World Journal of Radiology

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DOI: 10.4329/wjr.v6.i6.344

World J Radiol 2014 June 28; 6(6): 344-354
ISSN 1949-8470 (online)

REVIEW

Diffusion-weighted magnetic resonance imaging in management of bladder cancer, particularly with multimodal bladder-sparing strategy

Soichiro Yoshida, Fumitaka Koga, Shuichiro Kobayashi, Hiroshi Tanaka, Shiro Satoh, Yasuhisa Fujii, Kazunori Kihara

Soichiro Yoshida, Fumitaka Koga, Shuichiro Kobayashi, Yasuhisa Fujii, Kazunori Kihara, Department of Urology, Tokyo Medical and Dental University Graduate School, Tokyo 113-8677, Japan
Fumitaka Koga, Department of Urology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo 113-0021, Japan
Hiroshi Tanaka, Shiro Satoh, Department of Radiology, Ochanomizu Surugadai Clinic, Tokyo 101-0062, Japan
Author contributions: Yoshida S, Kobayashi S, Tanaka H, Satoh S, Fujii Y and Kihara K contributed to conception; Yoshida S and Koga F wrote the paper.
Correspondence to: Fumitaka Koga, MD, PhD, Department of Urology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. f-koga@cick.jp
Telephone: +81-3-38232101 Fax: +81-3-38241552
Received: December 29, 2013 Revised: April 10, 2014
Accepted: May 14, 2014
Published online: June 28, 2014

Abstract

Bladder-sparing strategy for muscle-invasive bladder cancer (MIBC) is increasingly demanded instead of radical cystectomy plus urinary diversion. Multimodal therapeutic approaches consisting of transurethral resection, chemotherapy, radiotherapy and/or partial cystectomy improve patients' quality of life by preserving their native bladder and sexual function without compromising oncological outcomes. Because a favorable response to chemoradiotherapy (CRT) is a prerequisite for successful bladder preservation, predicting and monitoring therapeutic response is an essential part of this approach. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a functional imaging technique increasingly applied to various types of cancers. Contrast in this imaging technique derives from differences in the motion of water molecules among tissues and this information is useful in assessing the biological behavior of cancers. Promising results in predicting and monitoring the response to CRT have been reported in several types of cancers. Recently, growing evidence has emerged showing that DW-MRI can serve as an imaging biomarker in the management of bladder cancer. The qualitative analysis of DW-MRI can be applied to detecting cancerous lesion and monitoring the response to CRT. Furthermore, the potential role of quantitative analysis by evaluating apparent diffusion coefficient values has been shown in characterizing bladder cancer for biological aggressiveness and sensitivity to CRT. DW-MRI is a potentially useful tool for the management of bladder cancer, particularly in multimodal bladder-sparing approaches for MIBC.

Key words: Diffusion magnetic resonance imaging; Bladder cancer; Urothelial carcinoma; Chemotherapy; Radiotherapy

Core tip: Diffusion-weighted magnetic resonance imaging (DW-MRI) is a functional imaging increasingly applied in the management of bladder cancer. This imaging offers unique information reflecting physiological character of the tissues by quantifying the diffusion of water molecules. DW-MRI provides accurate information for the diagnosis of bladder cancer in a noninvasive manner. Furthermore, growing evidence has emerged showing that DW-MRI can serve as an imaging biomarker of bladder cancer for assessing biologic aggressiveness and therapeutic sensitivity and for monitoring the therapeutic response. This review focuses on the potential role of DW-MRI in multimodal organ-preservation strategies for bladder cancer.

Yoshida S, Koga F, Kobayashi S, Tanaka H, Satoh S, Fujii Y, Kihara K. Diffusion-weighted magnetic resonance imaging in management of bladder cancer, particularly with multimodal bladder-sparing strategy. *World J Radiol* 2014; 6(6): 344-354 Available from: URL: http://www.wjgnet.com/1949-8470/full/v6/i6/344.htm DOI: http://dx.doi.org/10.4329/wjr.v6.i6.344

INTRODUCTION

Bladder cancer is the second most common genitourinary cancer in the United States and some 55600 new cases and 15100 deaths from bladder cancer are estimated to have occurred in 2012[1]. At the initial diagnosis, a third of all cases are diagnosed as muscle-invasive bladder cancer (MIBC)[2], and radical cystectomy has long been the treatment of choice for the treatment of localized MIBC. However, concern for patients' quality of life has strengthened the trend toward bladder-sparing approaches with various treatment modalities[3]. In this treatment approach, meticulous evaluation of the bladder cancer is essential. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a functional imaging technique increasingly applied to various types of cancer. Recently, growing evidence has emerged showing that DW-MRI can serve as an imaging technique that is useful for characterizing the pathophysiology of cancer. The biological behavior assessed with this imaging technique will play an important role in multimodal organ-preserving strategies for MIBC. Thus, this review focuses on the potential role of DW-MRI in multimodal organ-preservation strategies for MIBC.

