European Radiology (2019) 29:3881–3888
https://doi.org/10.1007/s00330-019-06119-6

ONCOLOGY

Usefulness of the inchworm sign on DWI for predicting pT1 bladder cancer progression

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Received: 28 October 2018 / Revised: 13 February 2019 / Accepted: 19 February 2019 / Published online: 19 March 2019

Abstract

Objective To evaluate the significance of the presence or absence of an "inchworm sign" on DWI for the recurrence and progression of T1 bladder cancer.

Materials and methods We retrospectively analyzed 91 patients with pT1 urothelial carcinoma who underwent DWI prior to transurethral resection between 2007 and 2016. DWI of the dominant tumors was scrutinized for inchworm signs at $b = 1000$ s/mm^2. The association of the presence of the inchworm sign with progression and recurrence was analyzed; progression was defined as recurrence to stage T2 or higher and/or N+, and/or M1.

Results An inchworm sign was seen in 65 cases (71%), while it was absent in 26 cases. Among the 65, 25 (38%) had confirmed tumor recurrence, while in the remaining 26, 14 (54%) had confirmed recurrence (median time post TURB = 7.9 and 10.1 months for each). At the time of recurrence, the tumor had progressed in one (2%) inchworm-sign-positive and seven (27%) inchworm-sign-negative cases. The progression rate of inchworm-sign-negative cases was significantly higher than that of inchworm-sign-positive cases (hazard ratio = 17.2, $p = 0.0017$), whereas there was no significant difference in the recurrence rate between two groups. The absence of an inchworm sign and histological grade 3 were independent risk factors for progression ($p < 0.001$ and 0.010, respectively).

Conclusions The absence of an inchworm sign on DWI was a significant prognostic factor for progression of T1 bladder cancer. Morphological evaluation of DWI signals may therefore be a useful adjunct to preoperative assessment of biological aggressiveness.

Key Points

- *An inchworm sign is a simple diagnostic criterion that characterizes only the shape of the tumor signal on DWI, and potentially serves as an imaging biomarker to predict clinical aggressiveness.*
- *The absence of an inchworm sign on DWI is a significant indicator of progression of T1 bladder cancer.*

Keywords Diffusion magnetic resonance imaging · Magnetic resonance imaging · Biomarkers · Prognosis · Urinary bladder neoplasms

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Abbreviations

ADC	Apparent diffusion coefficient
BCG	Bacillus Calmette-Guérin
CUETO	Club Urológico Español de Tratamiento Oncológico
DWI	Diffusion-weighted imaging
EORTC	European Organisation for Research and Treatment of Cancer
HR	Hazard ratio
MRI	Magnetic resonance imaging
NMIBC	Non-muscle-invasive bladder cancer
SI	Signal intensity
T2WI	T2-weighted MRI
TURB	Transurethral resection of the bladder

Introduction

Urinary bladder cancer is one of the most common urological malignancies. Despite its high recurrence rate (40–80%) [1], non-muscle-invasive bladder cancer (NMIBC) generally has a favorable prognosis. However, NMIBC is a potentially lethal and aggressive disease; more than half of high-grade T1 tumors develop into muscle-invasive bladder cancer (MIBC) or metastatic disease [2, 3]. During the follow-up of NMIBC patients, it is therefore important to assess the risk of progression, particularly in case of T1 disease.

There are currently three representative models to predict the risk of the recurrence and progression of NMIBC tumors: the European Organisation for Research and Treatment of Cancer (EORTC) [4], Club Urológico Español de Tratamiento Oncológico (CUETO) [5], and new EORTC models [6]. The CUETO model is based on the evaluation of seven prognostic factors with different weightings and the EORTC model on six; both scoring systems are relatively unwieldy in clinical settings. In 2016, the EORTC developed new nomograms that use T stage and histological grade to predict recurrence and progression in NMIBC patients treated with maintenance bacillus Calmette-Guérin (BCG) [5]. However, predictive abilities of the new EORTC model for progression are unsatisfactory. Previous studies reported that certain NMIBC tumor locations, mainly the bladder neck and/or trigone, are associated with worse outcomes [7–9]. We previously reported that bladder neck invasion, tumor grade, and stage are independent risk factors for progression of primary NMIBC [10, 11]. However, the significance of imaging techniques in predicting postoperative outcomes has not been widely reported.

