대한영상의학회지

T1-Staging for Urinary Bladder Cancer with the Stalk and Inchworm Signs with 3.0 Tesla MRI

3.0 테슬러 자기공명영상에서 Stalk 및 Inchworm Sign이 있는 방광암의 T1 병기 진단

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Purpose To evaluate the diagnostic utility of the stalk and the inchworm sign on preoperative MRI for detecting superficial bladder cancers, and to compare the diagnostic performance between the stalk and the inchworm sign.
Materials and Methods We retrospectively reviewed 240 patients (505 tumors) who had undergone radical cystectomy. The tumors were classified as follows: superficial or invasive tumors indicated by the stalk or inchworm sign on 3.0 Tesla MRI. We evaluated the diagnostic accuracy of the stalk and inchworm signs, by comparing each finding with the postoperative pathologic T stage. We compared diagnostic performance between them statistically.
Results The stalk and inchworm signs showed high specificity (93% and 91%, respectively), positive predictive values (89% and 90%, respectively), and acceptable accuracy (70% and 74%, respectively), but low sensitivity (54% and 61%, respectively) and negative predictive values (60% and 63%, respectively). There was no statistically significant difference between the two signs ($p > 0.05$).
Conclusion Superficial bladder cancers could be differentiated from invasive tumors using the stalk or inchworm sign on MRI.

Index terms Cystectomy; Urology; Urinary Bladder Cancer

INTRODUCTION

Treatment planning of urinary bladder cancer is based on distinguishing the superficial tumor (non-muscle-invasive tumor, T1-stage or lower) from the invasive tumor (muscle-invasive, T2-stage or higher). This is because the treatment options are quite

different. Transurethral resection (TUR) is performed on patients with superficial tumors, although some patients may have to undergo additional therapy such as intravesical chemotherapy, photodynamic therapy, and/or Bacillus Calmette-Guerin (BCG) immunotherapy (1). On the other hand, radical cystectomy (with ileal conduit or ileal neobladder formation), radiation therapy, and/or chemotherapy is performed on patients with invasive tumors (2). For patients with muscle-invasive tumors, radical cystectomy with curative intent is traditionally used. Other well-accepted indications of radical cystectomy are as follows: high-risk and recurrent non-muscle-invasive bladder tumors, BCG-resistant carcinomas *in situ*, high-risk T1-stage (grade 3) tumors, and extensive papillary diseases. Therefore, preoperative imaging studies are very important in patients with urinary bladder cancer to accurately differentiate between the two stages of urinary bladder cancer.

MRI is more useful and noninvasive than other diagnostic tools for staging urinary bladder cancer (3-5), and previous publications have reported that a combination of T2-weighted imaging (T2WI) and diffusion weighted imaging (DWI) is the best for the T-staging of urinary bladder cancer (6). 75% of urinary bladder cancers are the papillary type and 66% of these have stalks composed of fibrotic tissue, capillaries, inflammatory cells, and tissue edema (7, 8). Almost all papillary urinary bladder tumors with a stalk are pT1-stage or lower. The identification of a vascular stalk extending from the bladder wall may be an important observation to exclude invasion into the muscular layer (muscularis propria) of the urinary bladder by the tumor (8). Thus, in our study, we defined this observation on T2WI as 'stalk sign'. DWI is superior to T2WI for detecting a stalk and it has been shown to improve T-staging accuracy (9). Superficial tumors with stalks of thick hypointense submucosa beneath a C-shaped hyperintense tumor on DWI could be differentiated from invasive tumors without stalks (6). We defined this finding on DWI as 'inchworm sign' because it resembles the arch-like shape of an inchworm (6).
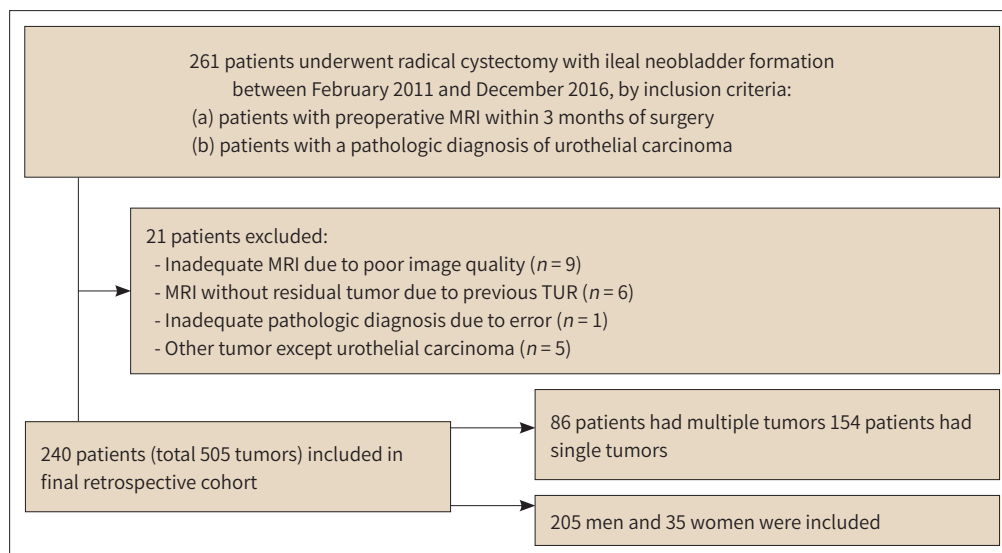
The purpose of this study was to preoperatively evaluate the diagnostic performance of stalk sign and inchworm sign in MR images for superficial tumors (T1-stage or lower) and to compare the diagnostic performance between stalk sign on T2WI and inchworm sign on DWI.

