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Original Article

Extramural venous invasion: a novel magnetic resonance imaging biomarker for adverse pathology in bladder cancer

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Abstract: Extramural venous invasion (EMVI) recognized on magnetic resonance imaging (MRI) is an unequivocal biomarker for detecting adverse outcomes in rectal cancer: however it has not yet been explored in the area of bladder cancer. In this study, we assessed the feasibility of identifying EMVI findings on MRI in patients with bladder cancer and its avail in identifying adverse pathology. In this single-institution retrospective study, the MRI findings inclusive of EMVI was described in patients with bladder cancer that had available imaging between January 2018 and June 2020. Patient demographic and clinical information were retrieved from our electronic medical records system. Histopathologic features frequently associated with poor outcomes including lymphovascular invasion (LVI), variant histology, muscle invasive bladder cancer (MIBC), and extravesical disease (EV) were compared to MRI-EMVI. A total of 38 patients were enrolled in the study, with a median age of 73 years (range 50-101), 76% were male and 23% were females. EMVI was identified in 23 (62%) patients. There was a significant association between EMVI and MIBC (OR = 5.30, CI = 1.11-25.36; P = 0.036), and extravesical disease (OR = 17.77, CI = 2.37-133; P = 0.005). We found a higher probability of presence of LVI and histologic variant in patients with EMVI. EMVI had a sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of 90%, 73%, 94% and 63% respectively in detecting extravesical disease. Our study suggests, EMVI may be a useful biomarker in bladder cancer imaging, is associated with adverse pathology, and could be potentially integrated in the standard of care with regards to MRI reporting systems. A larger study sample size is further warranted to assess feasibility and applicability.

Keywords: Bladder cancer, MRI, VI-RADS, histopathology, extramural venous invasion (EMVI), cancer staging, prognosis

Introduction

Extramural venous invasion (EMVI), is defined as the presence of tumor cells within blood vessels beyond the muscularis propria potentially directing tumor metastasis, it was first described in 1980 as an adverse pathologic feature in rectal cancer [1]. The evolution from a pathology-based to clinical staging system utilizing computerized tomography (CT) and magnetic resonance imaging (MRI) has allowed patient stratification for appropriate therapeutic management. For example, EMVI identified either preoperatively on magnetic resonance imaging (MRI-EMVI) or postoperatively in pathologic specimens (P-EMVI) as an independent prognostic predictor for adverse outcomes in rectal cancer [2]. MRI maintains a high specificity (96%) and moderate sensitivity (54%) for the histopathologic diagnosis of rectal cancer EMVI [1].

Precise determination and assessment of bladder cancer (BC) extent of muscle invasion and

extravesical involvement guide proper risk stratification and personalized therapy selection [3]. Recently, much emphasis has been placed on investigating predictors of outcome to better prognosticate and direct management of this aggressive disease [4]. Until now molecular and genetic biomarkers have been studied to prognosticate outcomes of patients with BC [4-6]. There is increasing interest in correlating these biomarkers with radiomic features, which are best obtained by MRI [4, 7-12].

MRI is being rapidly adopted for evaluating BC patients to assess adverse pathology and locoregional disease. Multiparametric magnetic resonance imaging (mpMRI) has high soft tissue contrast resolution, multiplanar imaging capable of demonstrating detrusor muscle invasion and extravesical extension [10, 13, 14]. There has been a growing body of evidence demonstrating that standardized imaging and reporting of mpMRI in BC using the VI-RADS (vesical imaging-reporting and data system), helps in risk stratification and better treatment planning for advanced disease [11]. The current VI-RADS scoring system is based on MRI tumor characteristics with T2W, DWI, ADC value, and DCE imaging sequences creating an overall risk of invasion score [11].

While the VI-RADS scoring system has been validated by several studies for assessment of muscle invasion, there is only one published study for extravesical disease [10, 12, 14, 15]. VI-RADS is not yet widely used in standard clinical practice [16]. Additional studies and potentially other MRI parameters may further validate the utility of VI-RADS in assessing extravesical disease. It is conceivable that EMVI may become a useful parameter in a variety of future VI-RADS validation studies by improving performance characteristics; However, this is not yet studied in BC.

