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Surgery in Motion

Assessing the Feasibility and Accuracy of High-resolution Microultrasound Imaging for Bladder Cancer Detection and Staging

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Abstract

Background: Magnetic resonance imaging (MRI) has been proposed as a staging tool for bladder cancer (BC), but its use has been limited by its high costs and limited availability. Microultrasound (mUS) is a novel technology capable of providing high-resolution images of the prostate.
Objective: To test the feasibility of high-resolution mUS in patients diagnosed with BC and its ability to differentiate between non-muscle-invasive BC (NMIBC) and muscle-invasive BC (MIBC).
Design, setting, and participants: This is an observational prospective study performed in 23 patients with a diagnosis of primary BC scheduled for an endoscopic treatment.
Surgical procedure: Micro-US was performed before transurethral resection of bladder tumor using the ExactVu system with an EV29L 29-MHz side-fire transducer (Exact Imaging, Markham, Canada).
Measurements: The endpoints were to test the feasibility, describe the normal bladder wall anatomy, identify the lesions, and compare the mUS findings with the histopathological results.
Results and limitations: Micro-US was accurate in differentiating the three layers of the bladder wall in all cases. Bladder cancers were clearly identified as heterogeneous structures protruding from the normal bladder wall. In 14 cases the lesions appeared confined to the lamina propria, and in all cases NMIBC was confirmed by the final pathological report. In the other patients, the lesions seemed to extend into the muscular layer, but MIBC was confirmed in five out of seven cases (71.4%) from the pathologist. The small sample size was the main limitation of the current study.
Conclusions: Our findings showed that mUS is able to differentiate the bladder wall layers and identify the bladder cancer stage. Further studies with a larger population and imaging correlation with MRI are warranted before its introduction in clinical practice.
Patient summary: In this report, a new imaging technique was tested for the characterization of bladder cancer. Microultrasound appears to be feasible and capable of discriminating between superficial and invasive tumors.

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1. Introduction

Bladder cancer (BC) is the second most common cancer in urology with respect to the incidence and prevalence [1]. BC is categorized as non-muscle-invasive BC (NMIBC) and muscle-invasive BC (MIBC), with the latter being typically associated with a poorer prognosis. Cancer staging and molecular subtype characterization are critical to the determination of the best therapeutic strategy [2]. The gold standard for assessing BC local stage is transurethral resection (TUR) used both to retrieve pathological samples for pathological analysis and to treat the patient. However, this approach is not risk free due to its invasiveness with the inherent surgical hazards, especially in patients with hemorrhagic diathesis.

T2-weighted and dynamic contrast-enhanced magnetic resonance imaging (MRI) recently replaced computed tomography urography (CTU) for the differentiation between NMIBC and MIBC [3]. Although imaging is not the gold standard to evaluate the invasiveness of BC, an MRI-based standardized reporting system, the Vesical Imaging Reporting and Data System (VI-RADS) [4], has recently been suggested in order to better define the lesions and improve peer-to-peer communication [5]. However, there are several factors that limit the diffusion of MRI for BC staging, such as the overstaging rate, procedure-related contraindications and costs, as well as the use of gadolinium-based contrast agents, which should be avoided in patients with impaired renal function [6].

Recently, 29-MHz high-resolution microultrasound (mUS) technology has been suggested as a potential noninferior alternative to multiparametric MRI (mpMRI) for the detection of clinically significant prostate cancer (csPCa) [7,8]. The benefit of this technology is extremely high resolution, down to 70 μm, which provides a significant improvement in the visualization of tissue details compared with standard US. In addition, since it is a US-based imaging technique, mUS provides the same benefits, such as real-time evaluation and cost effectiveness. Based on our previous experience with mUS technology for the detection of prostate cancer (PCa), we tested the hypothesis that high-resolution mUS assessment may effectively depict the anatomical structures of bladder wall and, thus, may be capable of discriminating between NMIBC and MIBC.

2. Patients and methods

This study included male and female adults referred to our tertiary urological center with the diagnosis of primary BC, diagnosed by either flexible cystoscopy or transabdominal ultrasonography, who were subsequently scheduled for endoscopic treatment. Patients with urethral, anal, and vaginal stricture; hip problems that do not allow the lithotomic position; previous pelvic surgery; and BMI >30 were excluded. The institutional review board and local ethical committee approved the study (Protocol ICH-2004-003 approved in September 2018), and all patients signed an informed consent form.