MATERIALS AND METHODS

STUDY POPULATION

The Institutional Review Board of Ewha Woman's University Mokdong Hospital (Seoul, Korea) approved this retrospective study and waived the requirement for written informed consent (IRB No. 2019-08-017-003). Between February 2011 and December 2016, 261 consecutive patients who had undergone radical cystectomy with ileal neobladder formation were retrospectively identified through the database from the Picture Archiving Communication System (PACS) at Ewha Woman's University Mokdong Hospital. Our study population was selected by using several inclusion criteria (Fig. 1). According the inclusion criteria, 240 patients (age range 30–88 years old; mean 65.6 years) were enrolled, and they consisted of 205 men (age range 30–88 years old; mean 65.4 years) and 35 women (age range 38–80 years old; mean 66.9 years).

Fig. 1. Flow chart of the study population.

261 patients underwent radical cystectomy with ileal neobladder formation between February 2011 and December 2016, by inclusion criteria:
(a) patients with preoperative MRI within 3 months of surgery
(b) patients with a pathologic diagnosis of urothelial carcinoma

21 patients excluded:
- Inadequate MRI due to poor image quality ($n = 9$)
- MRI without residual tumor due to previous TUR ($n = 6$)
- Inadequate pathologic diagnosis due to error ($n = 1$)
- Other tumor except urothelial carcinoma ($n = 5$)

240 patients (total 505 tumors) included in final retrospective cohort

86 patients had multiple tumors 154 patients had single tumors

205 men and 35 women were included

TUR = transurethral resection

MRI ACQUISITION

For appropriate imaging quality, moderate distention of the urinary bladder and reduction of the bowel motion were required. So, all patients were prohibited from urinating for 90 minutes before MRI examination. To reduce bowel motion, patients received gastroparesis agents (bropium, cimetropium bromide, 5 mg/mL; Bukwang Pharm., Seoul, Korea).

MRI was performed by using a 3.0 T MRI scanner (Intera Achieva 3.0 T; Philips Healthcare, Best, the Netherlands) equipped with RC SENSE-XL-Torso and RC Dual coils. The basic combination of MRI included the following sequences: axial, coronal, sagittal T2WI, axial T1WI, coronal fat-suppressed T2WI, dynamic contrast-enhanced T1WI, and DWI. T2WI was obtained as follows: repetition time (TR)/echo time (TE), 3588.73–4186.85 ms/90.0 ms; matrix, 552 × 229–576 × 256; slice thickness, 4.0–5.0 mm; interslice gap, 0 mm; number of excitations (NEX), 2.0; and field of view (FOV), 240 × 240. DWI was obtained on the axial plane with free-breathing fast spin-echo echo-planar imaging (TR/TE, 5000–6000 ms/76.39–63.96 ms; b values of 0, 100, and 1000 s/mm^2; matrix, 124 × 124; slice thickness, 4.0–5.0 mm; interslice gap, 0 mm; NEX, 8.0; and FOV, 250 × 250). Dynamic contrast-enhanced T1WI was obtained as follows: fat-saturated T1-weighted fast spin-echo imaging (TR/TE, 400–700 ms/8–10 ms; flip angle, 90°; matrix, 512 × 256; slice thickness, 4.0 mm; interslice gap, 0 mm; NEX, 1.0; and FOV, 240 × 240). 0.1 mmol/kg of gadobutrol (Gadavist; Bayer Schering Pharma, Berlin, Germany) was injected in each patient at a rate of 2–3 mL/s through a power injector followed by a 20 mL saline flush.

