VALIDATION OF VI-RADS FOR URINARY BLADDER CANCER ON MULTIPARAMETRIC 3T MRI AND HISTOPATHOLOGICAL CORRELATION

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CERTIFICATE

This is to certify that the thesis titled "VALIDATION OF VI-RADS FOR URINARY BLADDER CANCER ON MULTIPARAMETRIC 3T MRI AND HISTOPATHOLOGICAL CORRELATION" is the bonafide work of Dr. VATSALA VEERENDRA carried out under our guidance and supervision, in the Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur.

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DEDICATED TO MY PARENTS, &
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LIST OF ABBREVIATIONS

VI-RADS - Vesical Imaging-Reporting and Data System

mpMRI - Multi-parametric Magnetic Resonance Imaging

T2W - T2 Weighted

T1W - T1 Weighted

DCE - Dynamic Contrast Enhanced

DWI - Diffusion Weighted Image

ADC - Apparent-diffusion coefficient

CT - Computed Tomography

3T - Three Tesla

MIBC - Muscle invasive bladder cancer

NMIBC - Non Muscle invasive bladder cancer

TURBT- Transurethral resection of bladder tumour

AUC - Area under the ROC curve

ROC - Receiver operating characteristic

H&E - Hematoxylin & Eosin

VUJ - Vesico-ureteric junction

FOCUS-DWI - Field Of View Optimised And Constrained Undistorted Single Shot Diffusion Weighted Image

FOV - Field of View

HPE - Histopathological Examination

LUTS - Lower Urinary Tract Symptoms

KFT - Kidney function test

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INTRODUCTION

INTRODUCTION

Urinary bladder cancer is one of the most common malignancies of the urinary tract. It is a heterogeneous disease with a varying range of pathologic, cytogenetic, and natural history characteristics. Majority (~70%) of patients have superficial tumours that recur but are not life threatening whereas the rest have muscle-invasive disease that puts them at danger of dying from distant metastases (1).

Epidemiology

Bladder cancer is the world's eleventh most common cancer, with 573 278 new cases and 212 536 deaths estimated in 2020. Around 21,000 new cases of bladder cancer are diagnosed with approximately 11,000 resultant mortalities every year in India (2).

The incidence of urothelial carcinoma of the bladder varies considerably by geography, with the greatest rates in Western Europe and North America and the lowest rates in Eastern Europe and Asian countries (3).

Bladder cancer is the second most common malignancy in middle-aged and older adult males, following prostate cancer. Bladder cancer is most mainly encountered in those over the age of 50. A vast majority of bladder cancer patients (~73%) are above the age of 65 (4). The median age at diagnosis is 69 years in males and 71 years in females (5).

Smoking is one of the main risk factors for bladder cancer. Active smokers have a younger onset age than non-smokers. Males and females have the same relative risk for active vs non-smokers (4.0 and4.7, respectively), indicating converging smoking trends. Incidence rate in males is 9.5 whereas in females is 2.4 (6).

Environmental exposures account for most cases of bladder cancer. The surface epithelium (urothelium) that lines the mucosal surfaces of the entire urinary tract is exposed to potential carcinogens that are either excreted in the urine or activated from precursors in the urine by hydrolyzing enzymes.

Environmental risk factors may be implicated in large-scale population exposures as well. For example, high levels of arsenic in Antofagasta's drinking water have been linked to an increased risk of urinary tract cancer, which could explain part of the region's high incidence rates (7).

Workers in the painting, rubber, and aluminium industries are exposed to aromatic amines and other compounds that have been recognized as potentially carcinogenic to bladder (8).

Because of its link to schistosomiasis, a condition caused by parasitic worms (S. haematobium) in the urinary system found widespread in Egypt, bladder cancer has long been the most commonly diagnosed cancer there (8,9).

Inherited genetic factors are also thought to play a role in the development of bladder cancer (10).

Clinical features

Patients with bladder cancer classically present with painless hematuria (grossly visible or microscopic), although irritative voiding symptoms (frequency, urgency, dysuria) can be the initial manifestation.

The most common presenting symptom is hematuria, which is typically intermittent, gross, painless, and present throughout micturition. The likelihood of bladder cancer increases when the hematuria is gross (visible) rather than microscopic(11,12), with an incidence of bladder cancer of approximately 2 to 5 percent among patients with microscopic hematuria and 10 to 20 percent among those with gross hematuria (13–15).

The spectrum of urothelial bladder cancer at presentation includes non-muscle invasive, muscle invasive, and metastatic disease. The extent of disease reflects its natural history and determines treatment and prognosis.

Diagnosis

Cystoscopy is the gold standard for the initial diagnosis of bladder cancer. Cystoscopy is combined with urine cytology, which may detect lesions that might be missed at cystoscopy or lesions of the upper urinary tract (ureter, renal pelvis).

Patients with visible tumours are either biopsied or resected transurethrally to establish the histopathologic diagnosis and provide an initial assessment of the depth of invasion (mucosa, submucosa, muscularis propria).

Site-directed biopsies are indicated in patients with high-grade cancers and any suspicious erythematous and/or flat lesions. Biopsy of normal appearing urothelium and prostatic

urethra is indicated in patients with a positive urine cytology and no visually apparent tumour within the bladder.

TURBT combined with pelvic examination under anesthesia is the initial step in the staging evaluation and is required in order to assess the histologic grade and depth of invasion.

Imaging of the upper urinary tract by CT or MRI with intravenous contrast, or retrograde uretero-pyelography performed at the time of TURBT is indicated to rule out a second primary lesion, even for patients with an established diagnosis of urothelial carcinoma of the bladder.

When the initial evaluation identifies muscle-invasive disease, cross-sectional imaging with CT or MRI and laboratory evaluation is indicated to assess the extent of pelvic disease and exclude the presence of distant metastases.

Role of MRI-

The stages, grade, and biological potential of bladder cancer determine its management. Clinical, histological, and radiological examinations are used to gain an understanding of each of the above. This multimodal strategy decreases the possibility of an error from a single test, but it can create a staging uncertainty in case of conflicting results. Despite their seeming rigor, each modality relies on the operator, and individual concordance varies greatly. For example, surgeons' TURBT quality will vary, pathologists may have a disagreement on bladder cancer grading (10–29% discordance) and staging (15–56 % discordance), and radiologists may disagree on muscle invasion. However, excellent interobserver agreement has been reported VI-RADS in few studies (16).

- Because it does not use ionizing radiation, mpMRI is a safer and preferred modality to investigate people who are at risk for bladder cancer and for follow up imaging of patients to see their response to therapy.
- Advances in technology (both in software and hardware) have led to the development of mpMRI, which combines anatomic T2W with functional and physiologic assessment, including DWI and its derivative ADC maps, DCE MRI. **A** mpMRI has the potential to eliminate staging errors through improved anatomical visualization.
- Newer sequences like DWI gives both qualitative and quantitative information that depict changes in tumour cellularity and cell membrane integrity(17). Assessment of the reactive

tumour stalk morphology (distorted or absent stalk) on DWI has better diagnostic performance in predicting detrusor muscle invasion than conventional MRI (18).

Despite the growing use of mpMRI in local staging of bladder cancer, there was a lack of standardization in terms of protocol, reporting and aims of imaging. To overcome this VI-RADS was developed in July 2017. It began with a non-systematic literature review utilising Medline, PubMed, and Web of Science. The VI-RADS system was developed utilising a Delphi-style consensus process by various team members from Europe, North and South America and Asia, in a blend of electronic and face-to-face rounds. It was finally published in 2018 to standardize MRI acquisition and interpretation for urinary bladder cancer worldwide. MRI is less reliable to depict and stage carcinoma in situ (19). However, it is an excellent imaging modality to assess locoregional invasion.

An increasing body of data indicates that a positive positron emission tomography (PET) scan has a high predictive value for metastatic disease, and increasingly, fused CT-PET imaging is being used in the staging of patients (20).

Staging-

Table1: The American Joint Committee on Cancer (AJCC) TNM staging system for bladder cancer, 8th edition 2017 is as follows:-

T	**Primary Tumour**
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Urothelial carcinoma in situ: "flat tumour"
T1	Tumour invades lamina propria (subepithelial connective tissue)
T2 • pT2a • pT2b	Tumour invades muscularis propria Tumour invades superficial muscularis propria (inner half) Tumour invades deep muscularis propria (outer half)
T3 • pT3a • pT3b	Tumour invades perivesical tissue Microscopically Macroscopically
T4 • pT4a • pT4b	Extravesical tumour directly invades any of the following: Prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall Extravesical tumour invades prostatic stroma, seminal vesicles, uterus , vagina Extravesical tumour invades pelvic wall, abdominal wall

N	**Regional lymph nodes**
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (peri-vesical, obturator, internal and external iliac, or sacral lymph node metastasis)

N2	Multiple regional lymph node metastasis in the true pelvis (peri-vesical, obturator, internal and external iliac, or sacral lymph node metastasis)
N3	Lymph node metastasis to common iliac lymph nodes

M	Distant Metastasis
M0	No distant metastasis
M1 M1a M1b	Distant metastasis Distant metastasis limited to lymph nodes beyond the common iliacs Non-lymph-node distant metastases

Histological grade (G) For urothelial histologies, a low- and high-grade designation is used to match the current World Health Organisation/International Society of Urological Pathology (WHO/ISUP) recommended grading system:	
LG	Low grade
HG	High grade

For squamous cell carcinoma and adenocarcinoma, the following grading scheme is recommended:	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Table 2: AJCC Prognostic groups:

STAGE	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a T2b	N0 N0	M0 M0
Stage IIIA	T3a T3b T4a T1-T4a	N0 N0 N0 N1	M0 M0 M0 M0
Stage IIIB	T1-T4a	N2, N3	M0
Stage IVA	T4b Any T	Any N Any N	M0 M1a
Stage IVB	Any T	Any N	M1b

Source- nccn.org/professionals/physician_gls/pdf/bladder.pdf

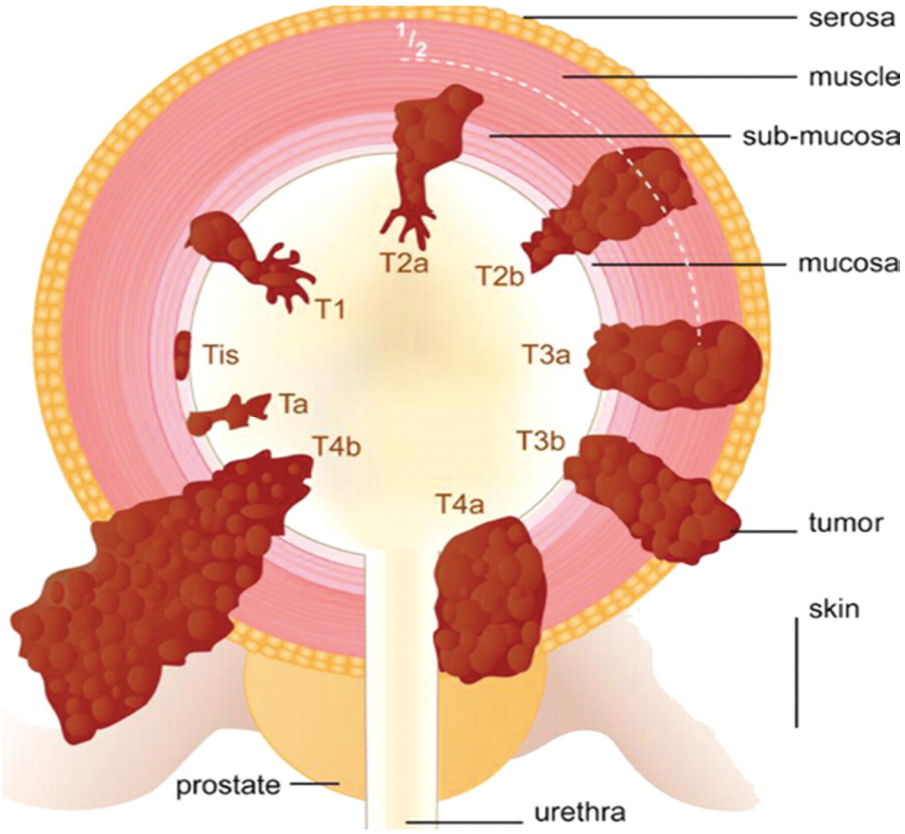


Figure 1: Drawing illustrates the layers of the bladder wall and tumour staging based on depth of invasion (17).

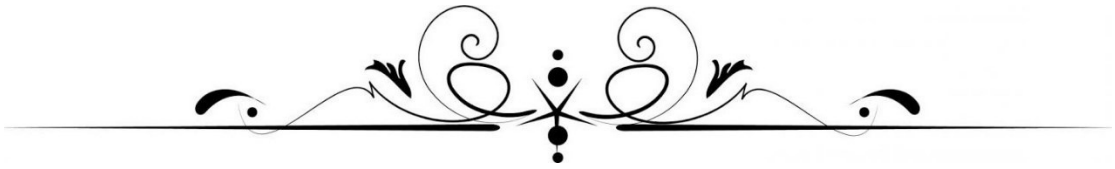
Treatment-

TURBT is the initial management of primary tumours that have not invaded the muscle (Ta and T1 lesions). Intravesical treatment may be required in patients who are at high risk of recurrence and/or progression. Following initial therapy, all patients are at risk for recurrence in the bladder and elsewhere in the urothelium and long-term observation is essential.

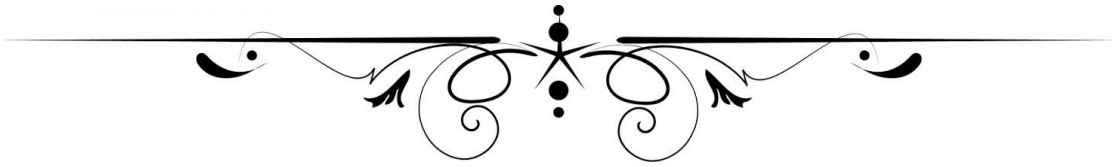
Patients with MIBC undergo a radical cystectomy with urine diversion as the treatment of choice. Neoadjuvant cisplatin-based chemotherapy is a part of the mainstay of care which increases overall survival. Adjuvant therapy may be advised for patients who underwent definitive surgery and are at a high risk of recurrence based on pathologic staging. Cisplatin-based chemotherapy and immunotherapy are two systemic medicines that are now available.

Trimodality treatment involving complete TURBT combined with radiation therapy with chemotherapy is offered as an alternative bladder-sparing strategy for individuals not keen to undergo radical cystectomy with urinary diversion for MIBC.

Combination cisplatin-based chemotherapy (such as methotrexate, vinblastine, doxorubicin, and cisplatin) or gemcitabine with cisplatin may prolong life and give symptomatic relief for patients with metastatic cancer. Checkpoint inhibitor immunotherapy is a therapeutic option for patients who are ineligible for platinum-based chemotherapy, as maintenance therapy after platinum-based chemotherapy, or who have treatment-resistant cancer (21).



REVIEW OF LITERATURE



REVIEW OF LITERATURE

Valeria Panebianco et al , created VI-RADS through consensus using existing literature. It describes standard imaging protocols and reporting criteria (including size, location, multiplicity, and morphology) for bladder mpMRI. They proposed a five-point VI-RADS score, derived using T2-weighted MRI, diffusion-weighted imaging, and dynamic contrast enhancement, which suggests the risks of muscle invasion. They included sample images to understand VI-RADS. While they did not advocate mpMRI for all patients with urinary bladder cancer, this imaging may compliment pathology or reduce radiation-based imaging. Bladder mpMRI may be most useful in patients with non–muscle-invasive cancers, in expediting radical treatment or for determining response to bladder-sparing approaches (19).

Hyung Kim et al , conducted a retrospective study which included 297 consecutive patients with 339 tumours who were previously diagnosed and subsequently underwent mpMRI (T2W,DW and DCE) between January 2015 and March 2019. Two radiologists assessed the score of muscle invasion using Cutoff values of $\geq$4 and $\geq$3 estimated from the best operating points of the areas under the receiver operating characteristic curve analyses using the Youden J statistic. The overall VI-RADS score showed 80.2% accuracy (272/339), with a cutoff value of $\geq$ 4, yielding 91.3% sensitivity (85/93), 76.0% specificity (187/246), 83.3% PPV (85/102), and 78.9% NPV (187/237). For an arbitrary overall score of $\geq$ 3 as the cutoff value, the accuracy was 63.7% (216/339); sensitivity, 94.6% (125/132); specificity, 43.9% (91/207); PPV, 51.6% (125/242); and NPV, 63.7% (91/97). An overall good performance of VI-RADS in the diagnosis of muscle-invasive tumours was obtained (22).

Huanjun Wang et al , conducted a retrospective study to determine the performance of the VI-RADS score in detecting muscle-invasive bladder cancer in a cohort of patients undergoing mpMRI before surgery. Both the VI-RADS score and its components were associated with muscle-invasive condition ($P < 0.001$). The area under the ROC curve for VIRADS for muscle invasion was 0.94 (95% confidence interval [CI]: 0.90, 0.98). The sensitivity and specificity of a VI-RADS score of 3 or greater were 87.1% (95% CI: 78%, 93%) and 96.5% (95% CI: 93%, 98%), respectively. The VI-RADS score was found to effectively define the likelihood of detrusor muscle invasion in bladder cancer and should be considered for evaluation of tumours prior to surgery (23).

Yoshiko Ueno et al , retrospectively evaluated data for 74 consecutive patients with bladder cancer who had undergone mpMRI before transurethral resection in a single institution from January 2010 to August 2018. Five readers assessed the probability of the presence of MIBCs using VI- RADS scores. The interobserver agreement was assessed by measuring intraclass correlation coefficients (ICC). The study demonstrated that interobserver agreement was excellent among five readers (ICC 0.85, 95% confidence interval 0.80-0.89) and the diagnostic performance of VI-RADS was represented as a pooled AUC of 0.90 (95% confidence interval 0.87–0.93) (16).

Jasmin Gmeiner et al, performed an IRB-approved retrospective, single-center, cross-sectional study which included 59 patients with BC who underwent 3 Tesla preoperative mpMRI including T2W, DWI and DCE) sequences. An independent evaluation according to VIRADS was performed by two radiologists in separate sessions, blinded to histological findings. Among bladder cancer patients, 26 (51%) were diagnosed as high grade and 14 (27.5%) as muscle invasive urothelial carcinomas in histological sections. The AUC for the overall VI-RADS score to predict muscle invasion was 0.986 (R1) and 0.992 (R2). The AUC to diagnose high grade bladder cancer was 0.908 (R1) and 0.905 (R2). There was no significance difference between the AUC of single parameters (T2w, DWI and DCE) compared to the total VI-RADS score ($P > 0.05$, respectively). Upon multivariate logistic regression, only the T2w VI-RADS score contributed independently to the diagnosis of high grade and muscle invasive bladder cancer ($P = 0.001$ (R1) and $P = 0.0022$ (R2) for high grade cancer; $P = 0.0007$ (R1) and $P = 0.0019$ (R2) for muscle invasiveness). The VI-RADS score was found to provide high diagnostic accuracy to diagnose high grade and muscle invasive BC. However, mpMRI parameters provided overlapping information and thus a biparametric, contrast free image acquisition was suggested without sacrificing diagnostic accuracy (24).

Kumawat Ghanshyam et al, conducted prospective cross-sectional study from March 2019 to March 2020. A total of 86 patients with the provisional diagnosis of bladder tumour were considered for final evaluation who underwent a 3T mpMRI to obtain a VIRADS score before they underwent a TURBT. The obtained data was correlated with final biopsy report for analysing muscle invasiveness of the tumour. A cut off of VIRADS$\geq$4 for prediction of detrusor muscle invasion yielded a sensitivity of 79.4%, specificity of 94.2%, positive predictive value (PPV) of 90%, negative predictive value(NPV) of 87.5%, and diagnostic accuracy of 86.37%. A cut off of VIRADS$\geq$3 for prediction of detrusor muscle invasion yielded a sensitivity of 91.2%, specificity of 78.8%, PPV of 73.8%, NPV of93.2%, and

accuracy of 83.7%. The AUC was 0.922 (95% confidence interval: 0.862-0.983). VIRADS score appeared to be an excellent and effective preoperative radiological tool for the prediction of detrusor muscle invasion in bladder cancer (25).

Ziyong Wang et al, performed a retrospective study on a total of 220 patients with bladder cancer from January 2017 to June 2019 who underwent mpMRI. Then, two radiologists with equivalent qualifications gave their diagnoses and scoring on the basis of the VI-RADS system followed by comparison with the pathological results after surgery. Among them, the pathological results were 113 cases of MIBC and 107 cases of non-MIBC. The results showed that there was a positive correlation between the pathological results and VI-RADS score ($r = 0.821$, $P < 0.05$). The AUC of the VI-RADS score was 0.960 (95% CI: 0.937, 0.983). When the VI-RADS score was above 3, the sensitivity, specificity and accuracy of predicting muscle-invasive bladder cancer were 82.3, 95.3 and 88.64%, respectively.

Thus proving the VI-RADS scoring system to be of good diagnostic value in predicting the degree of tumour invasion and guiding clinical decision-making and management (26).

