Differentiating malignant tumors from benign ones

Quantitative DCE-MRI parameters can be used to differentiate malignant tumors from benign ones. This application of research is mainly documented in breast and prostate cancer, where malignant lesions usually have higher K^{trans} than benign tumors and tumor-like growths.[6,7,13] Malignant lesions have rapid and high amplitude contrast medium wash-in followed by a relatively rapid wash-out, whereas benign lesions are characterized by contrast medium wash-in followed by persistent enhancement, due to a lower degree of angiogenesis.[17,18] These results are consistent with recently reported documents of malignant tumors in the head and neck including the sinonasal area.[19,20] Xian *et al*. demonstrated a significant difference in v_e between epithelial and nonepithelial malignant tumors and a significant difference in k_{ep} and v_e between malignant epithelial tumors and lymphomas in the sinonasal region.[20]

Tumors differ in their cellularity, and this difference may reflect their histologic composition and biologic aggressiveness. In a study that included carcinomas, lymphomas, benign salivary gland adenomas and benign cysts,[21] the mean ADC value of benign solid lesions significantly higher than that of malignant tumors was found. In the same way, investigators have found that benign liver

lesions, such as cysts and hemangiomas, have higher mean ADC values than malignant lesions, such as metastases and hepatocellular carcinoma (HCC).[22,23]

Monitoring treatment response in different sites

Many DCE-MRI studies have suggested that quantitative parameters can be used as potential markers for prediction of treatment response and long-term survival.[8,24] K^{trans} reflects a combination of tumor blood flow and microvascular permeability. On the other hand, K^{trans} values are also used to monitor response to cancer therapies.[25] In addition to K^{trans}, the other kinetic analysis of DCE-MRI data, v_e, v_p and k_{ep}, are also used to describe the uptake of low molecular weight gadolinium-medium contrast agents. The parameter v_e reflects the EES, which is composed of interstitial fluid and connective tissue arranged in a supportive frame structure and restricted by blood vessel walls and cell plasma membranes. Interestingly, controversy exists in the previous and current research, as other recently published papers exhibited the importance of v_e, v_p and k_{ep} as prognostic biomarkers of clinical outcome in patients with cancers of other regions.[26-28] Given the inherently different physiologic information that these parameters offer, we believe these parameters may play a complementary role in the evaluation of all oncological treatment response when used in combination with other quantitative and qualitative parameters. If confirmed in a larger trial, the prognostic significance of the DCE-MRI parameters would be useful to stratify patients in future clinical trials and to identify therapeutic regimen individually.

Diffusion-weighted imaging-MRI can be used to detect microstructural changes that precede changes in tumor size as an indication of tumor response to therapy. For many organs and tumor types, a tumor initially demonstrates decreased ADCs relative to the surrounding tissue due to diffusion restriction caused by high cell density in the tumor. Effective treatment on oncology results in tumor lysis, loss of cell membrane integrity, increased extracellular space. So, a positive response to treatment may tend to result in an increase in ADC.

These quantitative MRI parameters have been investigated extensively in the evaluation of treatment response in different malignant tumors. Recent research focusing on these aspects includes data on breast cancer, prostate cancer, colonic and rectal cancer, malignant liver lesions, and head and neck cancer.

Breast cancer

Diffusion-weighted imaging and DCE-MRI are under development for monitoring response to cancer therapies.[25] Incremental ADC increase over chemotherapeutic treatment cycles is found in a number of breast cancer studies[29-32] while the morphological change did not detect until second cycle of chemotherapy.[33] The increase in ADC values was due to both activation of apoptosis and presentation of cell death within the tumor,[34] which can be detected as early as 3 days after treatment.[35] Decrease in the transfer of gadolinium contrast from blood vessels to tumor tissue, measured by K^{trans}, is observed with cytotoxic therapy[29] and antiangiogenic therapies in breast cancer.[36] This result supports the idea that successful treatment where killing of tumor cells causes vascular shutdown due to loss of the proangiogenic cytokine may result in apoptosis of proliferating endothelial cells.[37]