Trimodality bladder-sparing strategy for MIBC

Favorable oncological and functional outcomes using bladder-sparing trimodality therapy combined with transurethral resection of bladder tumor (TURBT), chemotherapy and radiotherapy have been reported by several groups including Harvard University, the University of Paris and the University of Erlangen in Germany[4-6]. In most trimodality bladder-sparing approaches, patients who achieve complete response (CR) after the trimodal treatment are selectively subjected to consolidative therapies for bladder preservation, whereas those who do not achieve CR are advised to undergo early radical cystectomy. The 5-year survival rates after trimodality bladder-preserving trials were reported to be 50%-60%, which is comparable to those of radical cystectomy series[7, 8].

In the trimodality bladder preservation strategies, clinically tumor-free status after TURBT followed by chemoradiotherapy (CRT), as well as lower T stage and completeness of the TURBT, are important prognostic factors[6,9-11]. However, even the patients who clinically achieved CR after TURBT followed by CRT still may develop local tumor recurrence and lymph node metastases. Zietman *et al*[12] reported that two-thirds of non-MIBC (NMIBC) recurrences developed in the original MIBC sites. Tunio *et al*[13] also showed that 21% of the MIBC patients who achieved CR after trimodality therapy developed MIBC recurrence, and 69% of the recurrences arose from the original MIBC site. This problem could be due, in part, to subclinical viable bladder cancer cells remaining in the original MIBC site, which were missed by conventional imaging studies and biopsy-based evaluation[14].

Limitations of conventional radiological evaluations in bladder-sparing strategy for MIBC

Contrast-enhanced CT and conventional MRI are the standard techniques that have been used for the radiological evaluation of urinary system tumors. While CT is generally used to screen for metastasis, MRI plays a pivotal role in the staging of bladder cancer because of its superior soft tissue delineation, especially in the context of muscle-invasion. The diagnostic accuracy of MRI in differentiating MIBC from NMIBC is reported to be 75%-92%[15,16]. However, these anatomical imaging techniques are not ideal for tissue characterization and assessing tumor aggressiveness. Furthermore, these anatomical imaging techniques often overestimate the extent of tumor after TURBT and CRT due to the post-treatment changes. In multimodal organ-preserving strategies, generally, prior to CRT, TURBT is performed for debulking of the tumor. Both TURBT and CRT can induce local fibrotic and inflammatory changes, both of which manifest as bladder wall thickening[17]. Additionally, after the combined therapy, bladder cancer may regress and present as a flat lesion. Therefore, anatomical assessment of therapeutic response based on the response evaluation criteria in solid tumors on T2WI is not appropriate for discriminating small remnants of cancerous tissue from these secondary changes. Dobson *et al*[18] showed the utility of dynamic contrast-enhanced (DCE) MRI for discriminating cancerous tissue from radiation-induced fibrosis in thickened bladder walls. However, inflammatory changes secondary to treatments may persist for many years[19]. These false-positive results on DCE are often problematic, and they lower its specificity for detecting residual bladder cancer[19]. Thus, the utility of T2WI and DCE is still limited in monitoring the therapeutic response after TURBT and CRT[20].

DIFFUSION-WEIGHTED MRI IN CANCER

Biophysical basis and clinical application

The DW-MRI technique was initially devised by Stejskal and Tanner in 1965. Since 1985, DW-MRI has been mainly used for neuroimaging, especially for diagnosis of acute cerebral infarction and intracranial tumors[21]. With the recent advent of echo planar imaging, high gradient amplitudes, multichannel coils, and parallel imaging, DW-MRI of the abdomen and pelvis has become possible, and a growing number of studies have demonstrated the usefulness of this imaging technique in the diagnosis of malignant tumors of the abdomen[22,23]. Because the signal of DW-MRI is derived from the inherent tissue contrast,