Giovanni Barchetti et al, carried out a a retrospective study between September 2017 and July 2018 on 78 patients referred for suspected bladder cancer who underwent mpMRI prior to TURBT. All mpMRI were reviewed by two radiologists, who scored each lesion according to VI-RADS. In the final analysis, 75 patients were included, 53 with non-MIBC and 22 with MIBC. Sensitivity and specificity were 91% and 89% for reader 1 and 82% and 85% for reader 2 respectively when the cut off VI-RADS > 2 was used to define MIBC. At the same cut off, PPV and NPV were 77% and 96% for reader 1 and 69% and 92% for reader 2. When the cut off VI-RADS > 3 was used, sensitivity and specificity were 82% and 94% for reader 1 and 77% and 89% for reader 2. Corresponding PPV and NPV were 86% and 93% for reader 1 and 74% and 91% for reader 2. AUC was 0.926 and 0.873 for reader 1 and 2 respectively. Inter-reader agreement was good for the overall score ($K = 0.731$). Thus, proving VI-RADS to be accurate in differentiating MIBC from non-MIBC with overall good inter-reader agreement (27).

Francesco Del Giudice et al, conducted a prospective study on patients with suspected bladder cancer. They were offered mpMRI before TURBT. TURBT reports were then compared with preoperative VI-RADS scores to assess accuracy of mpMRI for discriminating between NMIBC and MIBC. High risk-Non MIBC Re-TURBT reports were also compared with preoperatively recorded VI-RADS scores to assess mpMRI accuracy in

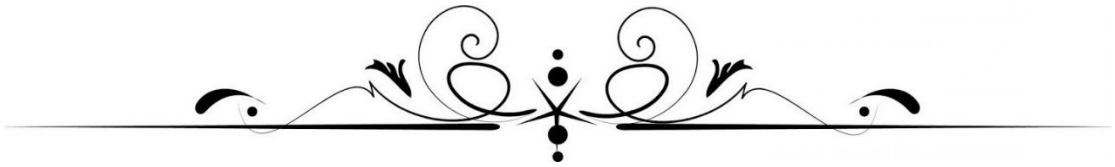
predicting Re-TURBT outcomes. A total of 231 patients were enrolled. mpMRI showed sensitivity, specificity, PPV, and NPV for discriminating NMIBC from MIBC at initial TURBT of 91.9% (95% confidence interval [CI]: 82.2–97.3), 91.1% (95% CI: 85.8– 94.9), 77.5% (95% CI: 65.8–86.7), and 97.1% (95% CI: 93.3–99.1), respectively. The AUC was 0.94 (95% CI: 0.91–0.97). Among High risk-Non MIBC patients (n = 114), mpMRI before TURBT showed sensitivity, specificity, PPV, and NPV of 85% (95% CI: 62.1–96.8), 93.6% (95% CI: 86.6–97.6), 74.5% (95% CI: 52.4–90.1), and 96.6% (95% CI: 90.5–99.3) respectively, to identify patients with MIBC at Re-TURBT. The AUC was 0.93 (95% CI: 0.87–0.97). Hence, confirming the accuracy of VI-RADS for discriminating between NMIBC and MIBC. Also it was seen that in future VI-RADS could improve the selection of candidates for Re-TURBT within High risk-Non MIBC patients (28).

Marwa Makboul et al, did a prospective study on 50 patients diagnosed as cancer bladder who were enrolled in this study and underwent mpMRI. All data were regrouped to evaluate the accuracy of each separate sequence and mp-MRI in distinguishing non-muscle invasive from muscle-invasive tumours, with VI-RADS score application and comparison with pathological findings, then interobserver agreement for detection of muscle invasion was calculated. Diagnostic accuracy of mpMRI in differentiation between MIBC and non-MIBC was (84%) with highest sensitivity (78%), very good agreement between mpMRI and histopathological data ($k = 0.87$), and highest AUC reaching 0.83, DCE-MRI sequence showed the highest accuracy in muscle invasion detection by (88%), with highest AUC 0.83. Diagnostic accuracy of VI-RADS score in detection of muscle invasion was 84%, with specificity and negative predictive value of 88% and AUC was 0.83. Interobserver agreement was strong with regards to diagnostic performance of mp-MRI and VI-RADS scoring for detection of muscle invasion reaching ($K = 0.82, p < 0.001$) and ($K = 0.87, p < 0.001$) respectively.

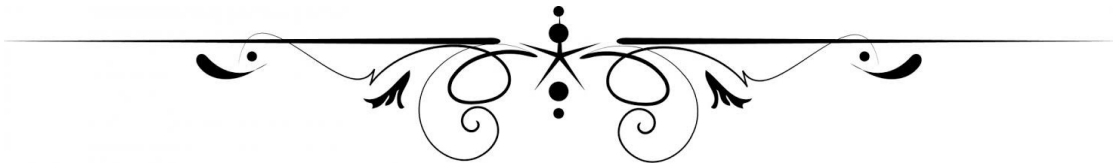
As a conclusion, mpMRI and VI-RADS scoring was considered as comprehensive and effective tool for determination of muscle invasion in cases of urinary bladder cancer (29).

Abdul Razik et al, evaluated the role of DWI in comparison with conventional MRI in determining the presence of muscle invasion in urinary bladder cancer through a prospective study conducted on 56 patients who presented with bladder cancer. After excluding 16 patients, 40 patients were finally included in the study who underwent MRI at 3T. Assessment of tumour morphology (papillary versus non-papillary), underlying bladder wall

distensibility, and perivesical fat infiltration was done on T2WI along with tumour stalk morphology on DWI. All the evaluated properties were found with significantly higher frequency in muscle-invasive tumours ($p < 0.001$). The finding of absent or distorted stalk on DWI had the highest sensitivity (87.5%) and specificity (97.6%). Conventional imaging attributes of non-papillary stalk morphology, restricted distension of underlying bladder wall, perivesical fat infiltration, as well as the previous DWI criterion were less sensitive (56.3%, 68.8%, 56.3% and 56.3%, respectively) in predicting muscle invasion. Thus, proving DWI to be better than conventional MRI sequences in prediction of detrusor muscle invasion in cases of bladder cancer (18).



HYPOTHESIS



HYPOTHESIS

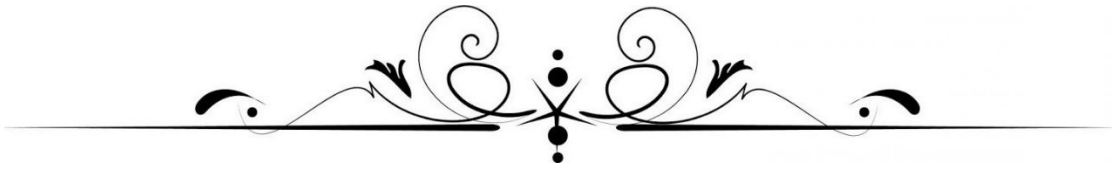
Multi-parametric MRI improves the diagnostic accuracy of muscle invasion in patients with urinary bladder cancer.

AIM & OBJECTIVES

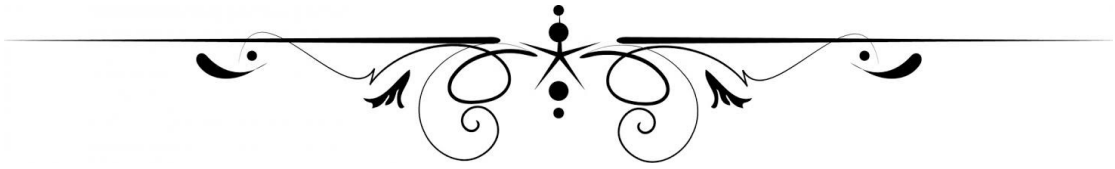
AIM AND OBJECTIVES

AIM: Validation of VI-RADS for urinary bladder cancer on 3T MRI.

OBJECTIVE: To assess the VI-RADS for the diagnosis of urinary bladder cancer and histopathological correlation in patients with suspected bladder cancer.



MATERIALS & METHODS



MATERIALS AND METHODS

STUDY DESIGN: Prospective study.

STUDY DURATION: One and half years.

STUDY SITE: Department of Diagnostic and Interventional Radiology, AIIMS Jodhpur.

STUDY GROUP: Suspected cases of urinary bladder cancer, visiting All India Institute of Medical Sciences (AIIMS), Jodhpur, who fulfilled the following criteria were enrolled in the study:

a) Inclusion Criteria:

1. All patients suspected of having urinary bladder cancer who had undergone bladder multiparametric MRI.
2. All patients who had undergone histopathological examination from bladder tumour after MRI.

b) Exclusion Criteria:

1. Age < 18 years.
2. Lack of histopathologic findings (unfit for anaesthesia, loss to follow up, etc)
3. Non-consenting patient.
4. MRI contraindications.

ENROLLMENT: Subjects who satisfied the above eligibility criteria were approached for participation in the study. An Information Sheet providing the details of the study was provided and the nature of the study was verbally explained. Written informed consent was obtained. Enrolment, recording of baseline information was done after written informed consent was obtained.

MULTIPARAMETRIC MRI PROTOCOL:

Patient preparation – patients were advised to take a low residue diet one night before. To reduce motion artefacts from bowel peristalsis, the use of an antispasmodic agent, a single dose of 20 mg scopolamine butyl bromide was given to the eligible patient, 20min before the procedure to reduce the bowel motility and related motion artefacts. Patients were required to

urinate 2 hours before the MRI examination, with no drinking or urination thereafter until the MRI examination was completed. Foley's catheter was clamped in a few patients for adequate distention of the urinary bladder.

MRI was performed in supine position on 3T clinical MRI system (GE Discovery MR 750 w 3T SYSTEM USA).

Sequences:

1. T2 weighted
2. DWI sequences (at b values 50,400 and 800 s/mm^2) and FOCUS-DWI in orthogonal plane (at b values 50,400 and 800 s/mm^2)
3. DCE MRI
4. T1 weighted

Technical Specifications:

All images included the whole urinary bladder, proximal urethra, pelvic nodes, and prostate if the patient is a male. In females, adjacent pelvic viscera (uterus, ovaries, fallopian tubes, and vagina) were also included.

High spatial resolution was achieved with the use of a phased-array external surface coil, thin sections (3-4 mm), and a large matrix. Preliminary localizer sequences were used to evaluate for appropriate coil placement and bladder distention.

1. T2-Weighted (T2W): High-resolution T2WI is required for accurate assessment of T staging. Fast spin-echo non-fat-suppressed T2WI (3500-4500 /91- 131) was acquired in three different planes (axial, coronal, and sagittal). Slice thickness of 3–4 mm with a small FOV and a large matrix was used to increase spatial resolution while maintaining the signal-to-noise ratio.

2. Diffusion-Weighted Imaging (DWI): The Brownian motion of water molecules is used in DWI sequences to provide information on tumour cellularity and cell membrane integrity. Free-breathing with a water-excited single-shot spin echo echo-planar sequence in axial and oblique sagittal plane perpendicular to tumour base was obtained. It is difficult to understand the anatomical details on DWI because the background signal is suppressed. Thus, for interpreting DWI, the locations of restriction should match or be close to the structures seen

on T2W imaging. To obtain an appropriate ADC map, at least two b value sequences are required, one of which should have a high b value of 800–1000 s/mm^2 to provide good contrast resolution relative to neighbouring tissues. The ADC may predict the histologic grade of bladder cancer in part (30).

Additional acquisition of FOCUS-DWI in a plane perpendicular to the tumour was acquired for better assessment of muscle invasion. FOCUS-DWI uses a small FOV as compared to conventional DWI with resultant higher and more consistent image quality, with non-inferior quantitative ADC values, making it an effective replacement in clinical practise. It overcomes the high sensitivity of conventional DWI to distortion caused by susceptibility mismatches generating magnetic field inhomogeneity (31).

3. Dynamic Contrast-Enhanced (DCE) MRI: DCE images were acquired using axial or sagittal fat suppressed three dimensional volumetric spoiled gradient-echo sequence before and after intravenous administration of 0.1 mmol/kg of standard gadolinium based contrast agent at the rate of 2 ml/sec up to total volume of 20 ml, followed by administration of 20 ml normal saline to flush the tubing. The initial contrast images were acquired at 30 seconds after initiating injection and followed by the same sequence 6 times at every 30 sec interval to depict an early enhancement of the inner layer followed by tumour enhancement. Late phase enhancement is not utilised for T staging owing to poor signal contrast among the inner, outer layers, and tumour.
Patients with deranged KFT underwent all sequences except DCE MRI.

4. Spin-echo T1-weighted (T1W) imaging was used to identify haemorrhage and clot in the bladder and bone metastasis.

Table 3: MRI parameters for image acquisition:-

Parameter Setting at 3.0 T	T2W axial	T2W coronal	T2W sagittal	DWI axial	FOCUS-DWI in orthogonal plane	DCE axial	T1W axial
TR (ms)	8800	13000	11300	2500 to 5300	4500 to 5050	3.8	820
TE (ms)	110	110	110	80	80	1.2	10
Flip angle(degree)	160	160	160	-	-	15	111
FOV (cm)	23	23	23	32	20	27	24
Matrix	400 x 256-320	288 x 220-290	300 x 300	128x 128	100 x 60-80	192 x 192	320 x 224
Slice thickness (mm)	3-4	3-4	3-4	3-4	3-4	1	3
Slice gap (mm)	0-0.4	0-0.4	0-0.4	0.3-0.4	0-0.3	0	3
Number of excitations	2-5	2-5	2-5	4-10	2-5	1	2
b values	-	-	-	50-400-800 s/mm^2	50-400-800 s/mm^2	-	-

Normal Anatomy Of The Urinary Bladder:

The urinary bladder is predominantly an extraperitoneal structure, with only the superior aspect of the bladder (bladder dome) covered by peritoneum. The inter-ureteric ridge joins both the ureteric orifices at the ureterovesical junction. The ureterovesical junction and the urethra are at the corners of the bladder trigone, which is a triangular area on the inferior wall of bladder. Moving outwards from the lumen following four layers are seen in the bladder wall- (a) the urothelium, which lines the bladder lumen; (b) the highly vascular lamina propria (submucosa); (c) the muscularis propria; and (d) the outermost serosa (17). [Figure 3]

MRI Semeiotics:

The detrusor muscle appears as a low-signal-intensity line on T2WI and as an intermediate-signal-intensity line on DWI and ADC maps, whereas the inner layer, which is made up of urothelium and lamina propria, is not visible using any of these techniques. On DCE-MRI, the inner layer shows early contrast enhancement and appears as a hyperintense line; the outer layers (muscularis propria) generally demonstrate a late and gradual enhancement.

MRI cannot completely describe the stratification of the bladder wall. The urothelium is very thin in comparison to the bladder wall's complete thickness. The thickness of the highly vascular lamina propria changes depending on the degree of bladder distention. For bladder cancer staging, the muscularis propria is a significant marker. Its distinction from the interior mucosa helps us classify bladder cancer, which eventually influences therapeutic therapy. The muscular layer of the bladder, also known as detrusor muscle, is made up of a complicated network of interlacing smooth muscle fibres which are oriented longitudinally and seldom evident separately. Due to the presence of fat tissue in between muscle fibres in the muscularis propria itself, the demarcation from the outermost layer of peri-vesical fat tissue is not well defined.

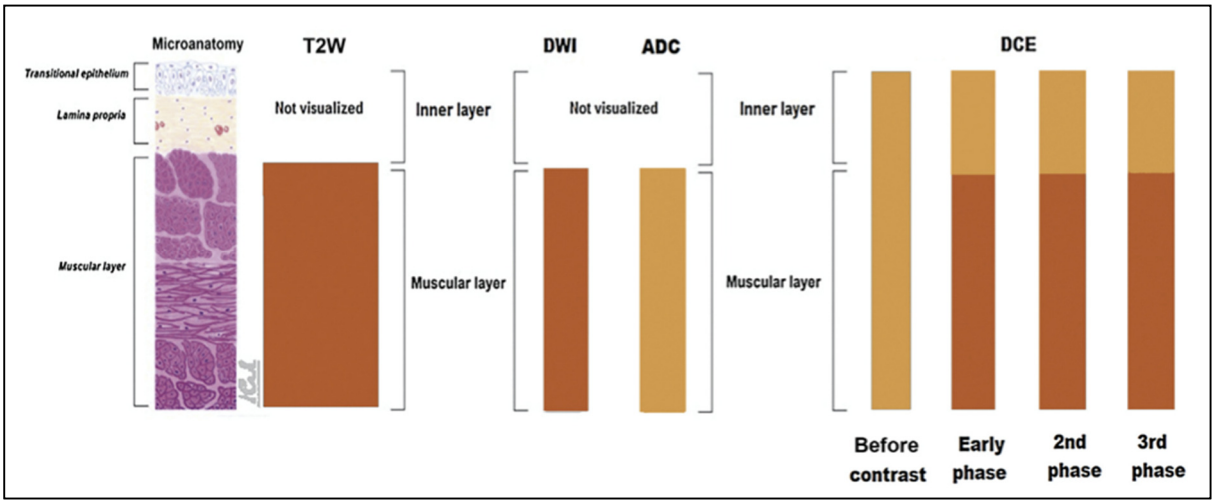


Figure 2– Schematic appearance of bladder wall anatomy and respective MRI appearances at T2WI, DWI, ADC, and DCE MRI. T2W images show low SI of muscular layer, and cannot visualize/discriminate the urothelium and the lamina propria. At DWI, the muscular layer appears as an intermediate SI line, while inner layer is not visualized; ADC maps shows intermediate signal of muscular layer compared with high signal of urine. The bladder wall components change appearance during the phases of DCE imaging (19).

It is difficult to distinguish the muscularis propria from the outermost layer in presence of certain pathologic features like dense fibrosis (seen in neoplastic growth), inflammatory processes, and tumour cells within the muscularis propria.

RECORDING BLADDER LESIONS:

- **MRI definition of the lesion:** Intravesical lesions with intermediate signal intensity as compared to urine and muscle on T2WI, a high signal intensity on DWI, a low signal intensity on corresponding ADC map and early postcontrast enhancement on DCE were documented as suspicious lesions.

- **Mapping**: According to literature, the trigone, bladder neck, and ureteral orifice regions account for about one-third of new tumours, with the lateral walls accounting for a rather higher percentage. Muscle invasion is usually more common in bladder neck tumours than in other malignancies (19). Multiple tumours were documented with description of tumour with the greatest disease load (largest) and with the most advanced stage on MR imaging.

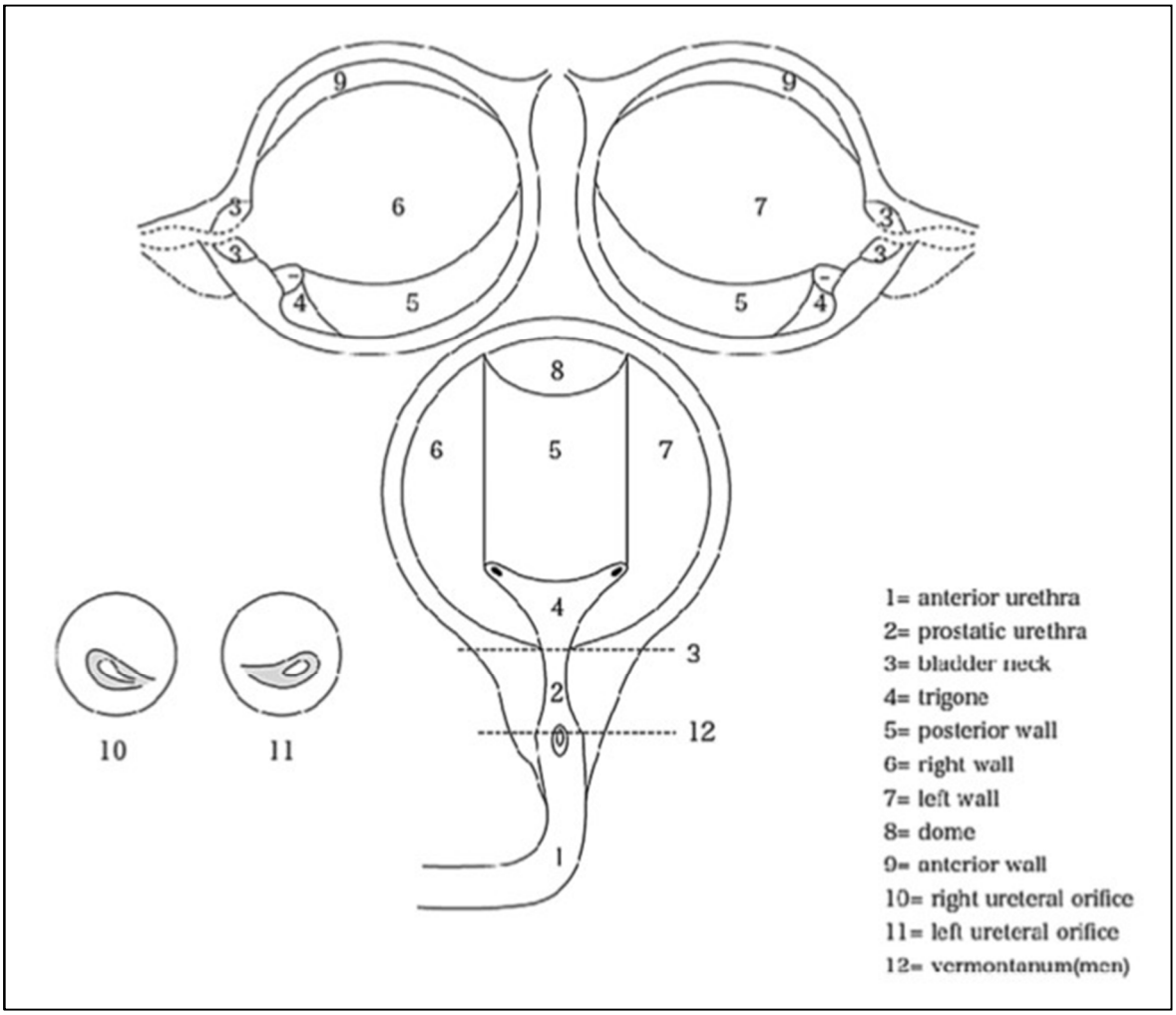


Figure 3: Schematic map used to record the tumour location (19).