A predictive model for the likelihood of the recurrence or progression of NMIBC that combines standard clinical factors with imaging results could be a valuable tool. Growing evidence suggests the particular usefulness of DWI in managing various malignant tumors [12, 13].

DWI is increasingly used to manage bladder cancer and yields both quantitative and morphological information [14, 15]. The apparent diffusion coefficient (ADC) could potentially serve as a biomarker of clinical aggressiveness. Kobayashi et al reported that ADCs were significantly lower in high-grade and high-stage bladder cancer [16]. Other papers have reported the usefulness of DWI in the morphological evaluation of bladder cancer, such as in detecting and staging [15]. Takeuchi et al proposed new staging criteria based on the shape of the DWI signal. On DWI, a significant proportion of T1 or lower-stage bladder cancers have an archlike shape of high SI with a low SI submucosal stalk, called the "inchworm sign." This sign provides useful information for differentiating T2 or higher-stage tumors [17]. The inchworm sign might reflect the micro-morphological features of Ta, T1, and T2 and provide information on the degree of microinvasion into the muscularis propria. To our knowledge, the significance of morphological evaluation of DW images in predicting postoperative outcomes has not been reported.

In the current study, we analyzed the importance of the inchworm sign in assessing the risk of recurrence and progression of T1 bladder cancer.

Materials and methods

Patients

Among the consecutive patients who underwent transurethral resection of the bladder (TURB) following a diagnosis of cTa/1N0M0 bladder cancer based on preoperative MRI between 2007 and 2016 in our department, 151 cases were diagnosed with pT1 urothelial carcinoma of the bladder. These patients underwent bladder MRI, including DWI, before TURB. During the study period, 16 patients (10.6%) were repeatedly diagnosed with recurrent pT1 bladder cancer. For these 16 patients, only data on the first diagnosis of pT1 bladder cancer were included; thus, 135 patients were enrolled in the study.

We excluded 19 (14%) of the enrolled patients because their index bladder cancer was < 10 mm on T2-weighted MRI (T2WI), 14 (10%) because muscle sampling was not performed, and 11 (8%) because the preoperative MRIs could not be fully analyzed. We analyzed data from the remaining 91 patients (67%).

The local ethics committee approved this retrospective study (M2000-2139).

Histopathological analysis

TURB specimens were classified by T stage according to the Union for International Cancer Control TNM Classification of Malignant Tumors, 2009. In cases where pathological diagnosis was not based on this classification, the tumor grade and T stage of the TURB specimens were histopathologically analyzed and re-classified by pathologists who were blinded to the clinical course and MRI findings. In patients with multiple pT1 tumors, only the evaluation of the index tumor was used in the analysis. The index tumor was defined as the largest pT1 tumor. The histological grade was the dominant grade of the index pT1 tumor according to the 1973 World Health Organization classification.

Imaging protocol

MRI was performed using a 1.5-Tesla imager (Intera Achieva, Philips) with a four-channel sensitivity encoding body-coil under free breathing. The MRI scan protocols are shown in Table 1.

Table 1 Protocol for diffusion-weighted MRI and T2-weighted MRI with a 1.5-T scanner

	DWI	T2WI
Type of sequence	Single-shot echoplanar imaging	FSE 3D
Orientation	Axial	Axial
Fat saturation	SPIR	None
Field of view (cm)	35	30
Matrix size	256 × 256	334 × 334
Number of slices	24	24
Slice thickness (mm)	5	0.8
Interslice gap (mm)	0.5	0.4
Repetition time (msec)	5000	4510
Echo time TE (msec)	65	100
Bandwidth (per pixel)	1880 Hz	336.3 Hz
Number of excitations	8	3

FSE fast spin echo, *SPIR* spectral presaturation with inversion recovery

Image analysis

A single radiologist (reviewer 1) with 4 years of experience in reading abdominal DWI data, blinded to the clinical and histological information, reviewed the MR images. The tumor size was measured on T2WI. DW images were reviewed at $b = 1000$ s/mm^2 along with anatomical information from T2WI. An inchworm sign on DWI was identified according to the criteria proposed by Takeuchi et al. An image with high SI from a tumor arising in the normal bladder wall and a low SI submucosal stalk was scored as positive for the inchworm sign (Fig. 1); an image with high SI from a tumor without submucosal components was scored as negative (Fig. 2).

