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Recent Progress of Diffusion Weighted Magnetic Resonance Imaging in Assessment of Tumor in the Body

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ABSTRACT In the last couple of years, as the development of new imaging techniques, diffusion-weighted magnetic resonance imaging (DW-MRI) has been applied increasingly in the evaluation of various diseases in the body, and has been adopted frequently as an imaging tool in clinical tumor assessment. As a completely non-invasive, highly sensitive, well-tolerated and relatively low cost technique, diffusion-weighted imaging (DWI) can supply both quantitative and qualitative information at the cellular level by exploring irregular diffusion motion of water molecules within tissues in the body. In this article, we summarized the recent application and reliability of DWI in tumor evaluation including tumor detection, tumor features, and outcome of early treatment response.

KEY WORDS: magnetic resonance imaging, diffusion-weighted, tumor.

Introduction

As a new promising image technique, diffusion-weighted magnetic resonance imaging (DW-MRI) explores the Brownian motion of water molecules in biological tissues. The motion of water molecules in vivo, unlike those in vitro where there is free diffusion, is restricted by the limitation of interactions with intracellular elements, macromolecules, hydrophobic cell membranes, and cell density. And it has been found that the degree of restriction to water diffusion in biological tissues is inversely proportional to the tissue cellularity and the integrity of cell membranes[1]. In areas of low cellularity, or where the cellular membrane has been damaged, the diffusion of water molecules is less restricted; where as in tissues of high cellular density is associated with numerous intact cell membranes, the diffusion of water is more limited.

The parameter value of "apparent diffusion coefficient" (ADC), which depends largely on the presence of barriers to diffusion within the water microenvironment such as cell membranes, tight junctions, fibers, macromolecules, and cell organelles is customarily used to represent the diffusion ability of different tissues in the body[2]. As the ADC value is estimated to be lower in tumor tissue with densely packed diffusion-hindering obstacles than in tissue with less densely packed obstacles such as tumor necrosis and benign tissue, the ADC value can effectively help radiologists in determining different types of tissue and tissue characteristics by quantitively evaluation. In clinical application, the diffusion sensitivity of the diffusion-weighted imaging (DWI) is determined by the parameter of "b value" which is

changed by altering the gradient amplitude, the duration of the applied gradient, and the time interval between the paired gradients. Water molecules with a larger degree of motion will show signal attenuation with smaller b values. By contrast, larger b values are usually required to perceive smaller diffusion distances because these show more gradual signal attenuation with increasing b values. DWI is commonly performed using 2 b values (e.g., b = 0 s/mm^2 and the other b values from 0 to 1,000 s/mm^2) to enable meaningful interpretation. Generally, the larger the b value is, the greater the degree of signal attenuation from water molecules. By observing the relative attenuation of signal intensity obtained from different b values, qualitive tissue characterization based on differences in water diffusion becomes possible[3]. Consequently, DWI can supply both quantitative and qualitative information of the biological tissue by calculating the ADCs of cell structures and using different b values.

Due to the low incidence of movement artifacts, the very high brain homogeneity and high signal-to-noise ratio (SNR), most early research on DW-MRI was performed in the brain, especially as a diagnostic tool for patients with ischemic stroke[4]. In the last couple of years, thanks to a series of technologic advances including echo-planar imaging (EPI), high gradient amplitudes, multichannel coils, and parallel imaging, high-quality diffusion-weighted (DW) images of body has been adopted increasingly in practice, thus making the clinical application of DW-MRI for tumor assessment in the body more and more popular.

Utilized in tumor detection and characterization

Brain

It has been well demonstrated in many pilot studies[5-7] that ADC measurements can significantly help discriminate capsular stage of brain abscesses from necrotic or cystic neoplasms which cannot be distinguished by conventional computed tomography and MR images. Recently, a study by Fertikh et al. has shown that the accuracy of ADC ratios in discriminating brain abscesses from cystic or necrotic neoplasms is very high (0.9 ± 0.04) and can be further improved using T2 rim characteristics (efficiency, 94.3%)[8]. In their study, ADC ratios were found significantly higher in neoplasms than in bacterial abscesses ($P < 0.01$) and in abscesses of unknown origin ($P < 0.001$), whereas the difference in ADC ratios between neoplasms and nonbacterial abscesses showed only a trend toward significance ($P = 0.062$). In addition, the ADC ratios in bacterial abscesses were similar to those in abscesses of unknown origin ($P = 0.68$).