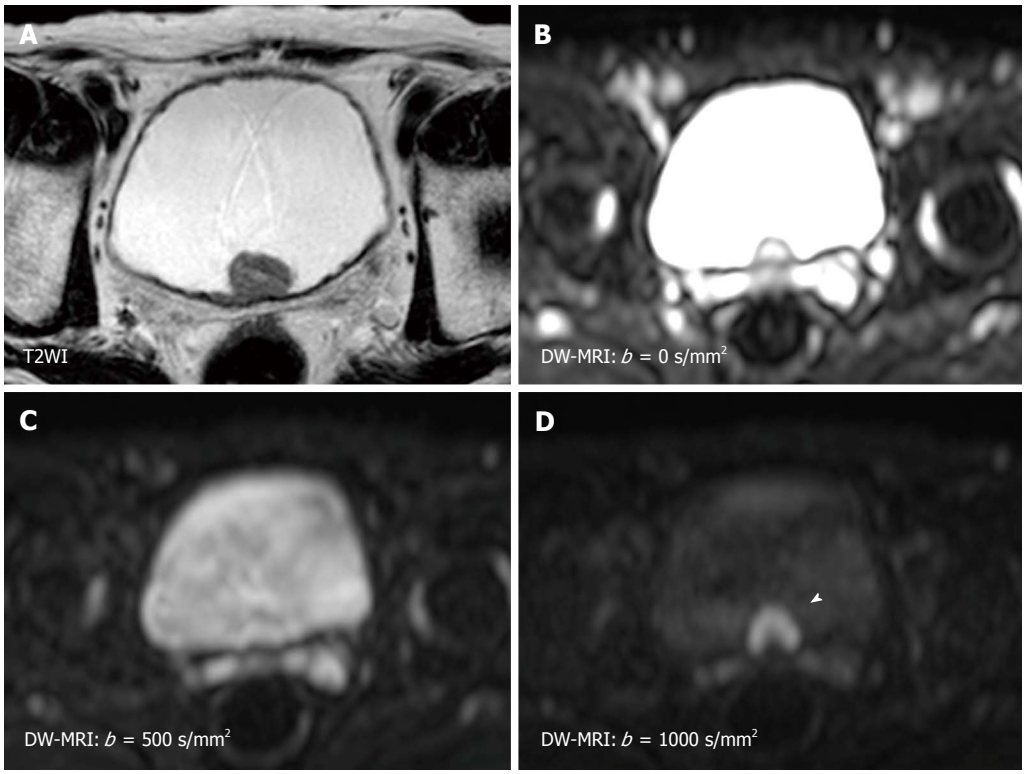

Figure 1 Magnetic resonance images of a 79-year-old man with non-muscle invasive bladder cancer (urothelial cancer, stage pTa, grade 2 > 3). A: T2WI shows a hypointense tumor at the trigone; B: The signal intensity of diffusion-weighted magnetic resonance imaging depends on both water diffusion and the T2 relaxation time; C: Due to the very long T2 relaxation time of urine, the signal of the urine in the bladder remains high on the diffusion-weighted magnetic resonance imaging with a *b*-value of 500 s/mm^2. This is known as the "T2 shine-through effect"; D: Using a *b*-value of 1000 s/mm^2 decreases the signal of the urine, as well as those of the seminal vesicles, while the bladder cancer (arrow head) shows little signal attenuation with the increased *b*-value.

this imaging technique requires no contrast agent and is applicable to patients with allergies to contrast agents or those with renal insufficiency. Furthermore, the addition of DW-MRI to a routine MRI examination requires only a few additional minutes and can be adopted for most current clinical MRI scanners.

DW-MRI is a functional imaging technique, the contrast of which results from quantifying the microscopic mobility of water molecules in tissue[22,23]. In biological tissues, the diffusion of water molecule is inversely correlated to the tissue cellularity and the integrity of cell membranes. In the area of tumor tissues, which have a high cellular density with intact cell membranes, water molecule diffusion is restricted, while the diffusion of water molecule is less restricted in areas of low cellular density. Areas where the diffusion is restricted generally show high signal intensity on DW-MRI, and malignant lesions typically show high signal intensity because of their higher cellularity, tissue disorganization, and decreased extracellular space, all of which restrict water diffusion. In recent years, an increasing number of studies have shown the usefulness of visual assessment of DW-MRI for detecting malignant tumors, and DW-MRI has quickly become a useful adjunct for assessing various types of tumors including bladder cancer[24-27].

Quantifying the degree of diffusion

The sensitivity of the diffusion is varied by changing the "*b*-value" which is proportional to the gradient amplitude, the duration of the applied gradient, and the time interval between the paired gradients[22,23]. Small *b*-values attenuate the signals of water molecules with a large degree of motion or a great diffusion distance. By using higher *b*-values, the perfusion in the intra-vascular space is restricted and slow-moving water molecules or small diffusion distances can be distinguished (Figure 1). Therefore, DW-MRI should be performed using three or more *b*-values including $b = 0$ s/mm^2, $b \geqslant 100$ s/mm^2, and $b \geqslant 500$ s/mm^2. Comparing the images obtained at different *b*-values is useful for characterizing the lesion. The apparent diffusion coefficient (ADC) value is assessed for quantitative evaluation of DW-MRI by evaluating the signal attenuation of tissue on DW-MRI with increasing *b*-values. Generally, the software automatically calculates the ADC values, and the calculated ADC values for each pixel of the image are displayed as a parametric map. By drawing regions of interests (ROI) on this ADC map, the ADC value of the delineated region can be easily obtained. However, because of their poor anatomical details, DW-MRI and ADC maps should be evaluated in combination with T1WI and T2WI, and the correlation with anatomical images is important to accurately set the ROI for the target lesion. Quantitative evaluation of DW-MRI by assessing the ADC value is potentially useful for tissue characterization based on the differences in water diffusion. The correlation of tumor ADC values with their

biological aggressiveness has been reported for various types of malignancies[28-30]. However, the reproducibility of the ADC value is an intrinsic limitation in ADC measurement because the ADC value depends on the MRI system and imaging protocol used. To standardize the ADC assessment, some trials using ADC ratio, calculated with respect to surrounding normal tissues, have been performed recently.

