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Pitfalls and Limitations of Diffusion-Weighted Magnetic Resonance Imaging in the Diagnosis of Urinary Bladder Cancer

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Abstract

Adequately selecting a therapeutic approach for bladder cancer depends on accurate grading and staging. Substantial inaccuracy of clinical staging with bimanual examination, cystoscopy, and transurethral resection of bladder tumor has facilitated the increasing utility of magnetic resonance imaging to evaluate bladder cancer. Diffusion-weighted imaging (DWI) is a noninvasive functional magnetic resonance imaging technique. The high tissue contrast between cancers and surrounding tissues on DWI is derived from the difference of water molecules motion. DWI is potentially a useful tool for the detection, characterization, and staging of bladder cancers; it can also monitor posttreatment response and provide information on predicting tumor biophysical behaviors. Despite advancements in DWI techniques and the use of quantitative analysis to evaluate the apparent diffusion coefficient values, there are some inherent limitations in DWI interpretation related to relatively poor spatial resolution, lack of cancer specificity, and lack of standardized image acquisition protocols and data analysis procedures that restrict the application of DWI and reproducibility of apparent diffusion coefficient values. In addition, inadequate bladder distension, artifacts, thinness of bladder wall, cancerous mimickers of normal bladder wall and benign lesions, and variations in the manifestation of bladder cancer may interfere with diagnosis and monitoring of treatment. Recognition of these pitfalls and limitations can minimize their impact on image interpretation, and carefully applying the analyzed results and combining with pathologic grading and staging to clinical practice can contribute to the selection of an adequate treatment method to improve patient care.

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Introduction

Urinary bladder cancer is one of the most common urinary tract malignancies, causing notable morbidity and mortality [1,2]. The management and prognosis of bladder cancer are based on T staging, pathologic grading of the tumor, and the presence or absence of metastatic disease. Clinical staging of the primary tumor with bimanual examination, cystoscopy, and transurethral resection of bladder tumor (TURBT) is associated with an inaccuracy rate from 23% to 50% [3–7]. Therefore, obtaining an accurate imaging study is important to facilitate choosing optimal management methods.

Magnetic resonance imaging (MRI) is a feasible and reasonably accurate technique for the local staging of bladder cancer preferred over computed tomography (CT) [2] not only because MRI provides multiplanar images but also because the tissue contrast resolution is high. Furthermore, the application of functional images such as

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diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE) to the anatomic images improves the accuracy of tumor detection and staging, and helps in monitoring posttherapy response and identifying recurrences [8–13].

DWI provides functional and structural information about biological tissues. It can be obtained rapidly and noninvasively without exposure to ionizing radiation and does not require gadolinium contrast administration. This is beneficial to a substantial group of bladder cancer patients who are allergic to contrast medium or who have renal dysfunction because it allows them to avoid contrast medium–induced nephrotoxicity and nephrogenic systemic fibrosis. DWI has played an important role in the multiparametric MRI and is a useful technique to increase the accuracy in detecting and evaluating the extent of bladder cancer [8–11,13]. In addition, it has also been applied to assess the biological behavior of bladder cancer. Apparent diffusion coefficient (ADC) value derived from DWI, which has been reported as a potential biomarker, could predict histopathological grading and reflect the aggressiveness of bladder cancer [14–18].

However, limitations exist, including a wide spectrum of cancer mimickers on DWI, intrinsic matters limiting the clinical applications of ADC values, inadequate patient preparation, presence of artifacts, and thinning of the bladder wall leading to inaccurate diagnosis, any of which could lead to under- or overstaging and impair the ability to determinate tumor aggressiveness. Moreover, difficult differentiation between benign lymph node and metastatic lymphadenopathy and interpretation of DWI in bone lesions also challenge the application of DWI to evaluate metastases. Although some studies have thoroughly reviewed the clinical use of DWI for bladder cancer assessment [19–21], pitfalls and limitations in the application of DWI to evaluate bladder cancer were not systemically reviewed. Full understanding of the limitations and careful avoidance of the pitfalls would promote more efficient use of DWI to assess bladder cancer.

Herein we described the biophysics of DWI and ADC, the histopathology of bladder cancer, the pitfalls and limitations in general utilization, and the clinical application of DWI for bladder cancer assessment based on our experiences and a review of the literature.