Prior to the endoscopic procedure, all patients underwent high-resolution mUS assessment in a lithotomic position. Micro-US imaging was performed using the ExactVu system with an EV29L 29-MHz side-fire transducer (Exact Imaging, Markham, Canada). Two urologists (G.L. and M.L.), who were routinely using mUS for the detection of PCa, and who were blinded to the number and location of the lesions, performed the assessment. Images and recording of the bladder were archived for retrospective analysis after TUR and pathological analysis. The bladder was previously emptied by catheterization and afterward filled with 50 cc of sterile saline solution. The mUS was performed transrectally in males and transvaginally in females, and a rectal enema was performed in the male population before the procedure.

The first endpoint was to investigate the feasibility of the procedure defined as the possibility to assess the bladder window. Under this setting, we investigated the differences between male and female populations considering the different anatomy. The second step was to define the features of a normal bladder wall with mUS. The mUS images were qualitatively evaluated and measured to estimate a "normal" picture. We identified the three layers of the bladder wall structure: the mucosa, the detrusor muscle, and the adventitia. We defined a normal bladder wall when all the layers were adequately represented, and no mass or layer interruption was identified. The third step was to recognize, describe, and differentiate the bladder wall lesions between NMIBC and MIBC. The investigators' description included site, size, and tumor margins. The fourth step was to correlate the mUS findings with the pathological report. All mUS image sets were interpreted while blinded to any histopathological information. An "en bloc" TUR was performed as previously described in patients with four or fewer lesions and tumors of ≤3 cm excluding those very close to the ostia, in the dome and/or the anterior bladder wall. All other patients received a standard bipolar TUR [9].

2.1. Pathological assessment

All specimens were fixed in 10% formalin, embedded in paraffin, cut, and stained with hematoxylin and eosin. Specimens were examined by two expert uropathologists (P.C. and M.G.E.) to assess the type, grade, and stage of the tumor. Malignant tumors were classified and graded according to the World Health Organization classification [10]. Tumor staging was defined according to the American Joint Committee on Cancer/Union for International Cancer Control TNM system [11].

3. Results

Twenty-three patients, 12 males (52.17%) and 11 females (47.83%), were prospectively enrolled in our study. Patients' mean age was 65.48 yr (standard deviation: ±12.78). Demographics and clinical features of the cases are summarized in Table 1. A case-by-case description is reported in Table 2.

3.1. Step 1: feasibility

The procedure was feasible in all female patients. We failed to evaluate two male patients because the prostate longitudinal diameter was longer than 5 cm and the bladder window was limited.

3.2. Step 2: normal bladder wall

After instillation of 50 cc of saline solution, the bladder appeared triangular in shape and its content anechoic. With mUS imaging, the bladder wall appears as a three-layered structure: the urothelium appearing hyperechoic, the detrusor muscle presenting as a normoechogenic homogeneous layer, and the adventitia appearing as a thin

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Table 1 – Descriptive characteristics of patients with primary bladder cancer evaluated with mUS

Patients	
Male	12 (52.17%)
Female	11 (47.83%)
Mean age (±SD)	65.48 (±12.78)
Smoking status	
Smoker	8 (34.78%)
Former smoker	6 (26.09%)
Nonsmoker	9 (39.13%)
Urine cytology	
Positive	2 (8.70%)
Negative	16 (69.56%)
Uncertain	1 (4.35%)
Not performed	4 (17.39%)
Hematuria	
Macrohematuria	11 (47.83%)
No	12 (52.17%)
Number of lesions, mean size (±SD)	19.66 (±15.62) mm
mUS stage (no.)	
NMIBC	14 (60.87%)
MIBC	7 (30.43%)

MIBC = muscle-invasive bladder cancer; mUS = microultrasound; NMIBC = non-muscle-invasive bladder cancer; SD = standard deviation.

hyperechoic layer (Fig. 1). The ureteric orifices appear as small, focal, round thickenings close to the bladder base.

3.3. Step 3: bladder wall with cancer

All cancers ≥5 mm in size were clearly visualized, appearing as heterogeneous structures protruding from the normal bladder wall. In NMIBC cases, lesions were not disrupting, or only focally disrupting, the hyperechoic line representing the urothelium (Fig. 2). In MIBC, tumors were clearly extending beyond this line into the muscular layer, showing a hyperechoic aspect (with or without a "starry sky" appearance) at the base of the lesion with the loss of the typical three-layer structure (Fig. 3). The endoscopic check showed a limit of resolution for the detection of bladder tumors ≤4 mm. No differentiation was performed between Ta and T1 tumors.

3.4. Step 4: pathological correlation

Tissue samples were obtained by standard or en bloc TUR depending on the number, size, and location of the lesions. The stage (NMIBC vs MIBC), grade, and margins (only for en bloc resection) were described. The pathologists confirmed all the 14 NMIBC patients; instead, two of the seven MIBC cases were downstaged to NMIBC at histopathological evaluation.

