

The role of multiparametric magnetic resonance in bladder cancer management

Rola multiparametrycznego rezonansu magnetycznego w terapii raka pęcherza moczowego

Katarzyna Kuźlik-Gołębiowska*¹, Anna Jurkowska¹, Dariusz Gołębiowski²,
Katarzyna Sklinda¹, Jerzy Walecki¹, Wojciech Rogowski²

¹ Department of Radiology, Centre of Postgraduate Medical Education, Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw, Poland

² Department of Urology and Oncological Urology, Centre of Postgraduate Medical Education, Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw, Poland

KEYWORDS:

- urinary bladder
- bladder cancer
- multiparametric MRI
- staging
- neoplasm invasion

ABSTRACT

Multiparametric magnetic resonance imaging with VI-RADS is a newly discussed method of diagnosing bladder cancer. There are more studies suggesting implementation of mpMRI with VI-RADS to the modern scheme of treating bladder cancer. It requires much more observation and trials to give a final recommendations. The aim of the summary is to present VI-RADS scale and possibilities that appear with the method. Many studies, that were made by departments of urology or radiology, showed promising results.

Background: estimation of bladder cancer depends on proper tumor staging, grading and assessment of its biological potential. It is provided by a multimodal approach using clinical, histopathological and radiological methods. Development of MRI provides the best imaging technique for locoregional staging in several other tumors. Lately it was adjusted in BCa preoperative evaluation leading to significant improvement in differentiating patients with NMIBCs and MIBCs.

Objective: this article aims to approximate the fundamentals of MRI in BCa and to provide an overview of the available data on the role of VI-RADS score in the diagnostic pathway of bladder cancer.

SŁOWA KLUCZOWE:

- pęcherz moczowy
- rak pęcherza moczowego
- wieloparametryczny MR
- ocena zaawansowania
- nacieki nowotworu

STRESZCZENIE

Obrazowanie metodą wieloparametrycznego rezonansu magnetycznego z VI-RADS jest nowo dyskutowaną metodą diagnostyki raka pęcherza moczowego. Pojawiają się kolejne prace sugerujące wprowadzenie mpMRI z VI-RADS do nowoczesnego schematu leczenia raka pęcherza moczowego. Do wydania ostatecznych zaleceń potrzeba jeszcze wielu obserwacji i badań. Celem podsumowania jest przedstawienie skali VI-RADS i możliwości, jakie wiążą się z tą metodą. Wiele badań przeprowadzonych przez oddziały urologii lub radiologii przyniosło obiecujące wyniki.

Informacje wstępne: postępowanie w przypadku raka pęcherza moczowego zależy od właściwego określenia stopnia zaawansowania nowotworu, klasyfikacji oraz oceny jego potencjału biologicznego. Zapewnia to podejście multimodalne z wykorzystaniem metod klinicznych, histopatologicznych i radiologicznych. Rozwój rezonansu magnetycznego (MRI) sprawił, że jest on najlepszą techniką obrazowania do oceny lokoregionalnej w wielu innych nowotworach. Ostatnio dostosowano go do oceny przedoperacyjnej BCa, co doprowadziło do znaczącej poprawy w różnicowaniu pacjentów z NMIBCs i MIBCs.

Cel: artykuł ma na celu przybliżenie podstaw MRI w BCa oraz przedstawienie przeglądu dostępnych danych na temat roli VI-RADS score w ścieżce diagnostycznej raka pęcherza moczowego.

Introduction

Bladder cancer (BC) is one of the most common tumors in Polish population. It is on the 4th place and the 5th place in terms of incidence and mortality among all other tumours in Poland (1). About 50% percent of bladder cancers are caused by cigarette smoking, but it is not the only cause. Exposure to aromatic amines, polycyclic aromatic hydrocarbons and some other chemicals in heavy industry is the second most important risk factor. Radiotherapy of pelvic organs (prostate, rectum) may also increase the risk of bladder cancer. In some parts of the world *Schistosoma Haematobium* may be a significant factor, which brings squamous cell bladder cancers on (2).

Urothelial cancer is the most common histological type of malignant bladder tumor. It represents 90% of all cases and most guidelines are referring to this histological type (3).