In this pilot study, we explored the feasibility of identifying EMVI on MRI of patients with BC and its potential utility in detecting adverse pathology.

Materials and methods

Following Institutional Review Board (IRB) approval, a retrospective review of the picture archiving and communication system (PACS) was conducted to include patients with BC who underwent mpMRI of the pelvis using a bladder protocol at our institution between January 2018 and June 2020. Demographic and clinical variables, including prior radiation therapy, chemotherapy or pelvic malignancy were retrieved from electronic medical records. Patients under 18 years of age, those with previous radiation treatment for BC, or other malignancies in the pelvis including gynecologic and prostate malignancies were excluded from the study. Following mpMRI, patients underwent transurethral resection of bladder tumor (TURBT). Further management included active surveillance, radical cystectomy and urinary diversion, or systemic chemotherapy, based on the pathologic stage of the disease and patient characteristics. BC stage was determined by pathological stage from cystectomy specimen (whenever performed) or a combination of TURBT pathology, clinical examination and radiologic findings (as a surrogate "clinical stage") otherwise.

MpMRI criteria and scoring

All mpMRI were reviewed and reported by two senior readers with sub specialization in body imaging and combined experience of more than 30 years. In the setting of interobserver variability a consensus was reached by the readers with regard to presence or absence of radiological EMVI.

Characterization of the lesion(s) for size, morphology, presence, and depth of muscularis propria invasion, presence of regional adenopathy, and presence or absence of EMVI were studied. The pattern of EMVI recognition was based upon presence of one of the following criteria on high resolution T2 weighted bladder images: 1) apparent intermediate signal intensity within slightly altered contour and caliber of vessels; 2) obvious irregular vessel contour or nodular expansion with demonstration of definite tumor signal [1, 2]. The MRI was performed using a 3 tesla MRI scanner (Siemens Healthcare) with four-channel and phased array pelvic coil with the patient in a supine position. Details of MRI of pelvis with and without contrast (bladder mass protocol) at our institution may be found in Supplementary Table 1. First spin-echo axial *T*1WI and high-resolution *T*2WI with more than two planes of multiplane (axial, sagittal or coronal) and without fat suppression

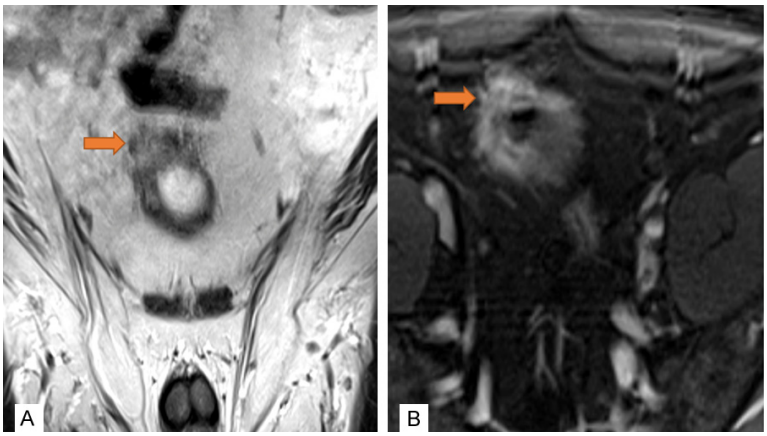

Figure 1. A, B. Coronal high resolution T2 weighted and post contrast T1 weighted gradient images show extramural vascular invasion (arrows). The vessels adjacent to the bladder dome shows irregular contour, nodular expansion with definite tumor signal.