To ensure interobserver concordance in assessment of the inchworm sign, two reviewers (reviewer 2: uro-radiologist, with 11-year experience of reading abdominal DWI data and 18-year experience of performing TURB; reviewer 3: urologist, with 6-year experience of reading abdominal DWI data and performing TURB) who were blinded to the clinical course and histological findings, independently evaluated the presence of an inchworm sign in the images of all subjects.

Follow-up

Cystoscopy, urinalysis, and urine cytology were used to follow-up patients every 3 months over the first 2 years post TURB, every 6 months over the next 3 years, and annually thereafter. In addition, yearly abdominal CT was performed for follow-up of the patients post TURB, according to EAU guidelines for NMIBC.

Statistical analysis

Associations between inchworm sign and clinicopathological variables were evaluated using Fisher's exact test. For statistical analysis, the tumors were divided into two groups according to the size criteria of the EORTC risk classification (< 3 and ≥ 3 cm). The distribution of time to progression or recurrence from the day of TURB was estimated and analyzed using the Kaplan-Meier method and log-rank test. Progression was defined as recurrence to stage T2 or higher and/or N+, and/or M1. Cox proportional hazards model was used to determine independent predictors for recurrence and progression. In this study, all cases were censored as of January 2018. Further, the observations were censored when the patients experienced recurrence during the follow-up period. Statistical analyses were performed using JMP 13 software (SAS Institute Inc.). $P < 0.05$ was considered significant.

Results

Patient and tumor characteristics

During the follow-up period (median 16.2 months [0.7–83.0]), disease recurred in 39 of 91 (43%) eligible patients (pTa, $n = 29$;

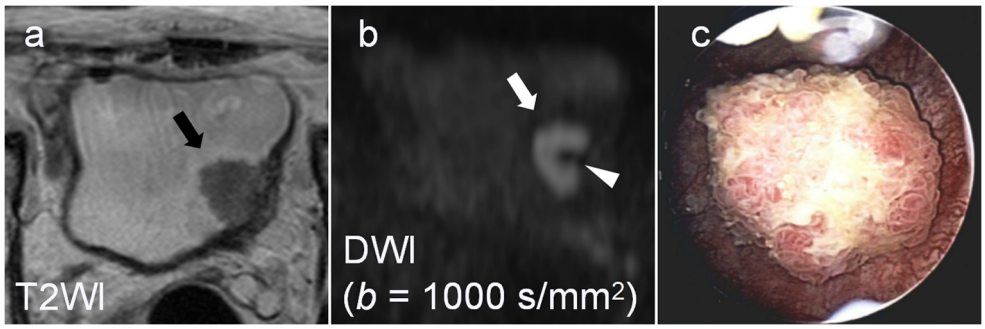

Fig. 1 Magnetic resonance (MR) images and cystoscopic findings from a 67-year-old man with histopathologically confirmed grade 2, pT1 bladder cancer. The patient experienced no recurrence in the follow-up period of 20 months after transurethral resection of the bladder tumor. **a** Transverse T2-weighted MR image shows tumor on the left bladder wall (black arrow). **b** Diffusion-weighted MR image at $b = 1000$ s/mm^2 shows a high signal from the tumor (white arrow) and a low signal intensity stalk (arrowhead) at a level corresponding to (**a**). The tumor signal characterizes this image as "inchworm-sign-positive." **c** Cystoscopy revealed a nodular-papillary tumor