- **Lesion Morphology:** Tumours were categorised into endophytic (showing intramural growth), exophytic (showing endoluminal growth), flat (showing non-mass effect) and mixed forms. The exophytic form were further divided into papillary broad based or pedunculated morphology. Papillary tumours with a stalk, as opposed to papillary tumours without a stalk or broad sessile malignancies, have a better prognosis. T1 stage tumours with stalks are larger (median diameter 21.5 mm) than those without stalks (13 mm) (19).

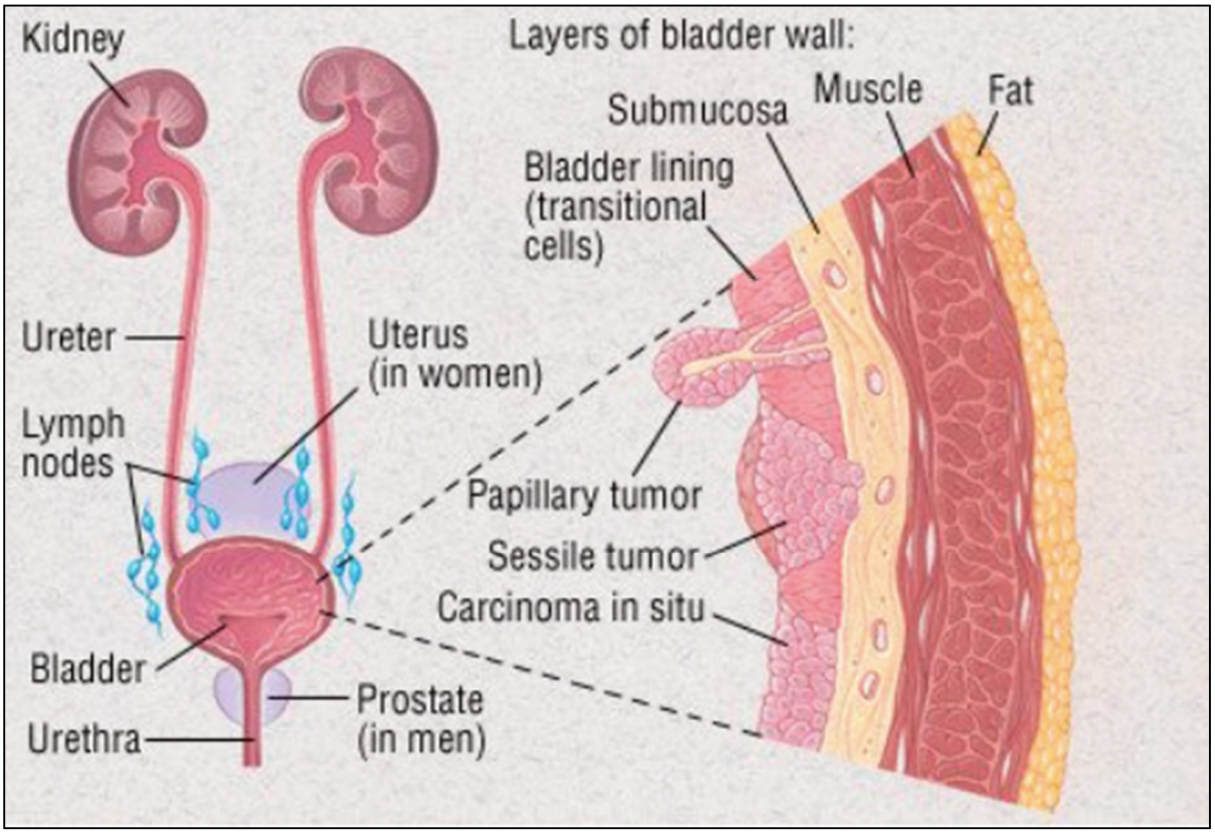


Figure 4: Schematic diagram showing histological layers of bladder along with various tumour morphology (Source-https://www.drugs.com/health-guide/bladder-cancer.html)

MRI SCORING and INTERPRETATION:

T2WI Assessment: On T2W images, muscle appears hypointense. Considering this as the initial primary MRI finding, any interruption in this muscle layer hypointensity was recognised as muscle invasion.

- Structural category (SC) 1: continuous low signal intensity line indicating the intact muscularis propria (lesion <1 cm; exophytic tumour with or without stalk and/or thickened inner layer).
- SC 2: continuous low signal intensity line indicating the intact muscularis propria (lesion >1 cm; exophytic tumour with stalk and/or high signal intensity thickened inner layer, if present, or sessile/broad-based tumour with high signal intensity thickened inner layer, if present).

- SC 3: absence of category 2 features with the presence of an exophytic tumour without stalk, or a sessile/broad-based tumour without a high signal intensity inner layer thickening but no obvious disruption of the low signal intensity muscularis propria.
- SC 4: disruption of the low signal intensity line, implying that the intermediate signal intensity tumour tissue has spread to the muscularis propria.
- SC 5: intermediate signal intensity tumour with trans-mural extension into the bladder wall and extravesical tissues, indicating the involvement of complete bladder wall and extravesical tissues.

Restricted wall distention is a conventional MRI feature which refers to the tethering of urinary bladder wall underneath the tumour. Restricted wall distention along with perivesical fat infiltration has shown significant association with histopathology. However, these findings may not be specific owing to tumour-induced reactive inflammatory and desmoplastic changes, as well as vascular proliferation which may mimic such imaging findings (18).

DWI Assessment: On the DWI, the tumour is hyperintense, while on the ADC map, it is hypointense. Muscularis propria may have intermediate signal intensity on DWI, whereas the stalk and inner layer show low signal intensity.

- DW category 1: continuous intermediate signal intensity of muscularis propria on DWI (lesion <1 cm, hyperintense on DWI and hypointense on ADC map, with or without stalk and/or low signal intensity inner layer thickening on DWI).
- DW category 2: continuous intermediate signal intensity of muscularis propria on DWI (lesion >1 cm, hyperintense on DWI and hypointense on ADC map, with low signal intensity stalk and/or low signal intensity inner layer thickening on DWI, or broad-based/ sessile tumour with low/intermediate signal intensity inner layer thickening on DWI).
- DW category 3: no category 2 findings (lesions corresponding to T2 category 3 findings) but without obvious disruption of low signal intensity muscularis propria.
- DW category 4: tumour with focal extension into muscularis propria showing high signal intensity on DWI and corresponding low signal intensity on ADC map.
- DW category 5: high signal intensity tumour on DWI with corresponding low signal intensity on ADC map extending to the entire bladder wall and extravesical fat.

The presence of low signal intensity tumour stalk on DWI favours the likelihood of NMIBC. The tumour stalk consists of submucosa with edema and fibrosis. An “inchworm sign” is seen in typical pedunculated papillary bladder cancers where a C-shaped high signal intensity area of tumour component is seen with a low signal intensity submucosal stalk.

Role of DWI -

- Detection and local staging of bladder cancer-by means of visual image interpretation [Figure 6] and quantitative ADC value analysis.
- ADC value has a role in characterising bladder cancer.
- ADC value helps in predicting the prognosis of bladder cancer.
- DWI helps in assessing post treatment response assessment and follow up.

Pitfalls of DWI-

- Inherent limitations in DWI interpretation due to relatively poor spatial resolution, a lack of cancer specificity, and a lack of standardised image acquisition protocols and data analysis procedures, which limit the use of DWI and the reproducibility of apparent diffusion coefficient values (32).
- The DWI signal is not limited to cancer cells; inflammatory changes and granulomas exhibit high signal intensity as well, simulating malignant tissue (21).
- Inadequate bladder distension, artefacts, bladder wall thinness, malignant mimickers of normal bladder wall and benign lesions, and in situ catheter can all complicate diagnosis and therapy monitoring (32). Thus, post TURBT changes may lead to false positive diffusion restriction (33).

DCE Assessment: When it comes to DCE MRI, both the tumour and inner layer show early enhancement at the same time and grade. In the early stages, the muscularis propria shows no enhancement to be identified as a low signal intensity line beneath the tumour. Based on the above features following categories are considered on DCE:-

- CE category 1: muscularis propria showing no early enhancement (lesions correlating to SC 1 findings).
- CE category 2: early inner layer enhancement with no early enhancement of muscularis propria (lesions correlating to SC 2 findings).
- CE category 3: no category 2 findings (lesions correlating to SC category 3 findings), but no obvious disruption of the low signal intensity muscularis propria.

- CE category 4: early tumour enhancement with focal extension into the muscularis propria.
- CE category 5: early enhancement of the tumour extending through bladder wall as well as extravesical fat.

DCE was not done in patients with deranged KFT (n=5) in our study. Only DCE-MRI can distinguish between T2a and T2b stages. When ADC and DCE-MRI are used simultaneously, the results are more accurate, hence a combination strategy was recommended (34).

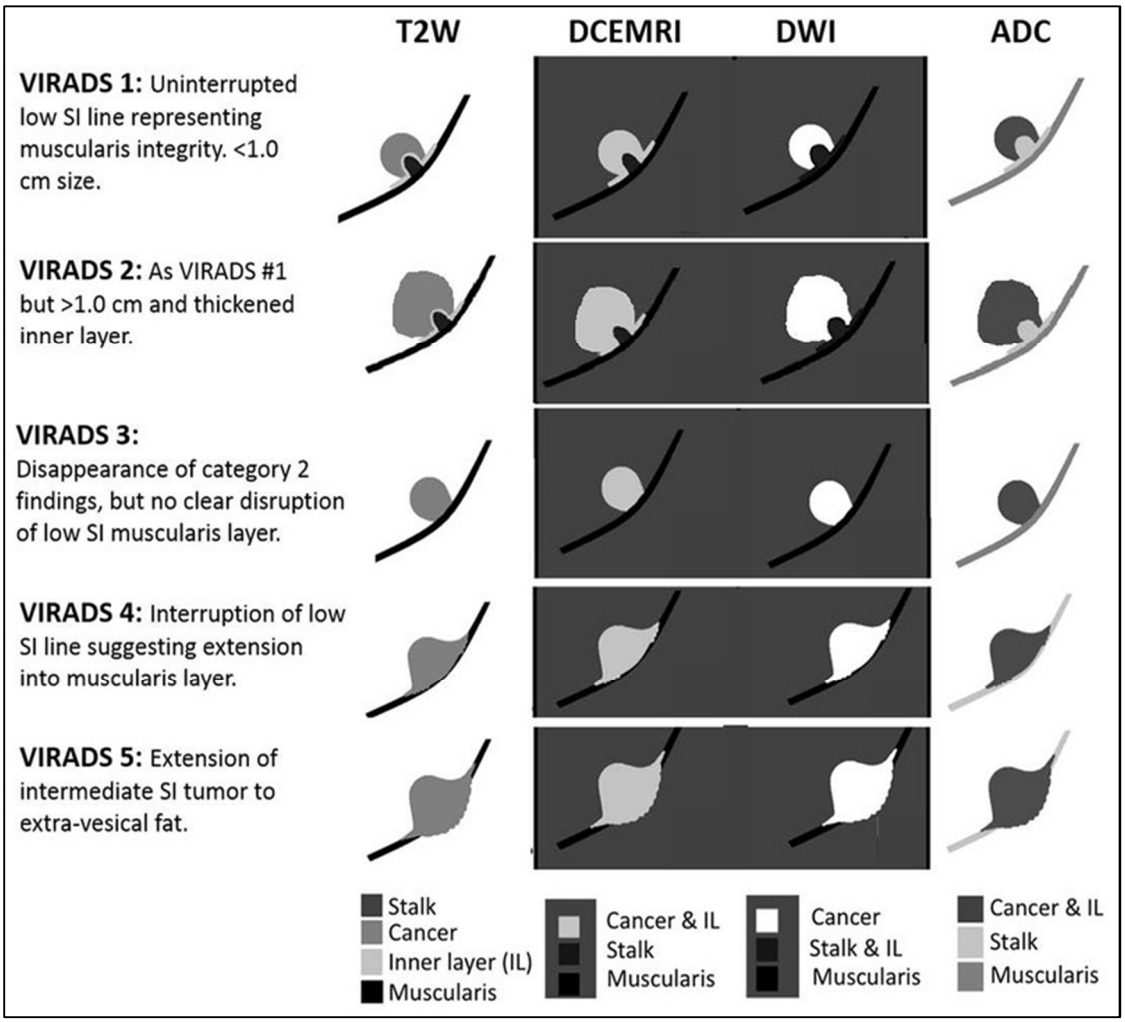


Figure 5: Schematic illustration of mpMRI appearances of VI-RADS scores 1–5 using T2, DCE MRI, DWI (19).

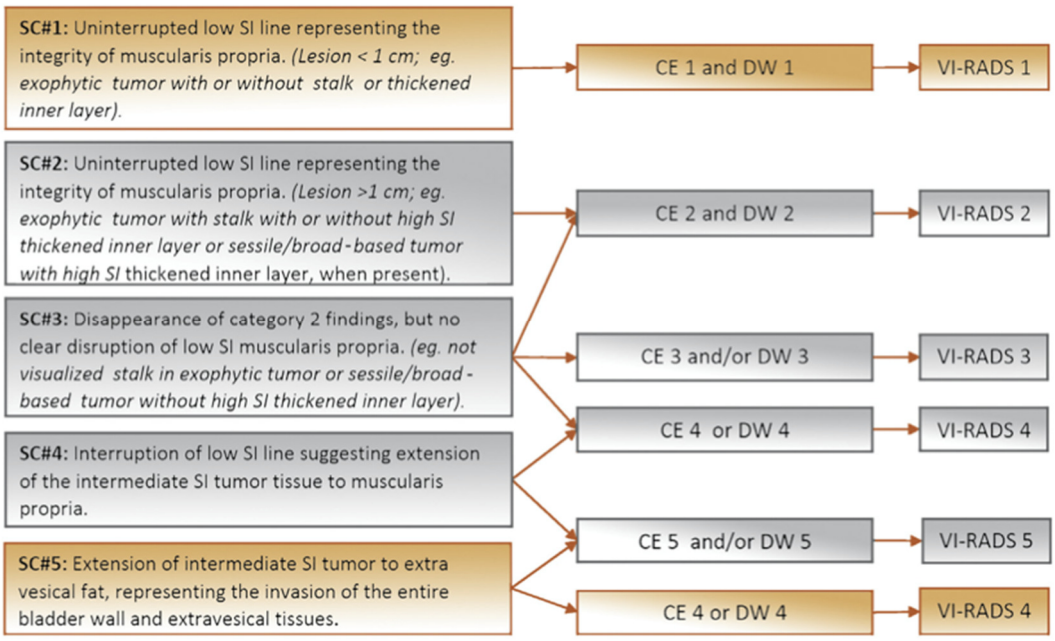


Figure 6 : Summary schematic representation of VI-RADS scoring. Scoring interpretation: for categories 1–3, the "first pass scoring" T2 sequence should be considered. For categories 4 and 5, the dominant sequences are DWI (first, when image quality is optimal) and DCE (second) (19).

Out of 31 patients in our study, 27 patients were biopsy naïve and underwent TURBT after prospective interpretation of VI-RADS scores. Four patients had a history of previous TURBT. MRI interpretation was done by two radiologists independently with an experience of 12 years and 2 years. Any discrepancy in VI-RADS scoring was resolved by consensus.

Statistical analysis:

SPSS software (Version 28.0) was used for statistical analysis of the data. For numerical variables, arithmetic mean, standard deviation and range was calculated. All categorical data were shown as number and proportion. The VI- RADS score and its components were dichotomized. Cross tables were applied and Pearson's Chi-square test was used to compare categorical variables. A p-value of less than 5% ($p<0.05$) was regarded as statistically significant. The ROC curve analysis and AUC was used to assess the VI-RADS score, as well as its components, for predicting a muscle-invasive tumour. The diagnostic performance of the dichotomized VIRADS score and its components for muscle-invasive tumours were evaluated by the calculation of sensitivity, specificity, PPV, NPV and accuracy.

OBSERVATION & RESULTS

OBSERVATIONS AND RESULTS

In our study a total of 39 patients with suspected urinary bladder cancer underwent mpMRI. Out of these 39 patients, 4 patients were excluded due to no evidence of malignancy (benign findings) on HPE report. Further 3 patients were lost in follow up leading to unavailability of HPE report and resultant exclusion. One patient was excluded due to evidence of prostate adenocarcinoma on HPE.

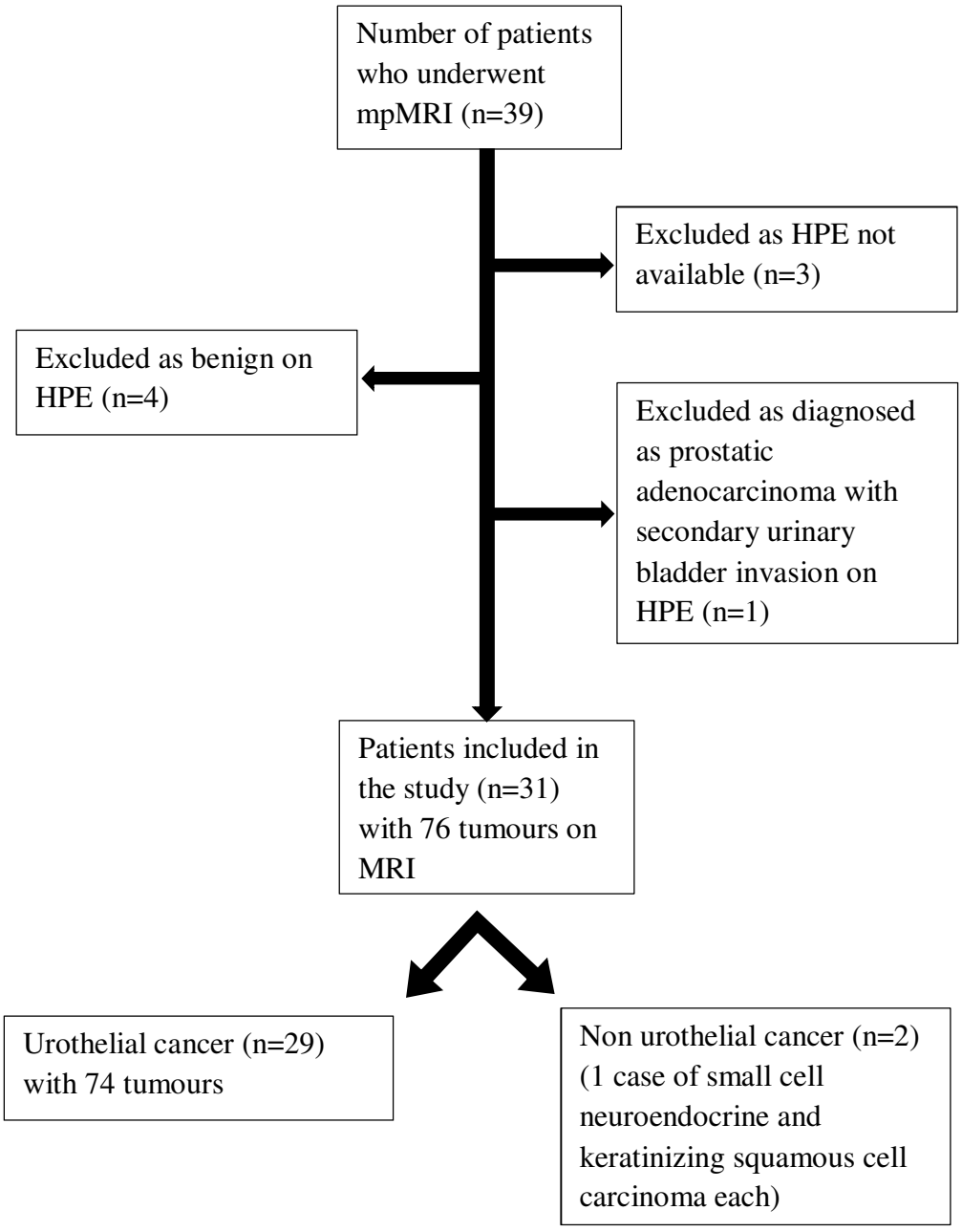


Figure 7: Flowchart of the patients in the study is shown below.

