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REVIEW ARTICLE

Staging of bladder cancer with multiparametric MRI

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ABSTRACT

The distinction of non-muscle-invasive bladder cancer and muscle-invasive bladder cancer is important for the selection of the optimal treatment. Multiparametric MRI (mp-MRI) has been an useful modality for the T staging of bladder cancer, and a systematic evaluation of mp-MRI is needed. The Vesical Imaging Reporting and Data System was designed to standardize the scanning and reporting criteria based on mp-MRI for clinical and research applications. This review briefly describes the method, interpretation, and timing of mp-MRI examinations in the clinical settings. Validation studies of Vesical Imaging Reporting and Data System and future perspectives are also considered.

INTRODUCTION

Bladder cancer is one of the most common diseases worldwide. There are approx. 430,000 incident cases of bladder cancer per year, with 165,000 deaths.¹ The majority of bladder cancers are urothelial cell carcinomas, and these can be divided into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). The first choice of treatment for NMIBC has been transurethral resection of the bladder tumor (TUR-BT) or intravesical chemotherapy or immunotherapy, whereas the first choice of treatment for MIBC has been cystectomy or systemic chemotherapy. Therefore, the distinction of NMIBC and MIBC is one of the most important issues in the treatment of bladder cancer.

For the staging of bladder cancer, CT and MRI are the important modalities of choice. Although CT is the first choice for N (node) or M (metastasis) staging, the accuracy of T (tumor) staging, especially for the distinction of NMIBC and MIBC, is insufficient.^{2,3} Multiparametric-MRI (mp-MRI) has recently become one of the most important modalities of choice for the T staging of bladder cancer. Meta-analyses of mp-MRI were published in 2017–18,^{4,5} and the Vesical Imaging Reporting And Data System (VI-RADS) was released in 2018 to standardize the scanning and reporting criteria based on mp-MRI.⁶ VI-RADS score might fit in several settings, not only for initial staging to avoid second look biopsy, but also for the evaluation of response to chemotherapy to avoid unnecessary total cystectomy. It might contribute to reduce total lifetime medical cost of bladder cancers.⁷

In this review, we briefly describe the method, interpretation and clinical timing of mp-MRI examinations, the staging method of mp-MRI using the VI-RADS, and clinical validation studies of mp-MRI based on the VI-RADS. We also discuss future perspectives regarding staging strategy using the VI-RADS with mp-MRI.

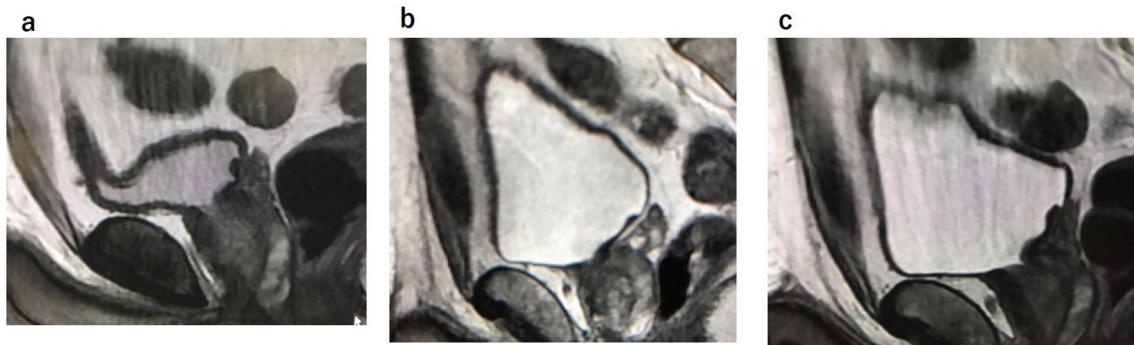
THE METHOD, INTERPRETATION, AND TIMING OF MP-MRI IN CLINICAL SETTINGS

The mp-MRI method

Adequate bladder distention is necessary for the optimal visualization of the bladder wall. To achieve sufficient distention, patients are asked to void 1–2 h before imaging or to drink 500–1000 ml of water 30 min before the examination.⁸ For the prevention of motion and susceptibility artifacts from bowel peristalsis, the administration of an intramuscular antispasmodic agent is recommended (Figure 1).⁹