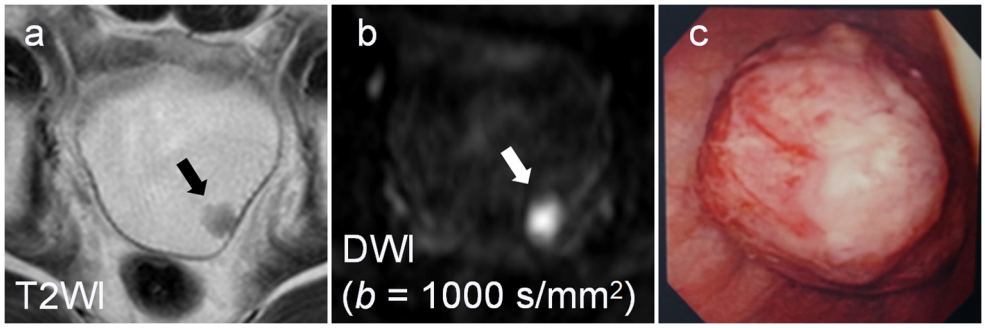

Fig. 2 Magnetic resonance (MR) images and cystoscopic findings from a 75-year-old man with grade 3, pT1 bladder cancer. The patient experienced recurrence of the pT2 bladder cancer 16 months after transurethral resection of the bladder tumor. **a** Transverse T2-weighted MR image shows a small tumor on the left bladder wall (black arrow). **b** Diffusion-weighted MR image at $b = 1000$ s/mm^2 shows a high signal from the tumor (white arrow) but no submucosal components at a level corresponding to (**a**). The tumor signal characterizes this image as "inchworm-sign-negative." (**c**) Cystoscopy revealed a nodular tumor

pT1, $n = 2$; pT2, $n = 8$); median time to recurrence was 8.6 months (2.2–45.2). Eight patients (21%) experienced progression to pT2 cancer post TURB (median time, 11.7 months [3.6–32.4]). The patient and tumor characteristics are listed in Table 2.

Imaging findings

The median tumor size measured on T2WI was 2.0 cm (1.0–8.0). On DWI at $b = 1000$ s/mm^2, reviewer 1 detected high signal intensity from all 91 tumors, with 65 (71%) positive and 26 (29%) negative for the inchworm sign.

Associations between inchworm sign and clinicopathological variables

We evaluated the association between an inchworm sign and clinicopathological variables listed in Table 2. A size larger than 3 cm, papillary structure, and a primary case were significantly associated with an inchworm sign ($p = 0.003$, 0.047, and 0.021, respectively).

Among the 65 inchworm-sign-positive cancers, 63 (97%) had a papillary structure, while 5 of the 26 (19%) inchworm-sign-negative cancers had a non-papillary structure on cystoscopy. The agreement between the papillary structure visualized via cystoscopy and an inchworm sign on DWI was poor ($\kappa = -0.097$).

Relationship between inchworm sign and clinical course of T1 bladder cancer

Among the 65 patients with inchworm-sign-positive cancer, 25 (38%) experienced bladder cancer recurrence (median time to post TURB, 7.9 months [2.2–45.2]). Progression to pT2 cancer was observed in only one patient (4%) at 11.6 months post TURB. Among the 26 patients with inchworm-sign-negative cancer, 14 (54%) experienced recurrence (median, 10.1 months [3.0–32.4]). Of these 14 patients, seven (50%) experienced progression to pT2 cancer (median, 11.8 months [3.6–32.4 months]). No significant difference existed in recurrence rates, irrespective of an inchworm sign (Fig. 3). The progression rate was significantly higher in the inchworm-sign-negative cancers than the inchworm-sign-positive cancers (hazard ratio [HR] = 17.2, $p = 0.0007$; Fig. 4); the 2-year progression-free rate was 41% for inchworm-sign-negative cancers and 98% for inchworm-sign-positive cancers.