Bladder cancer staging is performed by clinical examination, histopathological assessment and radiological features. Computed tomography is the most common imaging method among clinicians, but there are several potential clinical applications for MRI in the treatment of bladder cancer. MRI has superior soft tissue contrast resolution than CT, so it can be used for local staging of MIBC. If there are contradictions for administration of iodinated contrast during CT and full examination of urinary tract is required, it is possible to perform MRI urography. Studies showed that DWI-MRI is very promising in assessment to induction chemotherapy (4).

Management of bladder cancer mainly relies on differentiating NIMBC (Ta, T1 or Tis) from MIBC (stage T2 or higher) because the treatment methods differ markedly (5, 6).

Transurethral resection of bladder tumour (TURBT) is the first step towards acquiring a specimen for histological report. It is necessary to evaluate tumour's invasion of the muscle layer. Patients with an invasion of the bladder's muscle layer require radical cystectomy preceded by neoadjuvant chemotherapy. Some patient may be treated by trimodal therapy (TURB and radiochemotherapy). In case of failure radical cystectomy should be performed (5, 6).

Precise preoperative estimation is fundamental as the radical cystectomy surgery results in the lower quality of life and the high rate of complications (7). On the other hand transurethral resection quality differs among surgeons, and it appears to ¼ of MIBC is missed (8). Therefore, it was crucial to obtain an accurate imaging method to improve the efficiency of staging BC. A promising tool in this field appears to be Multiparametric MRI (mpMRI), which combines functional sequences such as DWI, DCEI and lymphotropic nanoparticle in addition to the anatomic T1- and T2-weighted images (9). Its success in management of prostate cancer convinced many radiologists and urologists to check capabilities for BC staging. Furthermore, recently the MRI reporting system for local bladder cancer staging (VI-RADS score) was presented (10).

Anatomy and MRI appearance

Urinary bladder is an organ located below the peritoneal cavity, in males between rectum and pubic symphysis, in females between uterus and pubic symphysis. The trigone is a triangular space between the two ureteral orifices and the internal urethral opening. The dome is covered by peritoneum and the bladder's base is attached inferiorly to neighboring structures. Histologically, the three main layers form bladder's wall: (I) bladder mucosa (embraces urothelium and connective tissue, lamina propria); (II) detrusor muscle (the muscularis propria) and (III) serosa (loose connective tissue). Bladder wall's thickness and bladder's volume depend on the degree of its distension. An average thickness of the lamina propria depends on the location. It is thicker at the dome than at the trigone. The muscularis propria is divided to three layers: inner longitudinal, middle circular, and outer longitudinal (11, 12) (Figure 1).

MRI does not have the necessary spatial resolution to visualize all the histological bladder wall layers. Normal bladder wall appears as a band of intermediate signal intensity

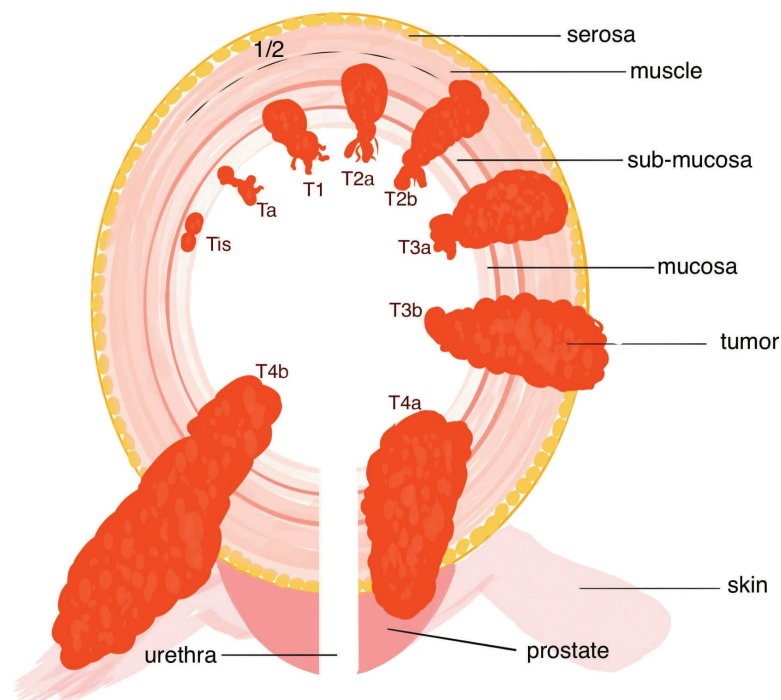


Figure 1. Bladder wall anatomy and local tumor staging of urinary bladder cancer, based on depth. See Table 1. for T definitions.

