Evaluation of Vesical Imaging-Reporting and Data System (VI-RADS) scoring system in predicting muscle invasion of bladder cancer

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Background: To investigate the accuracy of using the Vesical Imaging-Reporting and Data System (VI-RADS) scoring system in prediction preoperative muscle invasion of bladder cancer.

Methods: The study retrospectively reviewed consecutive patients with bladder cancer who received multiparametric magnetic resonance imaging (MRI) between January 2017 and June 2019. Clinical and pathological parameters were collected. Bladder tumors were re-evaluated with 5-point VI-RADS scoring system by two experienced radiologists independently. The VI-RADS score was compared with postoperative pathology for each tumor for determining muscle invasion. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each VI-RADS cutoff.

Results: A total of 126 patients were included in analysis, with 82 patients received transurethral resection of bladder tumor (TURBt) while 44 underwent radical cystectomy. Fifty patients were muscle-invasive bladder cancer and 76 were non-muscle invasive tumor confirmed pathologically. VI-RADS score was only predictive factor to muscle invasion in multivariate analysis. Setting VI-RADS score greater than or equal to 4 reached the best sensitivity and specificity of 94.00% and 92.11%, with PPV and NPV value of 88.68% and 95.89%.

Conclusions: VI-RADS score system is a promising and effective modality in determining detrusor muscle invasion of bladder cancer preoperatively.

Keywords: Bladder cancer; Vesical Imaging-Reporting and Data System (VI-RADS); multiparametric magnetic resonance imaging (mpMRI); muscle invasion; prediction

Introduction

Bladder cancer is the most common cancer in the urinary system with high morbidity and relapse rate. It is the fourth common cancer in men and the seventh the most common malignancy in the world. It is estimated that 80,470 new cases and 17,670 deaths from bladder cancer will occur in the United States in 2019 (1,2). Non-muscle invasive bladder cancer could be treated by transurethral resection (TUR) while muscle invasive bladder cancer must receive radical cystectomy as golden standard (3,4). Therefore, preoperative accurate staging is vital to ensure correct treatment choice and prognosis prediction.

Magnetic resonance imaging (MRI) has long been recognized as one of the best imaging modalities for

its high spatial and contrast resolution. The state of art multiparametric MRI (mpMRI), a combination of T2-weighted, diffusion-weighted and dynamic gadolinium-enhanced imaging sequences provided value in detection, localization and staging in bladder cancer patients (5). Several meta-analyses showed MRI had a good diagnostic performance for prediction muscle invasion of bladder cancer (6,7). However, previous studies lack uniform MRI evaluation criteria and therefore limit its promotion as an excellent staging method for bladder cancer.

In the year 2018, the Vesical Imaging-Reporting and Data System (VI-RADS) was released as a standard imaging protocol and reporting criteria (including size, location, multiplicity, and morphology) for bladder mpMRI (8). The novel scoring system classifies the possibility of muscle invasion into five stages, which could provide a more meticulous distinction between clinical T1 and T2 stage lesions that used to be hard to distinguish by conventional MRI interpretation. Before it could be widely accepted and adopted, its clinical validation should be tested. In our study, we aimed to retrospectively evaluate the accuracy by using VI-RADS to discriminate the muscle invasion in bladder cancer patients.

Methods

Patient selection and data collection

We retrospectively reviewed the medical information of consecutive patients who were diagnosed as bladder cancer in Shanghai Tenth People's Hospital between January 2017 to June 2019. Clinicopathological information including age, gender, tumor stage, grade was collected for those who received mpMRI before surgery, either transurethral resection of bladder tumor (TURBt) or radical cystectomy. After surgery the resected tissue or organ was sent for pathological evaluation routinely. For TURBt, a standard resection of tumor was performed by two experienced hands (X Yao and Y Yan) with the depth to at least detrusor muscle layer. The including criteria was (I) mpMRI was performed within 2 weeks before surgery; (II) the pathology was urothelial carcinoma. Patients with treatment prior to mpMRI, such as TURBt within 3 months, biopsy within 2 weeks or cystoscopy within 3 days were excluded due to possible judgment interference. The study was approved by the institutional review board of Shanghai Tenth People's hospital (No. 2019-321).

MRI Protocol

All exams were performed using a 3-T MRI scanner (Magnetom Verio: Siemens, Erlangen, Germany), equipped with an 8-channel phased-array coil. Patients were instructed to start drinking 500–1,000 mL of water in 30 min before scanning to obtain an optimally full bladder (around 300 mL). The scanning protocol of the pelvis include the whole bladder, proximal urethra, pelvic nodes and prostate if the patient is a male. If the patient is a female, uterus, ovaries, fallopian tubes, and vagina need to be included.