Patient wise data:

Gender distribution-

Total number of patients included in the study were 31. Out of the 31 subjects studied, 28 (90.32%) were male while only 3 (9.68%) were female suggesting male preponderance of the disease. [Figure-8]

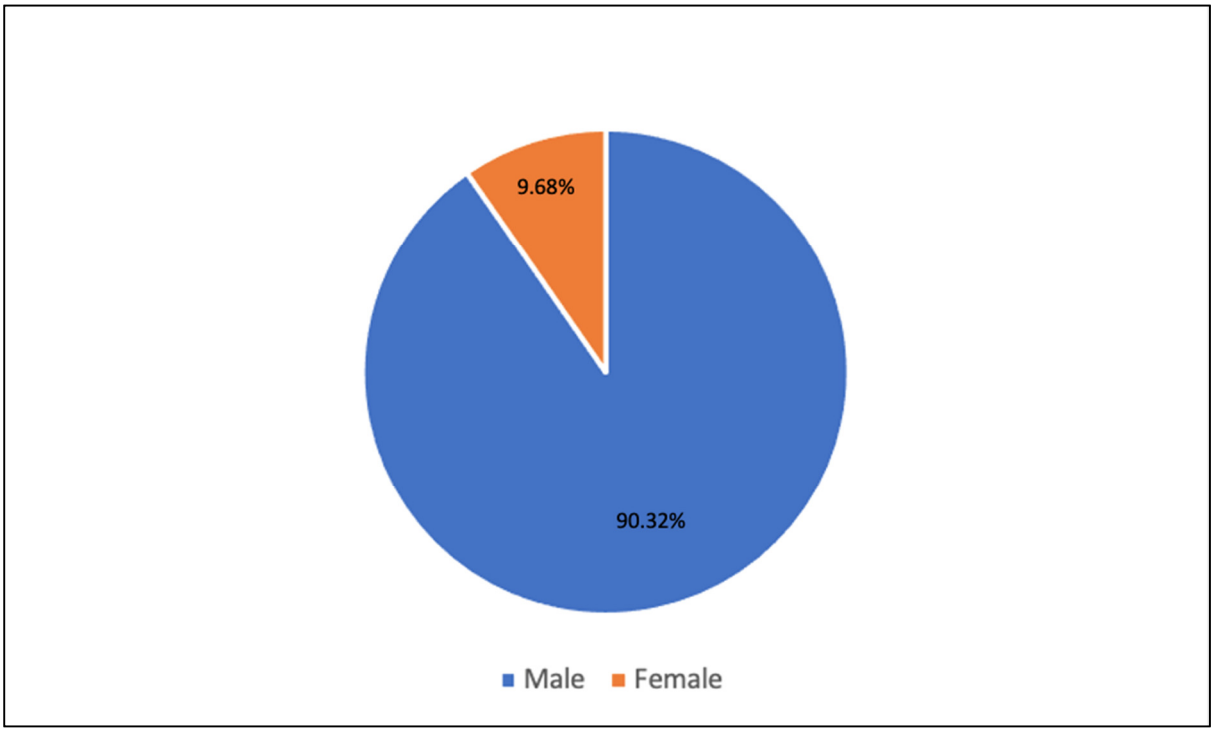


Figure 8: Pie chart for denoting gender distribution among patients of bladder cancer (n=31).

Age distribution-

The age of the patients ranged from 30 years to 80 years with the mean being 61.8 years (standard deviation: 13.1 years). [Table 4]

Out of 31 patients, 10 patients were in 71-80 years age group, 8 patients were in 51-60 years age group, 6 patients were in 61-70 years age group and 1 patient was in 21-30 and 31-40 years age group each. So, majority of patients (n=29, 93.55%) belonged to ≥40 years of age. [Figure 9]

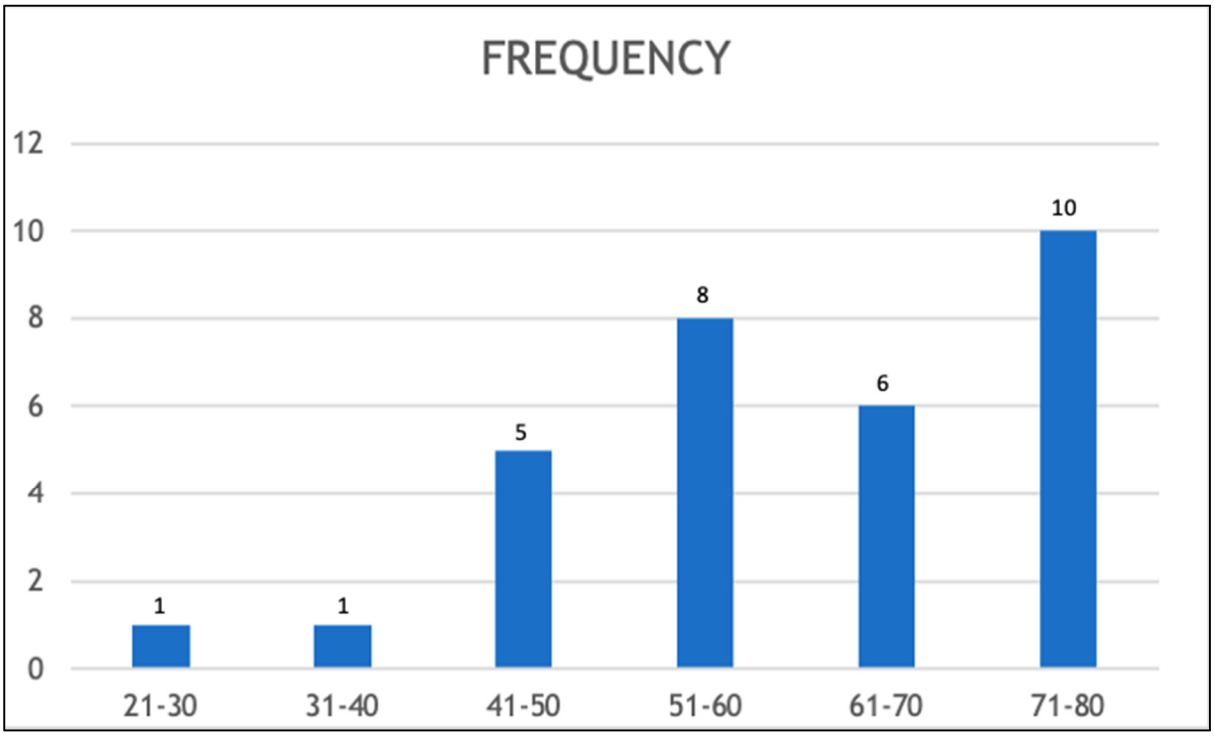


Figure 9: Bar chart showing age distribution among patients of bladder cancer (n=31).

Twenty out of 31 patients had single lesion in the urinary bladder whereas the rest 11 of them had multiple lesions. Eventually, a total number of 76 lesions were evaluated for tumour characteristics on MRI.

Four out of 31 patients included in our study had a prior history of TURBT (7 years, 3 years, 2 years, and 2 months before undergoing mpMRI respectively).

On HPE, 29 of these patients had urothelial cancer while the remaining 2 had non-urothelial cancer (1 case of small cell neuroendocrine and keratinizing squamous cell carcinoma each). During follow up, only 1 patient amongst these underwent radical cystectomy, whereas the rest 30 patients underwent only TURBT.

Out of 31 patients, 11 patients were in VI-RADS 2 category, 9 patients were in VI-RADS 5 category, 6 patients were in VI-RADS 4 category and 3 patients were in VI-RADS 3 category. No patient in our study had an overall VI-RADS category 1. However, 4 out of 76 lesions were classified as VIRADS category 1. [Figure 10]

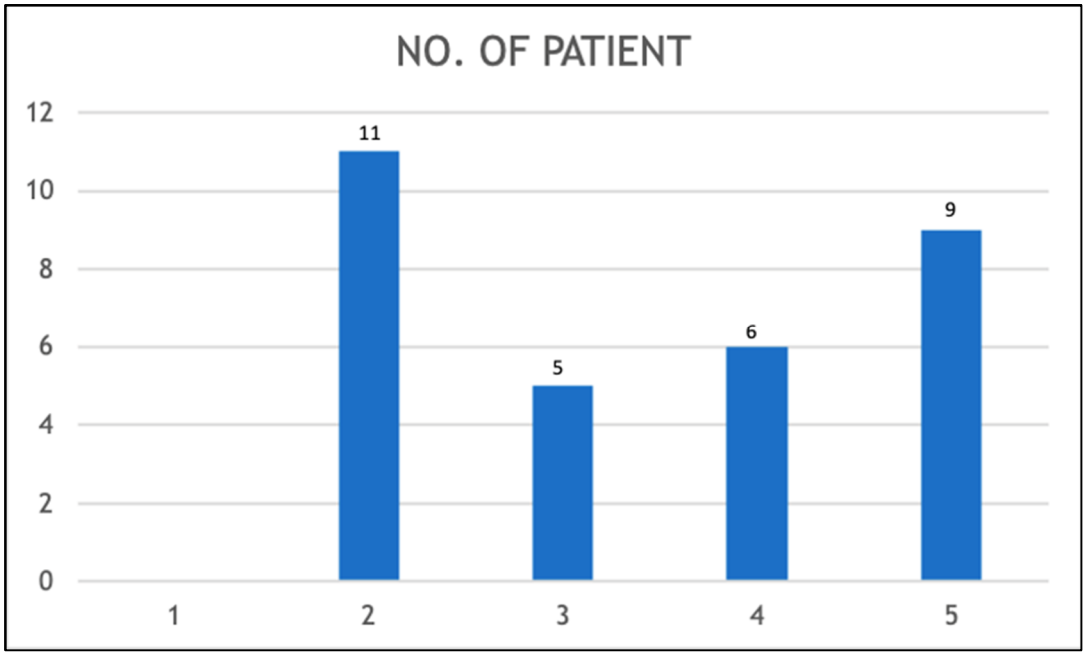


Figure 10: Bar chart showing number of patients with bladder cancer in each VI-RADS category (n=31).

Table 4: Patient characteristics and VI-RADS evaluation in cases of bladder cancer (patients=31)

Characteristics	Value (n=31)	VIRADS 2 (n=11)	VIRADS 3 (n=5)	VIRADS 4 (n=6)	VIRADS 5 (n=9)
Age(y) • **Mean ± SD** • **Range**	61.8±13.1 30-80	64±13.43 42-80	57.4±11.73 44-75	64.3±11.8 44-77	60.11±15.29 30-74
Sex • **Male** • **Female**	28 03	10(32.3%) 1(3.2%)	4(12.9%) 1(3.2%)	6(19.4%) 0	8(25.8%) 1(3.2%)
No. of lesions • **Single** • **Multiple**	20 11	6(19.4%) 5(16.4%)	4(12.9%) 1(3.2%)	3(9.7%) 3(9.7%)	7(22.6%) 2(6.5%)
Size of lesion (in mm) • **Mean ± SD**	49.7±27.3	36.8±22.9	57.4±7.2	56.1±13.4	57.1+40.5

The mpMRI predicted muscle invasion accurately in both cases of non-urothelial cancers (1 case of small cell neuroendocrine tumour and keratinizing squamous cell carcinoma each). Both of them were muscle invasive on MRI (small cell neuroendocrine carcinoma case had a VIRADS score of 4 and keratinizing squamous cell carcinoma case had a VIRADS score of 5) and HPE both.

In our study, all 11 (100%) patients with VIRADS score 2 had a non-muscle invasive bladder tumour on HPE. Three (60%) patients out of a total of 5 patients with VIRADS score 3 had a non-muscle invasive tumour on HPE while the remaining 2 (40%) showed muscle invasion on the final HPE. Out of 6 patients with VIRADS score 4, 5 (83.33%) had muscle invasive and 1 (16.66%) had non-muscle invasive tumours. A total of 14 (93.3%) patients out of total 15 with VIRADS score ≥4 had muscle invasion and 2 (6.66%) had no muscle invasion on HPE. All 9 (100%) patients with VIRADS score 5 had muscle invasion on the final biopsy.

When a VI-RADS score of ≥3 was considered as cut off, the sensitivity, specificity, PPV, and NPV of MRI in predicting detrusor muscle invasion in cases of bladder cancer were 100%, 73.33%, 80%, and 100% respectively.

However, when a VI-RADS of ≥4 was considered as cut off, the sensitivity, specificity, PPV, and NPV of MRI in predicting detrusor muscle invasion in cases of bladder cancer were 87.5%, 93.3%, 93.33%, and 87.5% respectively. [Table 5]

Table 5: Performance of VI-RADS score using ≥3 and ≥4 as cut off for detection of detrusor muscle invasion in cases of bladder cancer (patients=31, total lesions=76)

	VI-RADS ≥ 3	**VI-RADS ≥ 4**
Sensitivity	100%	87.5%
Specificity	73.33%	93.3%
Positive likelihood ratio	3.75	13.13
Negative likelihood ratio	0	0.13
PPV	80%	93.33%
NPV	100%	87.5%
Accuracy	87.10%	90.32%

In our study, it was found that overall VIRADS category along with its component scores on individual MRI sequences were effective in predicting detrusor muscle invasion. [Figure 11, Table 6]

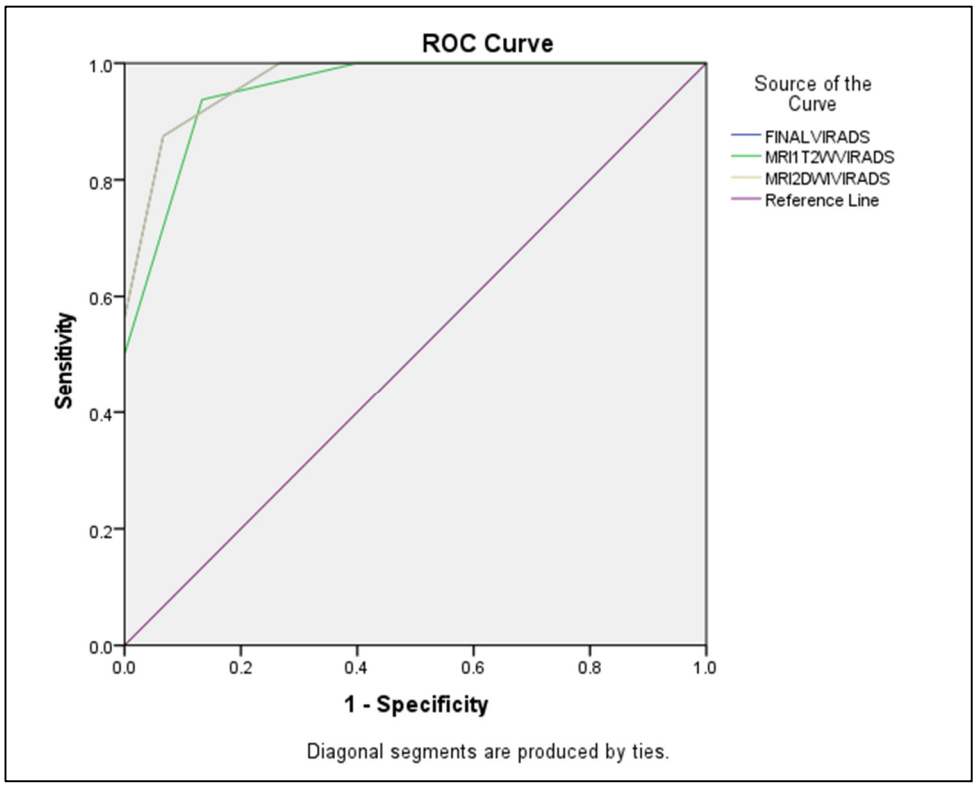


Figure 11: ROC curve analysis for predicting detrusor muscle invasion in bladder cancer for final VI-RADS category and its components.

Overlap of DWI VIRADS and final VI-RADS score curve was seen. Individual ROC curve for DCE could not be plotted because few patients (n= 5) with deranged KFT did not undergo contrast enhanced imaging.

Table 6: AUC values of ROC curve analysis for predicting detrusor muscle invasion in bladder cancer for final VI-RADS category and its components:

Test result variable	AUC	p-Value
Final VI-RADS	0.969	<0.001
T2WI	0.954	<0.001
DWI	0.969	<0.001

A comparison of nodal involvement on MRI with detrusor muscle invasion on HPE was done. Among 31 cases, 22 had no nodal involvement and 9 were node positive. 15 patients among node negative disease had non-invasive histopathology (68.2%) and rest of the 7 had invasion present on histopathology (22.6%).

Among node positive cases all of them had invasive disease on histopathology. [Table 7]

Table 7: Comparison of nodal involvement with detrusor muscle invasion on HPE

		HPE		Total
		Non invasive	Invasive	
Nodal involvement	**No**	15 (48.4%)	7 (22.6%)	22 (71%)
	Yes	0	9 (29%)	9 (29%)
Total		15 (48.4%)	16 (51.6%)	31 (100%)

Chi square statistic was used to examine association between nodal status and detrusor muscle invasion. There was a significant association at 5% significance level between nodal status and detrusor muscle invasion ($\chi 2$ =11.889, p=.001). Hence, null hypothesis was rejected. [Table 8]

Table 8: Association between nodal involvement and detrusor muscle invasion on HPE

	Value	p-Value
Pearson chi square	11.889	0.001

Thus, a significant association between nodal involvement and detrusor muscle invasion on HPE was found.

A comparison of nodal involvement with histological grade of tumour was done. Among 31 cases, 22 had no nodal involvement and 9 were node positive. 7 patients among node negative cases had low histological grade (31.8%) and rest of the 15 had high grade tumours (68.2.%) on histopathology.

Among node positive cases, only 1 of them had low grade tumour (11.1%) on histopathology while rest of 8 node positive cases had high grade (88.9%) tumour on histopathology. [Table 9]

Table 9: Comparison of nodal involvement on MRI with histological grade of tumour

		Histological grade		Total
		Low	**High**	
Nodal involvement	**No**	7 (22.6%)	15 (48.4%)	22 (71%)
	Yes	1 (3.2%)	8 (25.8%)	9 (29%)
Total		8 (25.8%)	23 (74.2%)	31 (100%)

Chi square statistic was used to examine the association between nodal status and histological grade of tumour. There was an insignificant association at 5% significances level between nodal status and grade of tumour ($\chi 2$ =1.430, p=0.232). Hence, null hypothesis was accepted. [Table 10]

Table 10: Association between nodal involvement and histological grade of tumour

	Value	**p-Value**
Pearson chi square	1.430	0.232

Thus, no significant association between nodal involvement and histological grade of tumour was found.

Evaluation of ADC values was done for predicting histological grade of tumour. For the largest lesion, if an ADC value cut-off of 1028.0 was considered then the sensitivity of 82.6% and a specificity of 87.5% was obtained for predicting histological grade. [Figure 12][Table 11]

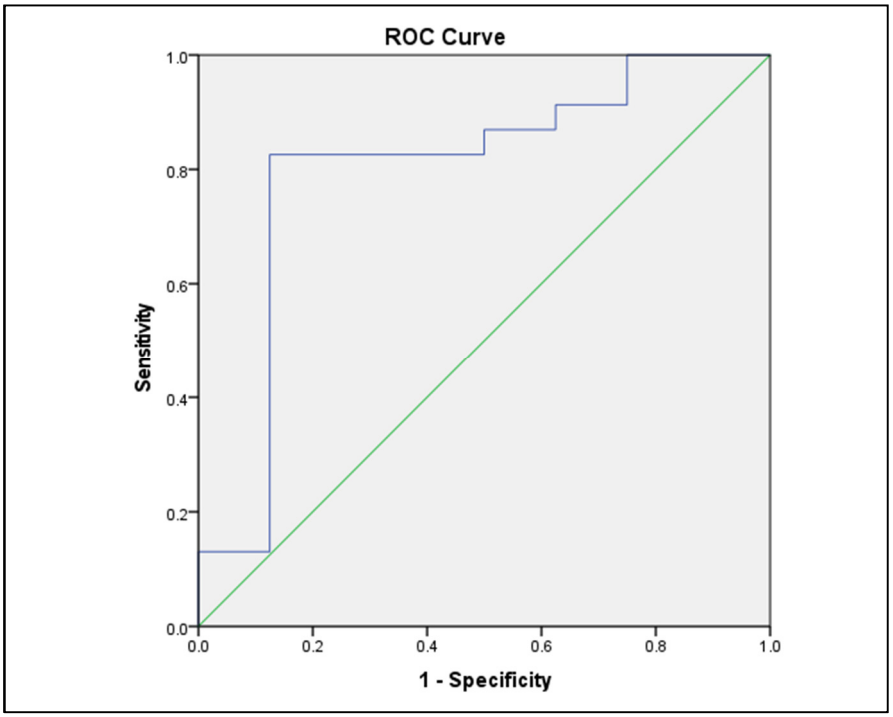


Figure 12: ROC curve analysis for predicting histological grade in bladder cancer with ADC for largest lesion

Table 11 : AUC values of ROC curve analysis for predicting histological grade of bladder cancer with ADC of largest lesion

	AUC	**p-Value**
ADC of largest lesion with histological grade	0.799	0.013

Thus, it was found that the ADC value of largest lesion can predict histological grade of the tumour.

One way ANOVA test was done to test the hypothesis that age of patient correlates with the VIRADS category. Participants were divided into 4 groups according to their VI-RADS status. The ANOVA result suggests that the two groups studied do not differ significantly (F=0.390, p-value=0.761) so, the age of the patient does not correlate with the VIRADS category.