Predicting treatment sensitivity

The important clinical implication of DW-MRI in multimodal organ preservation strategies for MIBC is the ability to predict therapeutic response prior to treatment. In a number of prospective studies in various types of cancers including brain tumors and cervical and rectal cancers[31-35], the potential of DW-MRI to predict the sensitivity to radiotherapy has been shown. The tumors with higher ADC values are less likely to respond to the treatment. The hypothesized mechanism underlying this relationship is the presence of necrosis reflected in a higher ADC value, which predicts a poor outcome related to hypoxia-mediated radioresistance. Meanwhile, soon after the initiation of chemotherapy and/or radiotherapy, immediate cell death can be observed after the commencement of the treatment, which is reflected as an early increase in the ADC value. In cervical cancer and rectal cancer, this early increase in ADC value is observed in patients who show good response to CRT, and can be a potential early biomarker for treatment outcomes[35-38]. Following this early ADC increase, edema and fibrosis cause a subsequent ADC decrease[35-37].

Monitoring treatment response

Importantly, the DW-MRI can be an imaging biomarker in monitoring treatment effect. In response to successful treatment, cell necrosis and loss of cell membrane integrity are induced, leading to increased water diffusion. Furthermore, tumor apoptosis induced by treatment results in cell shrinkage. These changes are reflected by increases in ADC value[22]. Clinical studies in many types of malignancies, including liver cancer, cerebral gliomas, and soft-tissue sarcoma, have demonstrated the correlation between therapeutic effect and changes in water diffusion in tumors[39-41].

CLINICAL APPLICATION OF DW-MRI IN BLADDER CANCER

Detecting bladder cancer

Since the first report by Matsuki *et al*[26] showing the utility of DW-MRI for detecting bladder cancer, a number of studies have shown the usefulness of DW-MRI for the diagnosis of bladder cancer[24-27]. On DW-MRI with a high *b*-value, bladder cancers generally show a hyperintense signal, while the signals of the surrounding tissues, including urine, are much less intense[26,42] (Figure 1). This good signal contrast is obtained between bladder cancer and the surrounding tissue. The sensitivity, specificity and accuracy for detecting bladder cancer were reported to be 90%-98%, 92%-93% and 91%-97%, respectively[24,25,27]. In several studies, quantitative analysis consistently showed restricted diffusion and lower ADC values in bladder cancer compared with the surrounding structures[26,42].

Detecting lymph node metastasis

MIBC has the potential to metastasize to lymph nodes and distant organs, and detecting metastatic lesion is another problem in managing MIBC. At the time of surgery, 25% of the patients who undergo radical cystectomy have a lymph node metastasis. Lymph node staging has been generally performed by CT or conventional MRI based on size criteria and morphological appearance, and the accuracy for staging nodal disease ranges from 73% to 90%[43]. On DW-MRI, benign lymph nodes show high signal intensity due to their highly cellular structures composed of lymphoid elements (Figure 2). The utility of DW-MRI has been shown in lymph node staging in various cancers[44-48]. Papalia *et al*[49] showed that malignant lymph nodes have a significantly lower ADC value than benign lymph nodes with sensitivity of 76.4% and specificity of 89.4% in a study that included 36 patients with bladder cancer undergoing radical cystectomy. However, there is a substantial overlap in ADC values between malignant and benign lymph nodes, and discriminating malignant nodes from benign nodes on DW-MRI is still challenging[50]. Recently, Thoeny *et al*[51] reported an excellent diagnostic accuracy of 90% in detecting pelvic lymph nodal involvement by the combined use of ultrasmall super paramagnetic iron oxide (USPIO) and DW-MRI. This agent is taken up by macrophages resulting signal loss in normal lymph nodes, while the signal of metastatic lymph nodes is not influenced[51-55]. Further studies are needed to confirm this encouraging result.

Detecting bone metastasis

DW-MRI for evaluating primary bladder cancer occasionally shows abnormal signals of pelvic bones or femur heads. Bone metastasis typically shows clear high signal intensity on DW-MRI[56,57]. However, as well as benign bone tumors, hematopoietic bone marrow also appears as a hyperintense lesion on DW-MRI because of rich hematopoietic cells[58,59]. These false-positive findings in detecting metastasis should be kept in mind for staging bladder cancer[60]. Furthermore, identifying microscopic metastases or developing metastases remains a challenge, and a third of MIBC patients have undetected metastases at the initial diagnosis[61].

