REVIEW

The role of MRI in muscle-invasive bladder cancer: an update from the last two years

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Purpose of review

Muscle invasive bladder cancer (MIBC) is aggressive and requires radical cystectomy and neoadjuvant therapy, yet over 40% of patients face recurrence. The loss of the bladder also significantly reduces quality of life. Accurate staging, crucial for treatment decisions, is typically done through transurethral resection (TURBT), but inconsistencies in pathology affect diagnosis in 25% of cases. MRI is the most precise imaging method for evaluating local tumor invasiveness. This review discusses recent advances in MRI for staging MIBC and predicting responses to neoadjuvant therapy.

Recent findings

Vesical imaging – reporting and data system (VI-RADS) accuracy may improve if combined with ADC maps and tumor contact length, while a bi-parametric MRI approach without contrast could reduce side effects without losing diagnostic precision, though evidence is mixed. VI-RADS shows promise in predicting neoadjuvant therapy responses, and the new nacVI-RADS score is in development. Non-Gaussian diffusion-weighted imaging techniques and machine learning could enhance accuracy but need more integration with mpMRI. VI-RADS may assist in evaluating responses in bladder-sparing regimens. Urodrill, an MRI-guided biopsy, aims to replace diagnostic TURBT but needs more accuracy data.

Summary

MRI in MIBC is evolving, offering potential for accurate local staging and reduced side effects by avoiding TURBT. Predicting neoadjuvant treatment response could guide personalized treatment and bladder preservation. Larger trials are needed to validate these findings.

Keywords

muscle invasive bladder cancer, peri-operative, staging, vesical imaging – reporting and data system

INTRODUCTION

Muscle-invasive bladder cancer (MIBC) represents 25–30% of newly diagnosed urothelial carcinoma cases [1] and it is classified as cT2–4N0M0 under TNM staging criteria [2]. The primary treatment is radical cystectomy (RC) [3], that for eligible patients is preceded by cisplatin-based chemotherapy [4], which improves overall survival (OS) by approximately 6% at 5 years [5]. Recently, phase II trials demonstrated the activity of neoadjuvant immune check point inhibitors (ICI), either alone or with chemotherapy [6–11].

Accurate diagnosis necessitates cystoscopy and transurethral resection (TURBT) to evaluate bladder wall invasion [3]. The precision of both resection and histopathological analysis relies upon operators expertise, with up to a quarter of patients being staged inaccurately [12].

MRI is currently the most reliable noninvasive method for predicting muscle invasion at the initial diagnosis and postneoadjuvant therapy, despite limitations in lymph node staging and accuracy following TURBT or BCG treatment [13]. The application of MRI in MIBC is growing, with recent advancements holding promise for improvements in treatment decisions.

This work aims to review the most recent MRI applications for local staging and treatment response evaluation in MIBC.

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KEY POINTS

- Muscle-invasive bladder cancer (MIBC) is an aggressive disease and its identification is inaccurate in up to a quarter of patients.
- In the last few years, vesical imaging – reporting and data system (VI-RADS) scoring system has demonstrated good performance for local staging assessment, yet novel MRI features such as non-Gaussian diffusion-weighted imaging sequences and morphological parameters can improve its accuracy.
- A bi-parametric MRI approach avoiding contrast administration seems to have comparable staging performance to standard multiparametric MRI.
- Machine learning methods have demonstrated good accuracy and hold the potential to overcome human readers' limitations.
- Treatment response assessment and prediction, especially to novel perioperative and bladder sparing strategy, is the big challenge for the very next years.

MRI IN DIAGNOSIS AND STAGING

In localized bladder cancer, muscle invasion assessment is crucial for treatment decisions, as non-muscle-invasive bladder cancer (NMIBC) is treated with transurethral resection or intra-vesical therapy, whereas MIBC often require RC [3].

MRI is a noninvasive imaging technique that utilizes electromagnetic fields and radio waves to perturb hydrogen atoms within the body [14] and It is particularly effective for visualizing soft tissues.

Multiparametric MRI (mpMRI) is the preferred approach for evaluating muscle-invasiveness, integrating T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast enhancement (DCE). Another parameter used is the apparent diffusion coefficient (ADC), which is calculated from DWI and represents the degree of water diffusion within tissues [15].

A meta-analysis of 24 studies conducted between 2000 and 2017 reported that MRI has a sensitivity of 0.92 [95% confidence interval (CI) 0.88–0.95] and a specificity of 0.87 (95% CI 0.78–0.93) for local T staging, with mpMRI demonstrating greater accuracy compared to other MRI methods [16].