4. Discussion

Our findings showed that bladder imaging with mUS is feasible and capable of describing normal bladder wall layers and BCs accurately. The concordance between mUS and histopathological results seems to confirm that mUS could be used as a noninvasive and potentially cost-effective staging device, although further data are warranted. Thus,

Table 2 – Case-by-case characteristics of the 23 patients enrolled in the study

	Gender	Age (yr)	Smoking status	Urine cytology	Macrohematuria	mUS staging	Site	No.	Size (mm)	pTNM	En-bloc vs traditional TUR	Description of the lesion
1	F	59	Former	Negative	No	NMIBC	Trigone	2	6–5	pTa LG	En bloc	Papillary
2	M	71	Yes	Negative	No	NMIBC	Left side wall	1	15	pTa LG	En bloc	Sessile
3	F	76	No	Negative	No	MIBC	Right side wall	1	15	pT1 HG	Traditional	Papillary
4	F	69	Yes	Negative	No	NMIBC	Right side wall	1	30	pTa HG	Traditional	Papillary
5	M	38	Yes	Negative	Yes	NMIBC	Right side wall	1	20	pTa LG	En bloc	Papillary
6	M	73	Yes	NA	Yes	NMIBC	Trigone, posterior wall	2	10–20	pTa LG	Traditional	Sessile
7	M	50	Yes	Negative	Yes	NA	Anterior wall	1	9	pTa LG	Traditional	Sessile
8	F	42	No	Negative	No	NMIBC	Trigone	1	20	pTa LG	Traditional	Papillary
9	M	79	No	Negative	Yes	MIBC	Right side wall	2	20–30	pT1 HG	Traditional	Flat
10	F	81	No	Negative	No	NMIBC	Multifocal	4	10–10–5–5	pTa LG	Traditional	Papillary
11	M	72	Former	NA	Yes	MIBC	Right side wall, trigone	1	55	pT2 HG sarcomatoid component	Traditional	Papillary
12	F	42	No	Negative	No	NMIBC	Left side wall	1	10	pTa LG	En bloc	Papillary
13	M	65	Former	Positive	No	MIBC	Trigone	1	40	pT2 HG	Traditional	Papillary
14	F	61	No	Negative	No	NMIBC	Left side wall	1	15	pTa LG	En bloc	Papillary
15	M	76	No	Negative	No	NA	Dome, anterior wall	2	15–5	pTa LG	Traditional	Sessile
16	M	63	Former	NA	Yes	MIBC	Left side wall, trigone	1	70	pT2 HG	Traditional	Sessile
17	F	76	No	Negative	Yes	NMIBC	Right side wall	1	9	pTa LG	En bloc	Papillary
18	F	62	Yes	Negative	No	NMIBC	Trigone	1	5	pTa HG	Traditional	Sessile
19	M	57	Yes	Positive	Yes	MIBC	Posterior wall, trigone	2	10–20	pT2 HG	Traditional	Papillary
20	F	85	No	Uncertain	Yes	NMIBC	Bladder neck	1	30	pTa HG	Traditional	Papillary
21	F	69	Former	Negative	No	NMIBC	Multifocal	5	10–10–40–30–10	pTa LG	Traditional	Papillary
22	M	69	Former	NA	Yes	MIBC	Left side wall	1	50	pT2 HG	Traditional	Papillary
23	M	70	Yes	Negative	Yes	NMIBC	Trigone	1	24	pT1 HG	Traditional	Sessile

F = female; HG = high grade; LG = low grade; M = male; MIBC = muscle-invasive bladder cancer; mUS = microultrasound; NMIBC = non-muscle-invasive bladder cancer; NA = not available; pTNM = pathological tumor-node-metastasis; TUR = transurethral resection.

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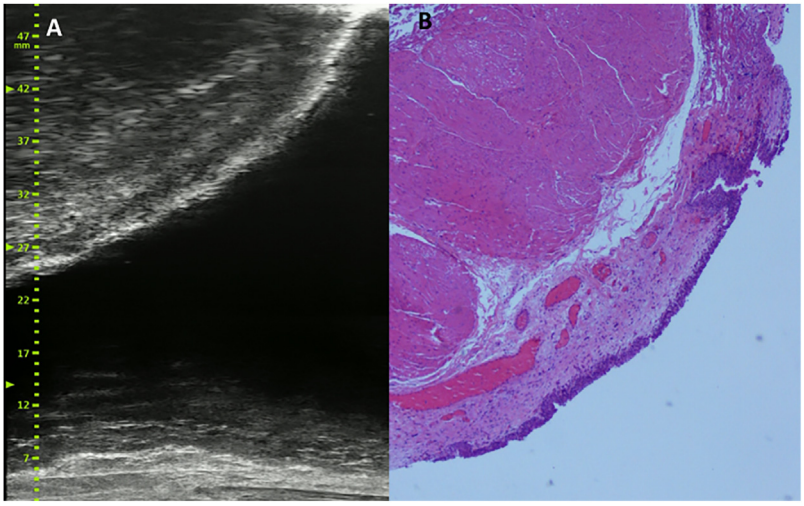