Role of inchworm sign as risk factor for recurrence and progression

Next, we examined risk factors for recurrence and progression. Of the clinicopathological factors including MRI findings, the absence of BCG therapy and a tumor larger than 3 cm were significantly associated with recurrence on multivariate analysis (HR = 2.8 and 2.2, respectively; $p = 0.003$ and 0.026, respectively; Table 3), while the presence of an inchworm sign had no significant impact.

The absence of an inchworm sign and histological grade 3 were significant and independent risk factors for progression ($p < 0.001$ and 0.010, respectively; Table 4). We used a composite of two factors (inchworm sign and tumor grade) in predicting the progression. This scoring model provides a better prediction of progression (c-index 0.88) than a model using only the "inchworm sign" (c-index 0.80). The progression-free survival curves were classified into three (Fig. 5).

Interobserver variability in identification of inchworm sign

We evaluated the interobserver variability in identifying the inchworm sign. Reviewers 2 and 3 independently analyzed the DW images of all eligible tumors and found 62 tumors (68%) and 64 tumors (70%) with inchworm signs,

Table 2 Characteristics of patients and tumors in 91 T1 bladder cancer cases, and associations between inchworm sign

Variables		No. IS + (%)	No. IS − (%)	*p* value
Median age/years (range)	69 (37–88)			
Month of median follow-up time/years (range)	16.2 (0.7–83.0)			
No. sex (%)				
Male	76 (84)	54 (71)	22 (29)	1.00
Female	15 (17)	11 (73)	4 (27)	
No. dominant grade (%)				0.06
Grade 3	52 (57)	33 (63)	19 (37)	
Grade 2	39 (43)	32 (82)	7 (18)	
No. tumor structure (%)				0.02
Papillary	84 (92)	63 (75)	21 (25)	
Non-papillary	7 (8)	2 (29)	5 (71)	
No. tumor size (%)				0.03
1–3 cm	61 (67)	39 (64)	22 (36)	
> 3 cm	30 (33)	26 (87)	4 (13)	
No. inchworm sign (%)				–
Positive	65 (71)	–	–	
Negative	26 (29)	–	–	
No. concomitant CIS (%)				1.00
No	78 (86)	56 (72)	22 (28)	
Yes	13 (14)	9 (69)	4 (31)	
No. second TURB (%)				0.48
Performed	52 (57)	39 (75)	13 (25)	
Not performed	39 (43)	26 (67)	13 (33)	
No. primary tumor (%)				< 0.01
Yes	83 (91)	63 (76)	20 (24)	
No	8 (9)	2 (25)	6 (75)	
No. BCG therapy (%)				0.35
No	51 (56)	34 (67)	17 (33)	
Yes	40 (44)	31 (78)	9 (23)	

CIS carcinoma in situ, *TURB* transurethral resection of bladder tumor, *BCG* bacillus Calmette-Guérin, *IS* inchworm sign

respectively. The interobserver variability between the three readers was excellent (Table 5).

Discussion

This study shows an inverse correlation between an inchworm sign and tumor progression, providing evidence that the absence of an inchworm sign is a predictor of tumor progression in T1 bladder cancer. Addition of morphological information obtained by DWI to standard clinical factors could serve as a valuable tool to support clinical decision-making in T1 bladder cancer patients.

Studies reported the usefulness of DWI signals in detecting bladder cancer [14, 15]. The signal shape on DWI has been used in the context of T staging. Takeuchi et al proposed that

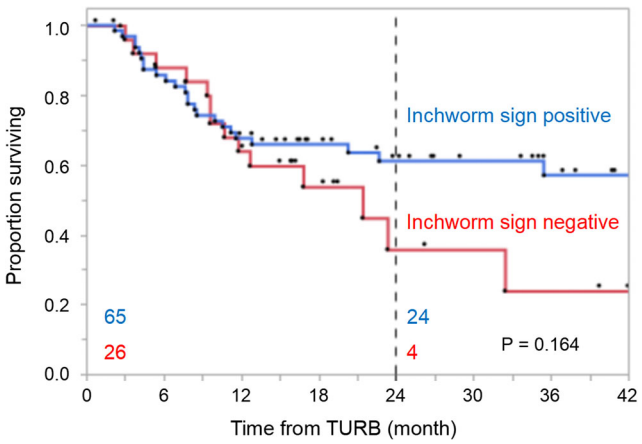

Fig. 3 Kaplan-Meier survival curves for recurrence-free survival stratified by the presence of an inchworm sign. The number of patients at risk is shown on the horizontal axis at 0 and 24 months