Source: own elaboration.

Table 1. TNM classification 2017 for upper tract urothelial cell carcinoma (13).

TNM = tumour, node, metastasis classification.

T – primary tumour	
TX Primary tumour cannot be assessed	
T0	No evidence of primary tumour
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	Renal pelvis: tumour invades beyond muscularis into peripelvic fat or renal parenchyma; Ureter: tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N – regional lymph nodes	
NX Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node ≤ 2 cm in the greatest dimension
N2	Metastasis in a single lymph node > 2 cm or multiple lymph nodes
M – distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

on T1-weighted images and as bands of low (inner) and intermediate (outer) signal intensity on T2-weighted images.

On T2-weighted images urothelium and lamina propria is not visualized. Muscularis propria appears as a low signal intensity line. On DWI images inner layer (urothelium and lamina propria) is not observed as well, but we can visualize muscularis propria as intermediate signal line. In ADC map bladder wall is of intermediate signal and the urine appears very bright. In DCE sequences urothelium and lamina propria enhance early as a hyperintense line and the muscularis propria shows slow and progressive enhancement as low signal line (10) (Figure 2, 3).

MRI – technical aspects

MRI timing

MRI is best performed before or at least 2 weeks after TURBT, bladder biopsy, or intravesical Bacille Calmette-Guerin (BCG) treatment because these procedures cause swelling and inflammation of the bladder wall and surrounding perivesical tissues. These lesions can complicate the interpretation of the study because they may look similar to BC (leading to an overestimation of regional staging).

Air remaining after cystoscopy or bladder catheterization affects diffusion weighted imaging (DWI), leading to artifacts and image distortion. Therefore, it is recommended that the interval between cystoscopy or catheter removal and MRI should be at least 2-3 days (10).

Patient preparation

In patients without contraindications, antispasmodic agents should be administered before the examination. These may be administered either intramuscularly or intravenously (an access line for contrast administration may also be used). Such management limits the occurrence of artifacts caused by peristaltic movements of the intestines.

Adequate bladder filling is also an important aspect of imaging. Optimally, the patient is advised to void 1-2 h before the study or drink adequate amount of water (500-1000 ml) 30 minutes before the MRI. Optimal volume of bladder during the procedure is around 300 ml. Without adequate bladder distension, the wall will appear thickened with irregular contours. This can lead to misdiagnosis of BC or overestimation of the lesions. On the other hand, overfilling the bladder may cause patient discomfort, motion artifacts, and thus difficulty in image interpretation (10, 14).

MRI protocols

A dedicated bladder mpMRI protocol should include at least T2-weighted imaging in three planes (axial, sagittal, and

