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@ciick.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.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

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, Fuji 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[7-9].

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[8-11]. 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,
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. In biological tissues, the diffusion of water molecules 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.

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. 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 $b = 0 \text{s/mm}^2$, $b \geq 100 \text{s/mm}^2$, and $b \geq 500 \text{s/mm}^2$. 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 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 radiosensitivity. 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[36-38]. Following this early ADC increase, edema and fibrosis cause a subsequent ADC decrease[39,40].

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[24]. 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[41-43].

CLINICAL APPLICATION OF DW-MRI IN BLADDER CANCER
Detecting bladder cancer
Since the first report by Matsuki et al[31] 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[28,44] (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%[45]. 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[44-46]. 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[49]. Recently, Thoeny et al[50] reported an excellent diagnostic accuracy of 90% in detecting pelvic lymph node involvement by the combined use of ultrasmall superparamagnetic 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[51-53]. 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[54,55]. However, as well as benign bone tumors, hematopoietic bone marrow also appears as a hyperintense lesion on DW-MRI because of rich hematopoietic cells[56,57]. These false-positive findings in detecting metastasis should be kept in mind for staging bladder cancer[58]. Furthermore, identifying microscopic metastases or developing metastases remains a challenge, and a third of MIBC patients have undetected metastases at the initial diagnosis[59].

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
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. reported the ability to discriminate MIBC from NMIBC with an accuracy of 63.6% in a study that included 106 patients. Takeuchi et al. 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. 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 of DW-MRI in characterizing bladder cancer has been consistently shown in multiple studies using quantitative analysis (Figures 4 and 5). Takeuchi et al. 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. 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 of DW-MRI in identifying different grades of bladder cancer.
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.\[66\]. ADC value can be a supplemental parameter for predicting the presence of metastasis, which
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
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[29]. 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 possibility 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 multimodality 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.