Fig. 1 – (A) Micro-US and (B) histopathological view of the normal bladder wall appearing as a three-layered structure consisting of the inner mucosa (hyperechoic), the detrusor muscle (medium homogeneous echogenicity), and the outer serosa (hyperechoic thin layer). US = ultrasound.

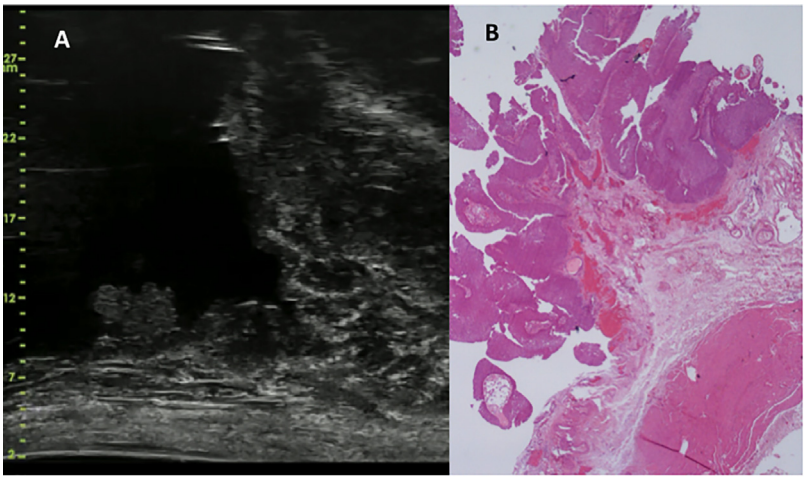

Fig. 2 – (A) Micro-US and (B) histopathological view of non-muscle-invasive bladder cancer: the lesion is not disrupting the hyperechoic line representing the lamina propria. US = ultrasound.

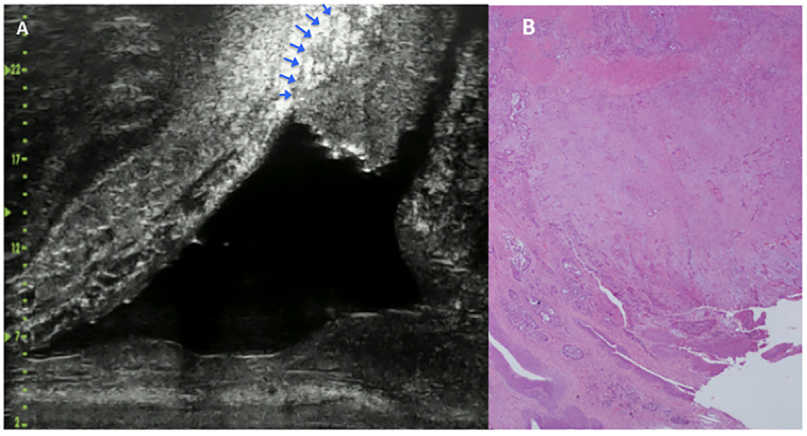

Fig. 3 – (A) Micro-US and (B) histopathological view (B) of muscle-invasive bladder cancer: the tumor is clearly extending into the muscular layer, showing a hyperechoic aspect at the base of the lesion associated with a "starry sky" pattern (blue arrows). US = ultrasound.

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high-frequency mUS may become an alternative tool in the BC treatment decision-making process.

For BC staging, CTU is generally performed. However, this imaging tool has its drawbacks, especially in the evaluation of tumor invasion into the muscularis propria [12]. To overcome these limitations, the use of MRI including functional sequences (mpMRI) has been suggested to be able to discriminate between NMIBC and MIBC [13]. This imaging technique could potentially improve BC diagnosis and staging, but it may also result in overstaging as tumor-associated fibrosis or inflammation can mimic the low signal intensity of the muscularis propria [14]. Thus, a VI-RADS, such as the Prostate Imaging Reporting and Data System (PI-RADS) for PCa, has been developed to help define and standardize the grade of BC invasion [5]. MRI and the VI-RADS may provide data about the extent of muscle invasion, exact location, and information to optimize the bladder-sparing trimodal therapy for MIBC for a more focused treatment and response evaluation [15]. However, the VI-RADS score still needs to be validated through the comparison of MRI descriptions with the histopathological results in different clinical situations. In addition, several potential drawbacks of MRI have to be considered, such as MRI is costly, there are multiple causes of artifacts, and image quality has to be excellent in order to get a correct interpretation of images by radiologists [16].