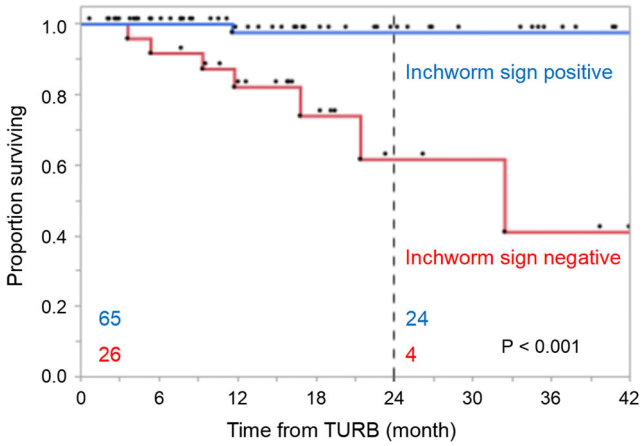

Fig. 4 Kaplan-Meier survival curves for progression-free survival (PFS) stratified by the presence of an inchworm sign. The number of patients at risk is shown on the horizontal axis at 0 and 24 months

the "inchworm sign" on DWI be used as an indicator of non-muscle-invasive disease [17]. They postulated that the low SI area between the tumor and muscle layer represented a mix of edematous submucosa, fibrous tissue, and capillaries that lifted the tumor up to form the tumor stalk. DWI and T2-weighted images improved accuracy in differentiating between Tis to T1 tumors and T2 to T4 tumors from 79 to 96% [17].

Table 3 Univariate and multivariate Cox proportional hazards analysis for time to recurrence in 91 patients with T1 bladder cancer

Variables	Univariate *p* value	HR	Multivariate *p* value
Age/years			
< 65 vs ≥ 65	0.89		
Sex			
Male vs female	0.31		
Histological grade (dominant)			
Grade 3 vs grade 2	0.61		
Tumor structure			
Non-papillary vs papillary	0.41		
Tumor size			
> 3 cm vs 1–3 cm	0.09	2.2	0.02
Concomitant CIS			
Yes vs no	0.91		
BCG therapy			
No vs yes	< 0.01	2.8	< 0.01
Inchworm sign			
No vs yes	0.18		
Second TURB			
Not performed vs performed	0.54		
Recurrence or primary			
Recurrence vs primary	0.68		

HR hazard ratio, *CIS* carcinoma in situ, *TURB* transurethral resection of bladder tumor, *BCG* bacillus Calmette-Guérin

Table 4 Univariate and multivariate Cox proportional hazards analysis for time to progression in 91 patients with T1 bladder cancer

Variables	Univariate *p* value	HR	Multivariate *p* value
Age/years			
< 65 vs ≥ 65	0.68		
Sex			
Male vs female	0.06		
Histological grade (dominant)			
Grade 3 vs grade 2	< 0.01	N/A	0.03
Tumor structure			
Non-papillary vs papillary	0.15		
Tumor size			
> 3 cm vs 1–3 cm	0.37		
Concomitant CIS			
Yes vs no	0.81		
BCG therapy			
No vs yes	0.77		
Inchworm sign			
No vs yes	< 0.01	17.2	< 0.01
Second TURB			
Not performed vs performed	0.80		
Recurrence or primary			
Recurrence vs primary	0.28		

HR hazard ratio, *CIS* carcinoma in situ, *TURB* transurethral resection of bladder tumor, *BCG* bacillus Calmette-Guérin