A retrospective review by Yamasaki et al.[9] on DW imaging with ADC calculated b values at 0, 250, 500, 750, and 1000 sec/mm^2, respectively, demonstrated that ADC was useful for differentiation of some human brain tumors. In their experiment, a significant negative correlation existed between ADC and astrocytic tumors in grades 2-4 classified according to World Health Organization Classification (grade 2 *vs.* grades 3 and 4, accuracy of 91.3%, $P < 0.01$; grade 3 *vs.* 4, accuracy of 82.4%, $P < 0.01$). ADC of dysembryoplastic neuroepithelial tumors (DNTs) was higher than that of astrocytic tumors in grade 2 (accuracy, 100%) and other glioneuronal tumors. ADC of malignant lymphomas was lower than that of glioblastomas and metastatic tumors (accuracy, 83.6%; $P < 0.01$). ADC of primitive neuroectodermal tumors (PNETs) was lower than that of ependymomas (accuracy, 100%).

Head and neck

DW-MRI can also help in the differential diagnosis of many disorders of the head and neck by calculating the ADC (i.e., differentiating carcinomas from lymphomas, or necrosis from abscess), though there is still some overlap between certain benign and malignant tumors in salivary glands[10]. de Bondt et al.[11] demonstrated in their latest research that the use of ADC values in combination with other MRI criteria (such as size and morphology) significantly improved the discrimination between malignant and benign lymph nodes. And the optimal ADC threshold was 1.0×10^{-3} mm^2/s with sensitivity and specificity being 92.3% and 83.9%, respectively.

Breast

DW-MRI becomes a valuable diagnostic tool in detecting and evaluating breast abnormalities[12]. A clinical trail of DW-MRI in detecting breast, which was performed with b values at 0, 750 and 1000 s/mm^2, showed that the mean ADC value of breast cancer was $(1.12 \pm 0.24) \times 10^{-3}$ mm^2/s, which was lower than that of normal breast tissue, and that the sensitivity of the ADC value for breast cancer using a threshold of less than 1.6×10^{-3} mm^2/s was 95%[13]. Lo et al.[14] also confirmed that diffusion-weighted imaging at 3T was highly sensitive in the detection of malignant breast lesions even with qualitative assessment alone, whereas ADC measurements offered quantitative assessment and increased the specificity to more than 90%. It seems that the breast tumor's ADC correlates inversely with its tumor cellularity[12]. However, in another research, almost concurrently, it was found that there was no correlation between the ADC values and cancer cellularities although the mean ADC values for breast cancer were significantly different from that of normal breasts[15]. So further studies are required to validate the results.

Lung

A preliminary study was performed by Matoba et al.[16] focused on DW-MRI with a split acquisition of fast spin-echo signals for diffusion imaging (SPLICE) se-

quence in tissue characterization of lung carcinomas by calculating the ADC value with relatively low b values. In their study, the mean ADC value of adenocarcinoma was observed significantly higher than that of squamous cell carcinoma and of large-cell carcinoma ($P < 0.05$); and in particular, the mean ADC value of well-differentiated adenocarcinoma was significantly higher than that of poorly differentiated adenocarcinoma and of squamous cell carcinoma ($P < 0.05$), which implys there was a negative correlation between mean ADC values of lung carcinoma and tumor cellularities. Consequently, we can educe from the study that ADC values of lung carcinoma might be considered as a differentiating parameter to distinguish different histological types of lung carcinoma.

Liver

The development of DWI for liver neoplasm has been behind the development of DWI in detecting the brain and pelvis due to its motion sensitivity and susceptibility variations. Recently, thanks to the advancement of parallel acquisition technique (SENSE) for single-shot echo-planar, DW-MRI has been applied increasingly in detecting liver for lesion characterization, liver metastases and in evaluating the response of the patients with hepatic metastases to therapy. Inanl et al.[17] postulated after their research in 2007 that DWI may help in the differential diagnosis of hydatid and simple cysts of the liver. In the prospective study (with b value at 1000 s/mm^2), both the signal intensity and cyst-to-liver signal intensity ratio of the hydatid cysts were observed significantly higher than those of simple cysts ($P < 0.001$); and both the ADC and cyst-to-liver ADC ratio of the hydatid cysts were significantly lower than those of simple cysts ($P < 0.005$). With a cut off value of 1.5, signal intensity ratio had a sensitivity of 77%, specificity of 86%, and positive predictive value of 83%.

