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# Diagnostic Value of the Vesical Imaging-Reporting and Data System in Bladder Urothelial Carcinoma with Variant Histology

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**Abstract**

The value of the Vesicle Imaging-Reporting and Data System (VI-RADS) in the diagnosis of muscle-invasive bladder cancer (MIBC) for urothelial carcinoma with variant histology (VUC) remains unknown. We retrospectively evaluated 360 consecutive patients with bladder cancer (255 pure urothelial carcinoma [PUC] and 69 VUC) who underwent multiparametric magnetic resonance imaging between 2011 and 2019. VI-RADS scores assigned by four readers were significantly higher for the VUC group than for the PUC group ($p < 0.05$). In the cohort of 122 pair-matched patients, there was no significant difference in VI-RADS score distribution between the PUC and VUC groups for all readers ($p > 0.05$). The area under the receiver operating characteristic curve for MIBC diagnosis via overall VI-RADS score was 0.93–0.94 for PUC and 0.89–0.92 for VUC, with no significant difference between the PUC and VUC groups ($p = 0.32$–$0.60$). These data suggests that VI-RADS scores achieved high diagnostic performance for detection of muscle invasion in both PUC and VUC.

***Patient summary:*** The Vesical Imaging-Reporting and Data System (VI-RADS) is a standardized system for reporting on detection of muscle-invasive bladder cancer via magnetic resonance imaging (MRI) scans. Our study shows that VI-RADS is also highly accurate for diagnosis for different variants of muscle-invasive bladder cancer, with good inter-reader agreement.

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Pure urothelial carcinoma (PUC) is the most common type of bladder cancer (BC). It is estimated that histological variant urothelial carcinoma (VUC) occurs in 10–25% of all BC cases, and VUCs are more frequent in the advanced

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and muscle-invasive stages, with poorer chemotherapy and radiotherapy responses [1–3].

The Vesical Imaging-Reporting and Data System (VI-RADS) is a standardized reporting system for detection of muscle-invasive BC (MIBC) via multiparametric magnetic resonance imaging (mpMRI) in patients with PUC [4]. VI-RADS is highly accurate in discriminating MIBC from non-MIBC (NMIBC) and has good inter-reader agreement in PUC [5–7]. However, the usefulness of VI-RADS in VUC remains unknown. We investigated the diagnostic performance of VI-RADS for MIBC assessment in VUC.

This bi-institutional study included 360 consecutive treatment-naïve patients who underwent bladder mpMRI before their first transurethral resection of bladder (TURB) between August 2011 and September 2019 (Fig. 1). MRI examinations were performed using a 1.5-T system with body array coils (Supplementary Table 1).

For each patient, the index tumor was defined as the tumor with the highest stage and selected for image analysis. The largest tumor was selected if more than one high-stage tumor were present. Three image sequences (T2-weighted imaging [T2WI], diffusion-weighted imaging [DWI], and dynamic contrast-enhanced [DCE]-MRI) were scored using the VI-RADS five-point scoring system [4] on a picture archiving and communication system workstation (Centricity Universal Viewer, GE Healthcare, Chicago, IL, USA).

Scoring was performed prospectively and independently by four blinded, board-certified radiologists. The final five-point VI-RADS overall score was compiled using the individual T2WI, DWI, and DCE-MRI scores according to the VI-RADS guideline [4]. The radical cystectomy specimen was used as the pathological reference standard for muscle invasion. If radical cystectomy was not performed or performed with neoadjuvant chemotherapy, TURB was used as the reference standard.

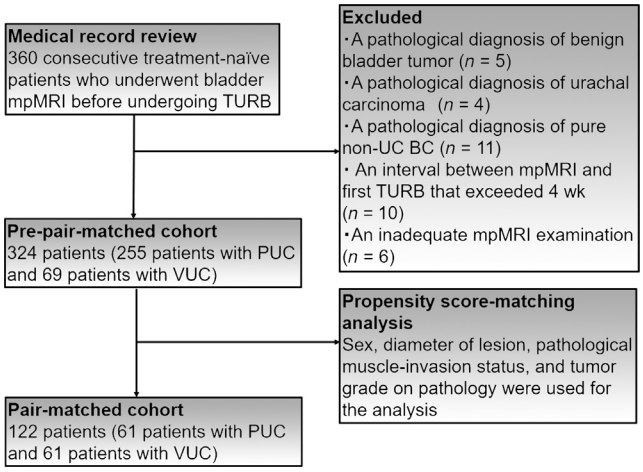


**Fig. 1 – Flowchart of patient inclusion. Patients with a pathological diagnosis of benign bladder tumor (*n* = 3 leiomyoma, *n* = 2 endometriosis), urachal carcinoma (*n* = 4), or pure non-UC BC (*n* = 6 pure squamous cell carcinoma, three adenocarcinoma, two small cell carcinoma) were excluded from the analyses. Patients with an interval between mpMRI and first TURB exceeding 4 wk (*n* = 10) or an inadequate mpMRI examination (*n* = 6 image degradation due to hip replacement) were also excluded. A total of 324 patients (255 PUC and 69 VUC) fulfilled the eligibility criteria. mpMRI = multiparametric magnetic resonance imaging; TURB = transurethral resection of bladder tumor; PUC = pure urothelial carcinoma; VUC = histological variant of urothelial carcinoma; BC = bladder cancer.**

Sex, lesion diameter, pathological muscle invasion status, and pathological tumor grade were used for the propensity score matching to select pair-matched patients in the PUC and VUC cohorts (Supplementary Table 2).

