

Diffusion Weighted Imaging in the Detection of Upper Urinary Tract Urothelial Tumors

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ABSTRACT

Purpose: Diffusion-weighted (DW) magnetic resonance imaging (MRI) provides information about the biophysical properties of tissues such as cell organization and density. DW imaging (DWI) is becoming important in the assessment of malignant tumors. The purpose of our study was to evaluate the capability and reliability of DWI in the evaluation of upper urinary tract urothelial tumors.

Materials and Methods: DWI was performed in seventeen patients with upper urinary tract urothelial tumor, previously diagnosed by either CT or retrograde pyelography. An histological evaluation was performed after surgical resection. Each MRI was carried out using a 1.5T superconductive magnet MRI system. DWI images were obtained with b value of 1000 s/mm² under normal breathing. The apparent diffusion coefficient (ADC) values were measured.

Results: In nine patients with renal pelvis tumors and seven patients with ureteral tumors, the lesions were shown as high-signal intensity in the corresponding region on DWI. In one patient with carcinoma in situ (CIS) of the ureter, the lesion was not depicted with DWI. The mean ADC value of the tumor was $1.125 \pm 0.217 \times 10^{-3}$ mm²/s and was significantly lower than those of the renal parenchyma ($1.984 \pm 0.238 \times 10^{-3}$ mm²/s, $p < 0.01$) and the urine ($2.941 \pm 0.315 \times 10^{-3}$ mm²/s, $p < 0.01$).

Conclusions: In our study, the renal pelvic and ureteral tumors except CIS were shown clearly with DWI. Although further studies are required, DWI may take the place of invasive retrograde urography for detecting tumors of the upper urinary tract.

Key words: *magnetic resonance imaging; transitional cell; neoplasm; renal pelvis; ureter*

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INTRODUCTION

Five percent of urothelial tumors occur from the ureter and renal pelvis or calyces, accounting for approximately 10% of upper urinary tract neoplasms (1). Upper urinary tract urothelial cancer is one of the most difficult lesions to be shown by imaging studies. Moreover, it is difficult to depict ureteral or renal pelvic small tumors. Conventionally, invasive

radiography, such as retrograde pyelo-uretrography using cystoscopy, has been the imaging modality in detecting urothelial tumors.

Diffusion-weighted (DW) magnetic resonance imaging (MRI) is a technique used to show water molecular diffusion in vivo. It provides information about the biophysical properties of tissues such as cell organization and density, microstructure, and microcirculation (2). DW imaging (DWI) has been

used in the field of neuroradiology. Recently, DWI has become increasingly important in the assessment of malignant tumors. Several authors have reported the usefulness of DWI in the detection of the abdominal and pelvic malignant lesion such as prostate cancer and colon cancer (3,4). The purpose of our study was to evaluate the efficacy and reliability of DWI in the assessment of upper urinary tract urothelial tumors.

MATERIALS AND METHODS

Patient Population

This was a retrospective study performed at Nagano Municipal hospital. Between June 2003 and March 2007, seventeen patients with upper urinary tract urothelial tumor underwent MRI examination including DWI. All patients had upper tract urothe-

lial tumor previously diagnosed either by computed tomography or by retrograde pyelography. Our Institutional Ethics Committee reviewed and approved the study protocol. Written informed consent was obtained from all patients.

The histological study was performed after surgical resection. The patients' characteristics are listed in Table-1.

Just before the examination, intramuscular or intravenous injection of 20 mg of butyl scopolamine bromide was administered to all patients.

Imaging Protocol

Each MRI was performed using a 1.5T super-conductive magnet MRI system (Signa, Twin Speed Excite version 12.0, GE Medical Systems, Milwaukee, WI.) with maximum gradient amplitude of 40

Table 1 – Patients' characteristics.