REFERENCES

1 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]
2 Tsukamoto T, Kitamura H, Takahashi A, Masumori N. Treatment of invasive bladder cancer: lessons from the past and perspective for the future. Jpn J Clin Oncol 2004; 34: 295-306 [PMID: 15535680 DOI: 10.1093/jjco/hyh048]
3 Gilbert SM, Wood DP, Dunn RL, Weizer AZ, Lee CT, Montie JE, Wei JT. Measuring health-related quality of life outcomes in bladder cancer patients using the Bladder Cancer Index (BCI). Cancer 2007; 109: 1756-1762 [PMID: 17365966 DOI: 10.1002/cncr.22556]
4 Houssset M, Maulard C, Chretien Y, Dufour B, Delanian S, Huart J, Colardelle F, Brunel P, Baillet F. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. J Clin Oncol 1993; 11: 2150-2157 [PMID: 8299129]
5 Kachnic LA, Kaufman DS, Heney NM, Althausen AF, Griffin PP, Zietman AL, Shipley WU. Bladder preservation by combined modality therapy for invasive bladder cancer. J Clin Oncol 1997; 15: 1022-1029 [PMID: 9060542]
6 Rödel C, Grabenbauer GG, Kühn R, Papadopoulos T, Dunst J, Meyer M, Schrott KM, Sauer R. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol 2002; 20: 3061-3071 [PMID: 12118019 DOI: 10.1200/JCO.2002.11.027]
7 Eisenberg MS, Dorin RP, Bartsch G, Cai J, Miranda G, Skinner EC. Early complications of cystectomy after high-dose pelvic radiation. J Urol 2010; 184: 2264-2269 [PMID: 20952024 DOI: 10.1016/j.juro.2010.08.007]
8 Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001; 19: 666-675 [PMID: 11517016]
9 Perdonà S, Autorino R, Damiano R, De Sio M, Morriva C, Gallo L, Silvestro G, Farace T, Femia A, Placido S, Di Lorenzo G. Bladder-sparing, combined-modality approach for muscle-invasive bladder cancer: a multi-institutional, long-term experience. Cancer 2008; 112: 75-83 [PMID: 18008364 DOI: 10.1002/cncr.23137]
10 Koga F, Kihara K, Yoshida S, Yokoyama M, Saito K, Masuda H, Fujiy, Nakawaki S. Selective bladder-sparing protocol consisting of induction low-dose chemoradiotherapy plus partial cystectomy with pelvic lymph node dissection against muscle-invasive bladder cancer: oncological outcomes of the initial 46 patients. BJU Int 2012: 109: 860-866 [PMID: 21854531 DOI: 10.1111/j.1464-410X.2011.10425.x]
11 Koga F, Yoshida S, Nakawaki S, Kageyama Y, Yokoyama M, Saito K, Fujiy, Kobayashi T, Kihara K. Low-dose chemoradiotherapy followed by partial or radical cystectomy against muscle-invasive bladder cancer: an intent-to-treat survival analysis. Urology 2008; 72: 384-388 [PMID: 18455771 DOI: 10.1016/j.urology.2008.03.017]
12 Zietman AL, Groeca J, Zehr E, Kaufman DS, Young RH, Althausen AF, Heney NM, Shipley WU. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: management and consequences of Ta, T1, and Tis recurrence within the retained bladder. Urology 2001; 58: 380-385 [PMID: 11549485 DOI: 10.1016/S0090-4295(01)01219-5]
13 Tunio MA, Hashmi A, Qayyum A, Mohsini R, Zaeem A. Whole-pelvis or bladder-only chemoradiation for lymph node-negative invasive bladder cancer: single-institution experience. Int J Radiat Oncol Biol Phys 2012; 82: e457-e462 [PMID: 21945107 DOI: 10.1016/j.ijrobp.2011.05.051]
14 Koga F, Kihara K. Selective bladder preservation with curative intent for muscle-invasive bladder cancer: a contemporary review. Int J Urol 2012; 19: 388-401 [PMID: 22409269 DOI: 10.1111/j.1442-2042.2012.02974.x]
15 Tekes A, Kamel I, Imam K, Szerf G, Schoenberg M, Nasir K, Thompson R, Blumen K. Dynamic MRI of bladder cancer: evaluation of staging accuracy. AJR Am J Roentgenol 2005; 184: 121-127 [PMID: 15615961 DOI: 10.2214/ajr.184.1.01840121]
16 Hayashi N, Tochigi H, Shiraishi T, Takeda K, Kawamura J. A new staging criterion for bladder carcinoma using gadolinium-enhanced magnetic resonance imaging with an endorectal surface coil: a comparison with ultrasonography. BJU Int 2000; 85: 32-36 [PMID: 10619941 DOI: 10.1046/j.1445-4110.2000.00358.x]
17 Raza SA, Jhaveri KS. MR imaging of urinary bladder carcinoma and beyond. Radiol Clin North Am 2012; 50: 1085-1110 [PMID: 23122040 DOI: 10.1016/j.rcl.2012.08.011]
18 Dobson MJ, Carrington BM, Collins CD, Ryder WD, Read G.
Hutchinson CE, Hawnaur JM. The assessment of irradiated bladder carcinoma using dynamic contrast-enhanced MR imaging. *Clin Radiol* 2001; 56: 94-98 [PMID: 11222646 DOI: 10.1053/crad.2000.0560]

Johanns RJ, Carrington BM, Jenkins JP, Barnard RJ, Read G, Isherwood I. Accuracy in staging carcinoma of the bladder by magnetic resonance imaging. *Clin Radiol* 1990; 41: 258-263 [PMID: 2304067 DOI: 10.1016/0003-980X(90)90006-7]

**Yoshida S**, Koga F, Kawakami S, Ishii C, Tanaka H, Numao N, Sakai Y, Saito K, Masuda H, Fujii Y, Kihara K. Initial experience of diffusion-weighted magnetic resonance imaging to assess therapeutic response to induction chemoradiotherapy against muscle-invasive bladder cancer. *Urology* 2010; 75: 387-391 [PMID: 19914691 DOI: 10.1016/j.urology.2009.06.111]

Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanas E, Lavel-Jeanlet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 1986; 161: 401-407 [PMID: 3763909 DOI: 10.1148/radiology.161.2.3763909]

Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am J Roentgenol* 2007; 188: 162-1635 [PMID: 17515386 DOI: 10.2214/AJR.06.1403]

Padhani AR, Liu G, Koh DM, Chenetert TL, Thoeny HC, Takahara T, Dziki-Jurasa A, Ross BD, Van Cauteren M, Collins DJ, Hammond DA, Rustin GJ, Taouli B, Choyke PL. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. *Neoplasia* 2009; 11: 102-125 [PMID: 19186405]

**Abou-El-Ghar ME**, Al-Assmy A, Refaie HF, El-Diasty T. Bladder cancer: diagnosis with diffusion-weighted MR imaging in patients with gross hematuria. *Radiology* 2009; 251: 415-421 [PMID: 19304915 DOI: 10.1148/radiology.2503080723]

Ceylan K, Taken K, Gecit I, Pirincci N, Gunes M, Tanik TH, Ceylan K. Diagnostic performance of diffusion-weighted magnetic resonance imaging in bladder cancer: potential utility of apparent diffusion coefficient values as a biomarker to predict clinical aggressiveness. *Eur Radiol* 2011; 21: 2178-2186 [PMID: 21688007 DOI: 10.1007/s00330-011-2174-7]

Costantini M, Belli P, Rinaldi P, Buﬁ E, Giardina G, Francechini G, Petrone G, Bonomo L. Diffusion-weighted imaging in breast cancer: relationship between apparent diffusion coefficient and tumour aggressiveness. *Clin Radiol* 2010; 65: 1005-1012 [PMID: 21070905 DOI: j.crad.2010.07.008]

**Yoshida S**, Masuda H, Ishii C, Tanaka H, Fujii Y, Kawakami S, Kihara K. Usefulness of diffusion-weighted MRI in diagnosis of upper urinary tract cancer. *AJR Am J Roentgenol* 2011; 196: 110-116 [PMID: 21718054 DOI: 10.2214/AJR.10.4632]

Kitajima K, Takahashi S, Ueno Y, Miyake H, Fujisawa M, Kawakami F, Sugimura K. Do apparent diffusion coefficient (ADC) values obtained using high b-values with a 3-T MRI correlate better than a transcranial ultrasound (TRUS)-guided biopsy with true Gleason scores obtained from radical prostatectomy specimens for patients with prostate cancer? *Eur J Radiol* 2013; 82: 1219-1226 [PMID: 23518144 DOI: 10.1016/j.ejrad.2013.02.021]

DeVries AF, Kremser C, Hein PA, Griebel J, Kreczy A, Othen D, Pfeiffer KP, Lukas P, Judmaier W. Tumor microcirculation and diffusion prediction therapy outcome for primary rectal carcinoma. *Int J Radiat Oncol Biol Phys* 2003; 56: 958-965 [PMID: 12892130 DOI: 10.1016/S0360-3016(03)02086-6]

Liu Y, Bai R, Sun H, Liu H, Zhao X, Li Y. Diffusion-weighted imaging in predicting and monitoring the response of uterine cervical carcinoma to combined chemoradiation. *Clin Radiol* 2009; 64: 1067-1074 [PMID: 19822230 DOI: 10.1016/j.crad.2009.07.010]

Mardor Y, Roth Y, Ochershvili A, Spiegelmann R, Tichler T, Daniels D, Maier SE, Nissim O, Ram Z, Baram J, Orenstein A, Pfeffer R. Pretreatment prediction of brain tumors’ response to radiation therapy using high b-value diffusion-weighted MRI. *Neoplasia* 2004; 6: 136-142 [PMID: 15140402 DOI: 10.1593/neo.03549]