A mp-MRI examination for bladder cancer consists of a T_2 weighted image (T_2 WI), a diffusion-weighted image (DWI), and a dynamic-contrast enhanced (DCE) image. To achieve high spatial resolution, 1.5 or 3.0 T MRI is recommended. Sensitivity and specificity were reported to be better with 3.0 T MRI as compared to 1.5 T MRI.^{4,5} T_2 WIs are usually obtained with two-dimensional (2D) fast spin echo (FSE) or three-dimensional (3D) spin echo acquisitions. On DWI, a spin echo EPI sequence combined with fat saturation is recommended. A high b-value (800–1000 s/mm²) is necessary for the visualization of bladder cancer. On DCE, a gadolinium-based contrast agent is administered with at a

Figure 1. Vesical wall distension is very important. (a) The bladder wall is less distended. (b) Void and drink 500–1000 cc of water after urination 1h prior to MRI. Antispasmodic agent is given. The bladder wall is well distended, and there is no motion artifact. (c) Over distended bladder wall without antispasmodic agent. Motion artifact occurs.



rate of 1.5–2.0 ml/s. The initial contrast image is obtained at 30 s after the injection of the contrast agent and is followed by the same sequences 4–6 times every 30 s for the visualization of inner layer enhancement (ILE) when the tumor is contrast-enhanced.¹⁰

The interpretation of mp-MRI findings

On T_2 WI, the urine, normal mucosa, and submucosa of the bladder wall is visualized as a high-signal intensity (SI) layer. The muscle layer of the bladder wall is visualized as a low-SI layer. As a result, in normal bladder wall the mucosa and submucosa are canceled out by urine (Figure 2a). On DWI, the urine, mucosa, and submucosa of the bladder wall are visualized as low-SI, and thus the mucosa and submucosa are canceled out by normal bladder wall.¹¹ The muscle layer of the bladder wall is visualized as intermediate-SI on DWI (Figure 2b). In some cases, part of the muscle layer is affected by motion artifact from peristalsis the colon or small intestine. On DCE, the mucosa and submucosa are often enhanced early after the administration of the contrast agent, but the muscle layer maintains its hypo-SI and is later contrast-enhanced (Figure 2C).

Bladder cancer shows iso- to slightly higher SI compared to the SI of the muscle layer on T_2 WI. In patients with muscle-invasive

tumors, the low SI of the muscle layer is often interrupted by the slightly high SI of the tumor. If the bladder cancer is iso-SI to the muscle layer, it is difficult to evaluate tumor invasion with T_2 WI alone. The SI values of bladder cancers are very high on DWI, but it is difficult to recognize anatomical structures on DWI. Comparisons of T_2 WI and DWI findings are thus necessary to identify the locations of tumors. For example, it was reported that the apparent diffusion coefficient (ADC) value of a bladder carcinoma was $1.18 \times 10^{-3} \text{ mm}^2/\text{s}$, which was significantly lower than that of urine ($3.28 \times 10^{-3} \text{ mm}^2/\text{s}$) and normal bladder wall ($2.27 \times 10^{-3} \text{ mm}^2/\text{s}$).¹² A bladder cancer tumor is enhanced early after the administration of contrast material. Hayashi et al¹⁰ reported that intact ILE adjacent to a tumor indicated stage T1 or lower.

There have been several important reports on mp-MRI for the T staging of bladder cancer. Takeuchi et al¹³ reported that a high-SI bladder cancer with the presence of a low-SI submucosal stalk or thickened submucosa suggests bladder cancer at stage T1 or lower. The submucosal components have shown low signal intensity on DWI, representing a mixture of edematous submucosa, fibrous tissue, capillaries, and mild inflammatory cell infiltration that result in a tumor stalk or thickened submucosa (Figure 3). The SI of the tumor stalks observed in cases of stage Ta or T1

Figure 2. Normal bladder wall. (a, b) The urine, normal mucosa and submucosa of the bladder wall has high signal intensity on T_2 WI and has low signal intensity on DWI. Therefore, normal mucosa and submucosa are not visualized on T_2 WI and DWI. (c) On dynamic contrast enhanced image, the mucosa and submucosa are often enhanced early after contrast material administration. DWI, diffusion-weighted image; T_2 WI, T_2 weighted image.