Among the 255 PUC and 69 VUC cases, 61 patients were selected for each cohort and matched on controlled background covariates. The median interval between mpMRI and first TURB was 2 wk (range 1–4). Among the 122 patients in the matched cohort, 34 PUC (55.7%) and 33 VUC (54.1%) had pathologically proven MIBC. Among the 20 high-risk NMIBC cases (9 PUC, 11 VUC), eight in the PUC group and ten in the VUC group underwent a second TURB, of which two PUC and three VUC cases were upstaged after the second TURB; 28 PUC and 34 VUC patients underwent radical cystectomy without prior chemotherapy. The clinical and pathological characteristics of the PUC and VUC cohorts before and after matching are presented in Supplementary Tables 1 and 3. In the cohort before matching, VI-RADS scores were significantly higher for VUC cases than for PUC cases for all readers ($p < 0.05$; Supplementary Table 4). In the pair-matched cohort, there was no significant difference in VI-RADS score distribution between the PUC and VUC cohorts for all readers ($p > 0.05$; Supplementary Table 5). Sessile/broad-based tumors and chemoradiotherapy were more common for the VUC than for the PUC cohort ($p < 0.05$; Table 1).

Scores for the three mpMRI sequences and the overall VI-RADS score for muscle invasion assessment for the PUC and VUC cohorts are shown in Supplementary Table 6. The Fleiss κ values for MIBC diagnosis in PUC/VUC for the four readers were 0.84/0.81 for the overall VI-RADS score, 0.75/0.68 for T2WI scores, 0.84/0.74 for DWI scores, and 0.84/0.77 for DCE-MRI scores; thus, reader consistency was good to excellent in both cohorts.

Cochran-Armitage test results show that for all T2WI, DWI, DCE-MRI, and overall VI-RADS scores, the proportion of cases with muscle involvement increased with increasing score, and the proportion of cases with no muscle involvement decreased with decreasing score ($p < 0.05$; Supplementary Table 6).

The PUC/VUC area under the receiver operating characteristic curve (AUC) for the overall VI-RADS score for MIBC diagnosis was 0.94/0.92 for reader 1, 0.94/0.91 for reader 2, 0.94/0.91 for reader 3, and 0.93/0.89 for reader 4 (Supplementary Table 7). There were no significant differences in AUC for overall VI-RADS score between the cohorts for all readers ($p > 0.05$). For the less experienced radiologists (readers 3 and 4), the DWI sensitivity was significantly lower in the VUC group than in the PUC group. However, the sensitivity and specificity of the other sequences (T2WI, DCE-MRI) and the overall score did not significantly differ between the two groups for all four readers ($p > 0.05$). Representative cases are shown in Supplementary Figures 1 and 2.

The higher VI-RADS scores for VUC than for PUC cases in overall cohort before matching can be attributed to the trend for more advanced cancers in the VUC group, since

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**Table 1 – Clinical and pathological characteristics of the pair-matched PUC and VUC groups**[a]

| Variable | PUC (*n* = 61) | VUC (*n* = 61) | *p* value[b] |
|---|---|---|---|
| Sex, *n* (%) | | | 1.00 |
| Male | 50 (82.0) | 49 (80.3) | |
| Female | 11 (18.0) | 12 (19.7) | |
| Median age, yr (range) | 73 (32–91) | 74 (53–98) | 0.33 |
| Median lesion diameter, mm (range) | 20 (4–55) | 19 (4–61) | 0.77 |
| Number of lesions, *n* (%) | | | 0.15 |
| Single | 38 (62.3) | 29 (47.5) | |
| Multiple | 23 (37.7) | 32 (52.5) | |
| Tumor shape, *n* (%) | | | <0.001* |
| Papillary tumor | 39 (63.9) | 19 (31.1) | |
| Sessile/broad-based tumor | 22 (36.1) | 42 (68.9) | |
| Preoperative chemotherapy, *n* (%) | | | 0.02* |
| Chemotherapy before radical cystectomy | 7 (11.5) | 17 (27.9) | |
| Chemoradiotherapy before radical cystectomy | 2 (3.3) | 6 (9.8) | |
| Pathological muscle invasion status, *n* (%) | | | 1.00 |
| Muscle invasion | 34 (55.7) | 33 (54.1) | |
| No muscle invasion | 27 (44.3) | 28 (45.9) | |
| Pathological T stage, *n* (%) | | | 0.74 |
| Ta | 5 (8.2) | 5 (8.2) | |
| T1 | 22 (36.1) | 23 (37.7) | |
| T2 | 25 (41.0) | 19 (31.1) | |
| T3 | 6 (9.8) | 10 (16.4) | |
| T4 | 3 (4.9) | 4 (6.6) | |
| Tumor grade on pathology, *n* (%) | | | 1.00 |
| High | 35 (57.4) | 35 (57.4) | |
| Low | 26 (42.6) | 26 (42.6) | |
| Pathological diagnosis, *n* (%) | | | – |
| Pure urothelial carcinoma | 61 (100) | 0 (0.0) | |
| Squamous differentiation | | 29 (47.5) | |
| Glandular differentiation | | 18 (29.5) | |
| Micropapillary variant | | 5 (8.2) | |
| Sarcomatoid variant | | 4 (6.6) | |
| Nested variant | | 2 (3.3) | |
| Plasmacytoid variant | | 2 (3.3) | |
| Lipid cell variant | | 1 (1.6) | |