Case N.	Age	Sex	Location	Tumor Size (mm)	Classification	Grade	pT	ADC Value (x10 ⁻³ mm ² /s)
1	73	M	Renal pelvis	10, multiple	Papillary	G1-2	pTa	1.06
2	61	M	Renal pelvis	20	Papillary	G2	pTa	1.09
3	58	F	Renal pelvis	40x35	Papillary and infiltrating	G2	pT3	0.884
4	84	M	Renal pelvis	40x45	Papillary and infiltrating	G2	pT4	1.2
5	72	M	Renal pelvis	20x60	Papillary	G2	pTa	1.1
6	56	M	Renal pelvis	45x60	Papillary	G2	pT1	1.33
7	75	M	Renal pelvis	35x50	Papillary	G1>2	pT3	1.68
8	78	F	Renal pelvis	20x30	Papillary	G2-3	pT3	1.26
9	66	M	Renal pelvis	50x35	Papillary and infiltrating	Sarcomatoid	pT3	1.11
10	72	M	Upper ureter	30	Papillary and infiltrating	G3 with SCC	pT3, pN0	1.17
11	77	M	Upper ureter	10	Papillary and infiltrating	G2	pT1	0.927
12	65	M	Middle ureter	10	Infiltrating	G1-2	pT1	1.02
13	72	M	Middle ureter	8	Infiltrating	G2	pT2+CIS	0.944
14	75	M	Lower ureter	8	Infiltrating	G2-3	pT2+CIS	1.00
15	75	M	Lower ureter	10	Infiltrating	G3	pT3	0.752
16	79	M	Lower ureter	15	Papillary	G1	pT3	1.22
17	72	M	Lower ureter		CIS	G3	CIS	

ADC = apparent diffusion coefficient; SCC = squamous cell carcinoma; CIS = carcinoma in situ.

Table 2 – Imaging parameters of diffusion-weighted imaging (DWI).

Type of Scan	Non-breath-hold	Scan percentage	100 %
Sequence	SE-EPI	EPI factor	64
Mode	Single shot	ASSET factor	2
Coil	8 Channel body	MPG	3 axis
Slice orientation	Axial	b-factor	1000s/mm ²
RT (repetition time)	5000 ms	NEX (number of excitations)	6
ET (eco time)	58.4 ms	Number of slices	48x2
Fat suppression	Water excitation	Slice thickness	5 mm
FOV (field of view)	350 mm	Slice gap	0 mm
RFOV% (receiver field of view)	100%	Acquisition time	240x2 sec.
Matrix	128		

mT/m and a maximum slew rate of 150 mT/m/second, with an 8-channel-body array coil. DW images were obtained in the axial plane under normal breathing in addition to conventional T1/T2 weighted MR images without contrast-enhanced imaging. We obtained multiple axial thin slices DWI and reconstructed 3D images and maximum intensity projection (MIP) images. The imaging parameters used for DWI are listed in Table-2.

Typically, presence of the tumor was defined when high signal intensity appeared on DWI. Radiological diagnosis was performed by the same radiologist (S.I.).

The apparent diffusion coefficient (ADC) values of the tumor, the renal parenchyma and the urine in the bladder were calculated in a circular region of interest for quantitative analysis (Figure-1). Statistical analysis was performed by an un-paired t-test. Results are reported as mean \pm standard deviation. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In nine patients with renal pelvic tumors, all lesions were shown as high-signal intensity in the renal pelvis or renal parenchyma on DWI (Figures-2 and 3), whereas conventional T1- and T2-weighted MRI was able to depict the lesion clearly in eight patients. In seven patients with a ureteral tumor, all

tumors were depicted in the corresponding region (Figures-1 and 4). The smallest depicted tumor was approximately 8 mm in diameter. However, conventional MRI was able to depict ureteral tumor in five patients. In a patient (case 17) with carcinoma in situ (CIS) in the lower ureter and in two patients (cases 13 and 14) with associated CIS, DWI and conventional MRI failed to show the corresponding lesions. The sensitivity and positive predictive value (PPV) of DWI for detecting the tumor were 94.1% (16 of 17) and 100%, respectively. The sensitivity and PPV of conventional MRI were 76.5% (13 of 17) and 100%, respectively.

DWI showed a hyper-intense signal in several normal structures such as spleen, lymph node, spinal cord and mucus in the small intestine. Swollen lymph nodes in a patient (Figure-4, case 10) were shown as high signal intensity by DWI; however, the lymph nodes did not contain malignant cells on histopathological examination.

Histopathologically all tumors were diagnosed as a urothelial carcinoma in the surgical specimens. The cytological tests were negative in five patients with low-grade tumors.

The mean ADC value of the tumor was $1.125 \pm 0.217 \times 10^{-3} \text{ mm}^2/\text{s}$, while the values of the renal parenchyma and the urine in the bladder were $1.984 \pm 0.238 \times 10^{-3} \text{ mm}^2/\text{s}$ and $2.941 \pm 0.315 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively. The mean ADC value of the urothelial tumor was significantly lower than those of the renal parenchyma and the urine ($p < 0.01$ and $p < 0.01$).