Characterizing histopathological features

Because the contrast of DW-MRI is based on difference in the degree of water diffusion between tissues, the spatial resolution of DW-MRI is generally low. However, using the clear contrast between bladder cancer and the surrounding tissues, the utility of DW-MRI for staging of

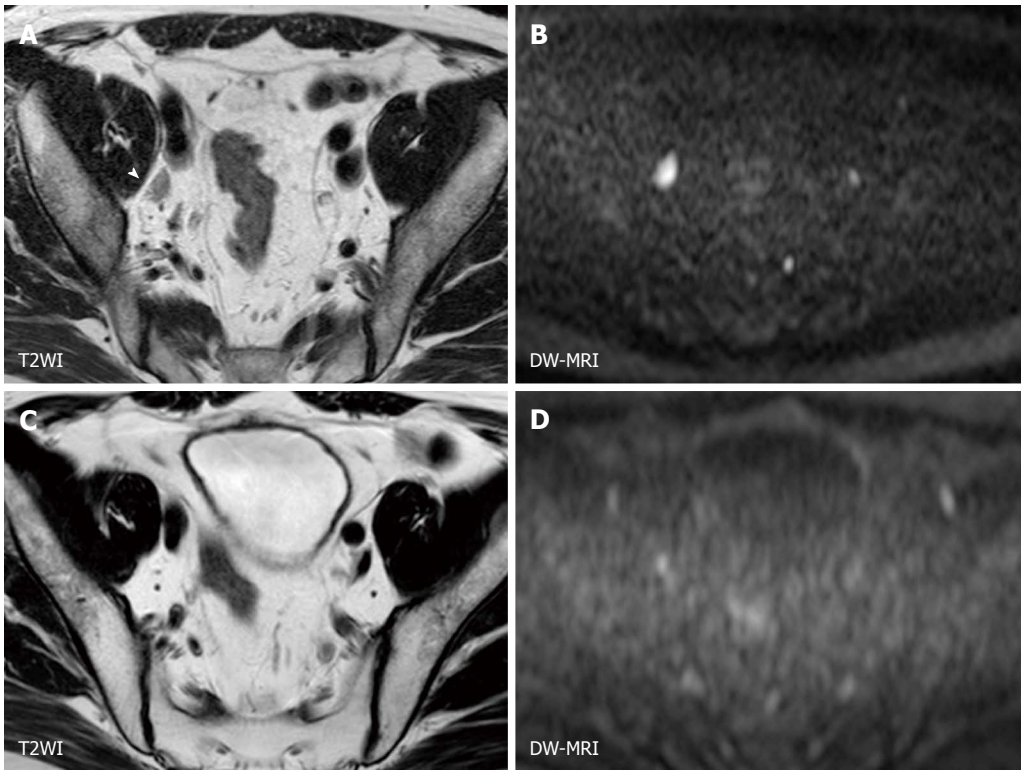

Figure 2 Magnetic resonance images of a 45-year-old man with muscle-invasive bladder cancer (urothelial cancer, stage cT3N1) before and after chemoradiotherapy. A: Before CRT, an enlarged right external iliac lymph node (arrow head) is visible on T2WI; B: The lymph node on the corresponding DW-MRI shows a hyperintense signal; C and D: After CRT, size reduction on T2WI (C) and signal attenuation on DW-MRI (D) in lymph node is evident, consistent with the expected treatment response. CRT: Chemoradiotherapy; DW-MRI: Diffusion-weighted magnetic resonance imaging.

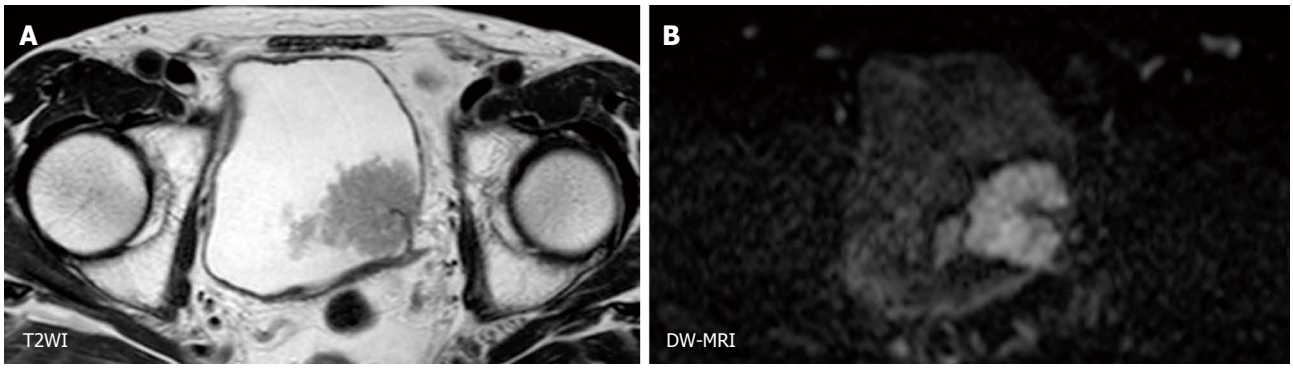

Figure 3 Magnetic resonance images of a 63-year-old man with non-muscle-invasive bladder cancer (urothelial cancer, stage pT1, grade 2 > 3). A: T2WI shows a large papillary tumor on the left bladder wall; B: DW-MRI displays a C-shaped high-signal tumor with a low-signal-intensity stalk connecting to the bladder wall. This C-shaped high signal is known as an "inchworm sign", which is a criterion for T staging in non-muscle-invasive bladder cancer (stage cT1 or less). DW-MRI: Diffusion-weighted magnetic resonance imaging.

bladder cancer based on the signal shape and contrast has been shown (Figure 3). On DW-MRI, bladder cancers generally show a hyperintense signal in distinct contrast to the hypointense signal of the submucosal layer and the intermediate signal of the intact bladder wall. On the basis of these findings, El-Assmy *et al*[62] reported the ability to discriminate MIBC from NMIBC with an accuracy of 63.6% in a study that included 106 patients. Takeuchi *et al*[63] reported that bladder cancer staging accuracy improved from 67 to 88% when DW-MRI was added to T2WI.