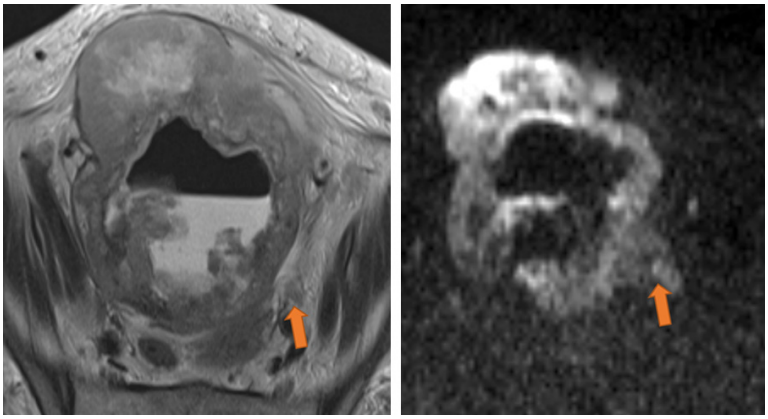

Figure 2. A, B. Axial high resolution T2 weighted and Axial Diffusion weighted B1000 images show extramural vascular invasion (arrows). The vessels adjacent to the bladder base shows irregular contour, nodular expansion with definite tumor and restricted diffusion signal.

were performed. Second, axial DWI was performed during free breathing with axial plane water-excited fat-suppressed single-shot spin echo-planar sequence and apparent diffusion coefficient (ADC) values of B0, B50 and B500 (mm^2/s) were calculated by placing the region of interest (ROI) manually within the most hypointense areas of the tumors. Finally, DCE-MRI was done using *T*1 fat-suppressed sequences before and after IV injection of contrast (DOTAREM, Bayer Pharma, Germany) with a dose of 0.1 mm/kg at a rate of 2 ml/s Dynamic images were obtained at 20 seconds (arterial phase), followed by 70 seconds (venous phase), then delayed phase at 3 and 10 minutes.

Pathology reporting criteria

Histopathologic assessment of surgical specimens was performed by our fellowship-trained uro-pathologist (S.L.). For pathologic diagnosis, grade, stage, presence of histologic variants, lymphovascular invasion, and EMVI was reported, if applicable. The pathologic definition for EMVI was initially described by Talbot et al in rectal cancer as the presence of tumor within an endothelium-lined space, which is either surrounded by a rim of smooth muscle or contains fibrin or red blood cells [17]. The updated College of American Pathologists (CAP) protocol for colorectal cancer subcategorized lymphovascular invasion into small vessel invasion (including lymphatics, capillaries, and postcapillary venules) and large vessel (venous) invasion (including extramural venous invasion and intramural venous invasion (IMVI)) [18]. Although recommended, reporting of EMVI and IMVI is not currently mandatory, and the CAP protocol for urinary BC has not included such a recommendation either.

In our study, pathologically identifiable EMVI showed endothelium-lined space surrounded by smooth muscle layers with different thickness or filled by tumor cells with fibrin and red blood cells (**Figures 1** and **2**). Other suggestive features for EMVI (which are described in colorectal cancer studies), such as 'orphaned arteriole' sign (a circumscribed tumor nodule adjacent to a muscularized artery without an obvious accompanying vein) and the protruding-tongue sign (a smooth bordered protrusion of tumor into pericolic fat), are also noted in our study [19]. However, we did not report these atypical findings as EMVI because these findings neither specifically indicate EMVI without

Table 1. Demographic data of the study population

Variable		Total (%)
Age		73 (50-101)
Gender	Male	29 (76%)
	Female	9 (24%)
Race	Caucasian	31 (82%)
	African American	5 (13%)
	Hispanic	2 (5%)
Smoking	Former smoker	22 (58%)
	Current smoker	10 (26%)
	Never-smoker	6 (16%)
Bladder Cancer Stage	NMIBC, < T1	5 (13%)
	MIBC, > T2	7 (18%)
	Extravesical, > T3	26 (68%)
Stage	Pathologic	12 (32%)
	Clinical	26 (68%)
Treatment	TURBT ONLY	18 (47%)
	RC	6 (16%)
	CRT	8 (21%)
	NAC + RC	6 (16%)
Histologic Variant	Pure Urothelial	29 (76%)
	Squamous	4 (11%)
	Micropapillary	3 (8%)
	Neuroendocrine	1 (3%)
	Glandular	1 (3%)
LVI		16 (42%)
mpMRI Characteristics	DCE	32 (91%)
	T2 Hyperintensity	28 (74%)
	DWI	27 (71%)
	EMVI	23 (62%)
	Low ADC value (Min < 700)	15 (42%)

additional immunohistochemical characterization nor diagnostic of EMVI based on these features alone on pathological evaluation.