Biophysical Basis and General Limitations of DWI and ADC

Biophysical Basis of DWI

DWI is a functional imaging technique that depicts differences in the microscopic mobility of water molecules, called *Brownian motion*; this mobility depends on the integrity of cell membranes and the cellularity of the underlying tissue, thus reflecting biologic abnormalities. Advancement of imaging techniques, such as echo planar imaging, parallel imaging, multichannel coils, and high gradient amplitudes, has enabled the application of DWI in the abdomen and pelvis [22,23].

The movements of water molecules within some normal tissues, including neurological tissue, lymphatic tissue, bowel mucosa, testis, and endometrium, are restricted because these are highly cellular tissues that show persistently bright on DWI, even at high *b*-values. Pathologic lesions, such as tumor and infarction, have been reported to be associated with impeded water diffusion. Tumor tissue has high cellular density, high nuclear-cytoplasmic ratio, and high extracellular disorganization [22], causing restricted water diffusion leading to high signal intensity (SI) on DWI and reduced ADC value. Restricted water molecular movement in infarction is mainly related to cytotoxic edema. Water diffusion is also impeded in fibrosis and in the presence of highly viscous fluids such as abscess; thus, these conditions have the same SI on DWI and ADC as malignancy [24,25]. Lesions with a high fluid content have a strong T2 SI that may be carried onto the DWI to mimic or obscure cancer as a T2 shine-through effect. This pitfall may be avoided by referring to the ADC map and discloses its true diffusivity.

Quantifying the Degree of Water Diffusion

The ADC value is quantitative assessment of the SI changes of tissue as an increase of *b*-values. The calculation of ADC value is acquired via a diffusion equation that requires two or more *b*-values. The ADC map is a gray-scale display of the quantitative analysis of DWI. The "*b*-value" is proportional to the amplitude and duration of the applied gradient and the time interval between the paired gradients [22,23]. Changing the *b*-value alters the sensitivity to detect water diffusion. The SI of tissues on small *b*-values DWI incorporates both the slow diffusion component of thermally generated water mobility and the fast diffusion component that results from the mobility within the capillary network, whereas the fast diffusion component is restricted on higher *b*-values DWI. Increasing the *b*-value of DWI would get higher lesion-to-tissue contrast; however, this would decrease the signal-to-noise ratio and demonstrate greater image distortion. Moreover, as the *b*-value increased, the ADC value decreased [26] because of the exponential diffusion signal decay. ADC values were statistically higher using dual–*b*-value than multi–*b*-value DWI [13,25,27–30]. Few studies compared the application of DWI with different *b*-values in bladder cancer evaluation [26,31]; and no optimal *b*-values were recommended until recently, when it was recognized that further evaluation with extended variant *b*-values is needed.

General Limitations of ADC Applications

To obtain the ADC value, one can simply draw an optimal-sized region of interest (ROI), which avoids the partial volume effect on the ADC map. However, because of the heterogeneity of lesions and because ROI only appears on one or a few lesion-containing slices, ROI analysis may not reveal the condition of the whole lesion. Some researchers suggested that drawing a volume of interest (VOI) during analysis [17] has the potential for less operator dependence than traditional partial lesion ROI analysis, but to determinate accurate tumor margin during drawing a VOI is also a challenge. Because of poor anatomical details on DWI and ADC maps, it is necessary to combine T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) to evaluate lesion and to set ROI or VOI appropriately [21]. Moreover, the measurement of ADC value relies on the use of MRI systems, imaging sequences, and parameters that limit the reproducibility of the ADC value. For example, the ADC threshold for prostate cancer measured on fast spin echo DWI was 18% lower than echo planar imaging DWI [32]. The variation of ADC values measured at 1.5 and 3 T was up to 5% based on phantom studies [33] and with 4% to 9% variation of gray and white matter of the normal brain. And the variation was up to 8% when different coils were used on the same scanner [34]. In addition, ADC value is also susceptible to biological changes such as age and body temperature that cause interpatient variation [35,36]. Some investigators studied on normalized ADC by calculating the ADC ratio of lesion to surrounding normal tissues, such as urine within bladder. Assessment of normalized ADC would be an alternative method to standardize