VESICAL IMAGING – REPORTING AND DATA SYSTEM

Vesical imaging – reporting and data system (VI-RADS), developed by Panebianco *et al.* in 2018 [12], is a 5-point scale used to standardize the interpretation of mpMRI in bladder cancer, assessing the likelihood of muscle invasiveness. Scores range from 1 (low probability) to 5 (high probability). Studies support its accuracy and inter-reader agreement, making it valuable in clinical practice [17,18■■]. Both VI-RADS 3 and 4 are used as cut-off for muscle invasion in clinical trials; however, recent findings suggest that VI-RADS 4 is more accurate. Additionally, VI-RADS 5 has shown accuracy in predicting fat invasion [19].

Concerns remain regarding variant histologies (VH). A retrospective study by Arita *et al.* demonstrated that VI-RADS had similar AUCs in both pure urothelial carcinoma (UC) and VH but noted that less experienced pathologists might underestimate muscle invasion in VH, with DWI being less sensitive in these cases [20■].

VESICAL IMAGING – REPORTING AND DATA SYSTEM "ESCALATION": MORPHOLOGICAL PARAMETERS AND UNCONVENTIONAL MRI SEQUENCES

Recently, studies have combined VI-RADS with other tools to overcome limitations. A retrospective study by Gong *et al.* showed that tumor-muscle contact margin, tumor cellularity index, and tumor longitudinal length associated with muscle invasiveness. The combination of these morphological parameters with VI-RADS significantly improves its area under the curve (AUC) [21■]. Moreover, a tumor contact length (TCL), which measures the interface between tumor and bladder wall, exceeding 3 cm has shown superior sensitivity and accuracy compared to a VI-RADS 3 score, supporting its utilization to distinguish uncertain cases of muscle invasion [22].

Although VI-RADS 2 lesions with a stalk have a low likelihood of MIBC, underdiagnosis remains a risk. Cai *et al.* developed a nomogram for assessing muscle invasion in such cases, achieving over 90% accuracy. This model incorporates several factors, including *tumor size* (cut-off at 3 cm), *stalk width*, and *morphology*, and normalized ADC values for both the tumor and stalk. ADC normalization involves dividing the ADC value of the target lesion by that of the psoas muscle. Authors found that low normalized tumor ADC and high normalized stalk ADC associated with muscle invasion [23]. Previously, they demonstrated that incorporating normalized tumor ADC into VI-RADS significantly improves muscle invasion detection, while adding *tumor size* to them offers no additional benefit [24].

Amide proton transfer-weighted imaging (APTw) is an MRI technique that informs about pH and protein concentration within lesions. Recently, Kong *et al.* have shown that incorporating APTw into the combination of VI-RADS and ADC provides benefit compared to VI-RADS alone or combined with ADC only [25].

VESICAL IMAGING – REPORTING AND DATA SYSTEM "DE-ESCALATION": BI-PARAMETRIC MRI

Increasing evidence suggests that omitting DCE in muscle invasiveness evaluation is feasible, potentially reducing costs [26] and avoiding contrast-related adverse events. Moreover, studies have reported that bpMRI is not inferior to mpMRI in terms of accuracy and inter-reader agreement [27–29].

However, there are still concerns regarding the reliability of bpMRI, particularly in the context of VH and the ureteral orifice location. Two different studies by Arita *et al.* evaluated bpMRI and mpMRI for diagnosing MIBC in tumors with VH [20▪,30]. They reported lower sensitivity and AUC for bpMRI compared to mpMRI, with a higher risk of under-diagnosis, especially for less experienced readers [30].

The ureteral orifice is a critical location for assessing muscle invasiveness, as lamina propria is thinner compared to the rest of the bladder. A recent study showed no significant AUC difference between bpMRI and mpMRI assessed by three radiologists, although accuracy was numerically higher with mpMRI for the least experienced reader [31].

DIFFUSION-WEIGHTED IMAGING

DWI is a functional MRI sequence that exploits water molecules diffusion to assess tissue cellularity, thus aiding to differentiate benign from malignant tissues. Several works support DWI and ADC for evaluating muscle invasion in BC [12], yet most studies rely on mono-directional axial measurements [32].

In 2023, Zhang *et al.* assessed a tri-directional DWI approach (axial, coronal and sagittal ADCs) and found that combining these values (TADC) yielded a higher AUC compared to single-directional ADCs, though the difference was not statistically significant. Additionally, normalizing ADC values improved diagnostic accuracy by reducing variability [33].

Recently, non-Gaussian DWI techniques like diffusion kurtosis imaging (DKI), which are based on the nonlinear diffusion of water molecules and associate with tissue structural complexity, have shown accuracy in detecting muscle invasion [34,35]. DKI-derived parameters, such as the Kapp heterogeneity coefficient and the Median Kurtosis are higher in MIBC compared to NMIBC lesions, indicating greater tissue complexity [35,36]. Studies have showed that combining DKI parameters with TCL further improves diagnostic accuracy, and DKI combined with bpVI-RADS outperforms bpVI-RADS using conventional DWI [35,37].

