Radiology

Bladder Cancer: Diagnosis with Diffusion-weighted MR Imaging in Patients with Gross Hematuria[1]

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Purpose: To prospectively evaluate the usefulness of diffusion-weighted (DW) magnetic resonance (MR) imaging for the detection of bladder neoplasms in patients with gross hematuria of lower urinary tract origin.

Materials and Methods: The study protocol received institutional ethical committee approval, and informed consent was obtained. Between April 2007 and March 2008, 130 consecutive patients with gross hematuria whose upper urinary tract had a normal appearance at ultrasonographic examination were prospectively enrolled. Mean age was 59.4 years (range, 45–75 years). All patients were evaluated by using T2-weighted high-spatial-resolution MR imaging of the urinary bladder, followed by DW MR imaging. Two radiologists independently interpreted the T2-weighted and DW images, and discrepancies were resolved by consensus. Agreement was evaluated by using the κ statistic. All patients underwent conventional cystoscopy. With cystoscopy and the final histopathologic findings as the reference standards, a comparison with imaging findings was performed by using the McNemar test.

Results: The consensus diagnostic performance of DW MR imaging for identification of bladder tumors was: sensitivity, 98.1% (104 of 106); specificity, 92.3% (24 of 26); PPV, 100% (104 of 104); negative predictive value, 92.3% (24 of 26); and accuracy, 97.0% (128 of 132). Two cases were falsely negative on T2-weighted MR images but were correctly diagnosed by using DW MR images. The agreement between DW MR imaging results and cystoscopic findings was excellent ($\kappa = 0.94$) for identification of bladder neoplasm. DW MR imaging had a sensitivity and PPV of 98.5% (128 of 130) and 100% (128 of 128), respectively, for determining the cause of hematuria.

Conclusion: DW MR imaging is a highly reliable imaging approach for identification of bladder tumors in patients with gross hematuria.

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Gross hematuria is an important finding that should be considered a sign of urologic malignancy until proved otherwise. Thus, hematuria necessitates complete evaluation of the entire urinary tract. For evaluation of the lower urinary tract, conventional cystoscopy is a standard diagnostic approach; however, this procedure has drawbacks, including its high cost and invasiveness. The latter may lead to iatrogenic bladder injury and urinary sepsis (1).

Computed tomography (CT) is commonly recommended as the initial radiologic approach for evaluating hematuria (1,2). CT has low sensitivity for detection of small bladder lesions. Adequate bladder distention and thin-section scanning are necessary to depict small bladder lesions on CT images. Therefore, in many cases, negative findings at CT warrant performance of conventional cystoscopy in patients with hematuria.

Virtual endoscopy is an imaging modality that has shown promising results for the diagnosis of bladder carcinoma. Currently, this is most commonly performed as CT-based virtual endoscopy (3,4), which requires air insufflation, or by magnetic resonance (MR) imaging–based virtual endoscopy (5). The problems of virtual cystoscopy include difficulty detecting flat tumors and differentiating small tumors and inflammatory lesions of the mucosa, especially in patients with suboptimal bladder filling.

Diffusion-weighted (DW) MR imaging is an established method used in the diagnosis of acute stroke (6) and extracranial tumors, such as hepatic, renal, prostatic, colonic, and cervical tumors (7–13).

The feasibility of using DW MR imaging in the detection of a urinary bladder carcinoma was evaluated in two prior studies (14,15). However, these studies suffered several limitations; the first was retrospective in nature, and neither included nonmalignant disease processes that commonly afflict the bladder.

Our study was conducted to prospectively evaluate the usefulness of DW MR imaging in the detection of bladder neoplasms in patients with gross hematuria of lower urinary tract origin.

Advance in Knowledge

- Diffusion-weighted (DW) MR imaging has high reliability for the diagnosis of bladder tumors.

Implication for Patient Care

- DW MR imaging is a promising modality with high sensitivity and specificity for the diagnosis of bladder tumors and could be a first-line diagnostic test in patients with gross hematuria.