IMAGE ANALYSIS

All MR images were reviewed by two radiologists (B.C.K and D.H.K, with 19 and 3 years of experience, respectively). Inter-observer agreement was performed and the two reviewers reached a consensus. Both reviewers were aware of the diagnosis of urothelial carcinoma but were blinded to other pathologic findings. In our study, only T2WI and DWI were reviewed

for stalk and inchworm sign, respectively. If the patient had multiple tumors, all tumors were used to evaluate the imaging features. The following image sets were reviewed after an interval of 1 week: axial, coronal, sagittal T2WI, and DWI. On the basis of the 1997 TNM system of the International Union Against Cancer (10), the reviewers classified the tumors of all patients into the two categories as follows; superficial tumors (T1 or lower stage) and invasive tumors (T2 or higher stage). If inchworm sign on DWI or stalk sign on T2WI was detected, the tumor was considered to be superficial, but if either sign was not detected, the tumor was judged to be invasive. In patients with multifocal tumors, the number of tumors and the maximum diameter of each tumor were independently measured by two radiologists.

HISTOPATHOLOGIC AND STATISTICAL ANALYSES

The postoperative pT-stage of urinary bladder tumors in all patients was obtained by pathologists in accordance with the 1997 International Union Against Cancer system (10). The reviewers retrospectively compared the preoperative T-stage from MR images with the postoperative pT-stage for all enrolled patients. The diagnostic significance of the inchworm and stalk sign was evaluated statistically. Chi-squared tests ($p < 0.05$) were used for the diagnostic accuracy of staging with stalk and inchworm sign. Statistical differences in diagnostic accuracy for each image set were evaluated by using Fisher's exact test. Statistical software (SPSS for Windows version 18.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. In this study, the null hypothesis was that the stalk sign group (or inchworm sign group) and postoperative pT1-stage or lower group were independent and $p < 0.05$ was considered to be statistically significantly dependent.

RESULTS

In 240 enrolled patients, a total of 505 tumors were detected. Table 1 summarizes the comparison between preoperative T stage of MR imaging (including stalk sign on T2WI and inch-

Table 1. Pathologic Staging with the Stalk Sign on T2WI and Inchworm Sign on DWI for All Enrolled Patients with Urinary Bladder Cancers ($n = 505$)

MR Finding	Stalk Sign on T2WI $n = 505$		Inchworm Sign on DWI $n = 505$	
	Stalk (+) $n = 174$	Stalk (-) $n = 331$	Inchworm (+) $n = 197$	Inchworm (-) $n = 308$
Pathology				
Superficial tumor*	158 (TP)	133 (FN)	178 (TP)	113 (FN)
Invasive tumor†	16 (FP)	198 (TN)	19 (FP)	195 (TN)

The stalk sign group (or the inchworm sign group) and the postoperative pathologic T1-stage or lower group were statistically significantly dependent ($p < 0.05$, chi-squared test).
*A superficial tumor was defined as postoperative T1-stage or lower, as determined by pathological examination.
†An invasive tumor was defined as postoperative T2-stage or higher on pathological examination.
DWI = diffusion weighted imaging, FN = false-negative group, FP = false-positive group, Inchworm (+) = with inchworm sign, Inchworm (-) = without inchworm sign, Stalk (+) = with stalk sign, Stalk (-) = without stalk sign, T2WI = T2 weighted imaging, TN = true-negative group, TP = true-positive group

worm sign on DWI) and postoperative T stage of pathologic result. True positive (TP) groups were defined as the tumors with stalk sign (or inchworm sign) and the pathologic confirmation of non-muscular invasion (Fig. 2). True negative (TN) groups were defined as the tumors that didn't have stalk sign (or inchworm sign) on MRI and had muscular invasion at the pathologic result (Fig. 3). False positive (FP) groups were defined as the tumors with stalk sign (or inchworm sign) and the pathologic confirmation of muscular invasion. TN groups were defined as the tumors that didn't have stalk sign (or inchworm sign) on MRI and didn't have muscular invasion at the pathologic result.