Prostate cancer

Apparent diffusion coefficient increase was found in response to both radiotherapy and antihormonal therapy,[38,39] and patients with high K^{trans} value before treatment were demonstrated response to chemoradiation therapy and prolonged survival.[7] In the evaluation of local tumor progression of prostate cancer after high-intensity focused ultrasonic ablation, DCE-MRI was more sensitive than T_2-weighted MRI with DWI, but T_2-weighted MRI with DWI was more specific than DCE-MRI[40] or T_2-weighted MRI alone.[41] In another study, multiparametric MRI, including DW-MRI, can achieve accuracy levels of 80–90% in the detection of recurrent prostate cancer after radiation therapy, which may have implications for determining presence or absence of local recurrence and subsequent local salvage therapy.[42]

Colonic and rectal cancer

Change of the ADC value in rectal cancer was unlike others. Pretreatment ADC values in rectal cancer patients were found to be negatively correlated with percentage size change of tumors after chemotherapy and chemoradiation: The presence of higher pretreatment ADC values reflected necrotic tumors that were resistant to therapy. Persistence of low ADC in responders after chemotherapy could represent a loss of a nonviable fraction of the treated tumor.[43] Another explanation is that this manifestation was attributed to the possible increase in fibrosis and proctitis in response to treatment.[44]

In the study by DeVries *et al*.,[45] a significant difference in the intratumoral frequencies of perfusion index values before therapy was found between patients responding to chemoradiation and those not responding. This finding allows the formulation of the hypotheses for advanced primary rectal carcinoma: The response to chemoradiation is determined by tumor microcirculation before therapy.

Malignant liver lesions

Several studies demonstrated that ADC increases correlated with response to systemic chemotherapy of liver metastases of breast and colorectal cancer.[46-48] In a study of 24 patients with unresectable HCC undergoing transcatheter arterial chemoembolization (TACE), mean tumor size was unchanged up to 4 weeks after TACE whereas reduction in tumor ADC was significant 1–2 weeks after therapy.[49] In this way, the use of DW-MRI seems to be an advantage over tumor morphology.

Magnetic resonance perfusion derived HCC parameters, K^{trans} and Kep, were sensitive imaging biomarkers. Higher baseline K^{trans} value and more substantial drop in K^{trans} and

K_{ep} at 2 weeks after therapy correlated with better clinical outcome.[50] This manifestation reflected the underlying tumor permeability changes induced by antiangiogenic therapy.

Head and neck cancer

Apparent diffusion coefficient value can be used as a biomarker for the prediction and early detection of response to concurrent chemoradiation therapy in head and neck cancer. Primary tumors and metastatic lymph nodes with lower ADC values are more likely to have a better response to the treatment.[51,52] Follow-up and early response to treatment have shown ADC increase in both primary tumor and nodal metastasis.[9,52-54] In complete responders significant increase in ADC was observed within 1-week of treatment that continued until the end of treatment.[51]

Malignant tumors responsive to chemoradiation therapy have significantly higher K^{trans} values before treatment than those partial response or no response.[8,20,24] The responders show prolonged survival in the follow-up study. These results support the idea that relatively higher blood flow in tumors associated with increased oxygenation levels may result in better access to chemotherapeutic drugs and radiosensitivity.[55] However, one study of squamous cell carcinoma in head and neck failed to show a significant difference in v_e, v_p and k_{eP} values between responders and nonresponders.[19]

Osteosarcoma

Diffusion-weighted-MRI may be useful in assessing response to cytotoxic chemotherapy. Tumors with no increase in ADC showed a poor response to chemotherapy on their histology results.[56,57] At mid-course of treatment, the ADC differential ($ADC_{post} - ADC_{pre}$) had 100% sensitivity and 57% specificity for predicting poor responders.[56] In another study, the patients with a good response had a significantly higher minimum ADC ratio ($[ADC_{post} - ADC_{pre}]/ADC_{pre}$) than those with a poor response.[57] DCE-MRI was also a prognostic factor for indicative of histologic response to neoadjuvant therapy. In the analysis by Guo *et al*.,[26] response was found as a time-dependent covariate and K^{trans}, v_p, and Δk_{ep} at week 9 were significantly different between responders and nonresponders.

Conclusion

As more individualized, biomarker-driven therapies are developed, and with cost incentives for comparative effectiveness research to assess these individualized therapies, the multidisciplinary nature of oncology research must be accommodated. The multiparametric MRI approach including anatomical and functional imaging techniques proves to be the optimal approach in the diagnosis of tumors and prediction and evaluation of treatment response.[30,58,59] However, prospective and multi-center studies must be conducted to assess quantitative MRI parameters as the most appropriate imaging biomarkers.

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