Statistical analysis

Association between MRI-EMVI and histopathologic features commonly associated with worse outcomes including lymphovascular invasion (LVI), variant histology, muscle invasive bladder cancer (MIBC), and extravesical disease (EV) was assessed using SAS v. 9.4. Continuous variables, frequency, and percentage categorical data were analyzed using Student t tests and Chi Square tests respectively. We also made combinations of three pathologic variables (LVI+ Histologic Variant+ MIBC or Extravesical disease) as a surrogate for overall adverse pathologic features (Meta-variable). We built a predictive model using logistic regression with Firth option, sensitivity, and specificity using diagnostic testing approach and agreement using percent agreement to identify associated factors. Although there was no indication of non-existence of maximum likelihood function due to small size, we believe logistic regression provided a better estimate of the actual results. Estimated statistics are expressed with 95% confidence intervals and statistical significance was set at a two-tail *P*-value of < 0.05.

Results

A total of 38 patients were enrolled in the study, 9 (24%) females and 29 (76%) males with a median age of 73 years (range 50-101). Of these, 10 (26%) were current smokers, 22 (58%) former smokers, and 6 (16%) never-smokers. Detailed demographic data of the cohort are shown in **Table 1**.

Overall, 22 (58%) patients had muscle invasive bladder cancer (MIBC) as compared to 16 (42%) who had non-muscle invasive bladder cancer (NMIBC). A total of 18 (47%) patients had extravesical (EV) disease as compared to 20 (53%) with organ confined (OC) disease. Of the 9 (24%) patients with histologic variants, squamous differentiation was the most common (11%), followed by micropapillary (8%), glandular (3%) and neuroendocrine (3%). Six (16%) patients received neoadjuvant chemotherapy (NAC), while eight (21%) underwent chemoradiation with bladder preservation. Radical cystectomy was performed in 12 (32%) patients of the entire cohort and 12/22 (55%) of the MIBC group (**Table 1**). There was no statistical significance between groups with regards to basic demographic variables, although clinical stages showed significant differences between the groups (**Table 2**).

The logistic regression analysis (C statistic, 0.70) can be found in **Table 3**. We found a high-

Table 2. Comparison of demographic and clinical parameters between MRI-EMVI groups

Variable		EMVI (+)	EMVI (-)	*P*-Value
Age	< 75	14	8	0.646
	> 75	9	7	
Gender	Male	18	4	0.510
	Female	5	11	
Race	Caucasian	18	13	0.501
	African American	3	2	
	Hispanic	2	0	
Smoking	Former smoker	13	9	
	Current smoker	6	4	
	Non-smoker	4	2	
Bladder Cancer Stage	NMIBC, < T1	0	5	< 0.001
	MIBC, > T2	0	7	
	Extravesical, > T3	23	3	
Treatment	TURBT ONLY	7	11	0.041
	RC	4	2	
	NAC + RC	6	0	
	CRT	6	2	
Histologic Variant	Pure Urothelial	15	14	0.104
	Squamous	4	0	
	Micropapillary	3	0	
	Neuroendocrine	1	0	
	Glandular	1	0	

er odd of presence of LVI (OR = 4.89, CI 0.92-26.1; P = 0.06) and histologic variant (OR = 16.38, CI = 0.77-348; P = 0.07) inpatients with EMVI (**Table 3**). There was a significant association between EMVI and MIBC (OR = 5.30, CI = 1.11-25.36; *P* = 0.04). The strongest association, however, was found between EMVI and extravesical disease (OR = 17.77, CI = 2.37-133; *P* = 0.005). We also made combinations of three pathologic variables (LVI+ Histologic Variant+ MIBC or Extravesical disease) as a surrogate for overall adverse pathologic features. Interestingly, there was a significant association between EMVI and either of the combinations of pathologic variables (**Table 3**).