Fig. 2. A 48-year-old man with pT1-stage invasive urothelial carcinoma.
A. Axial T2WI shows a high SI papillary mass with a low SI stalk at the right wall of the urinary bladder (arrow), referred to as stalk sign (TR/TE, 588.73–4186.85 ms/90.0 ms and FOV, 240 × 240).
B. Axial DWI shows a C-shaped and high SI mass with a low SI stalk connected to the right wall of the urinary bladder (arrow), referred to as the inchworm sign (TR/TE, 5000–6000 ms/76.39–63.96 ms and FOV, 250 × 250).
DWI = diffusion weighted imaging, FOV = field of view, pT1 = pathologic T1 stage, SI = signal-intense, T2WI = T2-weighted imaging, TE = echo time, TR = repetition time
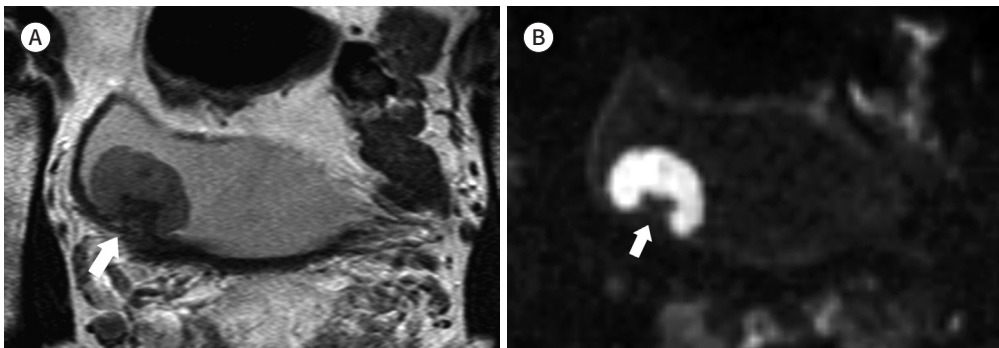
Fig. 3. A 76-year-old man with pT2-stage invasive urothelial carcinoma.
A. Axial T2WI shows diffuse wall thickening (arrowhead) with a mass (arrow) at the anterior wall of the urinary bladder (without stalk sign) (TR/TE, 588.73–4186.85 ms/90.0 ms and FOV, 240 × 240).
B. Axial DWI shows diffuse wall thickening (arrowhead) with a mass (arrow) at the anterior wall of the urinary bladder (without inchworm sign) (TR/TE, 5000–6000 ms/76.39–63.96 ms and FOV, 250 × 250).
DWI = diffusion weighted imaging, FOV = field of view, pT2 = pathologic T2 stage, T2WI = T2-weighted imaging, TE = echo time, TR = repetition time
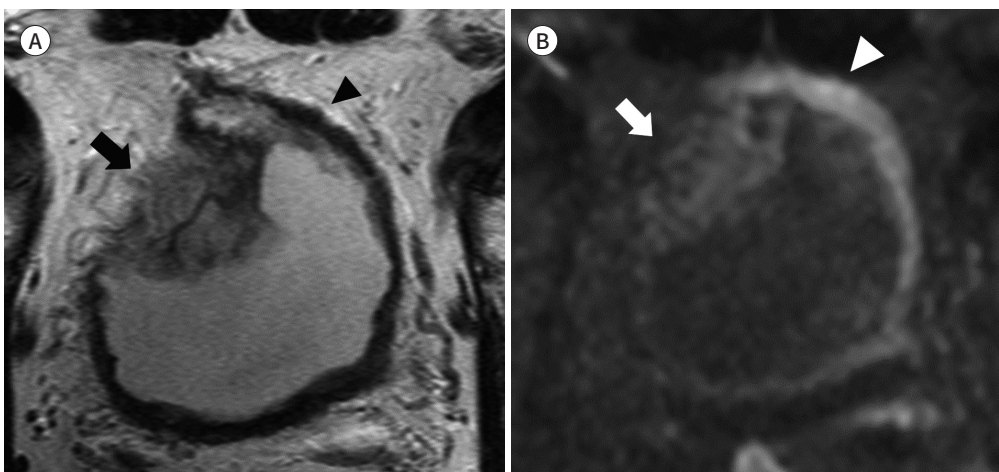
In addition, we sorted the tumors by size with a cut-off value of 10 mm for the larger diameter; 356 tumors were measured at more than 10 mm. Table 2 summarizes for tumors with more than 10 mm sizes the comparison between preoperative T stage of MR imaging and postoperative T stage of pathologic result. The definitions of TP, FP, TN, and FN groups in Table 2 were the same as in Table 1.