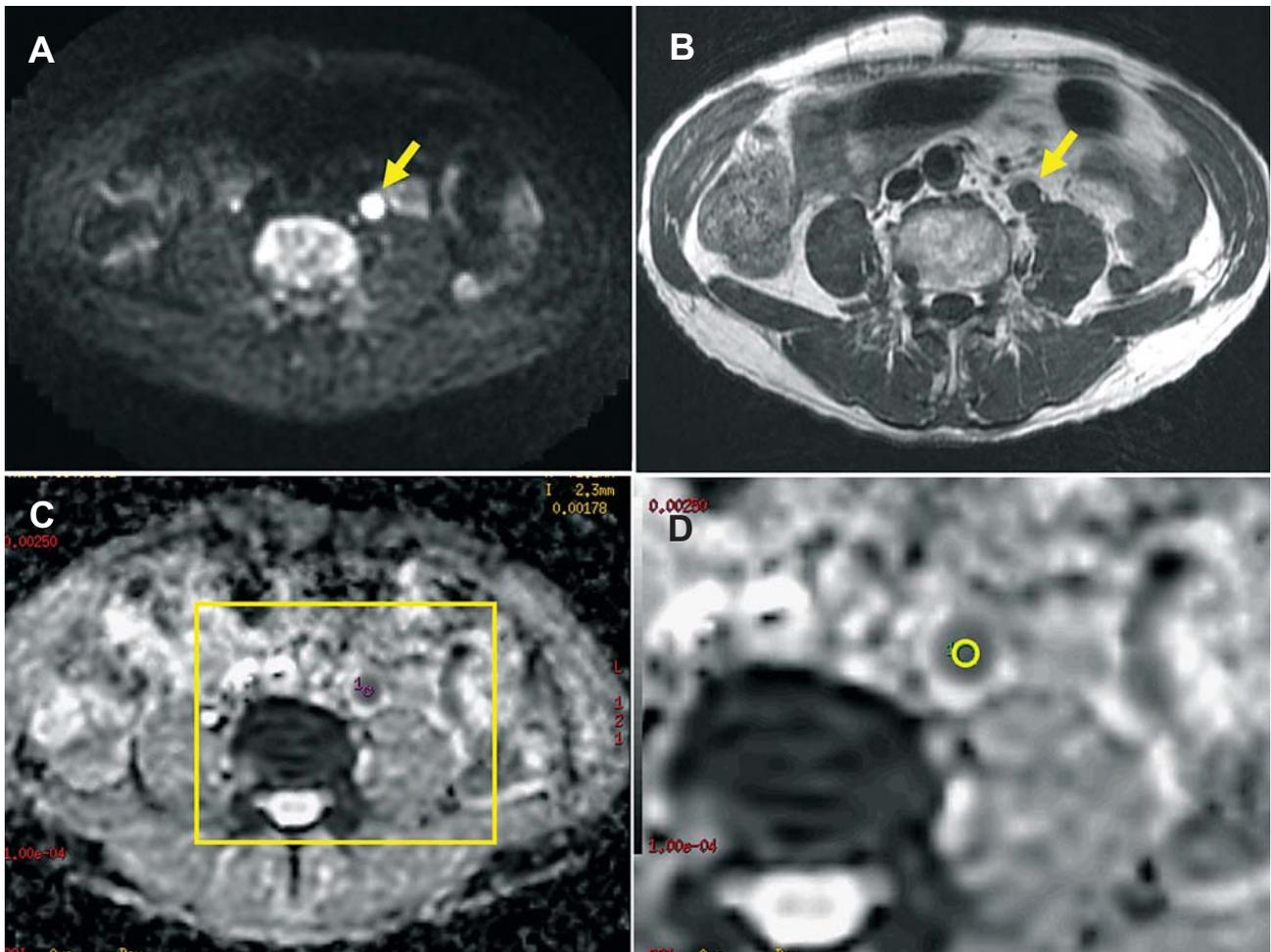


Figure 1 – Case 11: A 77-year-old man with left ureteral tumor. A) On axial diffusion weighted image, the tumor (arrow) is depicted as high intensity. B) On axial T1-weighted image, the tumor shows iso-signal to psoas muscle. C) On apparent diffusion coefficient (ADC) map, the ADC value was measured in a circular region of interest within the tumor. D) Magnified view of the ADC map in C.

Regarding the tumor classification, the mean ADC value of infiltrating tumor was significantly lower than that of papillary tumor ($0.929 \pm 0.122 \times 10^{-3} \text{ mm}^2/\text{s}$ and $1.245 \pm 0.215 \times 10^{-3} \text{ mm}^2/\text{s}$, $p < 0.05$).