Axial T1-weighted [repetition time/echo time (TR/TE), 600/11], turbo-spin-echo nonfat-suppressed T2-weighted in axial and coronal planes and turbo-spin-echo fat-suppressed T2-weighted in sagittal plane were performed.

Diffusion-weighted imaging (DWI) were performed with breathing-free spin-echo echo planar imaging (EPI) sequence in axial including high b value (800–1,000 s/mm^2) to display bladder cancer with high contrast to surrounding tissues;

Axial dynamic contrast-enhanced imaging (DCE) was performed after injection of gadopentetate administered at a dose of 0.1 mmol/kg at a rate of 1.5–2.0 mL/s. A 5–6 sets of CE images including three orthogonal planes were acquired 20–131 seconds after injection of contrast agents. Pre-contrast imaging was also needed.

Bladder MR imaging protocol parameters are summarized in *Table 1*.

MRI interpretation

MRI images were independently re-evaluated by two experienced radiologists (F Xu and T Xu), ignorant of the patients' medical history and pathological results, on the basis of 5-point VI-RADS scoring system. They have studied the VI-RADS algorithm for at least 1 week before practicing. Number of lesions, tumor size and their locations were recorded according to the schematic map (8). Hydronephrosis was defined as dilatation of the ureter due to bladder cancer obstruction at the time of surgery. When multiple lesions were presented, tumor size were measured as the diameter of the largest lesion, and VI-RADS score were considered as the highest one. When discordance was seen between two interpreters, consultation was conducted to reach consensus.

Table 1 MRI parameter setting

Parameters	TR (ms)	TE (ms)	Flip angle (degree)	FOV (cm)	Slice thickness (mm)	B value
T2WI cor	5,000	120	120	22	4	–
T2WI sag	4,000	85	140	30	5	–
T2WI tra	4,050	85	150	20	6	0, 50, 800, 1,000
DWI	4,500	72	90	26	6	–
DCE	3.9	1.4	9	26	3	–

MRI, magnetic resonance imaging; TR, repetition time; TE, echo time; FOV, field of view; T2WI, T2 weighted image; cor, coronal; sag, sagittal; tra, tranverse.

Statistical analysis

The cohort characteristics were described based on different VI-RADS score groups. Clinicopathological variables were compared dichotomized according to the muscle invasion status (stage T2 or higher). The Student t-test, Wilcoxon signed rank test, and Chi-square test were used to estimate differences of clinical and pathological characteristics between groups. Multivariate logistic regression model was performed to identify predictive factors of a muscle invasive tumor, using the variables statistically significant in univariate analysis. All statistical tests were two-tailed, with $P<0.05$ considered significant. Sensitivity, specificity, positive predictive value (PPV), and negative predictive (NPV) value were calculated using a 2×2 contingency table, and for each VI-RADS category used as cutoff. Statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 126 patients, with the mean age of 68 years old were enrolled in the study, including 104 males and 22 females. Eighty-two of them received TURBt while 44 underwent radical cystectomy. The number of patients with VI-RADS score of 1 to 5 were 16, 22, 35, 18 and 35 respectively. The characteristic of the cohort was listed in *Table 2*. Of all the patients, 76 were non-muscle invasive and the rest 50 were muscle invasive tumor. Patients with muscle invasive tumor had features of preoperative hydronephrosis, larger tumor size (≥3 cm), multifocality and higher VI-RADS score (all P<0.05) (*Table 3*). To figure out which factor remain the most vital in differentiating muscle invasive tumor, multivariate logistic analysis was performed and the result showed that only VI-RADS score

were statistically significant (P<0.001) (*Table 4*).

The ability of VI-RADS score to define the muscle invasive tumor were calculated according to different cut-off value. The sensitivity and specificity were 100.00% and 21.05% when the cut-off VI-RADS ≥2 was used. When the cut-off moves to VI-RADS ≥3, the sensitivity and specificity came to 100.00% and 50.00%, respectively. However, if VI-RADS score was set as ≥4, the sensitivity and specificity could be 94.00% and 92.11%, with PPV and NPV value were 88.68% and 95.89%. If the cut-off was set as VI-RADS ≥5, sensitivity fell to only 68.00% (*Table 5*).