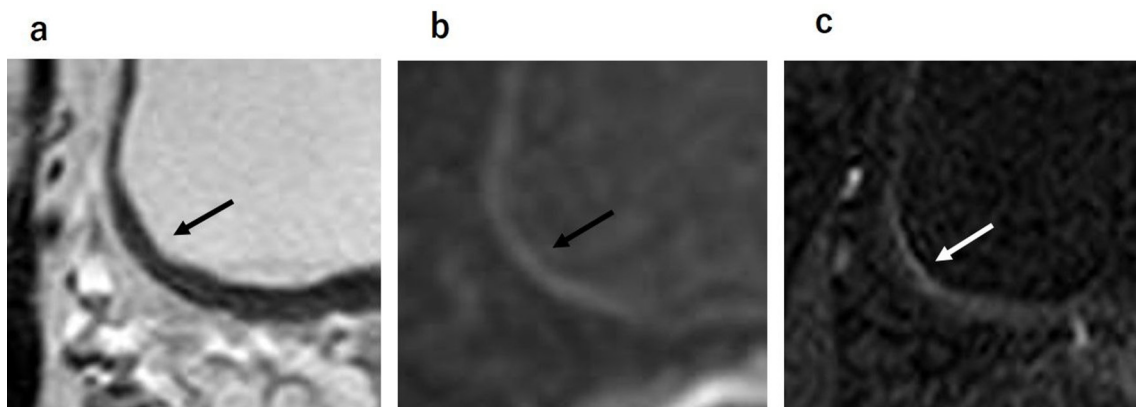
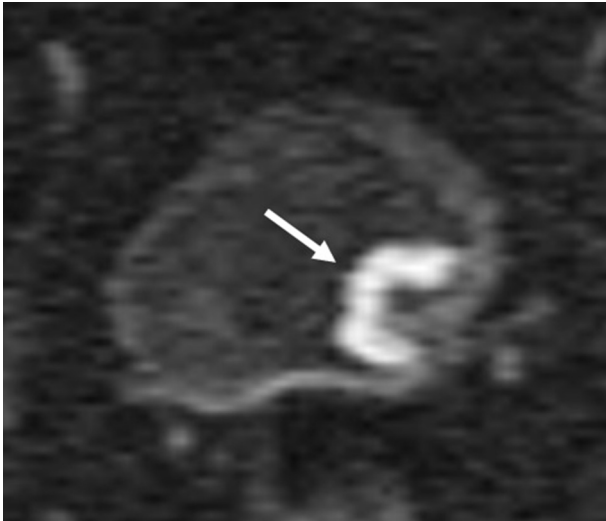


Figure 3. High SI bladder cancer over the low SI submucosal stalk or a thickened submucosa suggests bladder cancer with T1 or lower. Submucosal components showed low signal intensity on DWI. DWI, diffusion-weighted image; SI, signal-intensity.



bladder cancer varies on T_2 WI,¹⁴ and it is thus sometimes difficult to make a T-stage-based diagnosis of bladder cancer with a stalk on T_2 WI alone.

Wang et al¹⁵ reported that all of the <10.0 mm stage T1 or lower bladder cancer tumors without any stalks that they examined did not have ILE. In addition, all of the tumors without ILE had no stalks, of which 94.1% were stage T1 and 82.4% were <10.0 mm. Moreover, 20% of all of the tumors with discontinuous ILE and no stalk were NMIBC. According to that report, tumors with a dia. <10.0 mm would be NMIBC, and stalks are not usually seen in these tumors. On the other hand, tumors without ILE or with discontinuous ILE and no stalk would not be always MIBC (Figure 4).

Tekes et al¹⁶ reported that 81% of bladder tumors showed SI similar to that of muscle on T_2 WI, and over staging was the

Figure 4. Bladder cancer of stage T1. Tumor without ILE or with discontinuous ILE and no stalk are not the finding of muscle invasion. ILE, inner layer enhancement.