COMMENTS

MRI has been infrequently used in the primary assessment of upper tract urothelial cancer, and the MRI characteristics of this tumor have not been well described. MRI imaging is independent of excretory function and shows multiplanar imaging, which permits direct image acquisition in the plane

of tumor spread (5). Diffusion weighted imaging is an MRI technique and is the only imaging method that can evaluate the diffusion process in vivo. Diffusion is thermally induced motion of water molecules in biological tissues, which is called Brownian motion. The speed of diffusion of water molecules is different in the extracellular and intracellular component of the tissues. In the intracellular component, the diffusion is relatively slow because of the presence of cellular membranes (2). A malignant tumor often has a larger cell diameter and denser cellularity than normal tissue and the cell density may be indicative of tumor aggressiveness. Restriction of water diffusion is found to be a common feature of tumors (6). Apparent diffusion

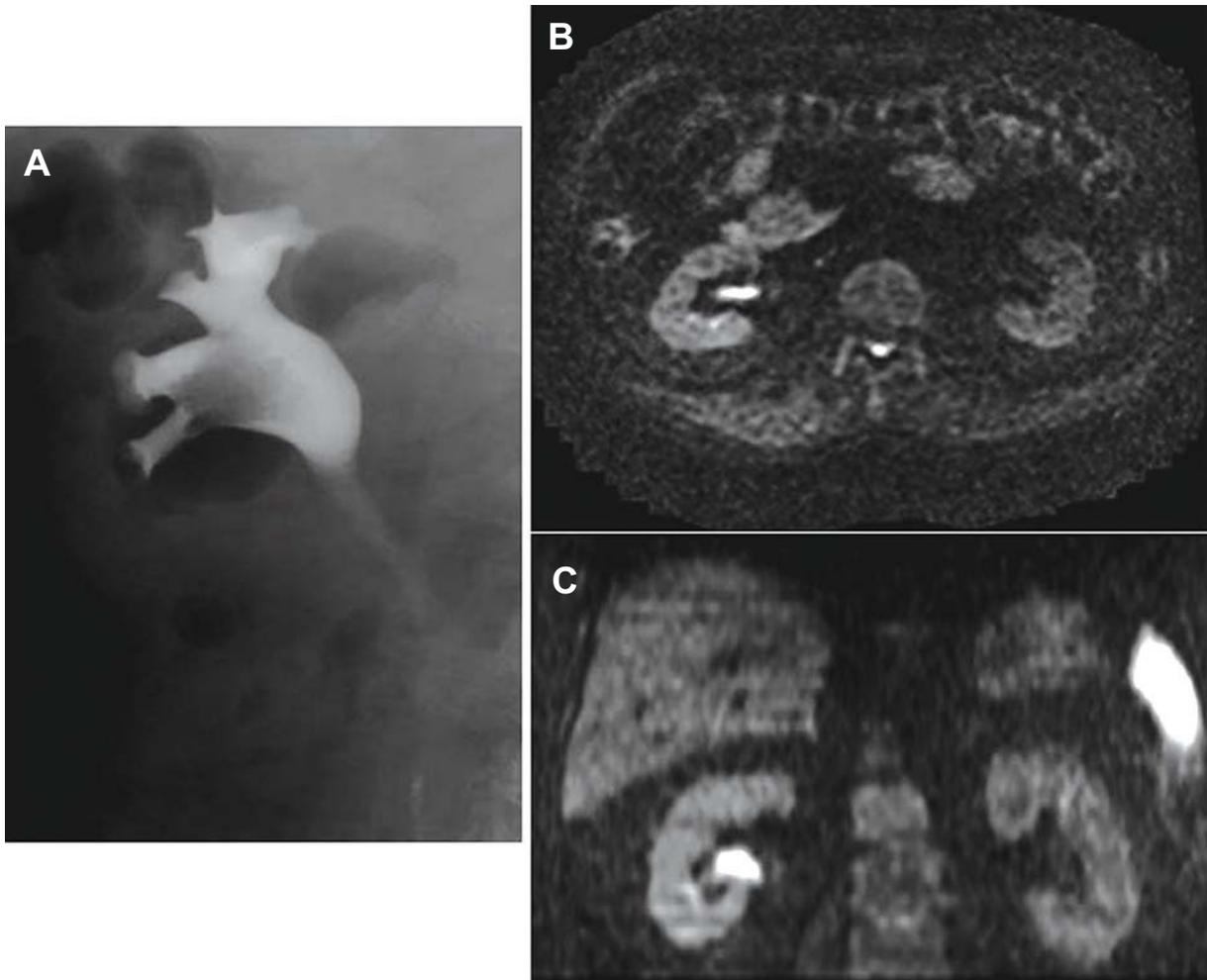


Figure 2 – Case 2: A 61-year-old man with right renal pelvic tumor. A) Retrograde pyelography shows a filling defect in the renal pelvis. B) On axial diffusion weighted image (DWI) and C) Maximum intensity projection image obtained from axial DWIs, the tumor is depicted in the right renal pelvis as high intensity.