Tumour characteristics and distribution:

Overall, a total number of 76 lesions were seen in 31 patients. Twenty out of 31 patients had single tumour while 11 patients had multiple tumoral lesions (a total of 56 lesions) ranging from 2 to 8 lesions per patient.

Each lesion was assigned a VI-RADS category. However, for the 11 patients with multiple lesions, the final VI-RADS categorization was done based on the lesion with highest VI-RADS score.

Tumour location and mapping-

Out of the 76 lesions, 21 lesions were large in size and were seen to cover multiple areas so, they could not be attributed to any one single area on lesion mapping. Among the remaining 55 lesions, 16 (29%) lesions were found on left lateral wall followed by 13 (23.6%) lesions on the posterior wall and 11 (20%) lesions on the right lateral wall of the urinary bladder. Two of the 21 lesions covering multiple areas were seen to involve bladder neck and prostatic urethra (area 2) extending from the inferior wall of urinary bladder. [Figure 13]

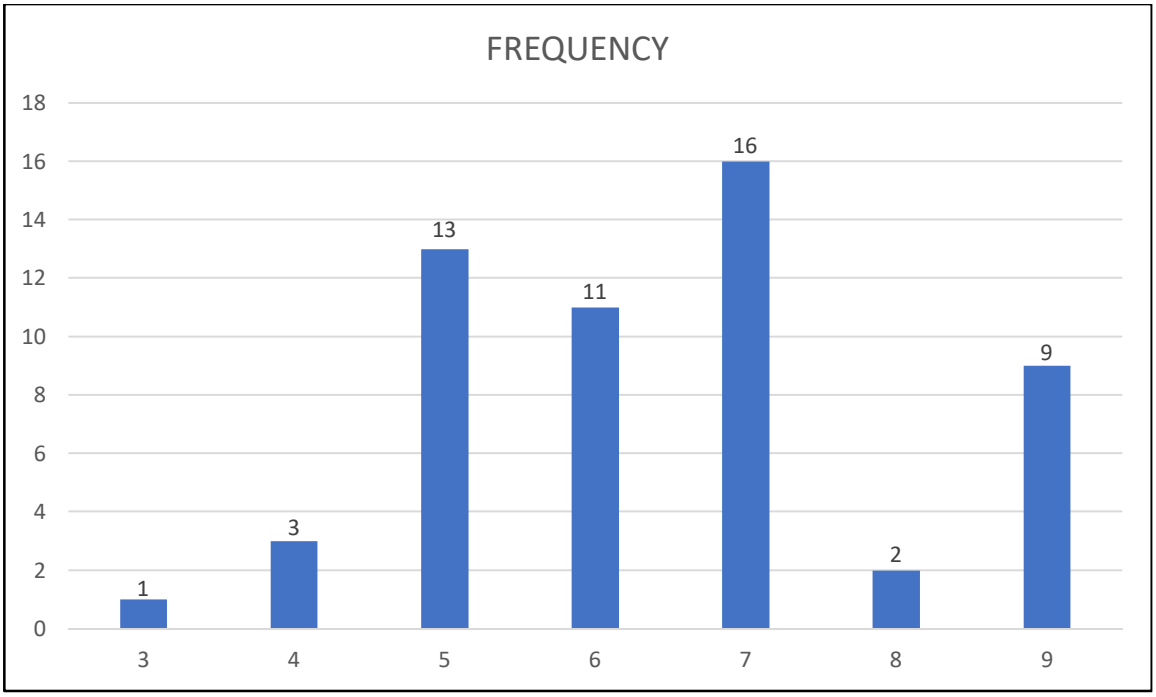


Figure 13: Bar chart for denoting anatomical location of lesions (n=55) in bladder cancer.

Note-Anatomical mapping reference chart has been shown on page number-23.

Tumour morphology-

Out of 76 lesion studied, 63 (82.89%) lesions had papillary morphology, 9 (11.84%) lesions had non-papillary morphology and the rest 4 (5.26%) lesions had mixed morphology.

On DWI, 60 (78.94%) out of the 76 lesions studied showed the presence of a stalk whereas 16 (21.05%) lesions had no stalk. On T2WI, stalk was seen in 59 (77.63%) out of 76 lesions while no stalk was appreciable in the rest 17 (22.37%) lesions.

Out of 76 lesions studied, 45 of them were less than 3 cm in size with a mean size of 2.2 $\pm$ 1.1 cm. Rest of the 31 lesions were more than 3cm in size with a mean of 5.6 $\pm$ 2.4 cm.

One way ANOVA test was done to test the hypothesis that size for largest lesion correlates with the VI-RADS category. Participants were divided into 4 groups according to their VI-RADS status. The ANOVA result suggested that the two groups studied did not differ significantly (F=1.325, p-value=0.287).

Tumour VI-RADS scoring-

Out of 76 lesion studied, 45 of them were assigned VI-RADS category 2, 11 lesions were of category 3, 7 lesions belonged to category 4, 9 lesions in category 5, and the rest 4 lesions belonged to category 1 [Figure 14]

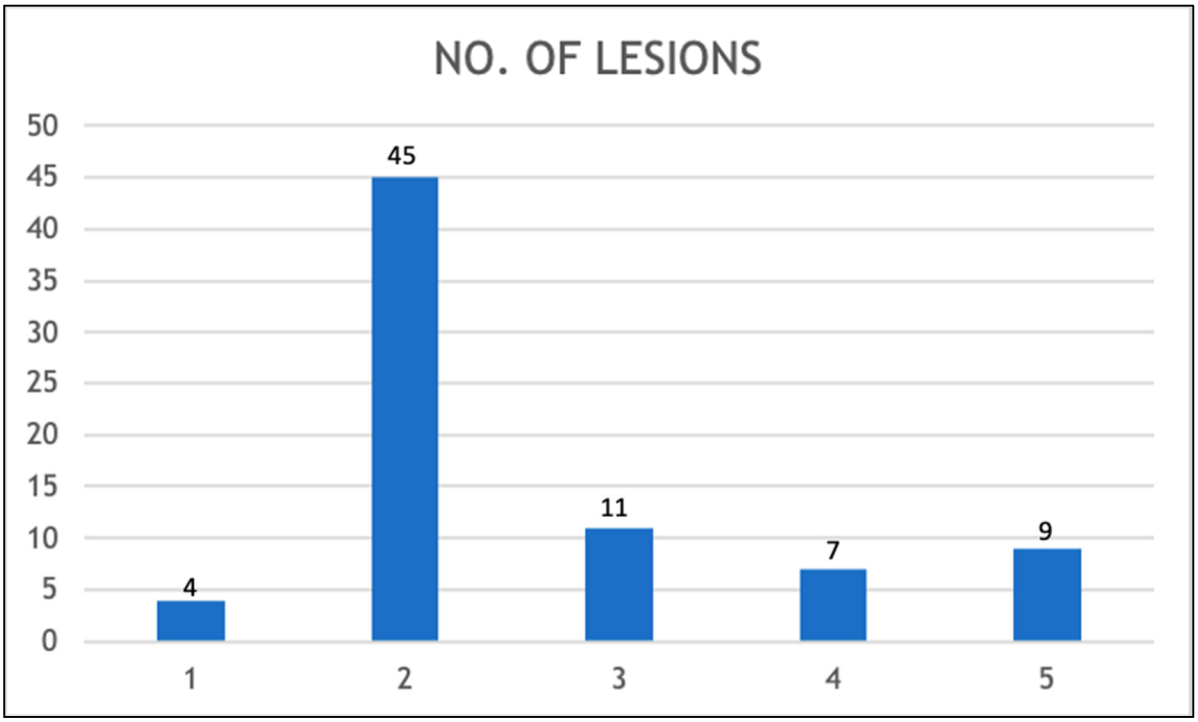


Figure 14: Bar chart for denoting final VI-RADS category of individual lesions (n=76) of bladder cancer.

A comparison of restricted wall distention with detrusor muscle invasion on HPE was done for the individual lesions. Out of total 76 lesions, 45 lesions (59.2%) had no restricted wall distention. Among these 45 lesions, 31 were NMIBC and 14 were MIBC. Restricted wall distention was present in rest of the 31 lesions of which 9 were NMIBC and 22 were MIBC. [Table 12]

Table 12: Comparison of restricted wall distention with detrusor muscle invasion on HPE

		HPE		Total
		Non invasive	Invasive	
Restricted wall distention	**No**	31 (40.8%)	14 (18.4%)	45 (59.2%)
	Yes	9 (11.8%)	22 (28.9%)	31 (40.8%)
Total		40 (52.6%)	36 (47.4%)	76 (100%)

Chi square statistics was used to examine the association between restricted wall distention and detrusor muscle invasion. There was a significant association at 5% significance level between restricted wall distention and detrusor muscle invasion ($\chi 2$ =11.696, df=1, p=.001). Hence, null hypothesis was rejected. [Table 13]

Table 13: Association between restricted wall distention and detrusor muscle invasion

	Value	p-Value
Pearson chi square	11.696	0.001

Thus, a significant association between restricted wall distention and detrusor muscle invasion on HPE was found for the individual lesions.

A comparison of restricted wall distention with histological grade was done for the individual lesions. Out of total 76 lesions, 45 lesions (59.2%) had no restricted wall distention. Among these 45 lesions, 14 were low grade and 31 were high grade lesions. Restricted wall distention was present in rest of the 31 lesions of which 4 were low grade and 27 were high grade lesions. [Table 14]

Table 14: Comparison of restricted wall distention with histological grade

		Histological grade		Total
		Low	**High**	
Restricted wall distention	**No**	14 (18.4%)	31 (40.8%)	45 (59.2%)
	Yes	4 (5.3%)	27 (35.5%)	31 (40.8%)
Total		18 (23.7%)	58 (76.3%)	76 (100%)

Chi square statistic was used to examine the association between restricted wall distention and histological grade. There was an insignificant association at 5% significances level between restricted wall distention and histological grade ($\chi 2$ =3.367, p=.067). Hence, null hypothesis was accepted. [Table 15]

Table 15: Association between restricted wall distention and histological grade

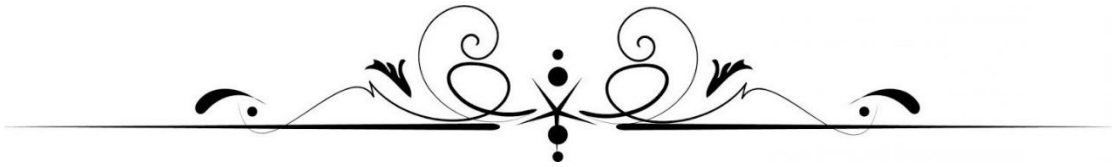
	Value	**p-Value**
Pearson chi square	3.367	0.067

Thus, no significant association between restricted wall distention and histological grade for the individual lesions was found.

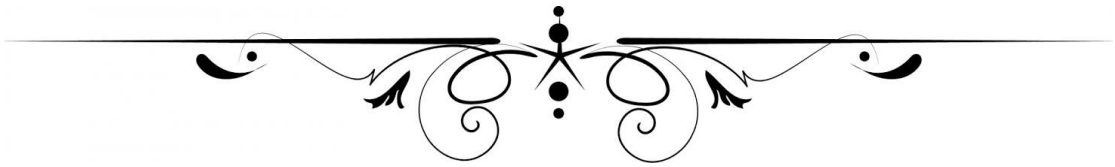
Out of 76 lesions studied, a total of 75 lesions were evaluated for advantage of FOCUS-DWI sequence. One patient with single lesion did not undergo the FOCUS-DWI sequence. We found the advantage of FOCUS-DWI sequence in 18 (24%) lesions out of 76 lesions. Thus adding significantly to the diagnostic efficiency. FOCUS-DWI in an orthogonal plane also increased our diagnostic confidence in the evaluation of these 18 lesions with regard to muscle invasion.

Many additional findings were also seen on MRI while evaluating the patients for bladder cancer. Presence of intraluminal clot was seen in 9 out of 31 patients included. Hydroureteronephrosis (HDUN) was seen in 8 patients with bilateral HDUN in 4 patients and unilateral HDUN in 4 patients.

Prostatomegaly (BPH) was seen in 10 patients. Evidence of inguinal testes, left VUJ calculus, liver metastasis, vascular invasion, diverticulosis was seen with a frequency of one case each. Bone metastasis was identified in visualised pelvic bones in 2 patients.



CASES



CASES

Case 1: A 56-years-old male presented with hematuria and abdominal pain for 4 days. VIRADS-2. HPE - low grade non-muscle invasive urothelial carcinoma.

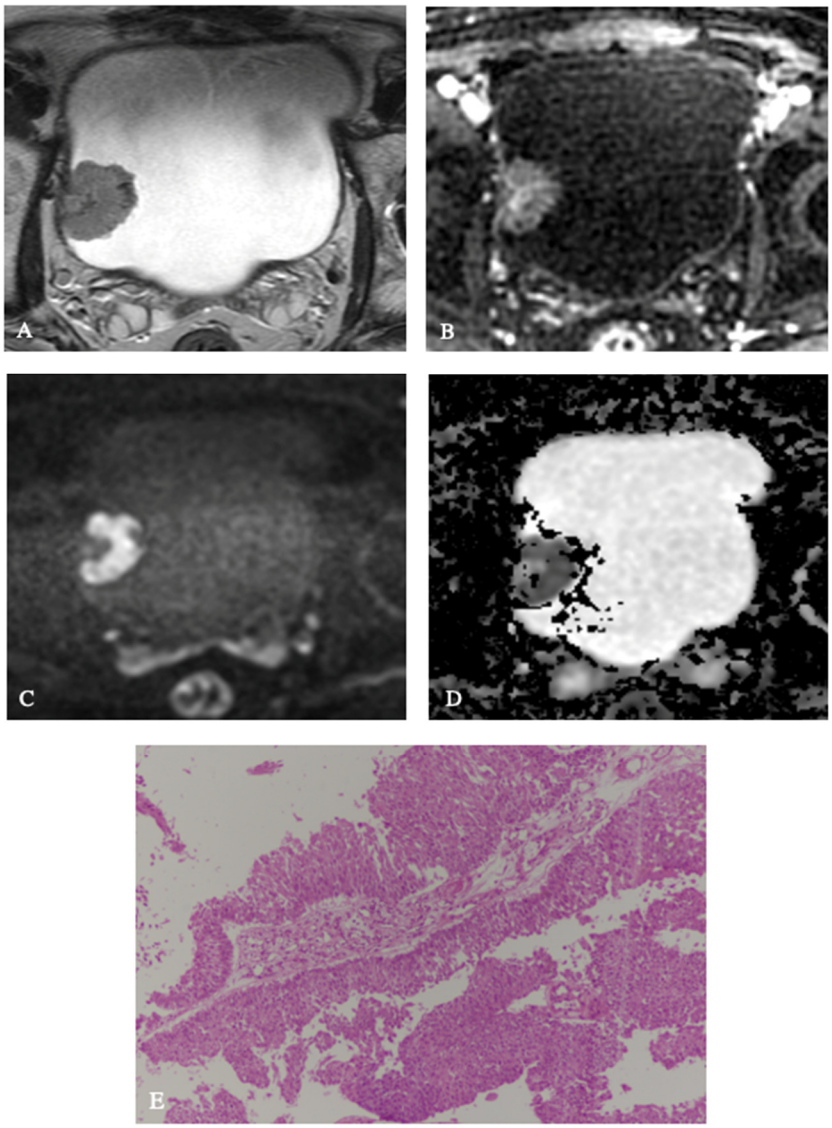


Figure: (A) Axial T2WI showing a hyperintense papillary lesion with a stalk along the right lateral wall (C) Axial DCE image showing an early enhancement of the lesion (C) DWI showing diffusion restriction within the lesion with hypointense stalk giving an "inchworm appearance" (D) ADC map showing corresponding low signal intensity (E) HPE image showing low grade papillary urothelial carcinoma, H&E stain, 10x.

Case 2: A 74-years-old male presented with gross painless hematuria for 2 days. VIRADS-5. HPE-high grade muscle invasive urothelial carcinoma.

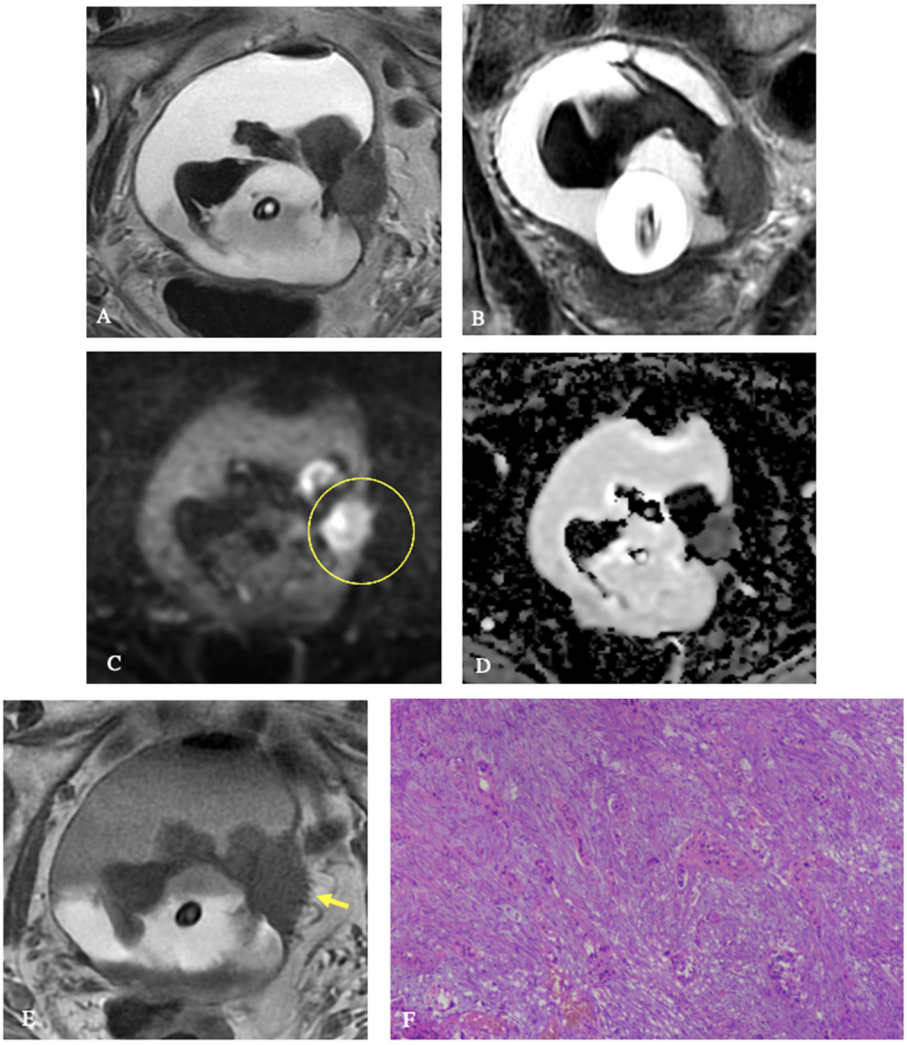


Figure: (A, B) Axial and coronal T2WI showing a hyperintense broad based lesion along the left lateral wall involving the left VUJ with Foley's bulb in situ (C) DWI showing restriction within the lesion with adjacent perivesical fat infiltration and spiculated outline {yellow circle} (D) ADC map showing significant corresponding low signal intensity (E) Axial T1WI showing presence of clot within the lumen with dependent hemorrhagic fluid in the UB lumen. Tumour infiltration into adjacent perivesical fat with irregular outline is also seen {yellow arrow} (F) HPE image showing deep muscle fascicles infiltrated by nests of tumour, H&E Stain, 10x.

Case 3: A 77-years-old male presented with burning micturition for 3 weeks and hematuria for 2weeks. VIRADS-4. HPE-high grade muscle invasive urothelial carcinoma with focal squamous metaplasia.