Materials and Methods

Patients

Our institutional ethical committee reviewed and approved the study protocol. Informed consent was obtained from all patients. Between April 2007 and March 2008, 130 consecutive patients who presented with gross (macroscopic) hematuria and who had normal findings from upper urinary tract ultrasonographic evaluation were prospectively enrolled. Exclusion criteria included upper urinary tract tumors or stones, a history of urinary tract trauma, contraindications to MR imaging (eg, pacemaker or metallic prostheses) or cystoscopy (eg, unfit for anesthesia or urethral stricture), and refusal to consent to the study.

The 130 patients were examined by using MR imaging and, subsequently (within 48 hours), conventional cystoscopy. The population included 107 (82.3%) men (mean age, 58.6 years ± 7.1 [standard deviation]; range, 45–73 years) and 23 (17.7%) women (mean age, 61.2 years ± 6.8; range 51–75 years). For the whole group, mean age was 59.4 years ± 7.4 (range, 45–75 years).

MR Technique

Patients were instructed to start drinking water one-half hour before the MR imaging examination and to arrive with a full bladder. In patients with a urethral catheter, 250–400 mL of sterile saline was used to distend the bladder. Bladder fullness was checked on localizer images, and the examination was delayed if the bladder was not full.

Patients were examined with a 1.5-T MR imager (Signa Horizon; GE Medical Systems, Milwaukee, Wis). Initially, high-spatial-resolution axial T2-weighted images of the bladder were obtained (repetition time msec/echo time msec, 7000–8000/90–102; bandwidth, 20–83 kHz; matrix, 256 × 256; section thickness, 3 mm; intersection gap, 1 mm; field of view, 20 cm). Then, with the patient free breathing, DW images were obtained in the axial plane by using a body coil and a monodirectional-gradient multisection fast spin-echo echoplanar sequence (8000/61.2; bandwidth, 142 kHz; matrix, 256 × 256; section thickness, 5 mm; intersection gap, 0 mm; field of view, 36 cm; signals acquired, seven; water signals acquired with b values of 0 and 800 sec/mm^2). Thirty to 54 sections were obtained in 60–120 seconds to cover the pelvis.

Image Analysis

Images were analyzed by using software (FuncTool; GE Medical Systems). Two radiologists (M.E.A., H.F.R., with 10 and 8 years experience, respectively, reading body MR images), who were blinded to the results of conventional cystoscopy, in-

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Abbreviations:
DW = diffusion-weighted
PPV = positive predictive value
SI = signal intensity

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Guarantors of integrity of entire study, M.E.A., A.E., H.F.R.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, all authors; clinical studies, M.E.A., A.E., T.E.; statistical analysis, A.E., H.F.R., T.E.; and manuscript editing, M.E.A., A.E., T.E.

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dependently interpreted the DW images. Discrepancies were resolved by consensus. A separate review of T2-weighted images by the same two radiologists was performed with the reviewers blinded to the DW imaging and cystoscopic findings. Both reviewers retrospectively reviewed any missed lesions.

Bladder tumors on images ($b = 800$ sec/mm^2) had high signal intensity (SI) relative to the bladder wall and surrounding urine. Prostatic and ureteric tumors also had high SI. Colonic lesions that were invading the bladder appeared as extravesical masses of intestinal origin with mural thickening and hyperintense mucosal foci. The bladder wall was considered thickened if it was greater than 3 mm thick.

Reference Standard

Conventional cystoscopy was performed by a urologist (A.E., with 3 years experience as a urology consultant), who was blinded to the results of MR imaging, by using a semirigid cystoscope while the patient received spinal anesthesia. In patients treated by radical cystectomy ($n = 72$), tumor appearance and size were established from the final histologic report; otherwise, tumor appearance and size were established at cystoscopy by using a ureteric catheter. Morphology was classified as fungating (overlying mucosa of the tumor was ulcerated, with fungation into the bladder lumen), nodular (intact mucosa overlying the tumor), or papillary (looked like a papilla).