coefficient (ADC) values are quantitative expressions of diffusion characteristics of tissues, and ADC values are related to the proportion of extracellular and intracellular components. Since a malignant tumor often has a larger cell diameter and cellularly denser than normal tissue the ADC values of tumors may decrease (7). Therefore, DWI shows the tumor as high signal intensity as well. Takahara et al. showed the potential capability of DWI as a screening tool for malignancy-like positron emission tomography. High-b-value DW-MRI images could be directly used for tumor detection because of the different cellular structures of healthy and neoplastic tissues. They reported a new DWI technique under normal breathing, which allows

acquisition of more slices with multiple signal averaging, a higher signal-to-noise ratio, and high-quality MRI images (3). We used multi-excitation for data acquisition under normal breathing as well. Additional advantages of this technique are that it is completely non-invasive, and does not require exposure to ionizing radiation. Furthermore, adding this DWI to a routine MRI protocol requires only few minutes and does not cause patient discomfort. DWI does not require the administration of intravenous contrast material, which may cause allergic reaction or renal toxicity.

DWI is available for several malignancies including abdominal and pelvic lesions such as liver, colon, uterus and kidney and prostate cancer (8-12).

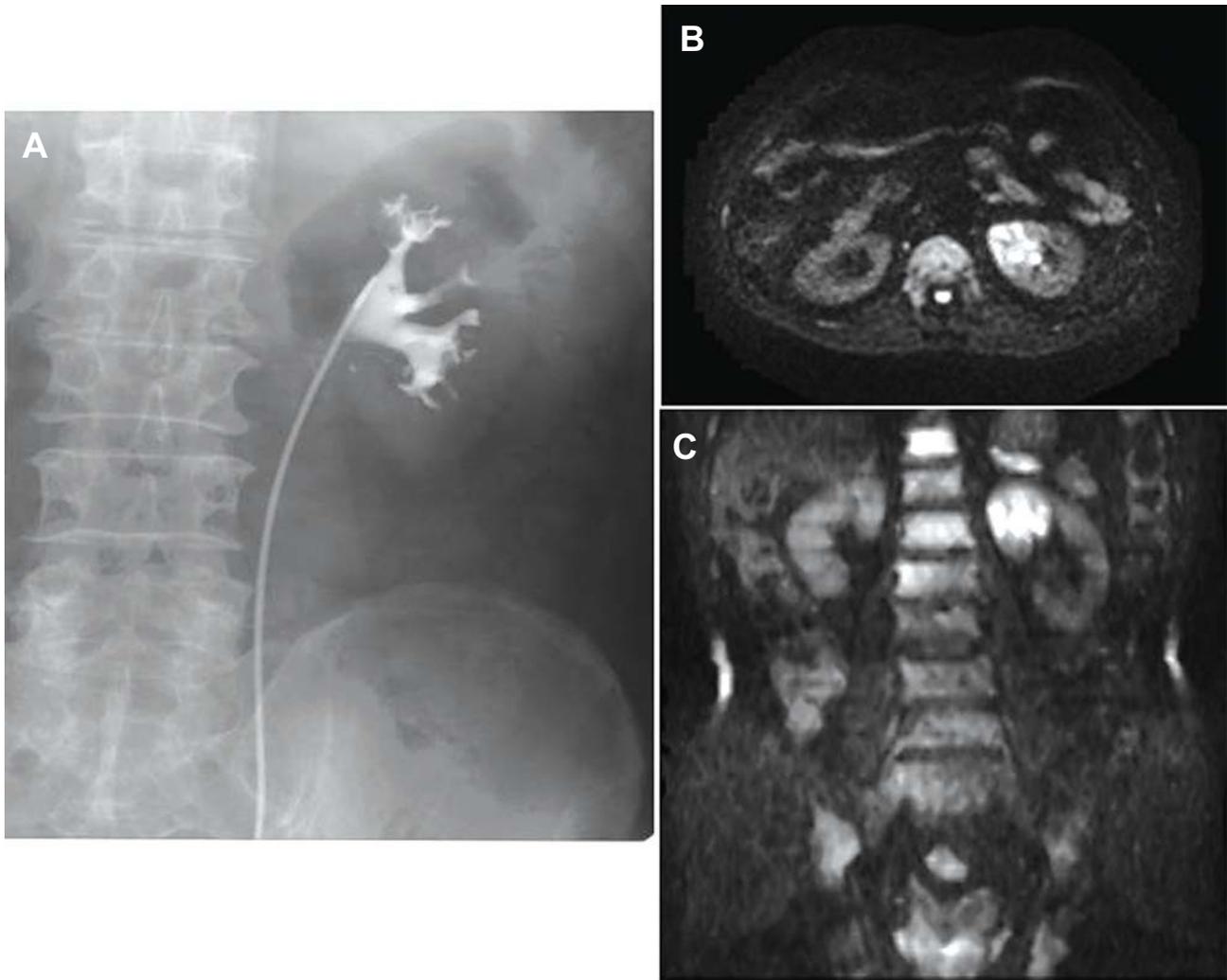


Figure 3 – Case 4: An 84-year-old man with left renal pelvic tumor. A) Retrograde pyelography shows small deformities in the upper calyx. B) On axial diffusion weighted image (DWI) and C) Maximum intensity projection image obtained from axial DWIs, the tumor is depicted in the parenchyma of upper part of the left kidney as high intensity.

Recently Yoshida et al. reported the application of DWI for a series of renal pelvic neoplasms (13), and Takeuchi et al. demonstrated the feasibility of this method for the detection of ureteral tumors (14), using DWI with diffusion gradient b-value of 800 s/mm². In these two reports, they demonstrated significantly lower ADC values of the tumors than of the surrounding tissues. Several authors have recently reported the feasibility of using DWI for the detection of a urinary bladder cancer (15-17).

In our study, the renal pelvic and ureteral tumors except CIS were clearly shown with DWI

regardless of the tumor grade. The mean ADC value of the urothelial tumor was significantly lower than those of the renal tissue and the urine. DWI may detect the tumor of upper urinary tract more distinctly because urothelial tumors were surrounded by a fluid collection or urine. We were able to demonstrate that the mean ADC value of the infiltrating tumor was significantly lower than that of papillary tumor. This may depend on the difference of cellular density between the tumor types. Although Takeuchi et al. recently reported that the mean ADC value of G3 bladder cancer was significantly lower than that of G1 and G2