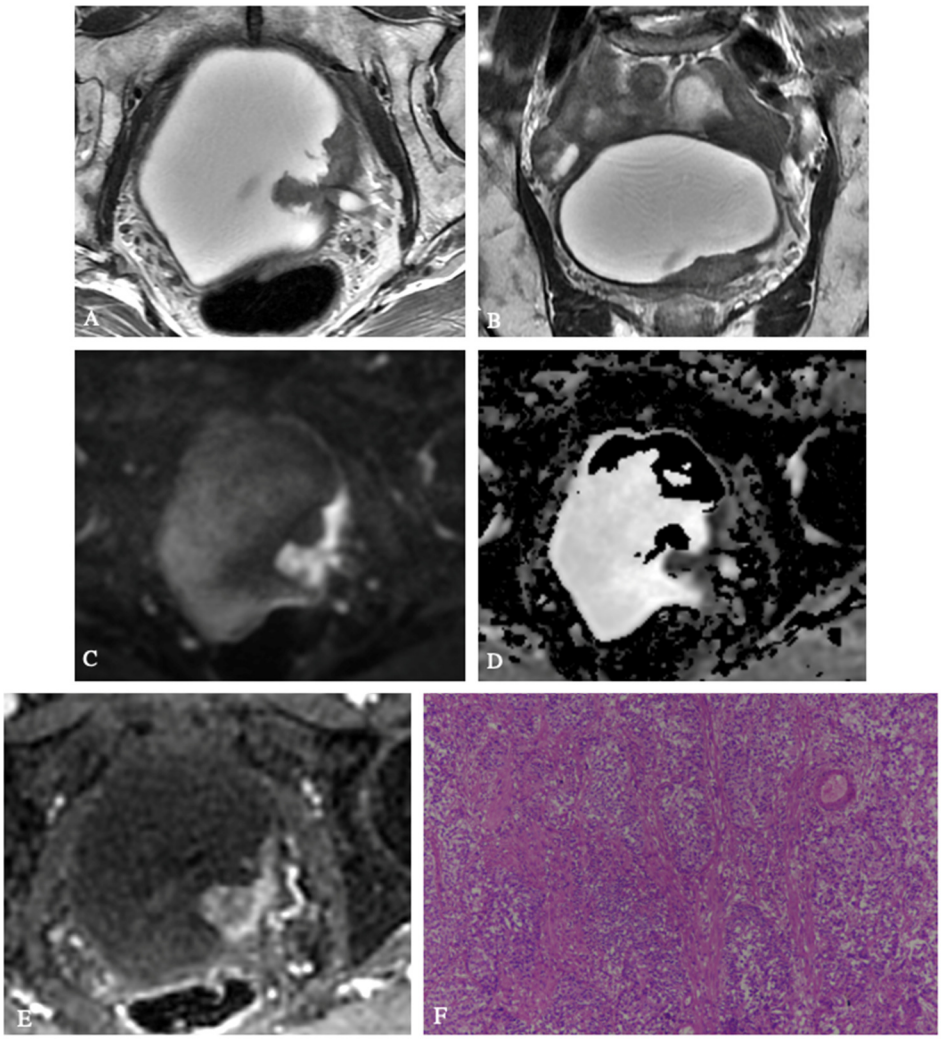


Figure: (A, B) Axial and coronal T2WI showing a hyperintense mixed lesion (with polypoidal and broad based component) along the left posterolateral wall with left VUJ involvement and resultant hydroureter (C) DWI showing restriction within the lesion muscle invasion (D) ADC map showing corresponding low signal intensity (E) DCE image showing early enhancement of the lesion (F) HPE image showing nests of tumour infiltrating muscularis propria, H&E Stain, 10x.

Case 4: A 65-years-old male presented with dysuria and occasional passage of clots for 4 months. DCE was not done for this patient owing to deranged KFT. VIRADS-4. However, histopathology was suggestive of non-muscle invasive high grade urothelial carcinoma with 80% squamous differentiation and sarcomatoid changes (False positive case of MRI)

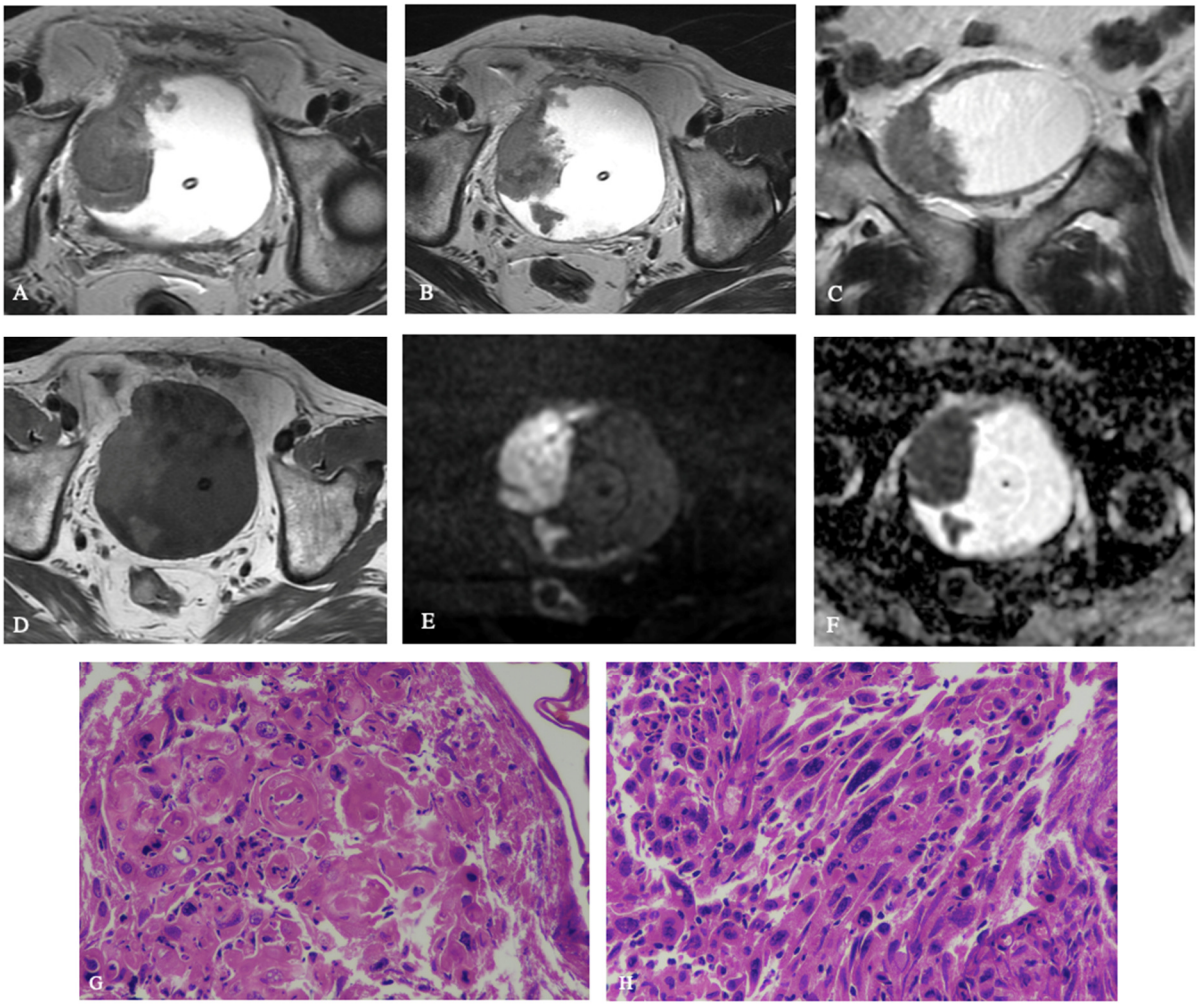


Figure: (A, B) Axial T2W images show a hyperintense broad based papillary lesion along the right anterolateral wall (C) coronal T2WI shows the disruption of the low signal intensity muscle layer (D) Axial T1WI shows the presence of intra-luminal clot (E) DWI showing hyperintense restriction within the lesion involving the muscle layer along with a distorted stalk displaced posteriorly (F) ADC map showing corresponding low signal intensity within the lesion (G) HPE image showing urothelial carcinoma with extensive squamous differentiation showing keratinization, H&E stain, 40x (H) HPE image showing sarcomatoid change in squamous component, H&E stain, 40x.

Case 5: A 60-years-old male presented with intermittent painless hematuria for 2 months. VIRADS-3. HPE-high grade muscle invasive urothelial carcinoma (False negative case of MRI).

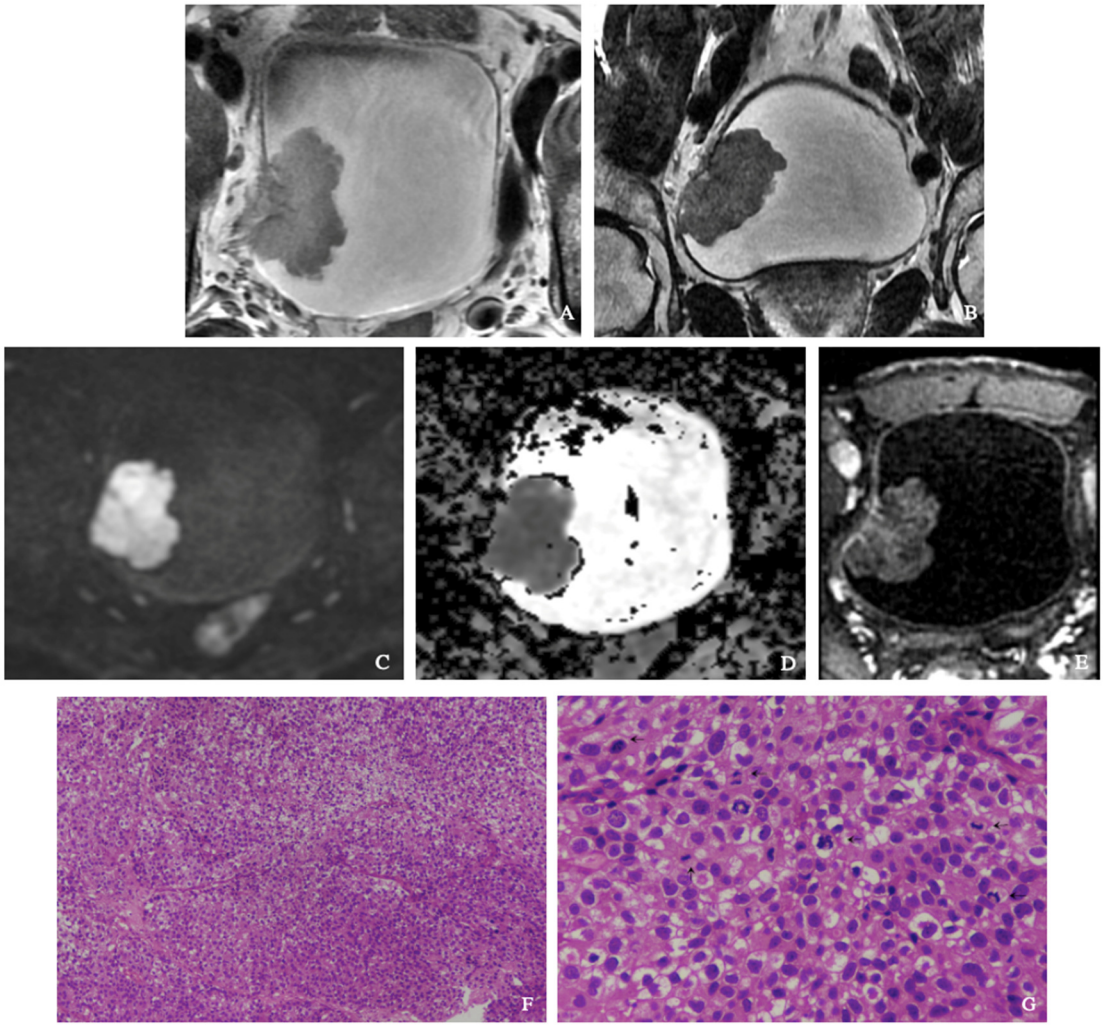


Figure: (A, B) Axial and coronal T2W images show a hyperintense papillary lesion with stalk and restricted wall distension along the right lateral wall (C) DWI showing restriction within the lesion with hypointense distorted stalk with a smooth outline (D) ADC map showing corresponding low signal intensity within the lesion (E) Axial DCE image showing early enhancement of lesion. So, a VI-RADS score of 3 was assigned. However, HPE was suggestive of MIBC. Hence, this case was a false negative of MRI (F) HPE image showing fused papillae in high grade invasive urothelial carcinoma, H&E Stain, 10x (G) HPE image showing many mitoses (arrows) in high grade invasive urothelial carcinoma, H&E Stain, 40x.

Case 6: A 60-years-old male presented with increased frequency, poor stream, and painless hematuria for 1 month. VIRADS-5. HPE-high grade muscle invasive urothelial carcinoma with squamous differentiation.

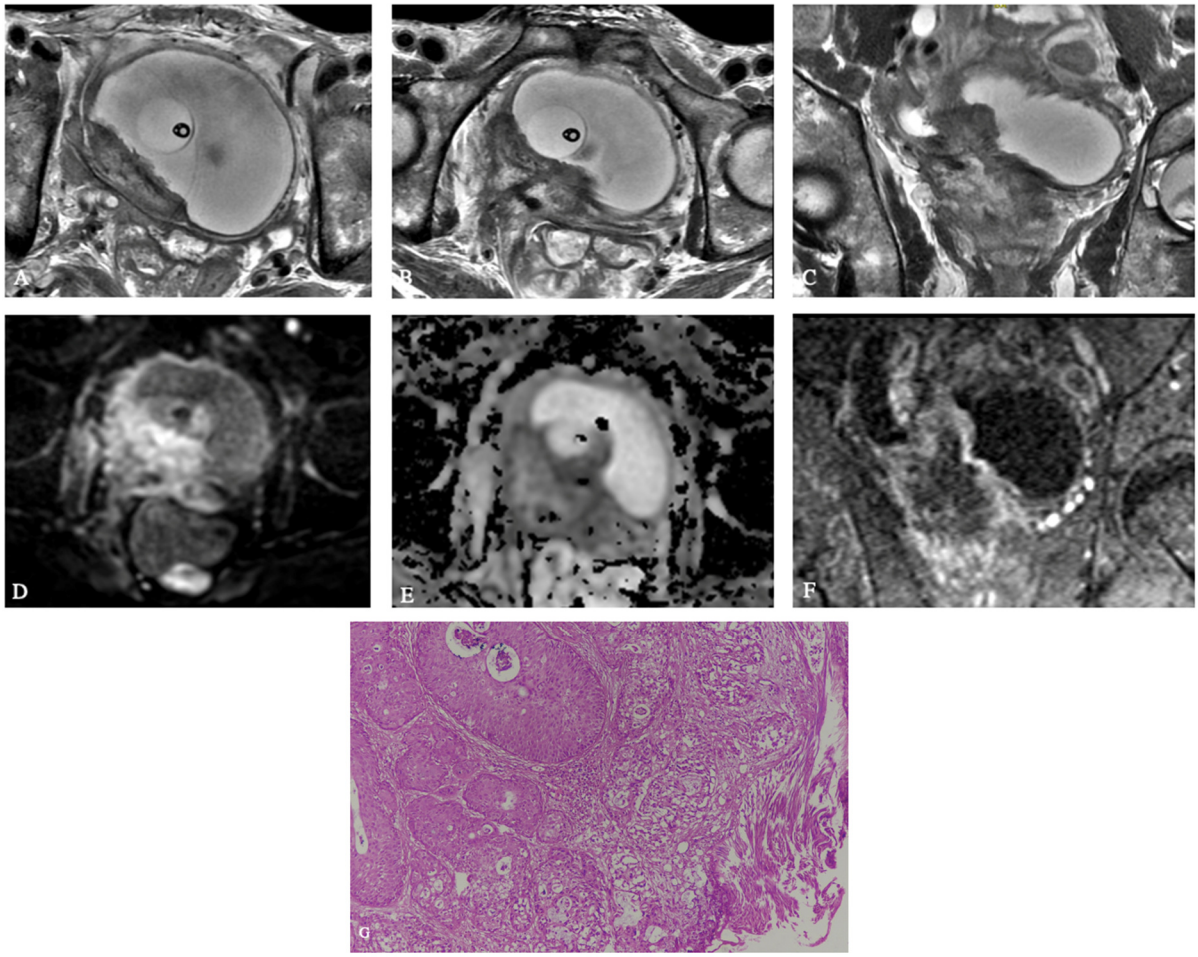


Figure: (A, B) Axial and (C) coronal T2W images showing a heterogeneous signal intensity non-papillary mass lesion along the right posterolateral wall causing restricted wall distension, extending into peri-vesical fat, prostate gland and involving right VUJ with upstream hydroureter (D) Axial DWI showing heterogeneous restriction within the lesion, right levator ani and right seminal vesicle (E) Axial ADC map showing corresponding heterogeneous low signal intensity within the lesion (F) Coronal DCE showing the heterogeneous predominantly peripheral irregular enhancement along the aforementioned lesion with central non-enhancing area(H) HPE image showing muscle invasive urothelial carcinoma, H&E Stain, 10x.

Case 7: A 57 years-old male presented with intermittent gross painless hematuria for 6 months. VIRADS-2. HPE-high grade non-muscle invasive urothelial carcinoma.

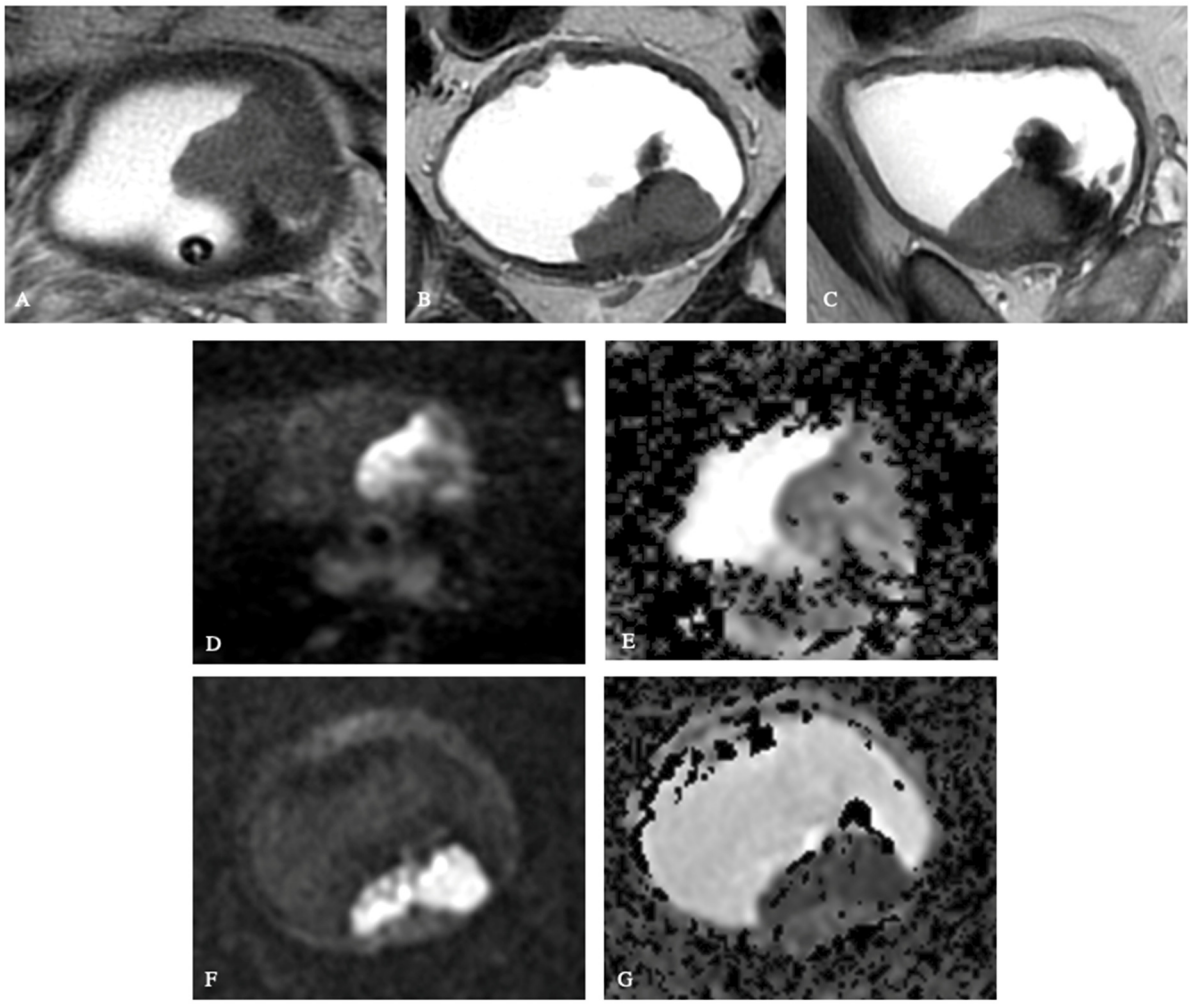


Figure: (A-C) Axial, coronal and sagittal T2WI showing papillary lesion with a stalk at left antero-inferior wall (D, E) Axial DWI and ADC map showing restriction within the lesion. As the lesion is oriented in an axial plane, axial DWI shows equivocal impression of muscle invasion (F, G) When lesion is imaged in a coronal plane (orthogonal to lesion orientation) with FOCUS-DWI whole lesion is better visualized with a clear absence of muscle invasion and thus was scored as VI-RADS 2.

Case 8: A 74-years-old male presented with passage of clots followed by urinary retention. H/o TURBT 2 months ago. VIRADS-5. HPE-High grade muscle-invasive urothelial cancer on radical cystectomy.