Statistical Analysis

The data were processed by using software (SPSS, version 15; SPSS, Chicago, Ill), with conventional cystoscopy or the final histopathologic report as the reference standard. We evaluated the sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy of DW and T2-weighted MR images as aids in the identification of bladder tumors, abnormal bladders (including both malignant and thickened bladders), and the cause of the hematuria.

To evaluate the performance and agreement of the two reviewers at identifying bladder tumors and extrabladder lesions, we applied the κ statistic. A κ of less than 0.20 was considered poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; and 0.81–1.00, excellent. A comparison of imaging findings with the results of cystoscopy and histologic examination was subsequently performed by using the McNemar test. A P value of less than .05 was considered to indicate a statistically significant difference.

Results

By using reference standard tests, bladder tumors were diagnosed in 106 (81.5%) of the 130 patients; cystitis, in 14 (10.8%); prostatic adenocarcinoma, in four (3.1%); benign prostatic hyperplasia, in three (2.3%); a ureteric tumor, in one (0.8%); and colonic carcinoma adherent to the bladder with secondary cystitis, in two (1.5%). In the 106 patients with bladder tumors, 123 lesions were identified with conventional cystoscopy. Ten patients had multiple lesions; five patients had two lesions, three patients had three lesions, and two patients had four lesions. The detection rates at different tumor locations on both DW and T2-weighted MR

Figure 1

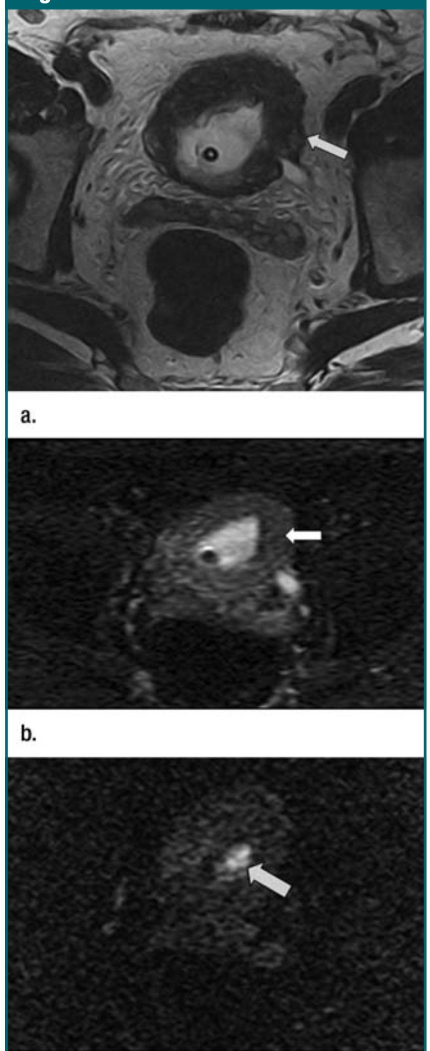

Figure 1: MR images of a 55-year-old man with a papillary bladder tumor. **(a)** Axial high-spatial-resolution T2-weighted image of the pelvis shows diffuse thickening of vesical wall (arrow). DW images obtained with b values of **(b)** 0 and **(c)** 800 sec/mm^2 show small hyperintense papillary growth at high posterior wall to the left (arrows).

Table 1

Detection of Bladder Tumors by Site on DW versus T2-weighted MR Images with Conventional Cystoscopy as the Reference Standard

Site*	No. of Tumors: DW MR Images	No. of Tumors: T2-weighted MR Images
Posterior wall ($n = 59$)	58 (98.3)	58 (98.3)
Right lateral wall ($n = 17$)	17 (100)	16 (94.1)
Left lateral wall ($n = 19$)	19 (100)	18 (94.7)
Anterior wall ($n = 18$)	18 (100)	18 (100)
Dome ($n = 10$)	9 (90.0)	9 (90.0)

Note.—Data in parentheses are percentages.

* Number of tumors at each site determined with conventional cystoscopy.