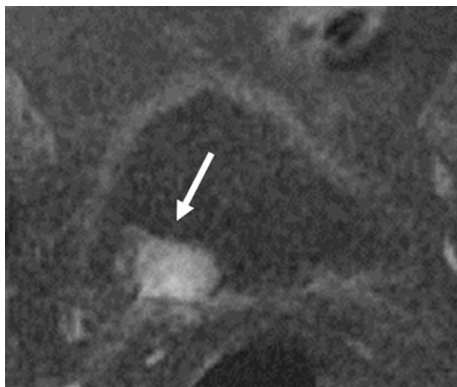
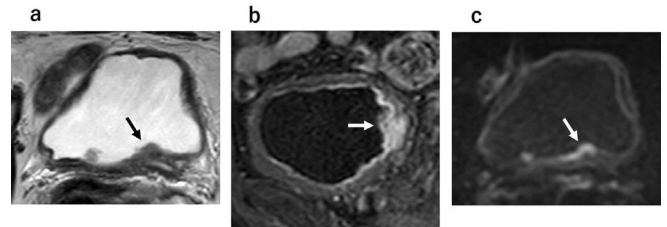


Figure 5. Bladder cancer of stage T1. (a, b) Inflammatory change or fibrosis, which are sometimes resemble tumor invasion, could cause over staging on T_2 weighted image or dynamic-contrast enhanced image. (c) On DWI, these inflammatory changes or fibrosis appear as low signal intensity, thus enable distinct from tumor invasion on DWI. DWI, diffusion-weighted image



most common error when evaluating the T-stage on T_2 WI. They noted that a low-SI area similar to a tumor reflecting inflammatory change or fibrosis (which are sometimes seen around tumor invasion) could cause over staging. In contrast, the improvement of the spatial resolution of DCE would enable the detection of muscle or perivesical-fat invasion, which is considered to be perivesical-fat invasion rather than tumor invasion. These findings can cause false positive findings of muscle or perivesical-fat invasion of bladder cancer. On DWI, these inflammatory changes or fibrosis appear as low SI and thus distinguishable from tumor invasion (Figure 5).

Although DWI is the most important sequence for the T-staging of bladder cancer. The images are often noisy with artefacts. They may obscure the tumor. This makes the diagnosis in all cases difficult. In these particular cases, an evaluation with T_2 WI and DCE is required instead of DWI (Figure 6).

The two recent meta-analyses of MRI for evaluations of bladder cancer^{4,5} revealed that the pooled sensitivity and specificity were 90–92% and 78–88%, and that 3.0 T MRI was better than 1.5 T MRI for differentiating NMIBC and MIBC. Sungmin et al⁴ mentioned that the sensitivity and specificity for distinguishing NMIBC and MIBC were highest with mp-MRI (94 and 95%). In the second meta-analysis,⁵ the sensitivity was slightly better with DCE (90%) than with DWI (86%), and the specificity was better with DWI (92%) than with DCE (64%). According to these

Figure 6. (a) (DWI sometimes causes motion artifact from colon or small intestine (arrow). (b, c) Evaluation with T_2 weighted image and dynamic-contrast enhanced image is needed instead of DWI. DWI, diffusion-weighted image

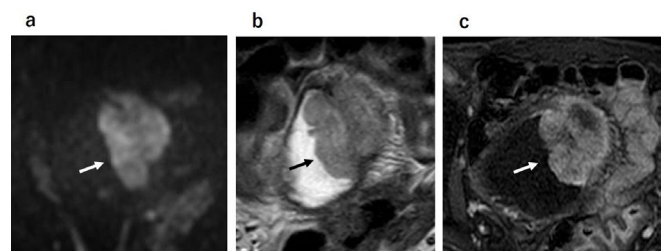
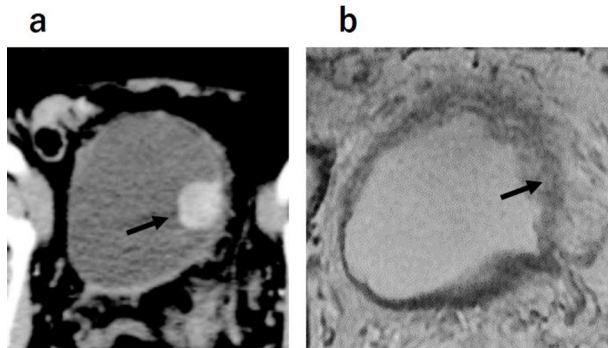


Figure 7. MRI obtained 2 weeks after TUR-BT. (a) Contrast enhanced CT. A tumor was detected on left-side wall. (b) There was thickness of left-side wall on T_2 weighted image. Inflammatory change appeared due to TUR-BT. TUR-BT, transurethral resection of the bladder tumor



meta-analyses,^{4,5} mp-MRI using DWI is the optimal protocol for the T-staging of bladder cancer.