The receiver operating characteristic (ROC) curve showed comparing with other parameters, VI-RADS score had the best ability to discriminate muscle invasive tumor (*Figure 1*). The area under curve (AUC) value was 0.966 (95% CI, 0.937 to 0.996) for VI-RADS, 0.681 (95% CI 0.580 to 0.781) for hydronephrosis, 0.879 (95% CI, 0.810 to 0.937) for tumor size, 0.392 (95% CI, 0.293 to 0.491) for number of lesions, respectively.

Discussion

In our retrospective study, we assessed the ability of mpMRI for detection of muscle invasion bladder cancer based on the newly released 5-point VI-RADS score. Overall, mpMPI showed a good performance with the accuracy of 92.8% when setting the cut-off value as VI-RADS 3.

To judge the muscle invasion would be crucial to decide the treatment strategy. Although several molecular panels have been figured out to predict muscle invasion in high risk non-muscle invasive tumor (9,10), the best of art currently was to perform TURBt, waiting for the pathological outcomes. However, the significant risk of residual tumor after primary TUR has been demonstrated (11). A systematic review demonstrated a 51% risk of disease

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Table 2 Characteristic of patients categorized to different VI-RADS score

Variable	Total	VI-RADS 1	VI-RADS 2	VI-RADS 3	VI-RADS 4	VI-RADS 5
Age, years						
Mean	68.0	66.4	68.0	67.6	67.2	68.2
Median [range]	67.6 [20–90]	65.5 [42–81]	68.5 [42–90]	68.0 [34–88]	65.5 [58–84]	70.0 [20–89]
Gender						
Male	104	12	18	29	17	28
Female	22	4	4	6	1	7
T stage						
Ta	31	13	9	9	0	0
T1	45	3	13	23	5	1
T2	19	0	0	3	10	6
T3	5	0	0	0	1	4
T4	26	0	0	0	2	24
Grade						
Low	24	9	9	6	0	0
High	102	7	13	29	18	35
Hydronephrosis						
Present	28	0	2	2	3	21
Absent	98	16	20	33	15	14
Size, cm						
<3	79	16	18	28	10	7
≥3	47	0	4	7	8	28
No. of lesions						
Single	78	9	16	15	11	27
Multiple	48	7	6	20	7	8
Location						
With neck or trigone	27	3	5	6	6	7
Without neck and trigone	99	13	17	29	12	28

VI-RADS, Vesical Imaging-Reporting and Data System.

persistence and an 8% risk of understaging in T1 tumors. Most of the residual lesions were detected at the original tumor location (12). This indicated mere TURBt cannot fully reflected the tumor de facto stage. Therefore, if preoperative imaging modality such as mpMRI could provide reliable staging information, the surgeon could be more confident in performing a curative TURBT.

Researches in the past decade have showed MRI as a useful method for the localization and assessment of bladder tumor extension and adjacent organ involvement. Dynamic contrast enhancing MRI are valuable indicators for assessing tumor angiogenic activity and tumor neovascularization (13). Diffusion-weighted MRI might have high specificity for the detection of suspected bladder cancer and invasion (14). To promote further generalization of mpMRI into research and clinical practice, an expert group recently issued a 5-point

Table 3 Characteristics of patients categorized to muscle invasiveness

Variables	Non-muscle invasive	Muscle-invasive	P value
Gender			0.726
Male	62	42	
Female	14	8	
Hydronephrosis			<0.001
Absent	70	28	
Present	6	22	
Location			0.534
With neck or trigone	16	11	
Without neck and trigone	60	39	
Size, cm			<0.001
<3	64	15	
≥3	12	35	
No. of lesions			0.009
Single	40	38	
Multiple	36	12	
VI-RADS			<0.001
1	16	0	
2	22	0	
3	32	3	
4	5	13	
5	1	34	

VI-RADS, Vesical Imaging-Reporting and Data System.

Table 4 Multivariate logistic regression model evaluating the risk factor of muscle invasiveness

Variable	HR	95% CI	P value
VI-RADS	25.090	6.969–90.334	<0.001
Hydronephrosis	0.343	0.036–3.241	0.350
Size	2.176	0.450–10.521	0.334
No. of lesions	0.261	0.054–1.274	0.097

VI-RADS, Vesical Imaging-Reporting and Data System; HR, hazard ratio; CI, confidence interval.