Figure 2

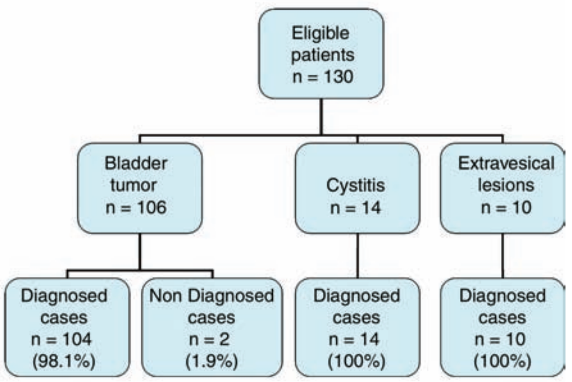

Figure 2: Flow diagram shows the diagnostic accuracy of DW MR imaging. Second row is findings with the reference standard. Third row is findings with DW MR imaging.

Table 2

DW versus T2-weighted MR Images for Detection of Bladder Tumors and Abnormality by Reviewer

Parameter	DW MR Imaging: Reviewer 1	DW MR Imaging: Reviewer 2	T2-weighted MR Imaging: Reviewer 1	T2-weighted MR Imaging: Reviewer 2
	Detection of Bladder Tumor			
Sensitivity	104/106 (98.1)	102/106 (96.2)	101/106 (95.3)	100/106 (94.3)
Specificity	24/27 (88.9)	24/28 (85.7)	24/28 (85.7)	24/29 (82.8)
PPV	104/104 (100)	102/102 (100)	101/101 (100)	100/100 (100)
NPV	24/26 (92.3)	24/28 (85.7)	24/28 (85.7)	24/29 (82.8)
Accuracy	128/133 (96.2)	126/134 (94.0)	125/134 (93.3)	124/135 (91.9)
	Detection of Abnormal Bladder			
Sensitivity	118/120 (98.3)	116/120 (96.7)	115/120 (95.8)	114/120 (95.0)
Specificity	10/13 (76.9)	10/14 (71.4)	10/14 (71.4)	10/15 (66.7)
PPV	118/118 (100)	116/116 (100)	115/115 (100)	114/114 (100)
NPV	10/13 (76.9)	10/14 (71.4)	10/14 (71.4)	10/15 (66.7)
Accuracy	128/133 (96.2)	126/134 (94.0)	125/134 (93.3)	124/135 (91.9)

Note.—Data in parentheses are percentages. NPV = negative predictive value.

Table 3

DW versus T2-weighted MR Images for Detection of Bladder Tumors and Abnormality at Consensus Review

Parameter	DW MR Imaging	T2-weighted MR Imaging
	Detection of Bladder Tumor	
Sensitivity	104/106 (98.1)	102/106 (96.2)
Specificity	24/26 (92.3)	24/28 (85.7)
PPV	104/104 (100)	102/102 (100)
NPV	24/26 (92.3)	24/28 (85.7)
Accuracy	128/132 (97.0)	126/134 (94.0)
	Detection of Abnormal Bladder	
Sensitivity	118/120 (98.3)	116/120 (96.7)
Specificity	10/12 (83.3)	10/14 (71.4)
PPV	118/118 (100)	116/116 (100)
NPV	10/12 (83.3)	10/14 (71.4)
Accuracy	128/132 (97.0)	126/134 (94.0)

Note.—Data in parentheses are percentages. NPV = negative predictive value.

images are listed in Table 1. Tumor appearance was fungating in 40 (37.7%) of the 106 patients, nodular in 35 (33.0%), and papillary in 31 (29.2%). Tumor length ranged from 3 to 85 mm (mean, 29 mm ± 20).

The histologic diagnosis was transitional cell carcinoma in 100 (94.3%) of the 106 patients with tumors and squamous cell carcinoma in six (5.7%). Muscle invasion by the tumor cells was present in 80 (75.5%) patients, while the remaining 26 (24.5%) had lamina invasion.

On DW MR images, the two reviewers initially agreed on the identification of four normal bladders, 14 thickened bladders, and 102 malignant bladders with 119 lesions. At consensus review, two additional tumors were noted in the bladders of two patients, so that two bladders originally classified as normal were then determined to be malignant. Thus, after consensus review, the two reviewers identified 104 malignant bladders with 121 lesions and 14 thickened inflamed bladders. The agreement between the two readers was excellent ($\kappa = 0.92$).