Dzik-Jurasa A, Domenig C, George M, Woller J, Padhani A, Brown G, Doran S. Diffusion MRI for prediction of response of rectal cancer to chemoradiation. *Lancet* 2002; 360: 307-308 [PMID: 12147356 DOI: 10.1016/S0140-6736(02)09520-X]

Sun YS, Zhang XP, Tang L, Ji JF, Gu J, Cai Y, Zhang X. Locally advanced rectal carcinoma treated with preoperative chemotherapy and radiation therapy: preliminary analysis of diffusion-weighted MR imaging for early detection of tumor histopathologic downstaging. *Radiology* 2010; 254: 170-178 [PMID: 20019139 DOI: 10.1148/radiol.2541082230]

Hein PA, Kremser C, Judmaier W, Griebel J, Pfeiffer KP, Kreczy A, Hug EB, Lukas P, DeVries AF. Diffusion-weighted magnetic resonance imaging for monitoring diffusion changes in rectal carcinoma during combined, preoperative chemoradiation: preliminary results of a prospective study. *Eur J Radiol* 2003; 45: 214-222 [PMID: 12595106 DOI: 10.1016/S0720-48X(02)00231-0]

Kremser C, Judmaier W, Hein P, Griebel J, Lukas P, de Vries A. Preliminary results on the influence of chemoradiation on apparent diffusion coefficients of primary rectal carcinoma measured by magnetic resonance imaging. *Strahlenther Onkol* 2003; 179: 641-649 [PMID: 14628131 DOI: 10.1007/s00066-003-1045-9]

**Harry VN**, Semple SJ, Gilbert FJ, Parkin DE. Diffusion-weighted magnetic resonance imaging in the early detection of response to chemoradiation in cervical cancer. *Gynecol Oncol* 2008; 111: 213-220 [PMID: 18774597 DOI: 10.1016/j.ygyno.2008.07.048]

Chen CY, Li CW, Kuo YT, Jaw TS, Wu DK, Jao JC, Hsu JS, Liu GC. Early response of hepatocellular carcinoma to transcatheter arterial chemoembolization: choline levels and MR diffusion constants–initial experience. *Radiology* 2006; 239: 448-456 [PMID: 16880781 DOI: 10.1148/radiol.2392051841]

Chenevert TL, McKeever PE, Ross BD. Monitoring early response of experimental brain tumors to therapy using diffusion magnetic resonance imaging. *Clin Cancer Res* 1997; 3: 1457-1466 [PMID: 9813831]

Einarsdóttir H, Karlsson M, Wejde J, Bauer HC. Diffusion-weighted MRI of soft tissue tumours. *Eur Radiol* 2004; 14: 959-963 [PMID: 14767604 DOI: 10.1007/s00330-004-2237-0]

**El-Assmy A**, Abou-El-Ghar ME, Refaie HF, El-Diasty T. Diffusion-weighted MRI in diagnosis of superficial and invasive urinary bladder carcinoma: a preliminary prospective study. *ScientificWorldJournal* 2008; 8: 364-370 [PMID: 18454244 DOI: 10.1100/tsw.2008.55]

Barentsz JO, Jager GJ, van Vierzen PB, Witjes JA, Strijk SP, Peters H, Karssemeijer N, Ruijs SH. Staging urinary bladder cancer: comparison of diffusion-weighted MR imaging and choline uptake in (11)C-choline PET/CT are correlated in pelvic lymph nodes in patients with prostate cancer. *Mol Imaging Biol* 2011; 13: 352-361 [PMID: 20490932 DOI: 10.1007/s13037-010-0337-6]
To determine if ultrasmall superparamagnetic particles of iron oxide (USPIO) can be used for the detection of metastases in normal sized pelvic lymph nodes of patients with bladder and/or prostate cancer.