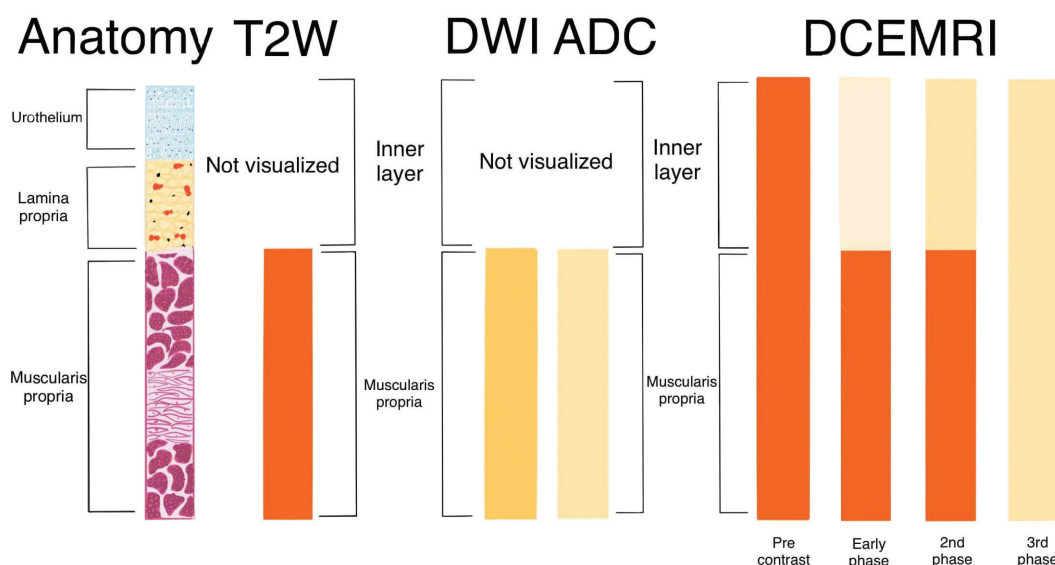


Figure 2. Schematic appearance of bladder wall anatomy and respective MRI appearances at T2W imaging, DWI, ADC, and DCE MRI (7).

Source: own elaboration.

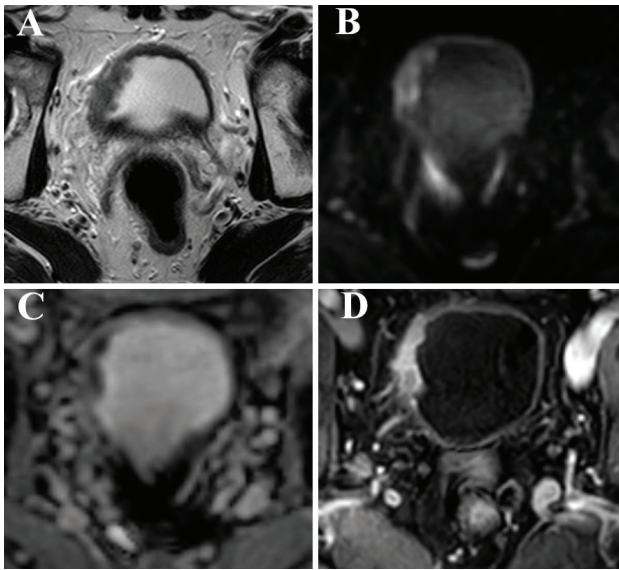


Figure 3. Urothelial carcinoma (stage T3b) in a 69-year-old man. In the right posterior wall, anteriorly to the ureteric orifice extensive tumor infiltration. Urothelium, muscularis propria, serosa are involved. Axial T2-weighted sequence (A), axial DWI sequence (B), axial ADC sequence (C), axial contrast enhancement sequence (D).

Source: own elaboration

coronal), Spin-echo T1-weighted (T1W) in the axial plane, DWI, and dynamic contrast-enhanced imaging (DCE MRI). Images should include not only the entire bladder, but also the proximal urethra, pelvic lymph nodes, prostate gland in men, uterus, ovaries, fallopian tubes, and vagina in women (15, 16). See Table 2.

mpMRI scoring

Using the "RADS" methodology, Panebianco et al. (10) proposed The Vesical Imaging-Reporting and Data System (VI-RADS) – the system using MRI images to inform about the probability of detrusor muscle invasion. The aim of VI-RADS is standardization of reporting criteria the risk of muscle invasion score, what could improve BC detection

and provides prognostic information useful before making decisions about treatment.

Presented in 2018 MRI scoring of bladder cancer is based on the combination of 3 sequences – T2-weighted anatomic imaging and functional MRI sequences – dynamic contrast-enhanced (DCE) imaging and diffusion-weighted MRI (DWI). Each sequence is an essential part and cannot be replaced (10).

T2W images and structural category (SC)

The T2W sequences is a first MR appearance to search. There are helpful ones, using to assess the appearance of the lesion (exophytic, with or without stalk, sessile /broad-based tumor, assessment of lesion size), the integrity of muscularis propria, the anatomy of the bladder (the thickening of inner layer, the invasion of bladder wall) and extravesical tissues. The structural category is defined by assessing the disruption of muscularis propria on this sequence. Based on this assessment, the lesion image is classified into 1 of 5 structural categories (SC).