The current study identified that the absence of an inchworm sign detected on DWI of T1 bladder cancer is a significant risk factor for progression and is more sensitive than a structural finding of a tumor on cystoscopy. Several studies have reported that substaging the depth of invasion of T1 bladder tumors is helpful to predict tumor progression. Orsola et al reported a 34% progression rate for T1 tumors deeply invading the lamina propria (T1b/T1c), opposed to an 8% progression rate for T1 tumors without deep lamina propria involvement (T1a), while the recurrence rates and recurrence-free intervals did not differ significantly [18]. Two other studies reported progression rates for T1a and T1b/c bladder cancer of 6.7–11% and 29–55% [19, 20], respectively, which are equivalent to rates of 4% and 50% for the inchworm-positive and inchworm-negative cancers, respectively, in our study [18, 21]. We infer that our results may represent a correlation between the inchworm sign and substage of T1 stage bladder cancer. Substaging according to the depth and extent of invasion into the lamina propria (T1m and T1e) is predictive of T1 bladder cancer behavior [22]. However, the usefulness of T1 substaging has been called into question because of identification difficulties and intra- and interobserver variability [23]. In contrast to the pathological substaging of T1 tumors in TURB specimens, the presence of

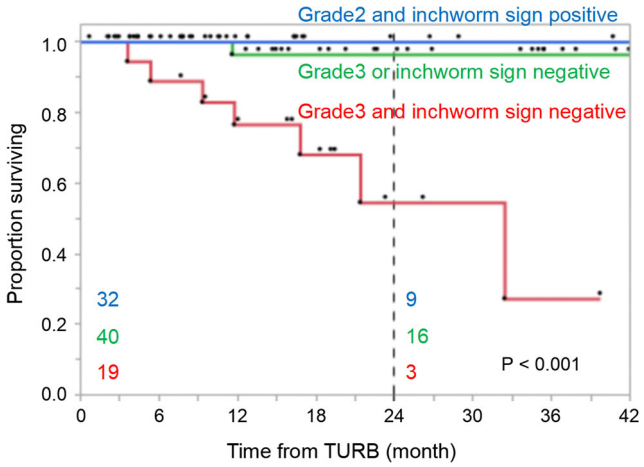

Fig. 5 Kaplan-Meier survival curves for progression-free survival (PFS) stratified by a scoring model comprising the presence of an inchworm sign and pathologic grade. The number of patients at risk at 0 and 24 months is shown on the horizontal axis

an inchworm sign is a simple finding, which can be easily identified in clinical settings.

The practical usefulness and reliability of this sign is ascertained by the excellent interobserver agreement between reviewers, a radiologist and urologist, in this study. An inchworm sign is a simple diagnostic criterion that characterizes only the shape of the tumor signal on DWI and qualifies as an imaging biomarker.

The small sample size and relatively short follow-up were the study limitations. To validate our results, further prospective studies using larger patient cohorts with longer follow-up are warranted. Since MR images depend on the coil systems, an analysis of images, vendors, and field strengths from large multi-clinical databases using different MRI scanners are desirable to justify our current results. Data of dynamic contrast-enhanced MRI are also necessary to overcome some inherent limitations in DWI interpretation such as relatively poor spatial resolution, lack of cancer specificity, and lack of standardized image acquisition protocols and data analysis procedures [24, 25]. External validation is also needed to confirm our results. To clarify the mechanisms responsible for high progression rates in inchworm-sign-negative bladder cancer, the association between inchworm signs and pathological substaging of pT1 tumors needs further analysis.

In conclusion, this study demonstrates that the absence of an inchworm sign on DWI is a significant predictor of progression of T1 bladder cancer. Morphological evaluation of DWI signals may be a useful adjunct to the preoperative assessment of biological aggressiveness.

Table 5 Interobserver variability between the three readers

	Reviewer 2	Reviewer 1 $\kappa = 0.92$ (*$n = 3$)
Reviewer 3	$\kappa = 0.95$ (*$n = 2$)	$\kappa = 0.92$ (*$n = 3$)

*The number of patients whose presence of inchworm sign was disagreed between the reviewers

Acknowledgments I gratefully acknowledge the work of past and present members of our department.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Soichiro Yoshida.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- observational
- performed at one institution

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