By using DW MR imaging, 10 patients were found to have multiple bladder lesions; five patients had two lesions, three had three lesions, and two had four lesions. The locations of the 121 focal bladder lesions on DW images included the posterior wall ($n = 58$), right lateral wall ($n = 17$), left lateral wall ($n = 19$), anterior wall ($n = 18$), and dome ($n = 9$). The diameter of the lesions ranged from 8 to 90 mm (mean, 33 mm).

DW MR imaging enabled detection of 121 of the 123 tumors noted at conventional cystoscopy, with two false-negative findings. All tumors identified were clearly shown on images ($b = 800$ sec/mm^2) to have high SI relative to the bladder wall and surrounding urine (Fig 1). Of the 16 neoplasms smaller than 10 mm at conventional cystoscopy, two (12.5%) were not detected on DW MR images. These two lesions with false-negative findings, confirmed as transitional cell carcinomas, were polypoid lesions with diameters of 3 and 4 mm. At retrospective review the reviewers still could not diagnose them.

Figure 3

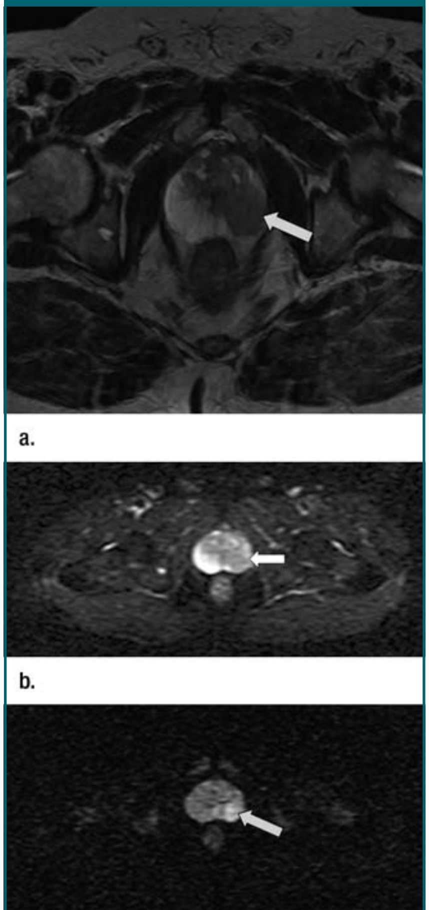

Figure 3: MR images of a 70-year-old man with prostatic adenocarcinoma. **(a)** Axial high-spatial-resolution T2-weighted MR image of the prostate shows area of low SI at left peripheral zone (arrow). DW images obtained with *b* values of **(b)** 0 and **(c)** 800 sec/mm^2 show this area with high SI (arrows).

Figure 4

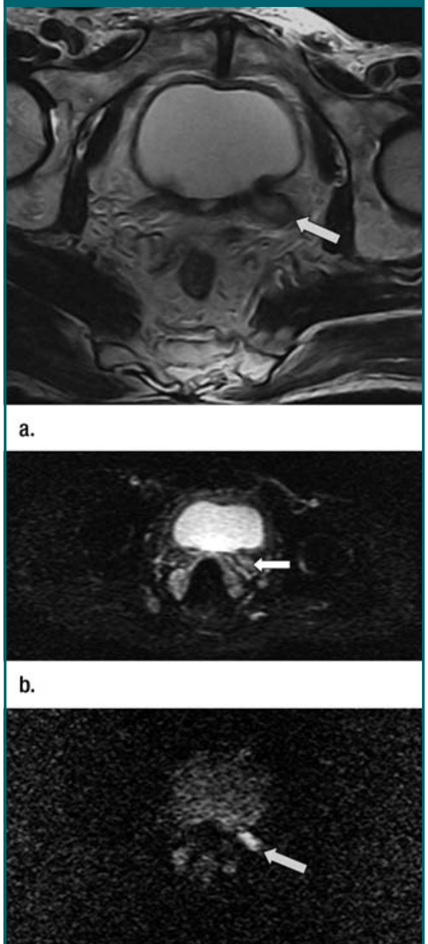

Figure 4: MR images of a 56-year-old man with a left ureteric tumor. **(a)** Axial high-spatial-resolution T2-weighted image of the pelvis shows abnormal SI (arrow) at the lower end of the left ureter. DW images obtained with *b* values of **(b)** 0 and **(c)** 800 sec/mm^2 show this area with high SI (arrows).