On structural category SC1 and SC2 uninterrupted hypointense line indicates the integrity of muscularis propria. SC3 signifies disappearance of category 2 findings, there is no evident disruption of hypointense muscularis propria.

Visible interruption of the hypointense line suggests extension of tumour tissue with intermediate SI into the muscularis propria (category 4), and if the tumour extends into extravesical fat, this indicates invasion of the entire bladder wall and extravesical tissues (category 5) (10, 17).

The principal sequences to estimate the presence of definitive muscular invasion are DWI and DCE MRI.

DCE images and contrast-enhanced (CE) category

DCE is used to define contrast-enhanced (CE) categories. There is assessed whether the lesions correspond to SC findings. Dynamic CE imaging can depict lesions smaller than 0.5 mm (18).

It is checked whether early enhancement of the muscularis propria is present (this is identifiable as a low SI line

Table 2. Abilities and outcomes of different MRI sequences (14).

MRI sequence	Abilities	Outcome
Spin-echo T1-weighted	To evaluate the perivesical fat planes for extravesical tumor infiltration, pelvic lymphadenopathy, and bone metastases	
T2- weighted	Tumor depth and extravesical disease spread	Efficiency in differentiating non-muscle invasive (NMIBC) from muscle invasive (MIBC): 40-67%
DWI (functional imaging technique reflecting proton diffusion properties in water)	Allows to differentiate inflammation and fibrosis associated with tumor from thickened submucosa caused by invasion	Efficiency in differentiating NMIBC form MIBC 63.6-92%, increasing to 98% adding T2WI; accuracy for identifying recurrent bladder tumors 91.6% with an excellent agreement between DWI and conventional cystoscopy finding
ADC maps	ADC maps could be a biomarker predicting histopathologic grading, aggressiveness, and tumor response to chemoradiation therapy; improves differentiation between benign and metastatic lymph	
DCEI	Evaluates response to chemotherapy – effectively distinguish residual tumor from chemotherapy – induced hemorrhagic inflammation	Overall accuracy in determining tumor stage: 52-93%

and should not be enhanced in the early phase – meaning CE category 1 and 2) and the presence and manner in which the tumor enhances. The lesion is classified as CE category 4 if the early enhancement extends focally to the muscularis propria and in category 5 if extends to the entire bladder wall and to extravescical fat, CE category 3 means that no conclusive destruction of low SI muscularis propria and no findings of category 2 was observed. All changes classified as CE categories correspond with the equivalent SC category (10).

A contrast-enhanced sequence is essential in VI-RADS. One study (5) investigated the effectiveness of assessment bladder cancer muscle-invasiveness on non-contrast MR imaging. Their results demonstrate that the contrast-free MRI protocol (consisting of T2W and DWI) shows a comparable diagnostic accuracy to the standard multiparametric MRI protocol for the detection of muscle-invasive bladder cancer, regardless of the reader’s experience.

DWI images and diffusion-weighted category (DW category)

DWI is the dominant sequence when image quality is optimal. DWI improves the accuracy in case of discordance between DCE and T2W sequences, when there are deflection of categories (6, 14). Based on the assessment for DWI /ADC is third category – DW category – diffusion-weighted category.

A lesion has high SI on DWI and low SI on ADC. On DWI muscularis propria may perform continuous intermediate SI (DW category 1 and 2), inner layer may be thickened and may have low (category 1 and 2) or intermediate (category 2) SI on DWI.

DW category 4 signifies that tumor extends focally to muscularis propria, category 5 – to the entire bladder wall and extravescical fat.

DW category 3 means that no clear destruction of low SI muscularis propria and no findings of category 2 was observed.

All changes classified as DW categories correspond with the equivalent T2 category findings (10, 18).

Final scoring

VI-RADS was created using 3 categories – structural category (SC), diffusion-weighted (DW) category, and contrast-enhanced (CE) category. This system using a 1-5 scale estimates the risk of muscle invasion:

- 1 – highly unlikely to be present,
- 2 – unlikely,
- 3 – equivocal,
- 4 – likely,
- 5 – invasion of the muscle and beyond the bladder is very likely.

A detailed information about the scoring can be found in the attached figures – 4 [taken from the original article of the Panebianco et al. (10)] and 5, based on this article.