Recently, the novel 29-MHz high-resolution mUS system has been developed, enabling about 300% higher resolution than conventional transrectal ultrasound systems, for prostate imaging [17,18]. Ghai et al. [17] developed the PCa risk identification system mUS (PRI-MUS), which could guide urologists to achieve accurate and reproducible results for PCa detection. With the PRI-MUS protocol, the authors achieved a mean accuracy of 0.60 ± 0.02, which is comparable with those reported by several studies performed using the MRI-based PI-RADS score [19,20]. Recently, Lughezzani et al. [8] confirmed that mUS could reliably exclude the presence of csPCa in the great majority of patients and that mUS is not inferior to MRI for the detection of csPCa in the peripheral zone of the prostate.

We decided to test the use of mUS technology for BC staging. In our preliminary experience, we were able to describe the normal anatomy and suggest a tumor characterization that found a correlation with the respective histopathological analysis in 90.5% of cases; 9.5% of cases were staged MIBC instead of NMIBC. The reason can be attributed mostly to the lack of expertise in the use of this technique in this specific setting and correlated with the learning curve. The main procedural limitation was that the probe shape was not designed for bladder visualization, which resulted in the failure to accurately stage two out of 23 (8.7%) patients.

The current study reports preliminary results regarding the role of mUS in the characterization of BC. In patients with TaG3 tumors, the persistence of BC reaches up to 41.4%, and disease persistence in T1 NMIBC ranges between 33% and 55% [21,22]. Therefore, the tumor may be understaged at first instance, and updated guidelines suggest a second resection for restaging. The possibility that MIBC is detected by a second resection of an initial T1 tumor ranges from 1.3% to 25%, and if the first pathological sample did not contain detrusor muscle, the rate of MIBC may increase up to 45%, making a second-look TUR mandatory. Micro-US accuracy in distinguishing NMIBC from MIBC could help avoid unnecessary re-TUR or guiding TUR when MIBC is suspected. Finally, in patients diagnosed with BC requiring anticoagulant therapy (eg, patients who underwent a recent cardiac surgery under dual antiplatelet therapy), the discrimination between NMIBC and MIBC could be useful to decide the kind and timing of treatment. As an example, the finding of an NMIBC by mUS could eventually promote expectant management of these patients or eventually guide a less invasive TUR.

Several limitations of the current study have to be acknowledged. First, the small sample size limited the statistical significance of our findings. Second, due to the exploratory nature of the current study, we did not perform any comparison between mUS and the available BC staging imaging tools, such as CTU and MRI. As a consequence, future efforts in larger populations comparing the diagnostic accuracy of the different imaging techniques are warranted. Third, the mUS probe was not specifically developed for bladder visualization, and this may limit the bladder window in male patients, especially in those with very large prostates. Fourth, the small number of patients included prevented us from determining whether other variables, such as tumor size and location, may act as confounders in discriminating between NMIBC and MIBC. Finally, since mUS provides only longitudinal sections of the bladder, its accuracy to determine the presence/characteristics of a lesion located in the lateral wall may be suboptimal.

5. Conclusions

High-frequency mUS is feasible and informative, and could be used for discriminating between superficial and invasive BC. Further studies aiming to prove the clinical relevance of this technique in a larger population are mandatory before its introduction in clinical practice.

Author contributions: Nicolò Maria Buffi 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.

Study concept and design: Saita, Lughezzani, Buffi, Nava.
Acquisition of data: Hurle, Colombo, Diana, Fasulo, Paciotti, Elefante, Lazzeri.
Analysis and interpretation of data: Saita, Lughezzani, Hurle, Diana.
Drafting of the manuscript: Saita, Lughezzani, Buffi, Diana, Lazzeri.
Critical revision of the manuscript for important intellectual content: Casale, Guazzoni.
Statistical analysis: Lughezzani, Diana, Fasulo, Paciotti.
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Appendix A. Supplementary data

The Surgery in Motion video accompanying this article can be found in the online version at https://doi.org/10.1016/j.eururo.2019.03.044 and via www.europeanurology.com.

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