The diagnostic performances of preoperative T-staging with stalk and inchworm sign are summarized in Table 3. To diagnose the preoperative T1-stage of urinary bladder cancer with MRI, stalk and inchworm sign showed high specificity (93% and 91%, respectively), positive predictive values (89% and 90%, respectively), acceptable accuracy (70% and 74%, respectively), but low sensitivity (54% and 61%, respectively) and negative predictive value (60% and 63%, respectively). Additionally, large tumors that were more than 10 mm had higher sensitivity (66% and 74%, respectively), negative predictive values (73% and 77%, respectively), and diagnostic accuracy (79% and 82%, respectively), while maintaining high specificity (91% and 90%, respectively), and positive predictive values (88% and 88%, respectively). Out of 505 tumors, 160 tumors had stalk and inchworm signs. Fourteen tumors had only stalk sign and 37 tumors showed only inchworm sign. However, there was no significant difference between stalk and inchworm sign for preoperative T-staging of urinary bladder cancer ($p < 0.05$, Fisher's test).

Table 2. Pathologic Staging with Stalk Sign on T2WI and Inchworm Sign on DWI for Urinary Bladder Cancers Larger than 10-mm Diameter (n =356)

MR Finding	Stalk sign on T2WI n = 356		Inchworm sign on DWI n = 356	
	Stalk (+) n = 134	Stalk (-) n = 222	Inchworm (+) n = 149	Inchworm (-) n = 207
Pathology				
Superficial tumor*	118 (TP)	60 (FN)	131 (TP)	47 (FN)
Invasive tumor†	16 (FP)	162 (TN)	18 (FP)	160 (TN)

The stalk sign group (or the inchworm sign group) and the postoperative pathologic T1-stage or lower group were statistically significantly dependent ($p < 0.05$, chi-squared test).
*A superficial tumor was defined as a tumor with postoperative T1-stage or lower on pathological examination.
†An invasive tumor was defined as a tumor with postoperative T2-stage or higher om pathological examination.
DWI = diffusion weighted imaging, FN = false-negative group, FP = false-positive group, Inchworm (+) = with inchworm sign, Inchworm (-) = without inchworm sign, Stalk (+) = with stalk sign, Stalk (-) = without stalk sign, T2WI = T2 weighted imaging, TN = true-negative group, TP = true-positive group

Table 3. Diagnostic Accuracy of Preoperative T-Staging with the Stalk and Inchworm Signs

	Sensitivity	Specificity	PPV	NPV	Accuracy
Total (n = 505)					
Stalk sign only	0.54	0.93	0.89	0.60	0.70
Inchworm sign only	0.61	0.91	0.90	0.63	0.74
Total (n= 356), more than 10-mm sized tumors					
Stalk sign only	0.66	0.91	0.88	0.73	0.79
Inchworm sign only	0.74	0.90	0.88	0.77	0.82

There was no significant difference between the stalk and inchworm sign for the T-staging of urinary bladder cancer ($p < 0.05$, Fisher's test).
NPV = negative predictive value, PPV = positive predictive value

DISCUSSION

Because the management of urinary bladder cancer (urothelial carcinoma) is quite different on the basis of the presence of detrusor muscle invasion, preoperative T-staging is very important for urologic radiologists. For classifying between superficial (T1-stage or lower) and invasive (T2-stage or higher) tumors, the diagnostic accuracy of dynamic contrast-enhanced MRI images has been reported to be 75–92% (3, 4, 11). In a previous study, Takeuchi et al. (6) reported the diagnostic accuracy for evaluating superficial tumors as 79% (only T2WI), 96% (T2WI with DWI), 88% (T2WI with dynamic contrast-enhanced image), and 98% (T2WI with DWI and dynamic contrast-enhanced image). Moreover, they reported that the identification of vascular stalk sign was useful to diagnose preoperative T-staging of urinary bladder cancer.