Table 5 Sensitivity, specificity, positive predict value and negative predict value for each cutoff

Variables	Sensitivity (%)	Specificity (%)	Positive predict value (%)	Negative predict value (%)
VI-RADS ≥2	100.00	21.05	45.45	100.00
VI-RADS ≥3	100.00	50.00	56.82	100.00
VI-RADS ≥4	94.00	92.11	88.68	95.89
VI-RADS ≥5	68.00	98.68	97.14	82.42

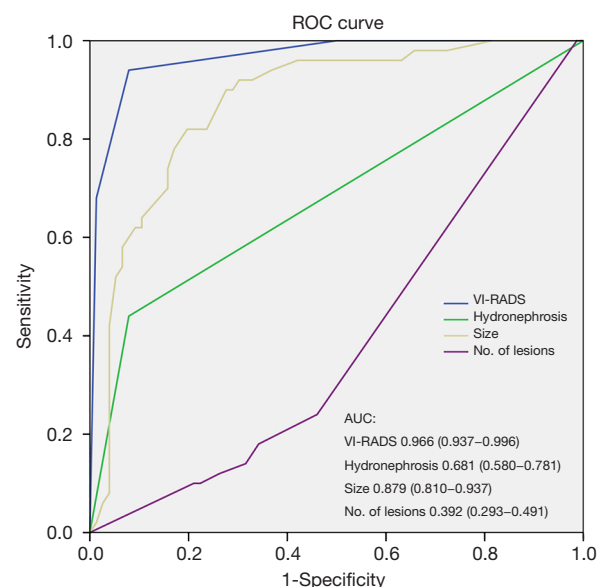VI-RADS, Vesical Imaging-Reporting and Data System.

Figure 1 Receiver operating characteristic (ROC) curve of different variables for predicting muscle-invasive bladder cancer. The area under curve and 95% confidence interval were showed in the lower right part (All P<0.05). AUC, area under the curve; VI-RADS, Vesical Imaging-Reporting and Data System.

scoring system in order to standardize its utility (8). The VI-RADS scoring system, however, is still in its early stage, and therefore demands further validation.

Our results showed that all lesions scored as VI-RADS 1 and 2 were verified as non-muscle invasive. For VI-RADS 3 lesions, 32 out of 35 were non-muscle invasive. When it comes to VI-RADS 4 and 5, the percentage of muscle invasive tumor were as high as 72.2% and 97.1%, respectively. Thus, when setting VI-RADS score greater than 3 as cutting off value, both the sensitivity and specificity could reach the best. To our knowledge, only several similar studies had investigated the discrimination ability of VI-RADS scoring system on muscle invasion,

most of which are small samples (15,16). Barchetti *et al.* including 78 patients showed VI-RADS score great than 3 had sensitivity of 77–82% and specificity 89–94% (16). Another largest study hitherto retrospectively reviewed 340 patients found that setting VI-RADS score great than 2 had best sensitivity and specificity of 87.1% and 96.5% respectively. For tumors scored as VI-RADS 3, 33.3% were confirmed to be non-muscle invasive cancer and 66.7% were confirmed to be muscle-invasive cancer (17). These indicate there is great uncertainty about the proportion of muscle invasion among VI-RADS 3 patients. Would VI-RADS score of 3 be a gray zone in defining the depth of tumor invasion warrant further researches.

Our study also analysis several preoperative factors supposed to be linked with muscle invasion, such as number of lesions, tumor size and hydronephrosis. Preoperative hydronephrosis were associated with advanced tumor stage and lymph node invasion (18). Tumor size great than or equal to 3 cm, multifocality were correlated with recurrence and progression for non-muscle invasive tumor to muscle invasion (19,20). Bladder neck and/or trigone involving were also predictive factors for progression and worse survival, possibly because of the proximity to vascular bed and thinness of lamina proper (21-23). However, together with VI-RADS score, these above factors were not statistically significant under multivariate analysis, indicating that preoperative mpMRI evaluation outweighed all the clinical variables in distinguishing muscle invasion.

Our study has limitations. First, it is a single-center, retrospective research with unavoidable selection bias. Patients who received mpMRI before operation were likely to bear heavier tumor burden and intended to receive radical cystectomy. Second, the image evaluation was performed by radiologists with expertise on urology. This could make its application in grass-roots hospital difficult for lack of experience. Third, 65% of pathology were evaluated by TURBt as golden standard, which might cause staging inaccuracy. Upstaging might occur in nearly one-third of patients who were initial Ta or T1 stage on TURBt after radical cystectomy (24). Whatever, our study provided one of the few evidences verifying the usefulness of VI-RADS score system.

Conclusions

To summarize, using VI-RADS score system in mpMRI could be a promising and effective method in differentiating muscle invasion of bladder cancer. Whether tumor of VI-RADS 3 invade detrusor muscle should be judge with caution. Therefore, further multi-centered, large research of its application is warrant.

Acknowledgments

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the institutional review board of Shanghai Tenth People's hospital (No. 2019-321).

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