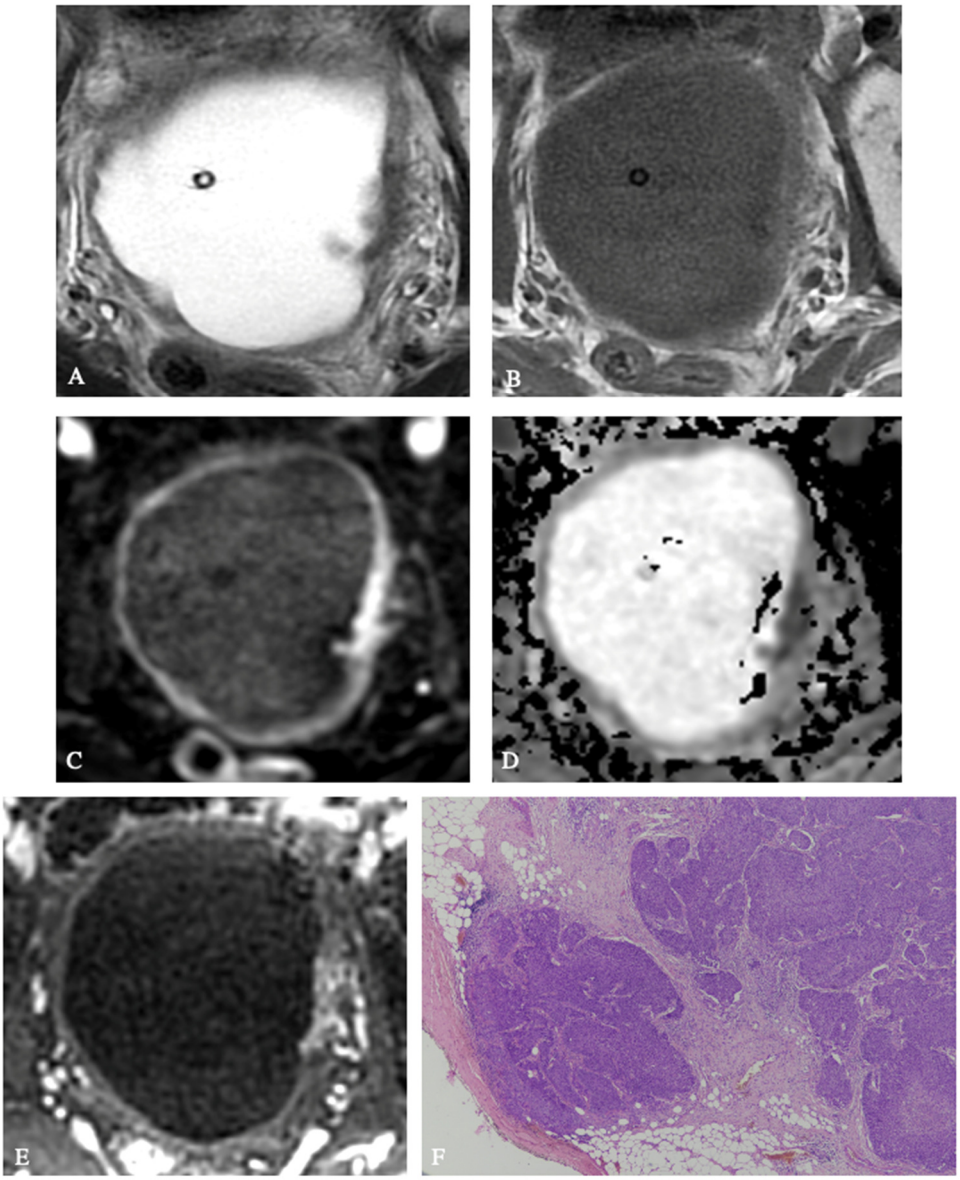


Figure: (A) Axial T2WI showing heterogeneously hypointense irregular thickening along the left lateral wall of urinary bladder- suggestive of residual lesion with muscle invasion (B) Axial T1WI showing perivesical fat involvement adjacent to lesion (C, D) Axial DWI and ADC map showing restriction along lesion involving the adjacent muscle layer and extending into peri-vesical fat (E) Axial DCE image showing heterogeneous enhancement along the lesion extending into adjacent perivesical fat (F) HPE image showing perivesical fat invasion with nests of tumour, H&E stain, 4x.

Case 9: A 77-years-old male presented with hematuria with passage of clots for 1 month. VIRADS-2. HPE-High grade non muscle-invasive urothelial cancer.

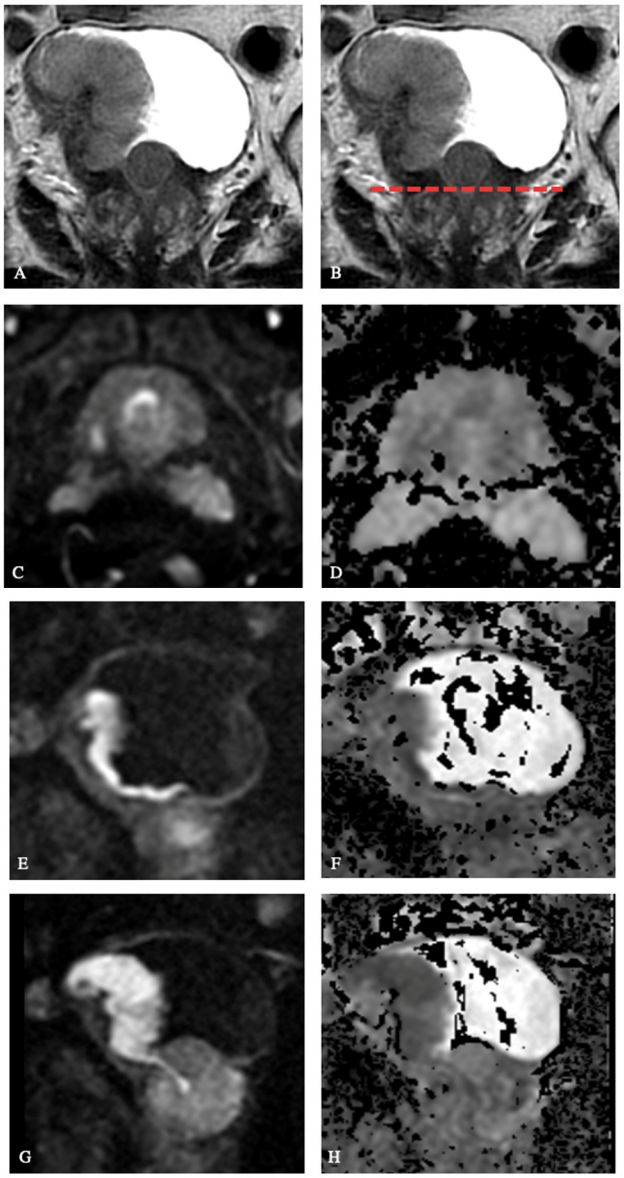


Figure: (A) Coronal T2WI showing hyperintense papillary lesion with hypointense stalk along right lateral wall. A BPH nodule is seen adjacent to lesion (B) Coronal T2WI showing the level at which DWI image is shown (C) Axial DWI showing restriction along the bladder neck. However, exact status of wall invasion cannot be commented upon (D) Axial ADC map showing corresponding low signal intensity (E, F) Coronal FOCUS-DWI image and corresponding ADC map showing the mixed papillary and flat nature of lesion without muscle invasion, clearly outlining the advantage of acquiring FOCUS-DWI in an orthogonal plane (G, H) Coronal FOCUS-DWI and ADC map showing spread of the lesion into bladder neck, extending beneath the BPH nodule. Axial DWI was not helpful for this type of spread of tumour.

Case 10: A 44-years-old male presented with hematuria for 1 month and lower urinary tract symptoms for 1 year. VIRADS-4. HPE-High grade non muscle-invasive urothelial cancer with carcinoma in situ and urethral involvement.

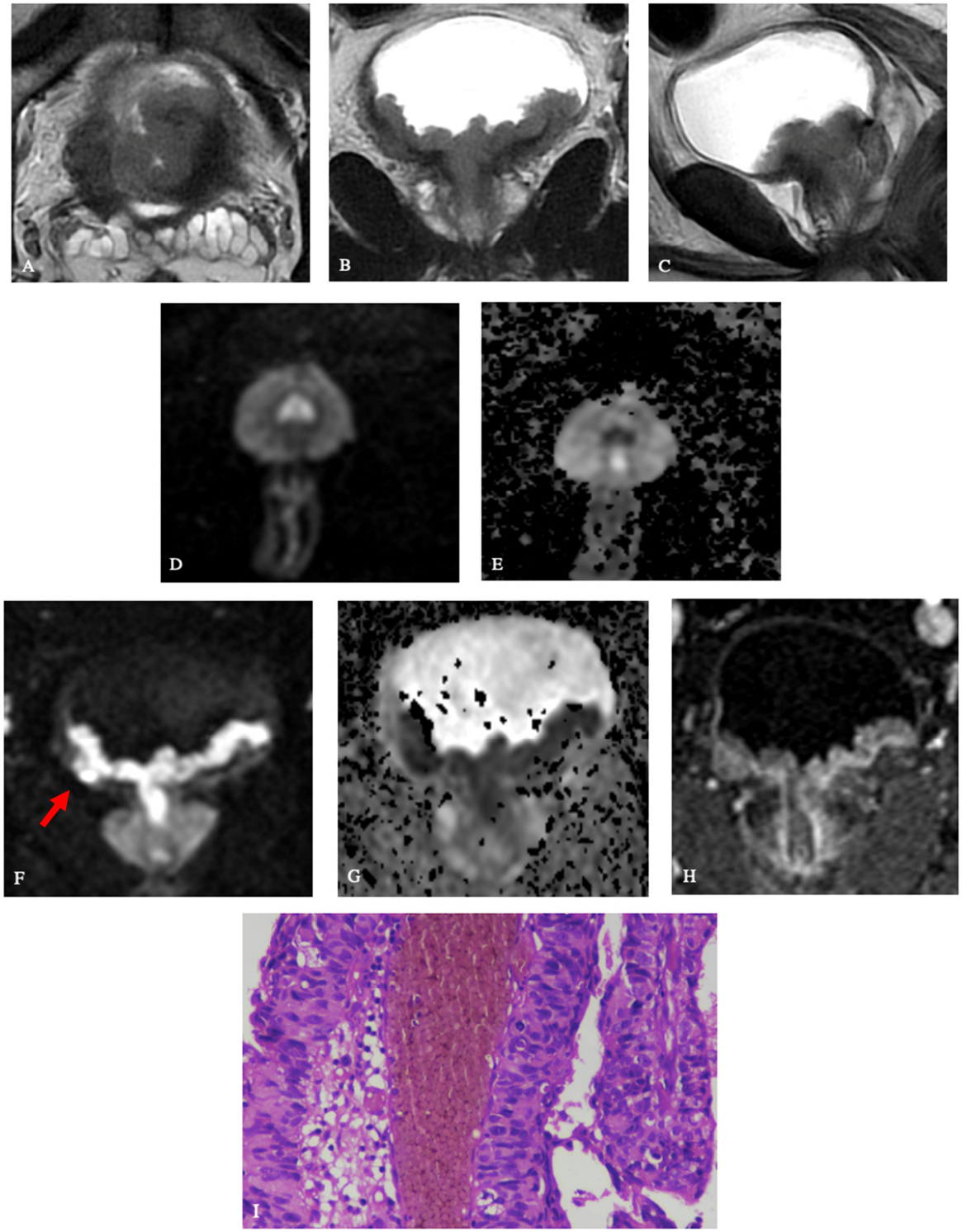
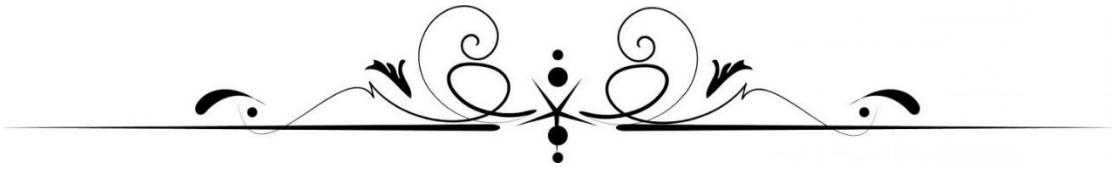
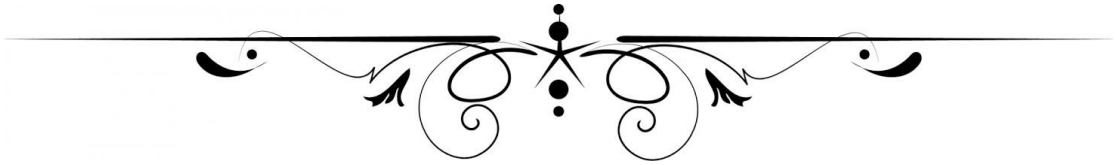


Figure: (A, B, C) Axial, coronal and sagittal T2WI showing hyperintense mixed type lesions (flat and papillary) with broad base along bladder neck and bilateral inferolateral wall. The lesion is seen involving bladder neck and prostatic urethra (D, E) Axial DWI and ADC map showing diffusion restriction and involvement of prostatic urethra (F, G) Coronal FOCUS-DWI and ADC map showing better visualization of tumour stalks and muscle invasion along the right inferolateral wall (red arrow) and extension of tumor along urethra. Coronal FOCUS-DWI shows a clear advantage in this case also over the axial DWI as the mass lesions are predominantly oriented in axial plane along the inferior wall (H) Coronal DCE showing early enhancement of lesion (I) HPE image showing carcinoma in situ, H&E stain, 40x.



DISCUSSION



DISCUSSION

Our study prospectively assessed VI-RADS to test its performance in the diagnosis of detrusor muscle invasion in cases of urinary bladder cancer. Out of 31 patients in our study, 27 patients were biopsy naïve and underwent TURBT after prospective interpretation of VI-RADS scores. Four patients had a history of previous TURBT. Our study assessed VI-RADS for each MRI parameter in the whole urinary bladder and surrounding perivesical fat before an overall score was determined. Our results showed that, in general, higher VI-RADS scores positively correlate with higher diagnosis rates of muscle invasive bladder cancer. Our study also showed that VI-RADS scores of 4 and 5 for each MRI parameter have a good diagnostic accuracy for detecting detrusor muscle invasion in cases of bladder cancer. Our results showed a superior diagnostic accuracy of muscle invasive bladder cancer with an overall score of ≥ 4 compared to that of ≥ 3.

We assessed the accuracy of VI-RADS for the detection of bladder cancer and identification of detrusor muscle invasion. A cut off ≥ 4 showed a higher specificity, PPV (93.33% each) than a cut off ≥ 3 (73.33% and 80%), and a lower sensitivity, NPV (87.50% each) than a cut off ≥ 3 (100% each). Hence, we concluded that a score ≥ 4 would be an optimal cut off to detect overall muscle invasive bladder cancer. However, a cut off ≥ 3 in keeping with the greater sensitivity will aid in detection of higher number of overall muscle invasive bladder cancers and can be utilized in conjunction with TURBT to increase the accuracy of detection of muscle invasion. Various other studies using radical cystectomy / guided biopsies as reference standards, showed a wide range of sensitivities and specificities for detection of detrusor muscle invasion in urinary bladder cancer. This has been summarized in Table 16.

Table 16: Comparison of studies which evaluated VI-RADS for detection of detrusor muscle invasion on MRI in urinary bladder cancer

Study	Cut off	Sensitivity (%)	Specificity (%)
Our study	≥4	87.5	93.3
	≥3	100	73.33
Huanjun Wang et al (23)	≥3	87.1	96.5
Hyung Kim et al (22)	≥4	91.3	76
	≥3	94.6	43.9
Kumawat Ghanshyam et al (25)	≥4	79.4	94.2
	≥3	91.2	78.8
Ziyong Wang et al (26)	>3	82.3	95.3
Giovanni Barchetti et al (27)	>2	R1-91	89
		R2-82	85
	>3	R1-82	94
		R2-87	89
Francesco Del Giudice et al (28)	≥3	91.9	91.1
J. Gmeiner et al (24)	>3	R1-92.9	95.1
		R2-100	92.5

Where R1 is reader one, R2 is reader two

The wide variation in sensitivity and specificity can be explained by the different cut offs, differences in MRI machines, MRI acquisition protocols, variability of VI-RADS scoring, biopsy protocol, differences in patient characteristics and user experience with the VI-RADS system. With the relatively recent genesis of this system, the existing inter-observer variability can be regarded as part of a learning curve which is expected to improve with larger and more variable studies. To the best of our knowledge, we prospectively evaluated VI-RADS, strictly adhering to their imaging protocols.

In our study, all 11 (100%) patients with VIRADS score 2 had a non-muscle invasive bladder tumour on HPE. Three (60%) patients out of a total of 5 patients with VIRADS score 3 had a non-muscle invasive tumour on HPE while the remaining 2 (40%) showed muscle invasion on the final HPE. Out of 6 patients with VIRADS score 4, 5 (83.33%) had muscle invasive and 1 (16.66%) had non-muscle invasive tumours. A total of 14 (93.3%) patients out of total 15 with VIRADS score $\geq$4 had muscle invasion and 2 (6.66%) had no muscle invasion on HPE. All 9 (100%) patients with VIRADS score 5 had muscle invasion on the final biopsy.

Out of 76 lesions studied, a total of 75 lesions were evaluated for advantage of FOCUS-DWI sequence. One patient with single lesion did not undergo the FOCUS-DWI sequence. We found the advantage of FOCUS-DWI sequence in 18 (24%) lesions out of 76 lesions. Thus adding significantly to the diagnostic efficiency. FOCUS-DWI in an orthogonal plane also increased our diagnostic confidence in the evaluation of these 18 lesions with regard to muscle invasion.

Further in our study, the presence of nodal involvement and restricted wall distention was seen to have a significant association with presence of detrusor muscle invasion in cases of urinary bladder cancer.

In a prospective study by *Sahar Mahmoud Abd elsalam et al*, 60 patients with urinary bladder mass lesions were evaluated for presence of detrusor muscle invasion and ADC values of tumours were calculated. ANOVA test was done to evaluate the statistical difference between mean ADC value of different tumour grades (G1, G2 and G3) which showed a statistically significant difference between the three groups (P value < 0.0001 and F was 66.9 at 2 degree of freedom). In accordance to results an inverse relationship was found between the mean ADC values and the histological grade of the bladder tumours (35).

In our study also, as mentioned earlier quantitative analysis of ADC value showed a significant association with the high grade on histology, thus helping in prognostication.

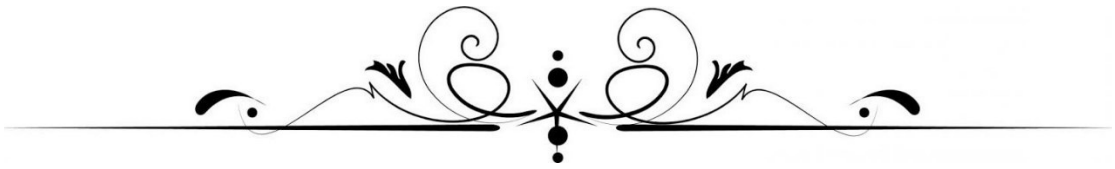
Thus, all the above mentioned imaging features - nodal involvement, restricted wall distention and quantitative analysis of ADC value along with additional FOCUS-DWI sequence aids to the diagnosis of detrusor muscle invasion and confident assignment of VI-RADS scoring in cases of urinary bladder cancer.

In our study, results suggested that in patients with VI-RADS score 3, the ratio of muscle-invasive to non-invasive tumour was 2:3, so this category of patients can be evaluated in conjunction with TURBT to increase the overall accuracy of diagnosis of muscle invasion pre-operatively, but in rest of VI-RADS score, there was good accuracy for the prediction of muscle invasion.

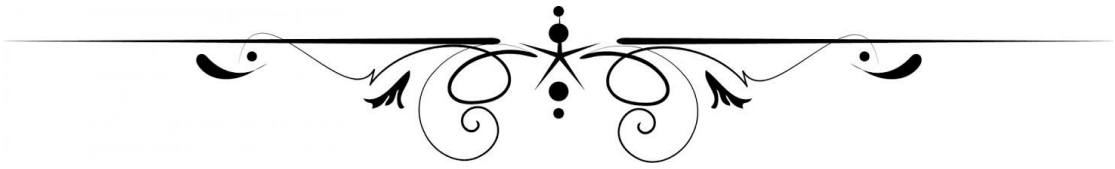
Because of the very high possibility of muscle invasion, it is clear from the preceding observation that in selected cases where we encountered a VI-RADS score of 4 or 5 in the preoperative setting, our target should only be a biopsy of the tumour with adequate depth, and these patients may be candidates for radical cystectomy in the future. As a result of the VI-RADS score validation, these patients can have earlier neo-adjuvant chemotherapy and radical cystectomy without delay, avoiding morbidity and saving cost on repeat TURBT.

At the same time, because there is little risk of muscle invasion in patients with VI-RADS scores of 1 or 2, our goal should be complete TURBT, and these are the individuals that might undergo repeated re-TURBTs routinely in the existing clinical scenario. As a result of the confirmation of the VI-RADS score in numerous studies, needless Re-TURBT in these low-risk patients should be avoided, and earlier intravesical treatment can be initiated if MRI strongly suggests non-muscle invasive malignancy.

Very few muscle invasive bladder cancers were missed by mpMRI. Hence, VI-RADS proved to be an accurate tool to diagnose overall bladder cancer on MRI and detect associated detrusor muscle invasion.