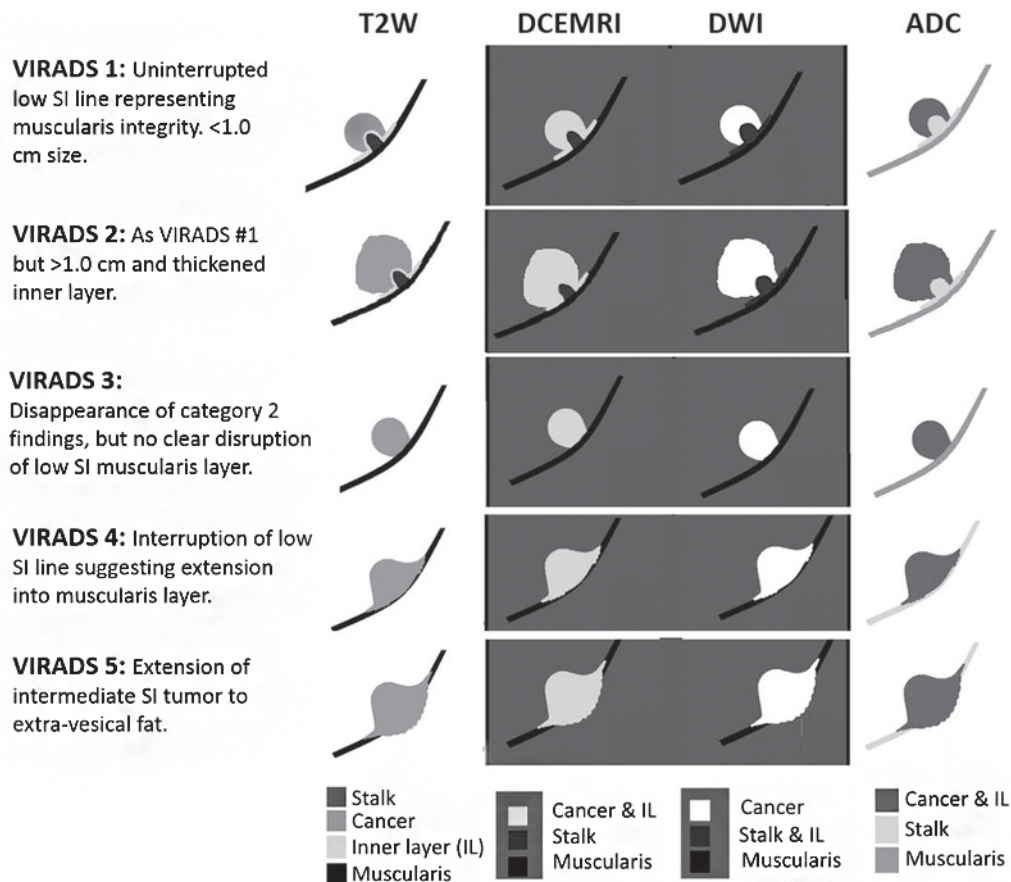


Figure 4. Schematic illustration of mpMRI appearances of VI-RADS scores 1-5 using T2, DCE MRI, DWI, and ADC weighted images. Source: Based on Panebianco et al. (10).