Furthermore, the utility of DW-MRI in characterizing bladder cancer has been consistently shown in multiple studies using quantitative analysis (Figures 4 and 5). Takeuchi *et al*[63] reported that the ADC value of grade 3 tumors was significantly lower than that of grade 1 and 2 tumors in a prospective study that included 40 patients. Avcu *et al*[64] also reported similar results showing an inverse correlation between the ADC value and the histological grade. The existence of a substantial overlap between the histological grades or stages poses a limit to qualitative analysis and the clinical application

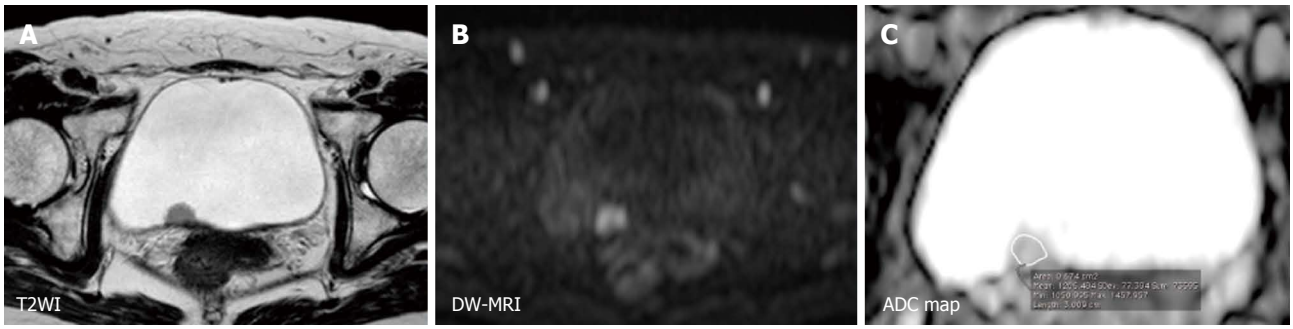

Figure 4 Magnetic resonance images of a 52-year-old woman with non-muscle-invasive bladder cancer (urothelial cancer, pTa, grade 2). A: T2WI shows a hypointense tumor at the posterior wall; B: DW-MRI displays the tumor as a high-signal mass; C: The corresponding ADC map demonstrates a lesser degree of restricted diffusion. The mean ADC value with the ROI positioned not extending over the tumor is 1.21 x 10^{-3} s/mm^2. DW-MRI: Diffusion-weighted magnetic resonance imaging; ADC: Apparent diffusion coefficient.