Figure 5

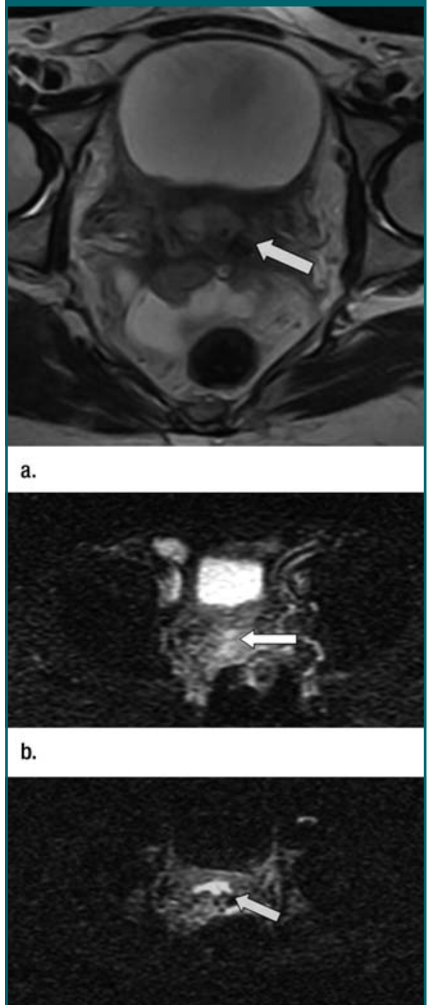

Figure 5: MR images of a 44-year-old woman with a colonic mass. **(a)** Axial high-spatial-resolution T2-weighted MR image of the pelvis shows retrovesical mass (arrow) adherent to the posterior vesical wall. DW images obtained with *b* values of **(b)** 0 and **(c)** 800 sec/mm^2 show retrovesical colonic mass (arrows) with foci of increased SI at its center. Mass is adherent to urinary bladder and associated with secondary cystitis.

Therefore, the reviewers' interpretations of DW MR images agreed with the findings at conventional cystoscopy for 104 malignant and 14 thickened inflamed (diffusely thickened) bladders (Fig 2). In two patients, abnormal malignant bladders were misdiagnosed as normal. The agreement between DW MR and conventional cystoscopic findings was excellent for both the identification of bladder neoplasms ($\kappa = 0.94$) and the determination of abnormal (malignant or inflamed) bladders ($\kappa = 0.95$). By using the McNemar test, no significant difference between DW MR imaging and cystoscopy was found ($P > .05$).

On T2-weighted MR images, the two reviewers identified all bladder tumors except for four (two of which were also missed on DW images) and accurately diagnosed all cases of cystitis. The four lesions with false-negative findings were polypoid lesions with diameters of 3, 4, 4, and 6 mm. At retrospective review the reviewers still could not diagnose these lesions.

The agreement between DW and T2-weighted MR imaging for the detection of bladder tumors and abnormal bladders was excellent ($\kappa = 0.96$ for both). By using the McNemar test, no significant difference was detected between DW and T2-weighted MR imaging ($P > .05$).

The sensitivity, specificity, PPV, negative predictive value, and accuracy of

DW and T2-weighted MR images for identification of bladder neoplasms and abnormal bladders are listed by reviewer in Table 2 and for both reviewers in consensus in Table 3.