Inferential statistics can be found in **Table 4**. EMVI had sensitivity and specificity of 90% and 73% respectively with negative predictive value (NPV) and positive predictive value (PPV) of 94% and 63% in detecting extravesical disease respectively. Other probabilities included sensitivity and NPV for LVI and MIBC, 82% and 87%, 64% and 81% respectively. Particularly, the presence of EMVI in mpMRI had 100% NPV and sensitivity in diagnosis of variant histology. Concurrently, the NPV of EMVI was more than 80% across all adverse pathological features and combinations (**Table 4**).

Regarding EMVI in pathology specimens (path-EMVI), there were a total of 10 MIBC cases in which pathology specimens were reviewed for path-EMVI features. Out of these, 4 (40%) patients had both MRI-EMVI and path-EMVI, 4 (40%) had MRI-EMVI but no path-EMVI, one patient had no MRI-EMVI but was found to have path-EMVI, and one patient neither had MRI-MVI nor path-EMVI. Given the heterogeneity of data and low numbers, no inferential statistics was performed.

Discussion

To our knowledge, this is the first pilot study to demonstrate that EMVI can be identified on mpMRI for BC and is associated with adverse pathologic features. Our study demonstrates that EMVI is a novel imaging biomarker, which has potential applications in risk stratification and therapy selection. As the VI-RADS evolves in BC management, EMVI could become a useful additional parameter to improve the performance characteristics. MpMRI is rapidly evolving into an essential tool for BC staging with its high soft tissue contrast resolution, multiplanar imaging, and ability to predict the depth of tumor invasion and extravesical extension [7, 8, 20, 21].

Standardized MRI reporting systems have been adopted for several organ systems including prostate (PI-RADS), breast (BI-RADS) and bladder (VI-RADS). The VI-RADS staging system has standardized MRI interpretation and identification of MIBC, the most critical determinant for directing therapy. In a large meta-analysis, the combined sensitivity and specificity of VI-RADS for detection of MIBC was 0.90 (95% CI, 0.86-0.94) and 0.86 (95% CI, 0.71-0.94) [9]. EMVI is an additional parameter that could be incorporated in the future updates of VI-RADS. The

Table 3. Association between Magnetic Resonance Imaging (MRI), Extramural Venous Involvement (EMVI) and Pathologic Adverse Features of the Bladder Cancer (Lymphovascular invasion (LVI), Histologic variant, Muscle-invasive bladder cancer (MIBC), Extravesical disease) or combination of them

EMVI vs. pathologic adverse Feature	OR	95% CI	*P* value
LVI	4.89	0.92-26.01	0.063
Histologic Variant	16.38	0.77-348.79	0.073
MIBC	5.30	1.11-25.36	0.036
Extravesical	17.77	2.37-133.08	0.005
LVI+ Histologic Variant + MIBC	6.85	1.37-34.35	0.019
LVI+ Histologic Variant + Extravesical	12.09	2.09-69.86	0.005

Table 4. Inferential statistics of MRI-EMVI for predicting adverse pathologic features

EMVI vs. pathologic adverse variable	Sensitivity	Specificity	PPV	NPV	Accuracy
LVI	81.82	56.52	47.37	86.67	64.7
Histologic Variant	100.0	39.13	46.15	100.0	60
MIBC	63.64	77.27	58.33	80.95	72.7
Extravesical	90.91	72.73	62.50	94.12	78.8
LVI+ Histologic Variant + MIBC	63.64	81.82	63.64	81.82	75.8
LVI+ Histologic Variant + Extravesical	81.82	77.27	64.29	89.47	78.8

inclusion may be an attractive strategy as our study demonstrates that EMVI is significantly associated with adverse pathology, which ultimately predicts prognosis [3, 22-24]. As a next logical application, EMVI may become useful in predicting disease outcomes on a long-term basis by portending distant metastatic disease by vascular invasion. While additional studies are needed to assess the value of EMVI, it is conceivable that EMVI may be a useful imaging biomarker in assessing and/or predicting response to neoadjuvant chemo or immunotherapy. EMVI identified by mpMRI could often be confirmed by focused evaluation of pathology specimens.