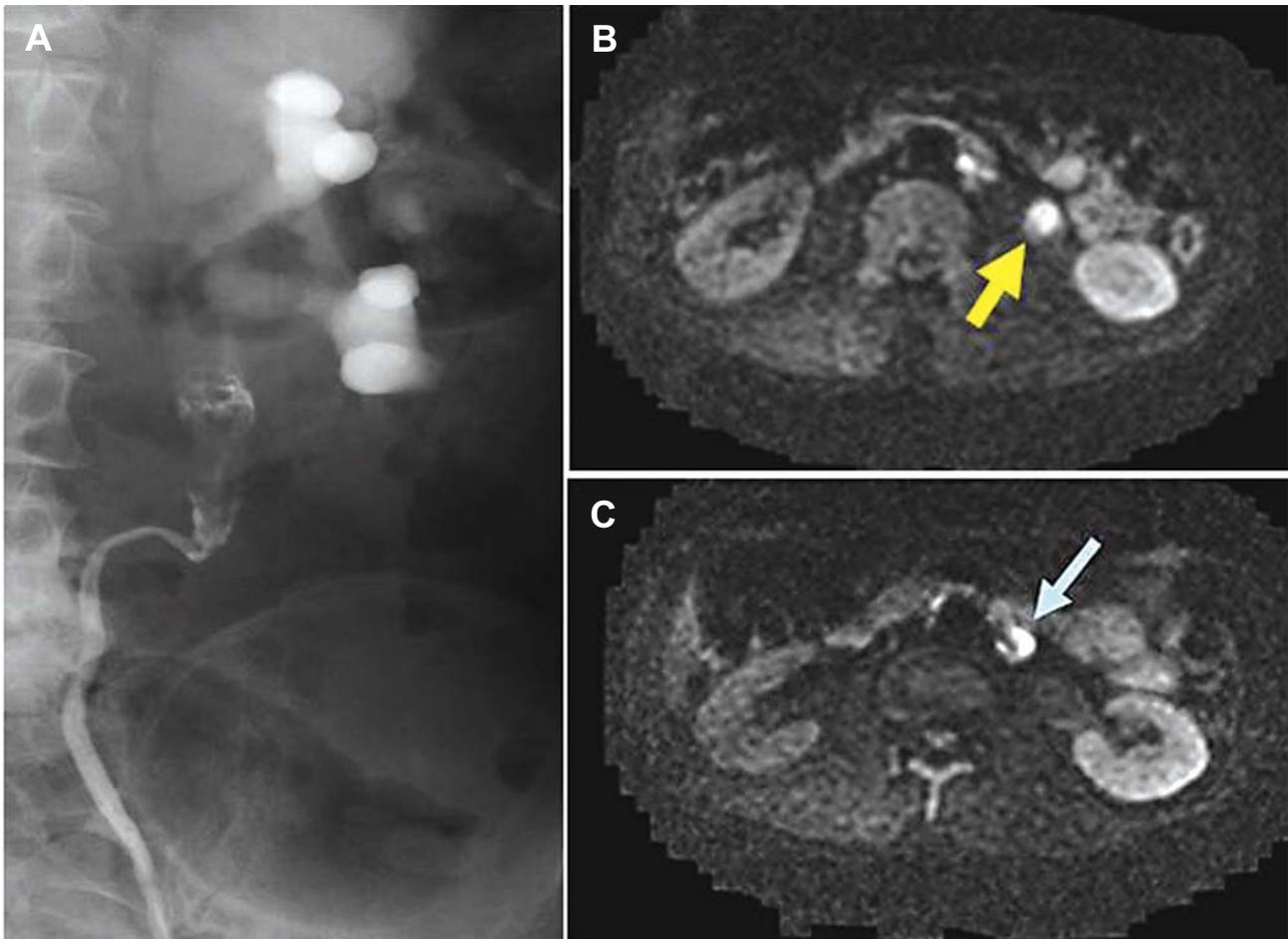


Figure 4 – Case 10: A 72-year-old man with left ureteral tumor. A) Retrograde pyelography shows a filling defect in the upper ureter. B) On axial diffusion weighted image, the tumor is depicted in the upper ureter as high intensity. C) An enlarged para-aortic lymph node is shown as high signal intensity. Histopathologically, the lymph node was not a metastatic lesion.

tumors recently (17), we were not able to demonstrate the difference in ADC value between tumor grades. This may be due to our small study population.

In our study, the smallest depicted tumor was approximately 8 mm in diameter. Yoshida et al. reported they were able to obtain high signal intensity of small renal pelvic tumors (5 mm and 7 mm in diameter) on DWI, despite unclear conventional morphological MRI (14). DWI may provide the information about the characteristics of a small mass even if the mass is not clearly depicted by conventional MRI techniques. The CIS lesion in case 17 could not be depicted either in DWI or in conventional MRI. This was also not possible in the associated CIS lesions in

the other patients. DWI may not be able to delineate the area of CIS at present because the lesion does not form a mass.

It might possibly be difficult to differentiate between malignant and benign tumors such as ureteral polyp by using conventional imaging studies and cytologic examination. Fujii et al. reported that the ADC values of uterine endometrial benign lesion including polyp and leiomyoma were significantly higher than that of the malignant lesion. They concluded that ADC measurement could provide useful information in differentiating malignant from benign uterine endometrial cavity lesions (18). Although we have no experience with the cases of benign urinary

tract tumors such as polyp or endometriosis, DWI and ADC value may nevertheless provide the information about the property of the mass (17,18).