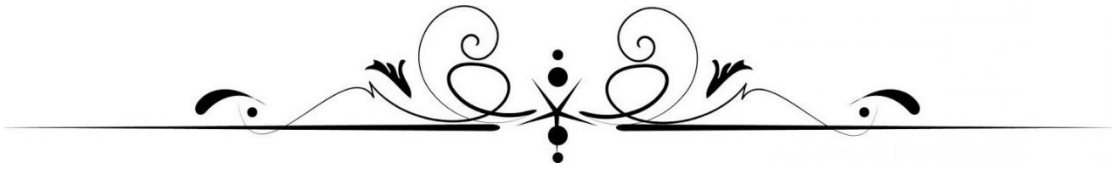


LIMITATIONS

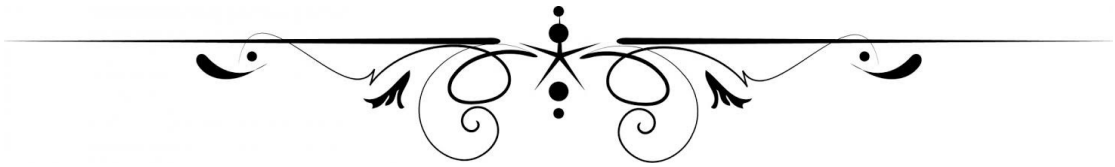


LIMITATIONS OF STUDY

- Our study is a single institute study with a small sample size so, a multicentric study with a larger cohort would be preferable for better validation.
- COVID -19 pandemic had a role to play in reducing the sample size of the study.
- The histopathological specimen from TURBT has an inherent risk of inaccurate and inadequate sampling due to operator variability, making it a less appropriate reference standard as compared to radical cystectomy specimen.
- Lesion to lesion comparison of VI-RADS with HPE was not done separately. However, VI-RADS scoring was given to the patient based on the lesion with highest score.
- Our study involved only 2 cases of non-urothelial malignancies in which VI-RADS scoring accurately identified muscle invasion. However, a larger cohort would be preferrable for validation of VI-RADS in less common non-urothelial malignancies.
- Follow up and comparison with repeat TURBT histopathology was not done.



CONCLUSION



CONCLUSION

- We found that the VI-RADS score is a reliable, convenient, and effective radiological tool for the pre-operative evaluation of patients with urinary bladder cancer and differentiation of muscle invasive bladder cancer from non-muscle invasive bladder cancer, which can aid in adequate management and prognostication of the patients.
- VI-RADS score of $\geq$ 4 shows a superior diagnostic accuracy for the detection of muscle invasive bladder cancer.
- VI-RADS score of 3 can be utilised in conjunction with TURBT staging to increase the sensitivity and accuracy of muscle invasion.
- As DWI is the most important sequence for detection of detrusor muscle invasion, so an addition of FOCUS-DWI sequence in an orthogonal plane increases the accuracy of VI-RADS and diagnostic confidence of the radiologist.

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ANNEXURES

ANNEXURE – 1

ETHICAL CLEARANCE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2083 **Date: 01/01/2020**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/1011**

Project title: **"Validation of VI-RADS for urinary bladder cancer on Multiparametric 3T MRI and Histopathological correlation"**

Nature of Project:	**Research Project**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Vatsala Veerendra**
Guide:	**Dr. Taruna Yadav**
Co-Guide:	**Dr. Pushpinder Singh Khera, Dr. Binit Sureka, Dr. Poonam Elhence, Dr. Gautam Ram Choudhary & Dr. Himanshu Pandey**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

Basni Phase-2, Jodhpur, Rajasthan-342005, **Website:** www.aiimsjodhpur.edu.in, **Phone:** 0291-2740741 Extn. 3109
Email: ethicscommittee@aiimsjodhpur.edu.in

ANNEXURE – 2

PARTICIPANT INFORMED CONSENT FORM

Participant identification number for this study: _____

Title of project: Validation of VI-RADS for urinary bladder cancer on Multiparametric 3T MRI and histopathological correlation .

Name of Principal Investigator: Dr. Vatsala Veerendra

Contact no 7291093180

The Contents of the information sheet dated ……. that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions. The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my medical records.

I agree to take part in the above study.

Date:_____

(Signatures / Left Thumb Impression) _____

Place: _____

Name of the Participant: _____

Son / Daughter / Spouse of:_____

Complete postal address:

_____

This is to certify that the above consent has been obtained in my presence.

Signature of the Principal Investigator: Place: Date:

1) Witness – 1

Signature ----------

Name:

Address:

2) Witness – 2

Signature ----------

Name:

Address:

ANNEXURE - 3

सहभागी सूचित सहमति फॉर्म

इस परीक्षण के लिए प्रतिभागी पहचान संख्या: _____

परियोजना का शीर्षक: **मल्टीपरामेट्रिक 3T एमआरआई और हिस्टोपैथिक सहसंबंध पर मूत्राशय के कैंसर के लिए VI-RADS की मान्यता**

प्रधान अन्वेषक का नाम: **डॉ वत्सला वीरेंद्र**

संपर्क नंबर 7291093180

सूचना शीट की सामग्री ..... प्रदान की गई थी, मेरे द्वारा विस्तृत रूप से पढ़ा गया / विस्तार से मेरे लिए, उस भाषा में, जिसे मैं समझता हूं, और मैंने पूरी तरह से सामग्री को समझा है। मैं पुष्टि करता हूं कि मुझे प्रश्न पूछने का अवसर मिला है। अध्ययन की प्रकृति और उद्देश्य और इसके संभावित जोखिम / लाभ और अध्ययन की अपेक्षित अवधि और अध्ययन के अन्य प्रासंगिक विवरण मुझे विस्तार से समझाए गए हैं। मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मैं किसी भी समय बिना किसी कारण के बिना किसी भी समय वापस लेने के लिए स्वतंत्र हूं, मेरी चिकित्सा देखभाल या कानूनी अधिकार के बिना प्रभावित हो रहा है।

मैं समझता हूं कि इस शोध में मेरी भागीदारी से मेरे बारे में एकत्रित की गई जानकारी और किसी भी मेडिकल नोट के कुछ हिस्सों को एम्स के जिम्मेदार व्यक्तियों द्वारा देखा जा सकता है। मैं इन व्यक्तियों को अपने मेडिकल रिकॉर्ड तक पहुंच की अनुमति देता हूं।

मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं।

तारीख: ----------

(हस्ताक्षर / बाएं अंगूठे छाप) ----------

जगह: _____

प्रतिभागी का नाम: _____

बेटा / बेटी / पति का: _____

पूरा डाक पता:

_____

यह प्रमाणित किया जाता है कि उपरोक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।

प्रधान अन्वेषक के हस्ताक्षर: **स्थान**: **तिथि**:

1) साक्षी - 1

नाम

हस्ताक्षर _____

पता

2) साक्षी - 2

नाम

हस्ताक्षर _____

पता

ANNEXURE - 4

PATIENT INFORMATION SHEET

1. Title of study: Validation of VI-RADS on Multiparametric MRI for urinary bladder cancer with histopathological correlation.

2. Aim of the study: We would like to invite you to take part in our study. The aims of our study is 'Validation of VI-RADS for urinary bladder cancer on 3T MRI'.

3. Histopathology correlation will be done with Biopsy specimen.

4. Benefits from the Study:
   (1) The study if successful, would give the urologist a clear and fast idea of the precise grading/staging along with volume distribution map of bladder cancer, without the need for multiple invasive bladder biopsies.
   (2) Better localization of cancer distribution will help in directing targeted biopsies for histopathological confirmation of suspicious cancer foci and in deciding feasibility of the focal therapies/active surveillance for low risk lesions, as opposed to a radical cystectomy.
   (3) Validate the routine clinical use of VI-RADS for the diagnosis of Bladder cancer using mpMRI.

5. Risks to the patients : There's no risk of death or any disability resulting directly due to imaging. No interventions or life-threatening procedure will be done.

6. Confidentiality: Your participation will be kept confidential. Your medical records will be treated with confidentiality and will be revealed only to doctors/ scientists involved in this study. The results of this study may be published in a scientific journal, but you will not be identified by name.

7. Provision of free treatment for research related injury. Not applicable.

8. Compensation of subjects for disability or death resulting from such injury, Not Applicable.

9. Freedom of individual to participate and to withdraw from research at any time without penalty or loss of benefits to which the subject would otherwise be entitled. You have complete freedom to participate and to withdraw from research at any time without

penalty or loss of benefits to which you would otherwise be entitled. Your participation in the study is optional and voluntary. The copy of the results of the investigations performed will be provided to you for your record. You can withdraw from the project at any time, and this will not affect your subsequent medical treatment or relationship with the treating physician. Any additional expense for the project, other than your regular expenses, will not be charged from you.

10. Costs and source of investigations, disposables, and drugs / contrast media,
    a. Institute charges for MRI pelvis - Exempted
    b. Contrast medium (Gadodiamide injection) – Exempted.

11. For further information and to report any side effects/complications, kindly contact:

    Dr. Vatsala Veerendra
    Junior resident
    Department of Diagnostic and Interventional Radiology
    AIIMS, Jodhpur
    Mob no 7291093180

12. I, Dr. Vatsala Veerendra, certify that translation to vernacular is accurate.

ANNEXURE - 5

रोगी सूचना पत्र

1.अध्ययन का शीर्षक: मल्टीपरामेट्रिक 3T एमआरआई और हिस्टोपैथिक सहसंबंध पर मूत्राशय के कैंसर के लिए VI-RADS का सत्यापन I

2. अध्ययन का उद्देश्य: हम आपको हमारे अध्ययन में भाग लेने के लिए आमंत्रित करना चाहते हैं। हमारे अध्ययन का उद्देश्य हैं: 3T MRI पर मूत्राशय के कैंसर के लिए VI-RADS की मान्यता I

3. हिस्टोपैथोलॉजी सहसंबंध बायोप्सी नमूने के साथ किया जाएगा।

4. अध्ययन से लाभ:

(1) यदि अध्ययन सफल होता है, तो मूत्राशय कैंसर के वॉल्यूम वितरण मानचित्र के साथ, सटीक ग्रेडिंग / स्टेजिंग के लिए मूत्रविज्ञानी एक स्पष्ट विचार प्रदान कर सकेगा, बिना कोई इनवेसिव मूत्राशय बायोप्सी किये।

(2) कैंसर वितरण के बेहतर स्थानीयकरण, खतरनाक कैंसर फॉसी की हिस्टोपैथोलॉजिकल पुष्टिकरण के लिए लक्षित बायोप्सी को निर्देशित करने में और कम जोखिम वाले घावों के लिए फोकल थेरेपी / सक्रिय निगरानी की व्यवहार्यता तय करने में मदद मिलेगी,

3. रोगियों के लिए जोखिम: इमेजिंग के कारण सीधे मौत या कोई विकलांगता का कोई खतरा नहीं है। कोई हस्तक्षेप या जीवन धमकी प्रक्रिया नहीं किया जाएगा।

6. गोपनीयता: आपकी भागीदारी को गोपनीय रखा जाएगा। आपके मेडिकल रिकॉर्ड को गोपनीयता के साथ इलाज किया जाएगा और केवल इस अध्ययन में शामिल डॉक्टरों / वैज्ञानिकों के लिए खुलासा किया जाएगा। इस अध्ययन के परिणाम एक वैज्ञानिक पत्रिका में प्रकाशित हो सकते हैं, लेकिन आपको नाम से पहचाना नहीं जाएगा।

7. अनुसंधान संबंधी चोट के लिए नि: शुल्क उपचार की व्यवस्था लागू नहीं।

8. ऐसी चोट से उत्पन्न विकलांगता या मृत्यु के लिए विषयों का मुआवजा, लागू नहीं।

9. किसी भी समय दंड या लाभ के नुकसान के बिना किसी भी समय भाग लेने के लिए और किसी भी समय शोध के लिए व्यक्ति को स्वतंत्रता की स्वतंत्रता, जिसके तहत विषय अन्यथा हकदार होगा आपको जुर्माना या लाभ के नुकसान के बिना किसी भी समय भाग लेने और अनुसंधान से वापस लेने की पूरी आजादी है, जिसके लिए आप अन्यथा हकदार होंगे अध्ययन में आपकी भागीदारी वैकल्पिक और स्वैच्छिक है किए गए जांच के परिणामों की प्रति आपके रिकॉर्ड के लिए आपको उपलब्ध कराई जाएगी। आप किसी भी समय परियोजना से वापस ले सकते हैं, और यह आपके बाद के चिकित्सा उपचार या उपचार चिकित्सक के साथ संबंध को प्रभावित नहीं करेगा। परियोजना के लिए कोई भी अतिरिक्त व्यय, आपके नियमित खर्चों के अलावा, आपसे शुल्क नहीं लिया जाएगा।

10. जांच, निष्पादन, और ड्रग्स / कंट्रास्ट मीडिया की लागत और स्रोत,

(1) एमआरआई के लिए संस्थान शुल्क - छूट दी गई

(2) कॉन्ट्रास्ट मध्यम (गादोडियामेड इंजेक्शन) - छूट दी गई

11. अधिक जानकारी के लिए और किसी दुष्प्रभाव / जटिलताओं की रिपोर्ट करने के लिए, कृपया संपर्क करें:

डॉ वत्सला वीरेंद्र

जूनियर निवासी

डायग्नोस्टिक एंड इंटरवेंशनल रेडियोलॉजी विभाग

एम्स, जोधपुर

संपर्क नंबर 7291093180

12. मैं, डॉ वत्सला वीरेंद्र, प्रमाणित करती हू कि स्थानीय भाषा में अनुवाद सटीक है।

ANNEXURE - 6

PATIENT PROFORMA

- Patient's Name:
- Age: Sex:
- Hospital Registration Number:
- Father's/Guardian Name:
- Address:

- Phone:
- Clinical history:

- Findings :-

1.Mapping lesion/s:

2.Morphology:

3.Measurements of the lesions:

4. Scoring :-

  - T2W-
  - DWI-

- DCE
- Final VI-RADS assessment (categories):

5.Transmural extension:

6.Adjacent organ invasion:

7.Nodes:

8.Bone/metastasis:

- MRI staging :

- Histopathology report of the TURBT guided biopsy specimen with staging:

ANNEXURE - 7

MASTER CHART

S.NO	AGE/ GENDER	NO OF LESIONS	LESION MAPPING	VUJ INVOLVEMENT (LT-LEFT) (RT-RIGHT)	MORPHOLOGY PAPILLARY (P) / NON-PAILLARY (NP) / MIXED	SIZE (mm)	RESTRICTED WALL DISTENTION	PERIVESICAL FAT INFILTRATION ON T1	T2 VIRADS	DCE VIRADS	ADC VALUE (mm2/sec)	DWI VIRADS	FINAL VIRADS	NODAL INVOLVEMENT	HPE
1	72Y/M	1	7	NO	P	11	NO	NO	2	2	820	2	2	NO	NMIBC
		2	8	NO	P	10.2	NO	NO	2	2	863	2	2		
		3	4	NO	P	28	NO	NO	2	2	971	2	2		
		4	5	NO	P	22	NO	NO	2	2	846	2	2		
		5	7	NO	P	62	YES	YES	4	3	805	2	2		
2	75Y/M	1	7	NO	NP	55	YES	YES	4	4	657	4	4	NO	MIBC
		2	8	NO	P	8	NO	NO	1	1	556	1	1		
3	59Y/M	1	7	NO	P	12.5	NO	NO	2	2	1431	2	2	NO	NMIBC
		2	5,7	NO	NP	3	NO	NO	1	1	1652	1	1		
		3	6	NO	P	20	NO	NO	2	2	1083	2	2		
4	56Y/M	1	6	NO	P	26	NO	NO	3	3	1296	2	2	NO	NMIBC
5	65Y/M	1	9,8	NO	P	9	NO	NO	1	1	1641	1	1	NO	MIBC
		2	9	NO	P	6	NO	NO	1	1	1369	1	1		
		3	7	NO	P	24	NO	NO	2	2	903	2	2		
		4	7	NO	P	20	NO	NO	2	2	1057	2	2		
		5	5	NO	P	42	NO	NO	2	2	1060	2	2		
		6	5	NO	P	14.6	NO	NO	2	2	1128	2	2		
		7	6	YES	P	70	YES	NO	4	4	1166	4	4		
6	69Y/M	1	6	NO	P	78	YES	NO	3	3	952	3	3	NO	MIBC
		2	8,5	NO	P	50	NO	NO	2	2	871	2	2		
		3	7	NO	P	50	YES	NO	3	3	1319	3	3		
		4	7	LT VUJ	P	80	YES	YES	5	5	933	5	5		
		5	5	NO	P	46	NO	NO	3	3	763	3	3		
7	67Y/F	1	4	RT VUJ	P	43	YES	YES	5	5	1029	5	5	YES	MIBC
8	50Y/M	1	7	LT VUJ	P	66	YES	NO	3	3	1287	3	3	NO	NMIBC
9	44Y/F	1	5,6	NO	P	45	YES	NO	3	3	1007	3	3	NO	NMIBC
		2	5,7	LT VUJ	P	31	NO	NO	2	2	1408	2	2		
		3	5,6	RT VUJ	P	21	YES	NO	3	3	1317	3	3		
		4	6	RT VUJ	P	19	NO	NO	2	2	1465	2	2		
		5	6	NO	P	20	NO	NO	2	2	1343	2	2		
		6	9,6	NO	P	23	NO	NO	2	2	1487	2	2		
		7	5	RT VUJ	P	19	NO	NO	2	2	1559	2	2		
		8	5	NO	P	58	YES	NO	3	3	1171	3	3		
10	77Y/M	1	5,7	NO	P	14	NO	NO	2	2	1043	2	2	NO	NMIBC
		2	5,7	NO	P	12.7	NO	NO	2	2	1235	2	2		
11	75Y/M	1	5	LT VUJ	P	60	YES	NO	3	NOT DONE	1049	3	3		NMIBC
12	65Y/M	1	9,6	NO	P	50	NO	NO	4	NOT DONE	857	4	4	NO	NMIBC (FALSE POSITIVE)
13	60Y/M	1	5,6	RT VUJ	NP	58.6	YES	YES	5	5	1071	5	5	YES	MIBC
14	60Y/M	1	6	NO	P	46	YES	NO	4	3	808	3	3	NO	MIBC (FALSE NEGATIVE)
15	40Y/M	1	5	NO	P	26	NO	NO	2	NOT DONE	1101	2	2	YES	MIBC
		2	5	NO	P	32	NO	NO	2		952	2	2		
		3	9	NO	P	17	NO	NO	2		1127	2	2		
		4	9	NO	P	25	NO	NO	2		1222	2	2		
		5	9	NO	P	35	YES	NO	4		810	4	4		
		6	6	NO	P	47	YES	NO	2		1384	2	2		
		7	7	NO	P	68	YES	YES	5		768	5	5		
16	77Y/M	1	5,7	LT VUJ	NP	45	YES	NO	4	4	786	4	4	NO	MIBC
17	74Y/M	1	7	LT VUJ	NP	36	YES	YES	4	4	859	5	5	NO	MIBC
18	43Y/M	1	3	NO	P	33	NO	NO	2	2	1032	2	2	NO	NMIBC
		2	7	NO	P	13	NO	NO	2	2	1038	2	2		
		3	9	NO	P	68	YES	NO	2	2	656	2	2		
		4	7	NO	P	40	NO	NO	2	2	850	2	2		
		5	9,6	NO	P	20	NO	NO	2	2	909	2	2		
		6	9	NO	P	22	NO	NO	2	2	848	2	2		
		7	9	NO	P	35	NO	NO	2	2	1042	2	2		
		8	6	NO	P	12	NO	NO	2	2	941	2	2		
19	60Y/M	1	6,4	BOTH VUJ	NP	11	YES	YES	5	NOT DONE	1027	5	5	YES	MIBC
20	57Y/M	1	9	NO	P	30	NO	NO	2	2	848	2	2	NO	NMIBC
21	42Y/M	1	9	NO	P	32	NO	NO	2	2	983	2	2	NO	NMIBC
		2	5	NO	P	26	NO	NO	2	2	1016	2	2		
		3	5	NO	P	12	NO	NO	2	2	1191	2	2		
		4	5	NO	P	11	NO	NO	2	2	1026	2	2		
		5	5	LT VUJ	P	27	NO	NO	2	2	1001	2	2		
22	67Y/M	1	4	NO	NP	28	YES	YES	5	5	784	5	5	YES	MIBC
23	58Y/M	1	7,4	NO	P	57	YES	NO	3	NOT DONE	652	3	3	YES	MIBC (FALSE NEGATIVE)
24	71Y/M	1	5,7	NO	P	10.9	NO	NO	2	2	559	2	2	NO	NMIBC
25	77Y/M	1	6	NO	MIXED	80	YES	NO	2	2	891	2	2	NO	NMIBC
26	74Y/M	1	7	NO	P	40	YES	YES	5	5	889	5	5	YES	MIBC
27	80Y/F	1	6	NO	P	26	NO	NO	2	2	1154	2	2	NO	NMIBC
28	70Y/M	1	7	NO	P	36	YES	NO	2	2	1146	2	2	NO	NMIBC
29	44Y/M	1	6,3,2	RT VUJ	MIXED	75	YES	NO	4	4	665	4	4	YES	MIBC
		2	7,3,2	LT VUJ	MIXED	75	YES	NO	3	3	616	3	3		
		3	8,6	NO	MIXED	53	YES	NO	2	2	1602	2	2		
		4	6,5	NO	NP	14	NO	NO	2	2	1530	2	2		
30	60Y/M	1	7	LT VUJ	NP	42	YES	NO	4	4	532	4	4	NO	MIBC (Small cell Cancer)
31	30Y/M	1	9,7,5	LT VUJ	NP	150	YES	YES	5	5	892	5	5	YES	MIBC (Invasive keratinising SCC)