Endometria

Currently, more and more clinical trails have confirmed that the ADC measurement on DWI has a great capability in differentiating normal tissues from cancerous endometria[18]. One study of DW-MRI with a single-shot echo-planar sequence and parallel technique showed that the mean ADC value of endometrial cancer was $(0.864 \pm 0.16) \times 10^{-3}$ mm^2/s, which was significantly lower than that of normal endometrium $(1.277 \pm 0.10) \times 10^{-3}$ mm^2/s ($P < 0.01$)[19]. Similar results have been obtained by McVeigh et al.[20] and Charles -Edwards et al.[21]

Prostate

Investigators have demonstrated in several studies[22-25] that adding an ADC map to T2-weighted values can enormously improve the diagnostic performance of MR imaging in prostate cancer detection, and ADCs are observed significantly lower in malignant than in non-malignant prostate tissue [26]. However, HK et al.[27] observed in their latest work that although dense prostate tumors had significantly lower ADC and T2 values than normal peripheral zone tissue ($P < 0.05$), no significant differences were detected between sparse tumors and normal tissue. Therefore, further evaluation is needed to ascertain the outcome.

Contribution of different b values in tumor detection

The low b-value (i.e., 50-150 s/mm^2) images of the DWI, which suppress the high-signal flow from the hepatic vessels, have been confirmed to be useful for the detection of metastasis since metastases commonly appear as high-signal intensity. Nasu et al. have perceived in their research that DWI has a higher accuracy (with sensitivity of 82% and specificity of 94%) than superparamagnetic iron oxide (SPIO)-enhanced MRI (with sensitivity of 66% and specificity of 90%) in detecting liver metastases[28]. A similarly high sensitivity of 86% and specificity of 94% in the detection of colorectal hepatic metastases by DWI has been observed by Dow-Mu et al.[29] in another study.

On the other hand, Ichikawa et al. reported a sensitivity of 91% and a specificity of 100% for the detection of colorectal cancer using high-b-value DW-MRI in 2006[30]. Then most recently, a similar high sensitivity (96.2%) and specificity (98.6%) in the detection of pancreatic adenocarcinoma using the same technique has been obtained in a study by Ichikawa et al.[31] again.

Role of ADCs in the prediction of early treatment response

DWI is being widely applied in assessing the response of tumor to treatment and therapeutic effects because of the interesting finding that the ADC value of the tumor usually changes before its morphological change. Research in rectal carcinomas[32,33], pancreatic[34] and cervical cancers[35], as well as gastrointestinal hepatic metastases[36,37] have shown the reliability of quantitative DWI in the prediction of response of cancers to chemotherapy and chemo-radiation treatment. In these studies, it has been well demonstrated that tumors with lower pretreatment ADC values respond better to chemotherapy, or radiation treatment than those with higher pretreatment ADC values. Cui et al.[36] demonstrated in their work that early increased ADC may be a suitable biomarker to indicate the response to treatment and the change in ADC occurs earlier than the change in tumor size in gastrointestinal carcinoma liver metastases. A similar conclusion has been made by Koh et al.[37] in 2007. And most recently, that a small high-b-value ADC in advanced pancreatic cancer patients treated with chemotherapy may predict early progression as has been corroborated by Niwa et al.[34]

The above observations are all consistent with the results of preclinical trials in animal models[38,39] and humans[40,41] in which an increased ADC was observed after a series of different therapeutic regimens were given. So it seems that the increase of ADC in necrotic tissue appears to be a universal response to therapy, regardless of the tumor type or therapeutic regimen. In theory, necrosis is the consequence of cellular damage resulting in the increases of ADC[42]. Because necrotic regions in a tumor usually have poor blood supply, it is difficult for chemotherapeutic drugs to reach these areas. Furthermore, tumor cells in necrotic areas are exposed to a more hypoxic and acidic environment, which diminishes the effectiveness of chemotherapy[39]. Of course, not all necrosis within tumor would be correlated to a high ADC. Coagulative necrosis, for example, without tumor cell liquefaction may not actually increase the ADC.

Conclusion

Diffusion weighted MRI has been shown to be a novel and powerful technique in oncology imaging by demonstrating its value in the clinical assessment of tumors. It is highly sensitive, completely non-invasive, relatively low cost, and can be done quickly. Moreover, due to its high accuracy in mass localization, future clinical research may demonstrate its application in targeting tumor margins for radiation therapy after further clinical researches. In conclusion, DW-MRI will increasingly become a significant and regular tool in the area of oncology imaging in the near future.

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