An enlarged lymph node may be a false positive structure in the diagnosis of malignant tumor with DWI. Ichikawa et al. reported that most metastatic lymph nodes were detected because of their high signal intensity, in some patients healthy lymph nodes also showed similarly high signal intensities (4).

The standard work-up for the patient with hematuria consists of urinalysis and cytologic analysis, cystoscopy and excretory urography (5). Additional imaging is often required. The diagnosis of urothelial cancers is usually made based on the cytological analysis of urine specimens, which are collected on cystoscopy or retrograde pyelography. These techniques are invasive and technically demanding. The preoperative cytologic studies were negative in five patients with low-grade tumors in our series. False negative cytologic results may occur in cases of low-grade lesions or in which the ureter is obstructed. MRI allows multiplanar images and MR urography can permit localization of ureteric obstruction. As previously mentioned, several reports have demonstrated the feasibility of DWI for the detecting upper and lower urinary tract tumor (13-17). Although further studies are needed to prove the value of DWI for detecting upper urinary tract tumor and for differentiating malignant from benign urothelial tumor, MRI adding DWI may become the first choice for imaging studies, and DWI may replace invasive retrograde urography and imaging studies using intravenous injection of contrast medium.

This is the third reported study on the application of DWI for the detection of the upper urinary tract urothelial cancer. However, this study has several limitations. It is a retrospective study, assessing only 17 patients, and only one radiologist evaluated the images. Further studies with larger clinical settings are necessary.