Whereas they regarded vascular stalk sign on T2WI as inchworm sign on DWI, we reviewed and compared these two types of sign (stalk sign and inchworm sign) in each sequence from pathologic specimens. Moreover, the diagnostic performances of stalk and inchworm sign were independently evaluated. Each diagnostic performance revealed high specificity, positive predictive values, diagnostic accuracy (Table 3). However, our data show low sensitivity and negative predictive values (Table 3) because TUR of bladder tumor might have been performed before MRI in a large number of the false-negative group previously at other hospitals before admission. Even though inchworm or stalk sign might have been initially seen, it might be lost after the TUR of the tumor, and thus they were categorized into the false-negative group. There have been a few reports that the histopathologic diagnosis of urinary bladder tumors with inchworm sign on DWI as muscle-invasive urinary bladder cancer showed false-negative results (7, 12). Moreover, the authors mentioned that although bladder tumors with stalks on MRI tend to be low T-stage (T1-stage or lower), the thickness of the bladder wall at the stalk's base should be evaluated carefully. In fact, we had a few false-negative cases diagnosed as T1-stage or lower with stalk or inchworm sign (Fig. 4), but the criterion of a thickened bladder wall is somewhat ambiguous and cannot be determined because the distensibility of the urinary bladder is very diverse.

Small-sized tumors (10 mm or smaller) with stalk sign might not be detected on MRI (especially on DWI), because of the current imaging limitation and small pixel size. In fact, there was a higher detection rate of stalk or inchworm sign in larger tumors with MRI (Table 3). The diagnostic accuracy for the larger tumor group was also higher than the other tumor groups. In several cases, stalk and inchworm sign did not always correspond, but there was no significant statistical difference between inchworm and stalk sign for preoperative T-staging of urinary bladder cancer.

Unlike previous studies (3, 4, 6-9), we enrolled many cohorts (a total of 240 patients with 505 tumors) with complete postoperative pathologic results by radical cystectomy, not TUR. Therefore, it was inspiring that the diagnostic performance of this study was quite excellent. Despite this strength, our study had some limitations. First, it was a retrospective study at a single center, so there might have been selection and/or information bias. Second, the types of gross pathology were mixed. We included papillary and non-papillary types (including diffuse type) of bladder cancer. Because vascular stalk sign is characteristic of the papillary type, the non-papillary type should have been excluded. Finally, in some cases, inflammatory changes due

Fig. 4. A 59-year-old man with pT3-stage invasive urothelial carcinoma.
A. Axial T2WI shows a high SI papillary mass (arrows) with a low SI stalk at the posteriolateral wall of the urinary bladder, referred to as stalk sign. It shows right hydronephrosis (arrowhead) (TR/TE, 588.73–4186.85 ms/90.0 ms and FOV, 240 × 240).
B. Axial DWI shows a very high SI papillary mass (arrows) with a low SI stalk at the posteriolateral wall of the urinary bladder, referred to as inchworm sign. It shows right hydrnephrosis (arrowhead) (TR/TE, 5000–6000 ms/76.39–63.96 ms and FOV, 250 × 250).
DWI = diffusion weighted imaging, FOV = field of view, pT3 = pathologic T3 stage, SI = signal-intense, T2WI = T2-weighted imaging, TE = echo time, TR = repetition time
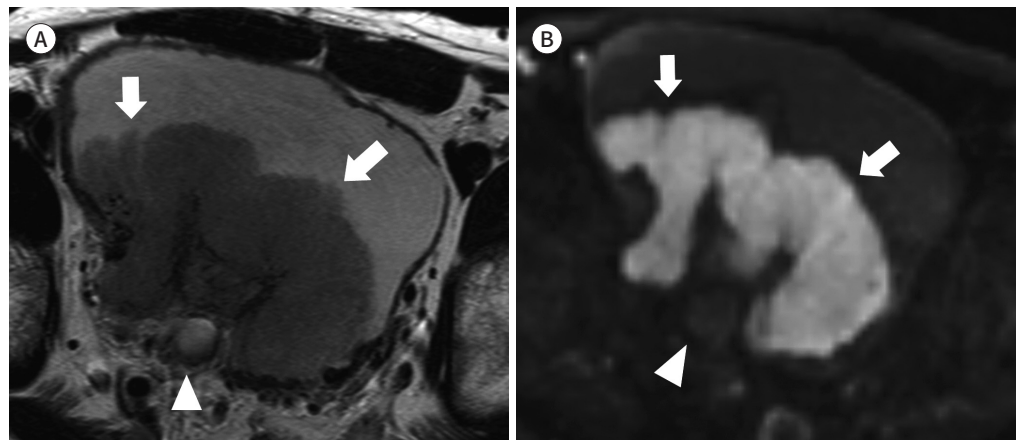
to previous biopsy or surgery (e.g. TUR of the bladder tumor) before MRI might have confused the assessment (13). Hence, further investigation is needed on multicenter-based cohorts, controlled types of gross pathology (only papillary type), and initial evaluation without any procedure before MRI.