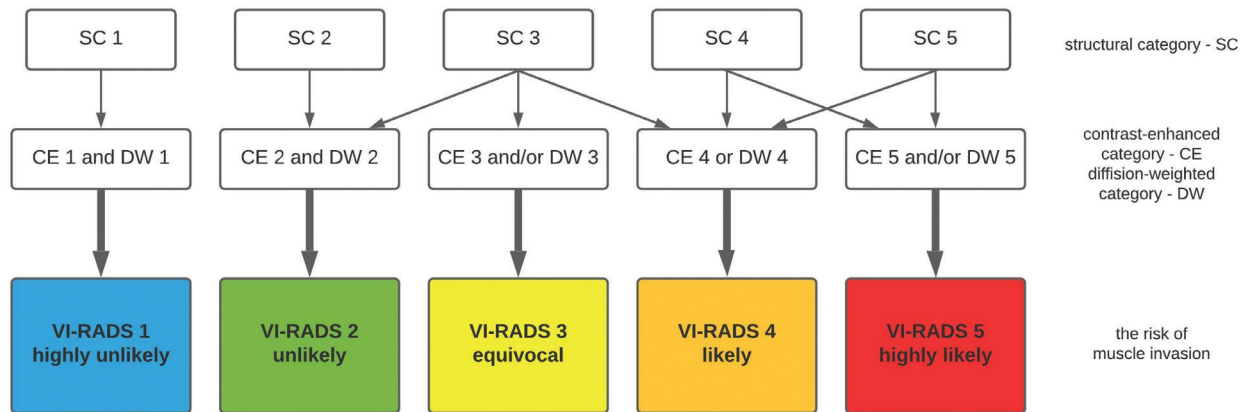


Figure 5. Summary schematic representation of VI-RADS scoring.

SI = signal intensity; CE = contrast-enhanced category; DW = diffusion-weighted category; SC = structural category.

Source: Based on Panebianco et al. (10).

Evaluation of VI-RADS in studies

A very important current step in the development of the VI-RADS is to conduct research and meta-analysis studies for effectiveness and inter-observer agreement of mpMRI.

Diagnostic performance of VI-RADS

The results obtained in the studies indicate that the standardizing VI-RADS is an effective comprehensive scoring system, with a high satisfactory sensitivity, specificity, and diagnostic value for determining the probability of invasion of the bladder detrusor muscle invasion in bladder cancer (6, 19, 20).

It is worth noting that significant improvement in sensitivity and specificity was noted when DW imaging included the use of a stronger field (3 T) (21). Further multi-centre validation studies involving devices with multiple magnetic field strengths (1.5-T or 3.0-T) should be conducted (6).

The VI-RADS score may be an effective image scoring method that defines the likelihood of the muscular invasion status of bladder cancer with VI-RADS 3 or VI-RADS 4 as the cut-off value (6), and the diagnostic efficiencies of VI-RADS 3 and VI-RADS 4 at the cut-off value are similar. According to one meta-analysis (22), VI-RADS criterion of 3 or greater before primary TURBT had a cumulative diagnostic accuracy of 94% in identifying MIBC. For comparison, the accuracy of MRI without VI-RADS in the primary assessment of bladder cancer staging ranges from 73% to 96% depending on the study (23).

It is important to note and emphasize that one study (5) highlighted that for tumors scored with VI-RADS at 3, two-thirds were muscle-invasive cancer and one-third were non-muscle-invasive cancer, suggesting the difficulty of determining the extent of tumor invasion when tumors were assessed by VI-RADS 3. For tumors rated as VI-RADS 1, 4, and 5, the VI-RADS system achieved 100% accuracy in predicting invasion of detrusor muscle. For tumors scored with VI-RADS 2, results were obtained suggesting a good prognostic performance for detrusor muscle invasion (95% were non-invasive muscle tumors and 5% were muscle-infiltrating tumors). These data imply that more attention should be paid to tumors with VI-RADS scores of 2 and 3.

The inter-readers agreement

An important issue is the question of the agreement for reviewers in categorizing according to the VI-RADS five-point scoring system among multiple readers with different levels of expertise. In studies evaluating the interobserver agreement of VI-RADS observed moderate to substantial (6), good to excellent agreement of VI-RADS to discriminate NMIBC from MIBC (23). That indicating excellent agreement in VI-RADS scoring (6) and supports the previously reported high reproducibility of VI-RADS (6, 23, 24, 25).

Studies evaluating the inter-readers agreement highlight potential problems and pitfalls in image interpretation, especially those not mentioned in the original VI-RADS criteria. Assessment of tumors located around bladder cervical orifice, bilateral ureteral orifices (18) and in the bladder triangle (20) is problematic, then there may be differences in scores on different planes and there has been some disagreement between readers in study (6). Further studies should determine whether this is associated with the special anatomical features of the bladder neck and ureteral orifices (6). Furthermore, cases with hydro-ureter should be interpreted with caution.

Studies also found that greater experience with VI-RADS was the most important predictor of reliability between readers, which may result in differences in score between centres, depending on familiarity and experience with categorisation according to the VI-RADS system (23).