RADIOMICS AND MACHINE LEARNING

Radiomics is an emerging field that combines quantitative analysis and machine learning to extract high-throughput quantitative features from radiological images [38], potentially offering more precise evaluation than conventional radiology by overcoming the limitation of reader interpretation.

Initial radiomics research for nonmetastatic bladder cancer began in 2017, and since then, several investigations have evaluated various models [39]. These studies have predominantly used T2W imaging, offering cost savings and reducing processing time compared to mpMRI, and avoiding the need for contrast administration [40,41]. Machine learning algorithms applied to T2W imaging have been reported to enhance accuracy and reduce processing time for muscle invasion assessment compared to human readers [40]. An indirect comparison of different studies indicates that 3D imaging improves diagnostic performance over 2D imaging, and multitask learning models exhibit higher accuracy than single-task approaches [41].

To ensure validation, models must be trained on dedicated patient groups and evaluated on both internal and external cohorts, with the latter comprising patients from other institutions. Studies have shown that deep learning models often lose accuracy when applied to external datasets, due to their training on local MRI data [40,42▪▪,43]. Similarly, human readers, who are familiar with local imaging style, also perform better with internal patients [42▪▪].

Li *et al.* developed a T2W-based deep learning model (DLM) and compared it with VI-RADS in a retrospective, multicenter study [42▪▪]. Using VI-RADS 4 as the cutoff for muscle invasiveness, the DLM demonstrated a higher AUC for assessing MIBC and reduced processing time compared to VI-RADS, though not statistically significant. The DLM showed significant superiority when evaluating VI-RADS 2–3 lesions, likely because it considers features beyond those included in VI-RADS, thereby better discriminating uncertain lesions.

Lesion segmentation is the process by which suspicious lesions are highlighted in MRI radiomics methods. While manual segmentation, where the reader manually delineates the lesion, is subjective and time-consuming, semi-automatic and automatic methods, such as Convolutional Neural Networks, use machine learning and artificial intelligence algorithms to improve efficiency and accuracy [40]. Ye *et al.* found no significant difference in AUC between semi-automatic and manual segmentation performed on the same machine learning model in both internal and external validation cohorts, indicating that semi-automatic methods can reduce processing time and variability without sacrificing accuracy [43].

Machine learning algorithms have also shown potential in distinguishing VH components from pure UC. A model integrating T2W imaging and ADC features achieved an AUC of over 0.900 in detecting squamous differentiation (SD) in a retrospective cohort of MIBC patients. This is crucial as initial TURBT has only a 60% sensitivity for detecting SD and identifying SD can influence treatment decision [44▪].

To date, no studies have explored machine learning algorithms based on mpMRI, highlighting a significant gap and potential for future advancements in the field of radiomics.

MRI-GUIDED BIOPSY

Preliminary data from a study by Bryan *et al.* indicated that one-third of patients diagnosed with MIBC via MRI were subsequently found to have NMIBC following TURBT, highlighting the need for histological confirmation [45]. However, TURBT, which requires general anesthesia, carries risks like bleeding and tumor cells dissemination and it is not curative for muscle-invasive lesions, delaying definitive treatment [46]. In response, Eriksson *et al.* developed Urodrill, a less invasive MRI-based biopsy device used under local anesthesia and tested it before TURBT in patients with VI-RADS 4–5 lesions to assess its diagnostic accuracy. Preliminary findings indicate it detected muscular invasion in six out of nine cases. Furthermore, it allowed molecular characterization with RNA sequencing, enabling early identification of VH. Authors stated that a randomized clinical trial comparing Urodrill with the standard diagnostic pathway is warranted [46].

MRI FOR SYSTEMIC TREATMENT RESPONSE EVALUATION

Currently, RC is the standard of care following systemic chemotherapy for patients with MIBC [3]. The development of new peri-operative systemic therapies and bladder-sparing approaches has driven progress in treatment evaluation with MRI.

NEOADJUVANT CHEMOTHERAPY

Cisplatin-based chemotherapy is the preferred neoadjuvant treatment for cisplatin-eligible MIBC patients according to Galsky Criteria [4,5]. Currently, no predictive biomarkers guide decisions, however, certain MRI features may have predictive value.

bpMRI demonstrated higher accuracy than mpMRI in evaluating residual tumors following neoadjuvant chemotherapy (NAC), with significantly higher specificity due to fewer false positives from DCE [47▪▪]. In 2022, Pecoraro *et al.* developed the nacVI-RADS scoring system, which incorporates two mpMRI timepoints, at baseline and after NAC completion, to assess response to NAC. Like the conventional VI-RADS, scores range from 1 to 5, indicating complete, partial or no radiological response. In a preliminary report, nacVI-RADS successfully predicted pathological response in all 10 patients tested [48], and further studies are ongoing.