The timing of the mp-MRI examination

Previous TUR-BT and intravesical chemotherapy usually cause edema and inflammation in the bladder wall. In such cases, it may be difficult to distinguish the remaining tumor from benign treatment-related effects¹⁷ (Figure 7). As a result, the T-stage of bladder cancer may be overestimated on MRI or CT. Treatment-related effects can persist for up to 18–24 months.¹⁸ In contrast, Takes et al¹⁶ concluded that the time interval between MRI and TUR-BT (≤ 60 and ≥ 61 days) was not a statistically significant factor. However, we recommend mp-MRI before TUR-BT or intravesical chemotherapy, because the initial appearance (peduncle, ILE, surrounding inflammatory change) of tumors is lost after TUR-BT on mp-MRI, and thus the VI-RADS cannot be used for T-staging. If TUR-BT was performed in a patient before mp-MRI, an interval of ≥ 8 weeks would be recommended for correct T-staging.

The mp-MRI staging method using the VI-RADS

Based on the reports of mp-MRI-based assessments of bladder cancer, Panebianco and Narumi et al⁶ released the VI-RADS

for local bladder cancer staging in May 2018. The aim of the VI-RADS is to standardize the scanning and bladder reporting format based on mp-MRI for clinical and research applications. In the VI-RADS, an mp-MRI examination consists of a combination of T_2 WI, DWI, and DCE imaging sequences (Table 1). On T_2 WI, ≥ 2 planes of multiplanar (axial, coronal, and sagittal) images without fat suppression are usually obtained with 2D fast spin echo; 3D spin echo acquisitions may be used as an adjunct to 2D acquisitions. On DWI, axial and sagittal/coronal breathing-free spin echo EPI sequences combined with spectral fat saturation is recommended. The scanning protocol of the DWI should be similar to T_2 WI to permit localization. On DCE, although either a 2D or 3D T1 gradient echo (GRE) sequence with fat suppression may be used, 3D acquisition is preferred to obtain higher spatial resolution.¹⁹ If 3D images are acquired with isotropic voxels on T_2 WI or DCE, an arbitrary plane perpendicular to the tumor-bladder wall interface can be reformatted.

The VI-RADS classifies the probability of bladder cancer invasion to muscle by using a 5-point scoring system:

VI-RADS 1; muscle invasion is highly unlikely

VI-RADS 2; muscle invasion is unlikely.

VI-RADS 3; muscle invasion is equivocal.

VI-RADS 4; muscle invasion is likely.

VI-RADS 5; muscle invasion is very likely.

The VI-RADS score is defined using individual categories of T_2 WI, DWI and DCE. Tumors with a dia. of < 10.0 mm and flat lesions were reported to be almost all non-muscle invasive,¹⁵ and these tumors were selected as Category 1. Category 2 is defined as tumors with a dia. ≥ 1 cm and a thickened inner layer. Category 3 is defined as the disappearance of Category 2 findings, but no clear disruption of a low-SI muscle layer. Category 4 is defined as the interruption of a low-SI line suggesting a muscle

Table 1. Examples of parameter setting for 3.0 T MRI

	T_2 WI	DWI	DCE
Parameter setting at 3.0 T			
TR (ms)	4690	2500–5300	3.8
TE (ms)	119	61	1.2
Flip angle (degree)	90	90	15
FOV (cm)	23	32	27
Matrix	400 × 256–320	128 × 128	192 × 192
Slice thickness (mm)	3–4	3–4	1
Slice gap (mm)	0–0.4	0.3–0.4	0
Number of excitations	2–3	4–10	1
b values (s/mm^2)		0–800 - 1000	

DCE, dynamic contrast enhanced; DWI, diffusion-weighted image; FOV, field of view; TE, echo time; TR, repetition time; T_2 WI, T_2 weighted image.