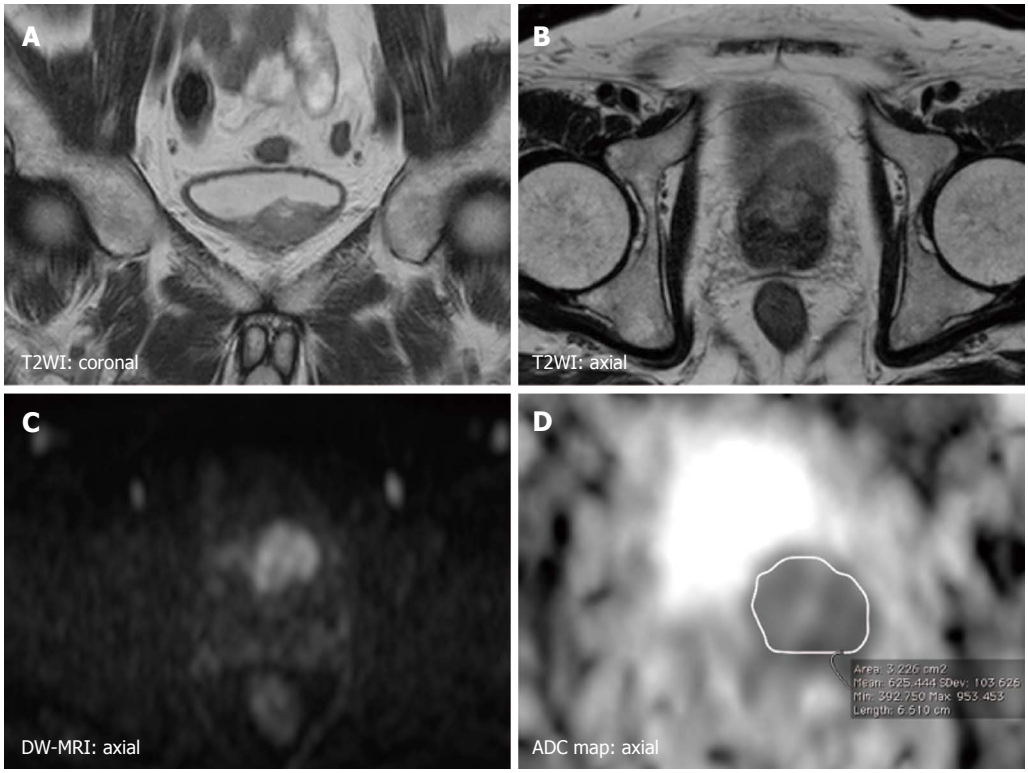

Figure 5 Magnetic resonance images of a 75-year-old man with muscle-invasive bladder cancer (urothelial cancer, stage cT4, grade 3). A and B: T2WI shows a large hypointense tumor at the bladder neck, invading the prostate; C: DW-MRI displays the tumor as a high-signal mass; D: The corresponding ADC map demonstrates restricted diffusion. The mean ADC value of the tumor is 0.63 x 10^{-3} mm^2/s. DW-MRI: Diffusion-weighted magnetic resonance imaging; ADC: Apparent diffusion coefficient.

of this technique. However, these studies indicated that advanced and aggressive bladder cancers tend to have a low ADC values. Actually, Kobayashi *et al*[27] found that clinically aggressive tumors, including MIBC and high-grade T1 tumors, had a significantly lower ADC value than the other less aggressive tumors. A threshold ADC value differentiated these two entities with 87% accuracy in a series of 121 patients. The underlying mechanisms whereby the ADC value reflects these tumor characters are thought to be the tumor cell morphological characters such as dense cellularity and large cellular size[22,23]. Recent studies have shown an inverse correlation between ADC value and the Ki-67 labeling index, a marker of cell proliferation, in bladder cancer[65-67]. These data suggest the potential of ADC value to serve as a quantitative biomarker characterizing the biological features of bladder cancer.

Predicting metastatic potential

The potential role of ADC values in predicting the metastatic potential of localized high-grade bladder cancers was shown in a small study that included 17 patients. This study showed that invasive high-grade bladder cancers with metastasis had lower ADC values than those without metastasis[68]. ADC value can be a supplemental parameter for predicting the presence of metastasis, which