PUC = pure urothelial carcinoma; VUC = histological variant of urothelial carcinoma; TURB = transurethral resection of bladder tumor.

[a] Sex, lesion diameter, pathological muscle invasion status, and pathological tumor grade were used for the propensity score matching to select pair-matched patients in the PUC and VUC groups.

[b] Age and lesion diameter were compared using a Wilcoxon signed-rank test. Sex, number of lesions, tumor shape, preoperative chemotherapy, pathological muscle invasion status, pathological T stage, and tumor grade on pathology were compared using Fisher's exact test.

* $p < 0.05$, statistically significant.

the VI-RADS score distribution did not significantly differ between PUC and VUC in the pair-matched cohort after adjustment for patient background and tumor characteristics.

Given the good interobserver agreement for VI-RADS scores and the high diagnostic accuracy for the PUC and VUC groups, it is appropriate to use VI-RADS scoring for evaluation of VUC patients.

In our study, less experienced radiologists underestimated the presence of muscle invasion in VUC, which exhibits heterogeneous or equivocal high signal intensity in the muscle layer on DWI owing to the high proportion of cytoplasm with relatively low cell density and microinvasion into the muscle layer [1,8].

Recent studies assessing VI-RADS based on biparametric MRI (T2WI, DWI) reported comparable diagnostic performance to conventional VI-RADS for patients with PUC [9,10]. According to our results, however, use of biparametric MRI by relatively less experienced readers may underestimate muscle invasion in VUC cases.

Our study had some limitations. First, the study was retrospective. Second, only one index tumor was chosen per patient. Third, TURB was used as the reference standard in 49.2% of the patients included. However, a second TURB was performed in 90.0% of high-risk NMIBC cases who did not undergo radical cystectomy. Fourth, the impact of the relative proportion of the variant histology on the VI-RADS score could not be assessed because 37.7% of VUC patients underwent chemotherapy before radical cystectomy. TURB could not adequately identify the relative proportion of variant histology in the resected specimen, and radical cystectomy could not reveal the relative proportion of variant histology because of systemic therapy receipt. Lastly, the sample size was relatively small. Future studies with larger sample sizes are warranted to analyze the diagnostic performance of VI-RADS for each VUC subtype. Further studies on pure non-UC are also expected.

In conclusion, the overall VI-RADS score had high diagnostic performance for detection of muscle invasion in both PUC and VUC.

***Author contributions***: Yuki Arita had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2022.07.006.

## References

[1] Wasco MJ, Daignault S, Zhang Y, et al. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. Urology 2007;70:69–74.
[2] Wang G, McKenney JK. Urinary bladder pathology: World Health Organization classification and American Joint Committee on Cancer staging update. Arch Pathol Lab Med 2019;143:571–7.
[3] Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol 2021;79:82–104.
[4] Panebianco V, Narumi Y, Altun E, et al. Multiparametric magnetic resonance imaging for bladder cancer: development of VI-RADS (Vesical Imaging-Reporting and Data System). Eur Urol 2018;74:294–306.
[5] Giudice FD, Flammia RS, Pecoraro M, et al. The accuracy of Vesical Imaging-Reporting and Data System (VI-RADS): an updated comprehensive multi-institutional, multi-readers systematic review and meta-analysis from diagnostic evidence into future clinical recommendations. World J Urol 2022;40:1617–28.
[6] Giudice FD, Pecoraro M, Vargas HA, et al. Systematic review and meta-analysis of Vesical Imaging-Reporting and Data System (VI-RADS) inter-observer reliability: an added value for muscle invasive bladder cancer detection. Cancers 2020;12:2994.
[7] Panebianco V, Pecoraro M, Giudice FD, et al. VI-RADS for bladder cancer: current applications and future developments. J Magn Reson Imaging 2022;55:23–36.
[8] Xylinas E, Rink M, Robinson BD, et al. Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy. Eur J Cancer 2013;49:1889–97.
[9] Ye L, Chen Y, Xu H, et al. Biparametric magnetic resonance imaging assessment for detection of muscle-invasive bladder cancer: a systematic review and meta-analysis. Eur Radiol. In press. https://doi.org/10.1007/s00330-022-08696-5.
[10] Delli Pizzi A, Mastrodicasa D, Marchioni M, et al. Bladder cancer: do we need contrast injection for MRI assessment of muscle invasion? A prospective multi-reader VI-RADS approach. Eur Radiol 2021;31:3874–83.