MULTI-MODALITY TREATMENT

Kimura *et al.* found that baseline VI-RADS scores in MIBC patients inversely correlated with pathological complete response (pCR) in a cohort of 78 patients treated with chemoRT followed by either radical or partial cystectomy. However, the accuracy of pretreatment VI-RADS in predicting pCR was unsatisfactory, with a value of 0.54 for VI-RADS $\leq$2 and 0.67 for VI-RADS $\leq$3. These findings suggest the need for further investigation into the newer nacVI-RADS method [48,49].

IMMUNOTHERAPY AND IMMUNE-BASED COMBINATIONS

Peri-operative immunotherapy for MIBC is an emerging research area, with limited data on the correlation between MRI biomarkers and treatment response. Necchi *et al.* were the first to report on peri-operative pembrolizumab activity in MIBC through the PURE-01 trial [6]. In a subsequent analysis involving 110 patients from PURE-01, who underwent mpMRI before and after neoadjuvant pembrolizumab, two VI-RADS features were associated with a major pathological response: pretreatment and posttreatment VI-RADS scores $\leq$3. The postpembrolizumab VI-RADS score $\leq$3 achieved the highest AUC (0.9), while the prepembrolizumab score correlated with a distinct baseline gene signature [50▪▪].

With the advent of immunotherapy-based combinations, numerous bladder-sparing trials have started. Accurate prediction of pCR is crucial for selecting candidates for organ preservation. However, there are only limited preliminary data on the potential role of MRI in this context. Galsky *et al.* examined the correlation between clinical CR (cCR) to a combination of gemcitabine, cisplatin, and nivolumab and the VI-RADS score from mpMRI after neoadjuvant therapy [51■]. cCR was defined as a negative bladder biopsy, negative urine cytology, and negative imaging for local and metastatic disease. While VI-RADS scores $\leq$2 were more frequent in cCR patients, 44% of non-cCR patients also had scores $\leq$2. Thus, while VI-RADS showed acceptable sensitivity, its low specificity suggests it cannot be solely relied upon to determine cCR [51■].

PROGNOSTIC MRI BIOMARKERS

Given the extended follow-up period required for patients with MIBC, there is less information available about prognosis compared to predictions of systemic therapy or radiotherapy responses. Nonetheless, understanding prognosis remains crucial, as clinical and pathological responses are surrogate markers for long-term outcomes.

According to Woo *et al.,* patients with both positive bpMRI and pathology after NAC exhibited worse disease-free survival (DFS) than those with negative results in either or both tests. Interestingly, no significant difference in DFS was observed between patients with both negative results and those with only one positive result [47■■].

The VI-RADS score assessed before RC has been suggested as a prognostic biomarker. In secondary analysis from the PURE-01 trial, a postpembrolizumab VI-RADS score of $\leq$3 was associated with longer PFS and OS [50■■]. A retrospective analysis of 219 patients by Zhuang *et al.*, indicated that a preoperative VI-RADS score $\geq$3 correlated with worse PFS and OS in NMIBC but not in MIBC. Instead, a VI-RADS score $\geq$4 was associated with poorer outcomes in MIBC [52■]. Two main limitations of VI-RADS as a prognostic tool were identified: its inability to predict outcomes in multiwall tumors and the lack of LN assessment, which could limit the detection of LN recurrence [52■].

Moreover, Fan *et al.* developed a radiomics model to identify high-risk MIBC patients, defined by the presence of TP53 mutations and low tumor mutational burden (TMB) in the RC specimen [53]. These patients exhibit significantly shorter 2-year DFS. Individuals with a history of immunotherapy and those who underwent chemotherapy or RT prior to MRI were excluded from the study. The model, based on manual segmentation and using features from T2WI, DWI, and ADC map, successfully predicted high-risk patients with an AUC greater than 0.900 in both the training and testing cohorts. Ongoing follow-up will provide data on 5-year DFS and OS [53].

CONCLUSION

MRI has the potential to enhance staging accuracy and prognostic capability in MIBC. While the VI-RADS score alone has demonstrated good accuracy in evaluating muscle invasiveness and predicting neoadjuvant treatment response, the integration of DWI sequences, biomarkers derived from ADC maps, morphological parameters, and machine learning algorithms could further enhance its performance. Conversely, avoiding DCE imaging does not appear to affect these outcomes. Despite these advancements, challenges persist in VH lesions staging, especially for less experienced readers. Future research should aim to refine these novel techniques and design prospective studies to evaluate long-term outcomes and MRI-based treatment decision-making. Given the expanding options for peri-operative treatment, selecting patients for more tailored therapies is crucial. Additionally, the ability to predict complete response to neoadjuvant treatment could facilitate the development of bladder-sparing strategies.

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Conflicts of interest

There are no conflicts of interest.

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