Eur J Cancer 2013; 49: 616-624 [PMID: 23084842 DOI: 10.1016/j.ejca.2012.09.034]

Lecouvet FE, El Mouedden J, Collette L, Coche E, Danse E, Jamar F, Machi JP, Vande Berg B, Osmouni P, Tombal B. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? Eur Urol 2012; 62: 68-75 [PMID: 22366187 DOI: 10.1016/j.eururo.2012.02.020]

Mosavi F, Johansson S, Sandberg DT, Turesson I, Sörensen J, Ahlström H. Whole-body diffusion-weighted MRI compared with (18)F-NaF PET/CT for detection of bone metastases in patients with high-risk prostate carcinoma. AJR Am J Roentgenol 2012; 199: 1114-1120 [PMID: 23069187 DOI: 10.2214/ajr.11.8351]

Ording Müller LS, Avenarius D, Olsen OE. High signal in bone marrow at diffusion-weighted imaging with body background suppression (DWIBS) in healthy children. Pediatr Radiol 2011; 41: 221-226 [PMID: 20652234 DOI: 10.1007/s00247-010-1774-8]

Steiner RM, Mitchell DG, Rao VM, Schweitzer ME. Magnetic resonance imaging of diffuse bone marrow disease. Radiol Clin North Am 1993; 31: 383-409 [PMID: 8446756]

Takeuchi M, Suzuki T, Sasaki S, Ito M, Hamamoto S, Kawai N, Kohri K, Hara M, Shimamoto Y. Clinicopathologic significance of high signal intensity on diffusion-weighted MR imaging in the ureter, urethra, prostate and bone of patients with bladder cancer. Acad Radiol 2012; 19: 827-833 [PMID: 22341371 DOI: 10.1016/j.acra.2012.01.013]

Proud GR, Griffin PP, Shipley WU. Bladder carcinoma as a systemic disease. Cancer 1979; 43: 2532-2539 [PMID: 455292]

El-Assmy A, Abou-El-Ghar ME, Mosbah A, El-Nahas AR, Refaie HF, Hekal IA, El-Diasty T, Ibrahim el H. Bladder tumour staging: comparison of diffusion- and T2-weighted MR imaging. Eur Radiol 2009; 19: 1575-1581 [PMID: 19247665 DOI: 10.1007/s00330-009-1340-7]

Takeuchi M, Sasaki S, Ito M, Okada S, Takahashi S, Kawai T, Suzuki K, Oshima H, Hara M, Shimamoto Y. Urinary bladder cancer: diffusion-weighted MR imaging—accuracy for diagnosing T stage and estimating histologic grade. Radiology 2009; 251: 112-121 [PMID: 19332849 DOI: 10.1148/ra diol.251108073]

Avcu S, Koseoglu MN, Ceylan K, Bulut MD, Unal O. The value of diffusion-weighted MRI in the diagnosis of malignant and benign urinary bladder lesions. Br J Radiol 2011; 84: 875-882 [PMID: 21224296 DOI: 10.1259/bjr/3091930]

Kobayashi S, Koga F, Kajino K, Yoshita S, Ishii C, Tanaka H, Saito K, Masuda H, Fujiy I, Yamada T, Kihara K. Apparent diffusion coefficient value reflects invasive and proliferative potential of bladder cancer. J Magn Reson Imaging 2014; 39: 172-178 [PMID: 23589321 DOI: 10.1002/jmri.24148]

Yoshida S, Kobayashi S, Koga F, Ishioh J, Ishii C, Tanaka H, Nakanishi Y, Matsuoka Y, Numao N, Saito K, Masuda H, Fujiy I, Kihara K. Apparent diffusion coefficient as a prognostic biomarker of upper urinary tract cancer: a preliminary report. Eur Radiol 2013; 23: 2206-2214 [PMID: 23494466 DOI: 10.1007/s00330-013-2805-2]