Figure 8. The category of T_2 WI. Category 1 to 5 are shown on schema and corresponding T_2 WI. Possibility of muscle invasion is higher with greater number of category. T_2 WI, T_2 weighted image.

Category	Muscle invasion	Findings	schema	MRI
1	Highly unlikely	< 10 mm or flat lesion		
2	Unlikely	Papillary or pedunculated high or low signal lesion, or non-papillary lesion with thickened high signal submucosa		
3	Equivocal	Disappearance of 1,2 Intermediate signal lesion does not occupy low signal muscle layer		
4	Likely	Intermediate signal lesion extends into muscle layer		
5	Very likely	Intermediate signal lesion extends into extravascular fat		

layer. Category 5 is defined as an extension of an intermediate SI tumor to extra vesical fat.

The VI-RADS scores 1 to 5 of each sequence are shown in Figures 8–10. The scoring is done based first on T_2 WI for the determination of morphology, because of the higher spatial

Figure 9. The category of DWI. Category 1 to 5 are shown on schema and corresponding DWI. Possibility of muscle invasion is higher with greater number of category. DWI, diffusion-weighted image.

Category	Muscle invasion	Findings	schema	MRI
1	Highly unlikely	< 10 mm or flat lesion		
2	Unlikely	Pedunculated and papillary lesion. Presence of low signal stalk or low signal area at tumor base.		
3	Equivocal	Disappearance of 1,2 High signal lesion does not extend into muscle layer		
4	Likely	High signal lesion extends into muscle layer		
5	Very likely	High signal lesion extends into extravascular fat		

Table 2. Sensitivity and specificity of VI-RADS in previous reports

	Number	Cut-off category	Sensitivity (%)	Specificity (%)	Interobserver agreement
Ueno Y et al.	74	≥4 ≥3	76 88	93 77	0.85
Barchetti G et al.	75	≥4 ≥3	82–91 77–82	85–89 89–94	0.73
Wang H et al.	340	≥3	87	97	0.92
Kim SH et al.	339	≥4 ≥3	91 95	76 44	0.85
Giudice FD et al.	231	≥3	92	91	0.81
Makboul M et al.	50	≥4	78	88	0.87

VI-RADS, Vesical Imaging Reporting and Data System. Category 3 or 4 was adopted for cut-off category of muscle invasion.

Figure 10. The category of DCE image. Category 1 to 5 are shown on schema and corresponding DCE. Possibility of muscle invasion is higher with greater number of category. DCE dynamic-contrast enhanced.

Category	Muscle invasion	Findings	schema	MRI
1	Highly unlikely	< 10 mm or flat lesion		
2	Unlikely	Pedunculated papillary lesion or presence of continuous submucosal contrast enhancement		
3	Equivocal	Disappearance of 1,2 And contrast-enhanced lesion does not extend into muscle layer		
4	Likely	Contrast-enhanced lesion extends into muscle layer		
5	Very likely	contrast-enhanced lesion extends into extravascular fat		

resolution of T_2 WI in the evaluation of the integrity of the muscle layer. The most commonly used sequence for determining the VI-RADS score is DWI (first) and DCE (second).⁶ DWI is used for the final category when DWI is available. DCE is used for the final category when the DWI results are suboptimal due to artifacts or noises. If DCE is also suboptimal, T_2 WI is used for the final category.

Reporting of mp-MRI using VI-RADS

One issue regarding the VI-RADS has been its diagnostic performance and reproducibility. Several research groups recently evaluated the diagnostic performance of the VI-RADS^{20–25} (Table 2). Overall, the sensitivity and specificity of the VI-RADS for bladder cancer staging have been 82–92% and 44–91% respectively when the cut-off VI-RADS score ≥3 was used. The sensitivity and specificity of the VI-RADS for bladder cancer staging have been 76–91% and 76–93%, respectively when the cut-off VI-RADS score ≥4 was used. Interobserver agreements were good or excellent in all of those reports.