In regards to extrabladder causes of hematuria, the two reviewers initially agreed on the identification of six hyperintense prostatic lesions (Fig 3), one hyperintense ureteric lesion (Fig 4), and two colonic lesions adhered to the bladder (these lesions appeared as extravesical masses of intestinal origin with mural thickening and hyperintense mucosal foci, Fig 5). By consensus, the reviewers decided that one additional prostatic lesion was present. Agreement between the readers was good (κ = 0.8). The sensitivity and PPV of DW MR imaging were both 100% (10 of 10) for detection of extrabladder lesions. On T2-weighted MR images, the two reviewers, by consensus, could identify all extrabladder lesions seen on DW MR images.

Among the 130 patients included in the study, we found that the sensitivity and PPV of DW MR imaging for identification of the cause of hematuria were 98.5% (128 of 130) and 100% (128 of 128), respectively, and those for T2-weighted MR imaging were 96.9% (126 of 130) and 100% (126 of 126), respectively.

Discussion

Hematuria is one of the most common problems in patients presenting to a urology service, and evaluation of the entire urinary tract is mandatory in order not to miss a malignancy. Refinements in diagnostic imaging and advances in endoscopy have improved the accuracy of diagnosing patients with hematuria while reducing morbidity. Evaluation of hematuria poses a number of risks to the patient, including contrast agent–induced renal failure, sepsis from instrumentation, radiation risks, contrast agent anaphylaxis, embolism from arteriography, and anesthesia risk during cystoscopy (16,17).

MR imaging does not involve the risks of ionizing radiation. In addition, the contrast agents used (gadolinium) are less toxic to the kidneys when given at recommended doses to patients without renal failure. Multiplanar imaging, rapid sequence imaging, specialized coils, and T1- and T2-weighted images can provide markedly enhanced resolution of tissue detail (16).

In DW MR imaging, the image contrast is influenced by the Brownian motion of water molecules. The SI is high if water molecules are restricted in their motion, which can be caused by cell membranes or, in the case of free fluid, by high viscosity. The MR SI is low if water molecules can diffuse freely (18).

The feasibility of using DW MR imaging for the detection of a urinary bladder carcinoma has been reported by Matsuki et al (14). In their study, all carcinomas in 15 patients were clearly shown to have high SI relative to the surrounding structures. The sensitivity and PPV of DW imaging in that study were both 100% for detection of carcinomas. However, that study had several limitations. First, it was a retrospective study of a small number of patients. In addition, all patients' MR examinations occurred after biopsy, which may have affected the results. Furthermore, all patients included in the study were known to have bladder tumors, thus there was case selection bias in the report. The same findings were also reported by El-Assmy et al (15). However, all included cases were known to have bladder tumors; thus, there again was a selection bias.

In our present study, findings on DW MR images showed excellent agreement with those at conventional cystoscopy. Reviewers could identify almost all bladder lesions and missed only two lesions that were less than 4 mm in diameter. The sensitivity and PPV for the diagnosis of bladder tumors were 98.1% and 100%, respectively. These results are in agreement with those reported by Matsuki et al (14). For enabling identification of the cause of hematuria, the sensitivity and PPV of DW MR imaging were 98.3% and 100%, respectively.

The results of our study suggest a high reliability of DW MR imaging for the diagnosis of bladder and extrabladder lesions in patients with gross hematuria. In addition, DW MR images can provide information regarding lesion size, number, and location to surgeons who perform conventional cystoscopy.

Our study had limitations. First, most of the tumors we studied were large (mean length, 29 mm), so it would be critical to assess smaller tumors to assess the reliability of DW MR imaging. Second, the value of DW versus T2-weighted MR imaging for staging of bladder tumors was not assessed. Finally, we did not apply this technique to differentiate tumor tissue from scars and reactive tissue after chemotherapy and radiation therapy.

One disadvantage of DW MR imaging includes failure to visualize the lumen of the urethra, as is routinely seen at conventional cystoscopy. Another disadvantage is that patients with metal prostheses or implants can not be adequately examined.

In conclusion, our study shows DW MR imaging has high reliability for the diagnosis of bladder tumors, which is similar to that of conventional cystoscopy. This noninvasive method could be efficiently used for evaluation of patients with hematuria of lower urinary tract origin.

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