In 2018, the Vesical Imaging-Reporting and Data System (VI-RADS) scoring system was introduced. The object of this system was to standardize imaging and reporting of bladder cancer staging with multiparametric MRI. The VI-RADS had a five-point score, that suggested the possibility of muscle invasion. In according to VI-RADS, stalk sign and inchworm sign were included in the feature of score 2. In previous study (14), the accuracy, sensitivity, specificity, PPV, and NPV of a VI-RADS score of 3 or greater were 63.7%, 94.6%, 43.9%, 51.6%, and 63.7%. In other study (15), they showed the sensitivity (87.1%) and specificity (96.5%). There are some differences of the measurements in each article, but all of them believe that the stalk (VI-RADS score 2) is useful for predicting muscle invasive tumor. In conclusion, we can easily diagnose superficial urinary bladder cancers (T1-stage or lower) from invasive tumors (T2-stage or higher) by detecting stalk sign on T2WI and inchworm sign on DWI by 3.0 Tesla MRI.

Author Contributions

Conceptualization, K.B.C.; data curation, K.B.C., K.D.; formal analysis, K.B.C., K.D.; funding acquisition, K.B.C., C.J.; investigation, K.B.C., K.D.; methodology, K.B.C., C.J.; project administration, all authors; resources, K.B.C., C.J.; software, K.B.C., K.D.; supervision, K.B.C., C.J.; validation, K.B.C., K.D.; visualization, K.B.C.; writing—original draft, K.B.C., K.D.; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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대한영상의학회지

3.0 테슬러 자기공명영상에서 Stalk 및 Inchworm Sign이 있는 방광암의 T1 병기 진단

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목적 본 연구의 목적은 수술 전 표재성 방광암(T1 또는 그 이하 병기)을 확인하기 위한 자기공명영상의 stalk sign 및 inchworm sign의 진단적 능력을 평가하는 것이다. 또 다른 목적은 두 sign 간의 진단적 능력의 차이를 비교하는 것이다.

대상과 방법 방광전절제술을 시행 받은 총 240명의 환자들(505개의 종양들)을 후향적으로 검토하였다. 모든 종양은 3.0 테슬러 자기공명영상에서 T2 강조영상의 stalk sign 또는 확산강조영상의 inchworm sign을 발견함으로써 표재성 종양 및 침윤성 종양으로 분류하였다. 이를 수술 후 병리학적 T 병기와 비교함으로써 통계학적으로 진단적 의의를 평가하였고 두 sign 간의 진단적 능력 차이를 비교하였다.

결과 Stalk sign 및 inchworm sign은 높은 특이도(93%, 91%), 양성예측도(89%, 90%), 정확도(70%, 74%)를 보였으나 낮은 민감도(54%, 61%)와 음성예측도(60%, 63%)를 보였다. 두 sign 간의 진단적 능력에서 통계학적 유의미한 차이는 없었다($p > 0.05$).

결론 수술 전 T2 강조영상의 stalk sign과 확산가중영상의 inchworm sign을 발견함으로써 표재성 방광암을 쉽게 진단할 수 있다.

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