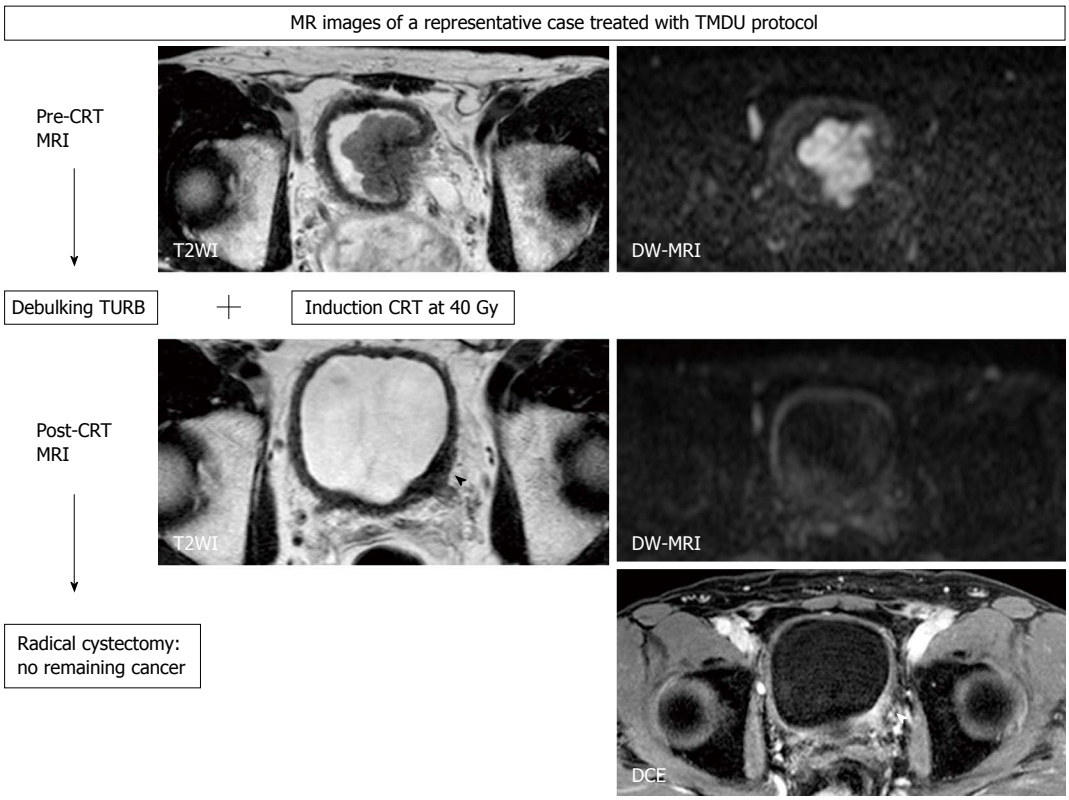

Figure 6 Magnetic resonance images of a 61-year-old man with muscle-invasive bladder cancer (urothelial cancer, stage cT3, grade 3) treated with the Tokyo Medical and Dental University protocol consisting of transurethral resection of bladder tumor and induction chemoradiotherapy (CRT) followed by radical or partial cystectomy. T2WI shows a large hypointense tumor at the bladder neck, invading the prostate. At the diagnosis, DW-MRI with a *b*-value of 1000 s/mm^2 displays a hyperintense lobulated mass. After TURBT and CRT, this lesion shows wall thickening (arrow head) on T2WI and enhancement on DCE, while the abnormal signal on DW-MRI is diminished to normal signal intensity. Histopathologic examination of the cystectomized sample reveals no remaining bladder cancer, revealing the findings of post-CRT T2WI and DCE to be false-positive findings reflecting post-treatment changes in bladder tissues. TURBT: Transurethral resection of bladder tumor; CRT: Chemoradiotherapy; DW-MRI: Diffusion-weighted magnetic resonance imaging; DCE: Dynamic contrast-enhanced.

has a great impact on treatment decisions.

POTENTIAL ROLES OF DW-MRI IN MULTIMODALITY BLADDER-SPARING STRATEGIES

Novel bladder-sparing approach incorporating consolidative partial cystectomy with pelvic lymph node dissection

We started a pilot study of a selective bladder-sparing protocol incorporating consolidative partial cystectomy with pelvic lymph node dissection after induction low-dose chemoradiotherapy (LCRT) in 1997 at Tokyo Medical and Dental University (TMDU)[10,11,14,69-71]. Consolidative partial cystectomy with pelvic lymph node dissection is intended to eradicate possible remaining subclinical residual tumor tissue in the original MIBC sites and micrometastases in the pelvic lymph nodes. Candidates for bladder preservation are selected based on the extent, location, and post-LCRT status of the tumor. More than one-third of MIBC patients without any metastasis meet our criteria for partial cystectomy. Partial cystectomy with pelvic lymph node dissection was performed in 70 patients following LCRT. A functional native bladder was preserved in 91% of patients, and none has developed MIBC or lymph node recurrence[10,14].

Predicting sensitivity to CRT

In the majority of CRT-based bladder-sparing protocols for localized MIBC, patients who achieve a clinical CR are subjected to consolidative treatment with CRT for bladder preservation. In these protocols, treatment effect cannot be histologically evaluated. In the above-mentioned bladder-sparing protocol incorporating partial cystectomy, histopathological therapeutic effects of LCRT can be assessed, which is one of advantages of the TMDU protocol. By comparing DW-MRIs taken before and after LCRT with this therapeutic effect, the utility of DW-MRI for predicting treatment sensitivity and in monitoring therapeutic response can be evaluated[20,67].

We found a significant inverse correlation between LCRT sensitivity and ADC value of the tumor[67]. LCRT-sensitive MIBCs had significantly lower ADC values than LCRT-resistant MIBCs. With a defined cut-off ADC value, the sensitivity, specificity and accuracy in predicting LCRT sensitivity were 92%, 90%, and 91%, respectively. These findings are consistent with previous reports on other tumors including brain, cervix and rectum[31-35]. However, the presence of necrosis is not common in

MIBC, which is understood to be the background of the correlation between lower ADC values and favorable CRT response. One possible explanation of this correlation found in MIBC is that the relationship between the proliferative activity and the ADC value of MIBC; highly proliferating MIBCs show low ADC values[65,67]. Because favorable CRT response in highly proliferating MIBC has been reported[72,73], a low ADC value would be predictive of a better CRT sensitivity of MIBC.

Monitoring response to CRT

We also showed the utility of DW-MRI in monitoring the therapeutic response of MIBC treated with LCRT, as has been reported for other cancers. The sensitivity/specificity/accuracy of T2WI, DCE, and DW-MRI in predicting pathologic CR were 43%/45%/44%, 57%/18%/33%, and 57%/92%/80%, respectively[20]. DW-MRI improved the accuracy for detecting the remaining cancer after LCRT, primarily due to its increased specificity (Figure 6). However, the low sensitivity in detecting small lesions is a notable limitation, which makes it difficult to detect microscopic residual cancers, as is the case with the other imaging techniques. Further studies are necessary to evaluate the potential of DW-MRI as an imaging technique in the context of bladder-sparing approaches. Multiple approaches, including DW-MRI and biopsies to monitor the therapeutic response, may improve the accuracy of these techniques. However, the limits discussed here in detecting remaining cancers justify partial cystectomies to eliminate the possibly of remaining microscopic tumors in the original invasive cancer site, even in the patients who achieve clinical CR after CRT.

CONCLUSION

Recent studies have shown that the DW-MRI is a unique imaging technique that provides qualitative and quantitative information on biological features of bladder cancer, and is potentially useful as an imaging technique in the management of bladder cancer, particularly in multimodal bladder-sparing strategies for MIBC. Further large prospective studies are needed to clarify the practical roles of DW-MRI in the management of bladder cancer.

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