Advantages and disadvantages of VI-RADS

Advantages of VI-RADS

Descriptions of bladder imaging examinations may differ between clinical centers. The introduction of VI-RADS as a diagnostic standard would make it possible to standardize the method of describing bladder tumors using MRI (23).

The aim of the VI-RADS is to strive for higher reliability among readers for diagnostic results compared with only subjective interpretation of MRI sequences.

mpMRI is currently the best method in imaging of pelvic soft tissues. Its resolution can differentiate layers of the bladder wall and enables evaluation of tumor invasion (11). According to Del Giudice (4, 26) mpMRI is a good tool

to differentiate NMIBC and MIBC. The same author also made a meta-analysis of 8 studies that were built to investigate the effectiveness of mpMRI before TURBT. Across all these studies there was agreement that mpMRI with VI-RADS scoring differentiate NMIBC and MIBC very well, but there is need to more studies to allow avoiding reTURBT after MRI (23).

Furthermore the group also identified VI-RADS 5 score as independent unfavourable predictive indicator for patient with MIBC (23).

Carando and al. stated that mpMRI could possibly allow to avoid a second TURBT (20).

Disadvantages of VI-RADS

There is an agreement between authors of many studies that there is a need to test mpMRI in clinical practice before it could be established as a crucial part of bladder cancer management (6, 20, 24, 25, 26, 27).

There are some other limitations mentioned in the searches.

Quality of diagnostics highly depends on capabilities of MRI-device. 1.5T or 3T MRI-device is a minimum which is required to correctly evaluate bladder using VI-RADS. mpMRI also requires radiologists that are highly trained and qualified in imaging of the genitourinary system (11).

mpMRI cannot detect carcinoma in-situ (CIS). Diagnose of CIS determines further management of disease like BCG therapy and risk of progression to MIBC. None of current imaging methods is good for detecting CIS and it is required to use cystoscopic examination. In this case photodynamic diagnosis (fluorescence cystoscopy) is more useful than any other method (28).

MRI showed mixed results of detecting lymph node invasion. Sensitivity ranges from 41% to 100% (29). PET with MRI is noticeably superior to MRI alone if we are considering lymph node evaluation (95% for FDG PET/MRI vs 76% for MRI alone) (30).

Current place of mp-MRI with VI-RADS

Multiparametric resonance imaging is currently not established in protocols of diagnostic and staging of bladder cancer according to 2020 EAU Bladder Cancer Guidelines (31). It needs further publications to form a clear statement about the diagnostic method.

Currently management of bladder cancer depends on the pathological report after the first TURBT.

Conclusions

Bladder cancer, as one of the most common cancers in the population, is a significant clinical problem. It is crucial to constantly improve methods of management which should lead not only to radical treatment but also provide the highest possible quality of life for patients. The method that currently seems to be the most promising in this field is MRI. Despite its limitations, the necessity for careful planning and appropriate patient preparation, it is an important element in the assessment of tumor invasiveness, which directly affects therapeutic decisions. The recently developed VI-RADS scale unifies the MRI staging system and improves interdisciplinary communication and cooperation between practitioners.

Although the VI-RADS scale is not included in 2020 EAU recommendations, it can be expected that in the future it will become an approved method. Currently there is not enough evidence that we could state undoubtedly that mpMRI is useful in management and staging of BC. MRI is undoubtedly more patient-friendly, non-invasive and linked to lower risk of complications than second TURBT. There is the need for a further analysis of this topic. If we can also prove that it is cost effective compared to endoscopic procedures, it would be a straight road to changing current guidelines, like in case of prostate cancer and mpMRI with PI-RADS.

Abbreviations:

MRI	– magnetic resonance imaging,
mpMRI	– multiparametric MRI,
BCa	– bladder cancer,
MIBC	– muscle invasive bladder cancer,
NMIBC	– non-muscle-invasive bladder cancer,
CIS	– Carcinoma in-situ,
TURBT	– transurethral resection of bladder tumour,
RC	– radical cystectomy,
DWI	– diffusion-weighted imaging,
DCE	– dynamic contrast enhancement,
DCEI	– dynamic contrast-enhanced imaging,
ADC	– apparent diffusion coefficient,
SI	– signal intensity.

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