Yoshida S, Koga F, Kobayashi S, Ishii C, Tanaka H, Nakanishi Y, Matsuoka Y, Numao N, Saito K, Masuda H, Fujiy I, Kihara K. Role of diffusion-weighted magnetic resonance imaging in predicting sensitivity to chemoradiotherapy in muscle-invasive bladder cancer. Int J Radiat Oncol Biol Phys 2012; 83: e21-e27 [PMID: 22414281 DOI: 10.1016/j.ijrobp.2011.11.065]

Rosenkant AB, Mousi TC, Spierer B, Melamed J, Taneja SS, Huang WC. High-grade bladder cancer: association of the apparent diffusion coefficient with metastatic disease: preliminary results. J Magn Reson Imaging 2012; 35: 1478-1483 [PMID: 2282896 DOI: 10.1002/jmri.23590]

Yoshida S, Saito K, Koga F, Yokoyama M, Kageyama Y, Azuma K, Matsuura T, Yabuki H, Hara M, Shimamoto Y, Kihara K. Comparison of diffusion-weighted imaging with dynamic contrast-enhanced MRI in prediction of pelvic lymph node metastases in patients with bladder cancer. Acad Radiol 2011; 18: 532-538 [PMID: 21359877 DOI: 10.1016/j.acra.2010.10.018]

Yoshida S, Saito K, Koga F, Yokoyama M, Kageyama Y, Azuma K, Matsuura T, Yabuki H, Hara M, Shimamoto Y, Kihara K. Comparison of diffusion-weighted imaging with dynamic contrast-enhanced MRI in prediction of pelvic lymph node metastases in patients with bladder cancer. Acad Radiol 2011; 18: 532-538 [PMID: 21359877 DOI: 10.1016/j.acra.2010.10.018]
Masuda H, Kobayashi T, Kawakami S, Kihara K. C-reactive protein level predicts prognosis in patients with muscle-invasive bladder cancer treated with chemoradiotherapy. *BJU Int* 2008; 101: 978-981 [PMID: 18190628 DOI: 10.1111/j.1464-410X.2007.07408.x]

70 Kageyama Y, Okada Y, Arai G, Hyochi N, Suzuki M, Masuda H, Hayashi T, Kawakami S, Okuno T, Ishizaka K, Kihara K. Preoperative concurrent chemoradiotherapy against muscle-invasive bladder cancer: results of partial cystectomy in elderly or high-risk patients. *Jpn J Clin Oncol* 2000; 30: 553-556 [PMID: 11210165]

71 Kageyama Y, Yokoyama M, Sakai Y, Saito K, Koga F, Yano M, Arai G, Hyochi N, Masuda H, Fujii Y, Kawakami S, Kobayashi T, Kihara K. Favorable outcome of preoperative low-dose chemoradiotherapy against muscle-invasive bladder cancer. *Am J Clin Oncol* 2003; 26: 504-507 [PMID: 14528080 DOI: 10.1097/01.coc.0000037665.11701.22]

72 Matsumoto H, Wada T, Fukunaga K, Yoshihiro S, Matsuyama H, Naito K. Bax to Bcl-2 ratio and Ki-67 index are useful predictors of neoadjuvant chemoradiation therapy in bladder cancer. *Jpn J Clin Oncol* 2004; 34: 124-130 [PMID: 15078907]

73 Rödel C, Grabenbauer GG, Rödel F, Birkenhake S, Kühn R, Martus P, Zörcher T, Fürsich D, Papadopoulos T, Dunst J, Schrott KM, Sauer R. Apoptosis, p53, bcl-2, and Ki-67 in invasive bladder carcinoma: possible predictors for response to radiochemotherapy and successful bladder preservation. *Int J Radiat Oncol Biol Phys* 2000; 46: 1213-1221 [PMID: 10725634]

P- Reviewers: Msaouel P, Plataniotis G  S- Editor: Ji FF  L- Editor: A  E- Editor: Zhang DN