Traditionally, EMVI is diagnosed in postsurgical pathology, defined as tumor involvement of veins beyond the muscularis propria. Our histologic assessment of surgical BC specimens confirmed the presence of pathologic EMVI in some study subjects. In rectal cancer, EMVI has been well described as a strong poor prognostic marker [1, 25-27]. Similarly, we could study the significant pathological EMVI in BC prognostication. Detection of EMVI in preoperative MRI imaging could alert pathologists to study BC specimens in detail for EMVI by focusing on location identified on imaging. Arguably, confirmation of EMVI in pathology specimens could be used to further risk stratify patients in addition to conventional pathological staging. Such novel information may allow for adjuvant therapy for patients at higher risk of disease recurrence while sparing such toxic therapy(s) for the remaining patients who are less likely to benefit.

Despite the potential benefit of identifying EMVI in pathology specimens, the current CAP protocol has not recommended routine reporting of EMVI because the identification of EMVI is challenging on hematoxylin and eosin (H&E) stained slides. Guided by the current CAP protocol for urinary BC, the evaluation of tumor invasion into perivesical tissue can be satisfied by reporting the presence or absence of microscopically or macroscopically identifiable tumor invasion [18]. Extensive sampling for EMVI is not required by CAP protocol. Limited sampling of perivesical tissue decreases the chance of identifying EMVI, especially when it is present at the periphery, away from the center of the tumor. Moreover, the smooth muscular wall of the vein can be effaced by tumor invasion which leaves the endothelium-lined space indistinguishable from an adjacent desmoplastic reaction in the background, unless fibrin or red blood cells are present in the space as evidence of EMVI. It is a reasonable concern that

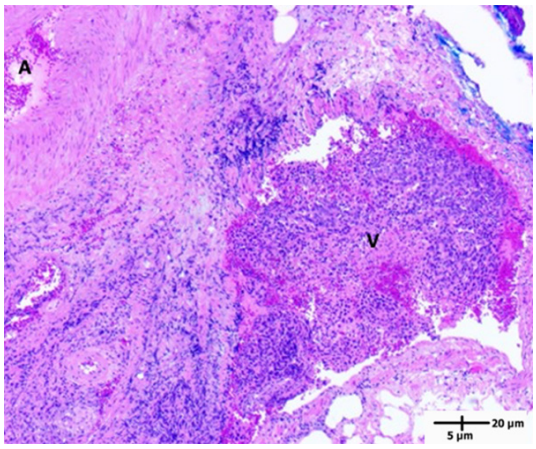

Figure 3. Extramural venous invasion in a vein containing fibrin and red blood cells (labeled V). Note the adjacent paired artery (labeled A). H&E stain ×40.

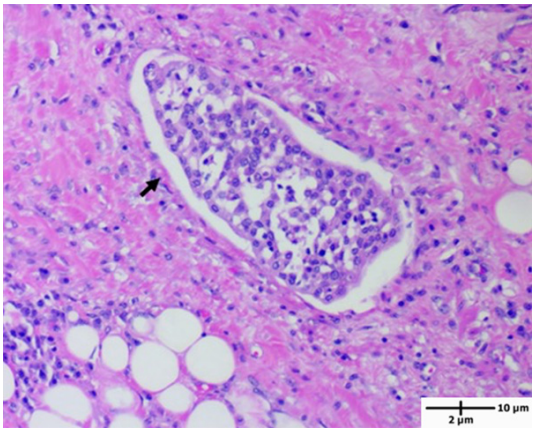

Figure 4. Extramural venous invasion in a venule. The arrow indicates a rim of smooth muscle. H&E stain ×100.

EMVI would be underdiagnosed in the current pathological assessment for urinary BC. Pathological specimen evaluation guided by pretreatment EMVI on MRI may improve the accuracy of detecting EMVI. Our histologic assessment of surgical BC specimens confirmed the presence of pathologic EMVI with corresponding MRI images (**Figures 3** and **4**).