According to these results, the diagnostic performance of the VI-RADS is good. The sensitivity was slightly higher when the cut-off VI-RADS ≥3 was used, whereas the specificity was slightly higher when the cut-off VI-RADS ≥4 was used. The

Figure 11. Current Algorithm for T staging of bladder cancer. Clinical algorithm as the gold-standard of MIBC is TUR-staging first, followed by MRI staging. MIBC, muscle-invasive bladder cancer; TUR-BT, transurethral resection of the bladder tumor.

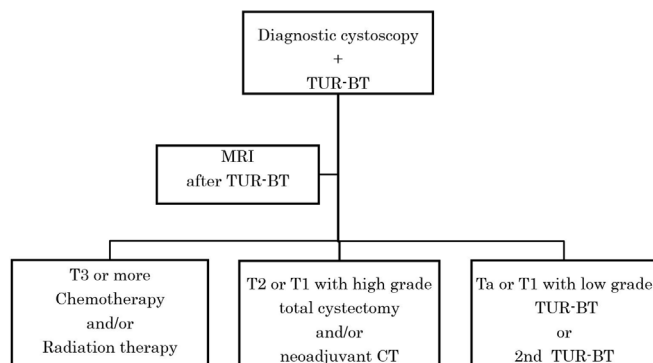
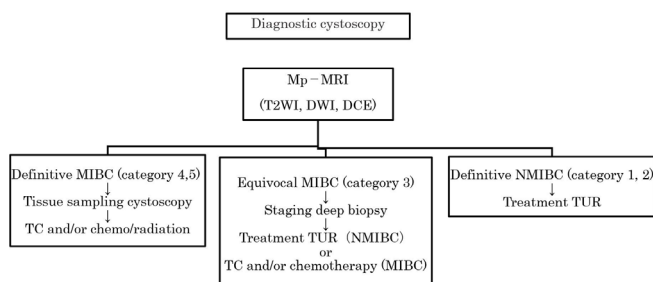


Figure 12. Proposed New Algorithm of VI-RADS with mp-MRI to stratify patients. Mp-MRI can be used as first line method for stratification of diagnosis to distinguish apparently MIBC (VI-RADS 4, 5) from apparently NMIBC (VI-RADS 1, 2). Staging biopsy may be used for selective cases of equivocal MIBC (VI-RADS 3). DWI, diffusion-weighted image; MIBC, muscle-invasive bladder cancer; mp-MRI, multiparametric-MRI; NMIBC, non-muscle-invasive bladder cancer; T_2WI , T_2 weighted image; TUR-BT, transurethral resection of the bladder tumor.



diagnostic ability of the VI-RADS for the T-staging of bladder cancer has been comparatively good, but there are still some false-positive or false-negative cases. Further multi-institutional and meta-analyses are needed for a more thorough validation of the VI-RADS.

Possible clinical algorithm using the VI-RADS in the future

The current clinical algorithm used at many institutions as the gold standard of MIBC is TUR-staging first, followed by MRI staging (Figure 11). However, the TUR-staging is not perfect. It was reported that 48 and 46.7% of bladder cancers were under staged in the first- and second-look staging, respectively in a study in which total cystectomy was applied as the gold-standard.²⁶ At present, MRI can be used as a first-line method for the stratification of diagnoses to distinguish apparent MIBC (VI-RADS score 4, 5) from apparent NMIBC (VI-RADS score 1, 2). A staging biopsy may be used for selective cases of equivocal MIBC (VI-RADS score 3) (Figure 12). In this way, we can reduce the total number of second look staging biopsy possibly resulting in reduction of total diagnostic cost. Future studies should justify this staging algorithm by comparing TUR-staging biopsy and MRI staging applying total cystectomy as the gold-standard.

CONCLUSION

Mp-MRI has been an important method for the T-staging of bladder cancer. We need to know the characteristics of each sequence of mp-MRI for bladder cancer. As VI-RADS scoring is an excellent tool, we proposed diagnostic strategy with mp-MRI before TUR-BT using VI-RADS scoring in patients with bladder cancer. Multi-institutional studies are awaited comparing TUR-BT staging and mp-MRI scoring using the VI-RADS.

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