CONCLUSIONS

In our study, the renal pelvic and ureteral cancers except CIS were shown clearly with DWI regardless of the tumor grade. We demonstrated that

an infiltrating tumor had lower ADC values than that of papillary tumor. Although further studies with larger clinical settings are required, DWI may replace invasive retrograde urography or conventional imaging using intravenous injection of contrast medium in detecting tumors of the upper urinary tract.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Urothelial carcinoma of the upper urinary tract accounts for 5% of all urothelial carcinomas and 10% of all renal tumors. Patients with a history of urothelial carcinoma are at high risk of developing synchronous or metachronous urothelial carcinoma. This known multifocality requires thorough examination of the entire urinary tract in high-risk patients

(1). The diagnosis is difficult by conventional morphological imaging, since urothelial carcinomas may be overlooked with suboptimal examinations and even though the examination is sufficient, small lesions may not be detected due to volume averaging (2).

Excretory urography or computed tomography (CT) was used to evaluate high-risk patients (3).

Multiphasic CT urography offers superior detection of calculi, urothelial tumor, and parenchymal tumor over excretory urography and allows accurate staging of detected lesions at the same examination. However, when the patient has a contraindication to iodinated contrast material, retrograde pyelography or MRI is often used to image the upper urinary tract (4). MR imaging, including MR angiography and MR urography, offers comparable evaluation in patients who cannot tolerate iodinated contrast material and in whom multiplanar, vascular, and collecting system imaging is required (3,4).

Recently a new MRI technique, called diffusion-weighted MR imaging (DW-MRI) has been applied in various abdominal diseases, especially in detecting tumors without the need for contrast administration (5). Different from conventional anatomical MR imaging DW-MRI provide functional information (5). By studying molecular diffusion, the ultrastructural characteristics of tissue can be studied in vivo through sampling water molecules and by exploiting the natural sensitivity of MRI to the motion (2).

The research of Nishizawa et al. has shown the superiority of DW-MRI in detecting urothelial tumors with a very high accuracy, demonstrated with excellent images. Also in a study by Yoshida et al. two cases of highly suspected upper urinary tract neoplasm had been detected clearly on DW-MR images, despite unclear conventional morphological MR images (2).

Malignant masses are easily discernible against suppressed background signal with visual assessment of DW-MR images (PET like images).

This method may be obtained after a routine abdominal MR imaging protocol approximately in 3 to 5 minutes without an additional cost. The additional benefit of DW-MRI is the ability to determine quantitative indices, which may be important in the assessment of tumor cellularity, and disease response to treatment methods and follow-up (2,5).

Further investigations will probably increase the use of functional imaging methods and especially DW-MRI in genitourinary diseases.

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EDITORIAL COMMENT

A combination of morphological imaging modalities using iodinated radiocontrast media, such as excretory urography and computed tomography with urinary cytologic examination, has been used for diagnosing upper urinary tract cancer (UUTC). However, these media may cause renal insufficiency. Contrast-induced nephropathy due to iodinated radiocontrast media is currently the third most common cause of acute renal failure in hospitalized patients (1). Diffusion-weighted magnetic resonance imaging (DWI) is a functional imaging technique with no contrast agent and is applicable to patients with allergies against contrast agents or existing renal insufficiency. Furthermore, the addition of DWI to a routine MRI examination can be readily adopted for most current clinical MRI scanners with only a few minutes and no additional equipment.

DWI has been reported to be a useful technique to detect UUTC in a noninvasive manner because of clear contrast between high signal intensity of UUTC and well-restrained signal intensity of the surrounding tissue (2). This study has confirmed the above points. The location (pelvis or ureter) and the size of the UUTC seem to have little impact on diagnostic potentiality because of good contrast between the tumor and the surrounding tissues, even if the tumor burden was small (8 mm in this paper, 5 mm in our experience). The impact in the degree of diffusion within the tumor on the estimation of grade or depth has recently been shown on DWI in some malignancies, including bladder cancer (3). In this study, ADC values of the infiltrating tumor were significantly lower than that of papillary tumor. However, overlap among ADC values between them

seems to exist. Also, overlap among ADC values for tumor, renal parenchyma and collecting system exists. Further investigations should be performed to clarify the clinical importance of ADC values in evaluating tumor aggressiveness.

The current study also showed the limitation of DWI technique in assessing the UUTC. Depicting carcinoma in situ (CIS) lesions is also challenging in DWI, as well as in other conventional imaging modalities. The DWI contrast reflects molecular diffusion, not the presence of existing cancer cells. Therefore, it remains challenging to distinguish a malignant disease from nonmalignant lesions, such as benign neoplasms, hematomas, abscesses and inflammatory condition.

We have to keep in mind that we could not gain anatomical information from DWI. Addition of DWI to anatomical imaging increases the accuracy of MRI to UUTC.

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