Our study has identified another potential novel application of MR imaging of BC to identify variant histology. Histologically, BC comprises 75% pure urothelial carcinoma and 25% variant histology. Variant histology demands recognition due to its aggressive behavior and the need to alter therapy [13, 22]. Interestingly, our study showed a trend in association between EMVI and variant histology. Further studies with larger sample size are required to show a more robust association between EMVI and variant histology. The current VI-RADS system does not address variant histology and description of EMVI on MRI may provide an opportunity for novel application of VI-RADS in detecting variant histology.

With high NPV (> 80%) for adverse pathological features including variant histology, MIBC, LVI and EV, MRI-detected EMVI can provide additional risk stratification for therapy selection. For example, while NAC is standard of care for certain MIBC and EV disease, it provides a modest 5-10% survival benefit with substantial side effects [28]. The EMVI could be used as part of the armamentarium of predictors of response to NAC in addition to several known molecular biomarkers such as ERCC2, ERBB2 and epithelial tumor markers [4-6]. Unlike response to chemotherapy, aggressive tumors associated with adverse pathology and high mutational burden respond better to immunotherapy [29, 30]. It would be interesting to explore whether EMVI predicts better response to immunotherapy because of significant association with adverse pathology.

As a pilot study, our study is not without limitations. We evaluated a small patient cohort, although we discovered a strong statistical association between EMVI and adverse pathology. The study is underpowered for detecting association of EMVI with other high-risk features such as histologic variants, which are less frequent and present in < 25% of the study cohort. Some confidence intervals are relatively wide indicating relative instability in this parameter and caution to be exercised with interpretation of the magnitude of association. The study by design is focused on EMVI in BC and therefore we did not report using VI-RADS. However, as our sample size increases in the future, studies are planned to assess incorporation of EMVI in the VI-RADS. We could not demonstrate direct correlation between radiologic and pathologic EMVI. This might have resulted from a small sample number with insufficient data, limitations of reviewing pathologic specimens retrospectively, effect of neoadjuvant chemotherapy. Future prospective studies specifically sampling the perivesical tis-

sue to study EMVI on pathology specimens will allow more definitive correlation with MRI imaging.

Conclusions

Our pilot study is the first to describe feasibility of EMVI by MRI in patients undergoing staging workup for BC. EMVI is associated with adverse pathologic features and can be used as a novel imaging biomarker to detect adverse pathology. Potentially, EMVI could be incorporated into standard MRI reporting systems such as VI-RADS to improve performance characteristics including extravesical disease, response to treatment and prognostication.

Disclosure of conflict of interest

None.

Abbreviations

EV, Extravesical; OC, Organ-confined; NAC, Neoadjuvant chemotherapy; mpMRI, multiparametric magnetic resonance imaging; VI-RADS, Vesical Imaging-Reporting and Data System; T2WI, T2-weighted-image; DWI, Diffusion-weighted imaging; ADC value, Apparent diffusion coefficient; DCE, Dynamic contrast-enhanced; EMVI, Extramural venous invasion.

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Supplementary Table 1. MRI Pelvis without and with contrast (Bladder Mass) Protocol

Plane	Sequence	TR/TE: msec	FOV: mm	*Slice thickness/Gap: mm	Comments
3 Plane	LOC				Gradient sequences
Coronal	T2 Haste*	1500/90	440	5/1	Large Field of View
Sagittal	T2	4000-5000/90-120	200	3/0	High Resolution
Axial	T2	4000-5000/90-120	200	3/1	High Resolution
Axial	T2 FS	6200/93	240	4/1	Coverage from aortic bifurcation
Axial	T1	556/10	240	4/1	Non contrast, nonfat sat
Axial	Diffusion	5700/66	260	4/1	B: 0, 500, 1400
Coronal	T2	6800/110	250	4/1	
Coronal	T1	550/10	250	4/1	Non contrast, nonfat sat
Axial	T1 FS 3D	4.3/1.54	240	3/0	Pre contrast
Axial	T1 FS 3D	4.3/1.54	250	3/0	Post contrast Arterial, Venous, 3 min delay
Axial	T1 FS	4.3/1.54	240	4/1	Can run after 3 min T13D
Axial	T1 FS 3 D	4.3/1.54	240	3/0	10 min delay

*HASTE: Half Fourier Acquired Single Shot Turbo Spin ECHO.