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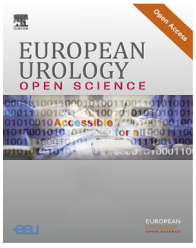

Brief Correspondence

Urodrill - a novel MRI-guided endoscopic biopsy technique to sample and molecularly classify muscle-invasive bladder cancer without fractionating the specimen during transurethral resection

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Abstract

The current diagnostic pathway for patients with muscle-invasive bladder cancer (MIBC), which involves with computed tomography urography, cystoscopy, and transurethral resection of the bladder (TURB) to histologically confirm MIBC, delays definitive treatment. The Vesical Imaging-Reporting and Data System (VI-RADS) has been suggested for MIBC identification using magnetic resonance imaging (MRI), but a recent randomized trial reported misclassification in one-third of patients. We investigated a new endoscopic biopsy device (Urodrill) for histological confirmation of MIBC and assessment of molecular subtype by gene expression in patients with VI-RADS 4 and 5 lesions on MRI. In ten patients, Urodrill biopsies were guided by MR images to the muscle-invasive portion of the tumor via a flexible cystoscope under general anesthesia. During the same session, conventional TURB was subsequently performed. A Urodrill sample was successfully obtained in nine of ten patients. MIBC was verified in six of nine patients, and seven of nine samples contained detrusor muscle. In seven of eight patients for whom a Urodrill biopsy sample was subjected to RNA sequencing, single-sample molecular classification according to the Lund taxonomy was feasible. No complications related to the biopsy device occurred. A randomized trial comparing this new diagnostic pathway for patients with VI-RADS 4 and 5 lesions and the current standard (TURB) is warranted.

Patient summary: We report on a novel biopsy device for patients with muscle-invasive bladder cancer that facilitates histology analysis and molecular characterization of tumor samples.

The standard workup for hematuria comprises computed tomography (CT) urography, urine cytology, and flexible cystoscopy, and patients diagnosed with bladder cancer subsequently undergo transurethral resection of the bladder (TURB) under general anesthesia. For patients with non–muscle-invasive bladder cancer (NMIBC), the aim of

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TURB is to remove all tumor. However, in muscle-invasive bladder cancer (MIBC), TURB is incomplete and further definitive treatment is required with neoadjuvant chemotherapy (NAC) and radical cystectomy (RC), although histological verification of MIBC is required. Major concerns with the current pathway for patients with MIBC are that TURB delays definitive treatment, potentially disseminates tumor cells into the bloodstream [1], and is associated with morbidity and risks of bleeding and perforation [2,3].

Thus, the ideal diagnostic pathway would separate Ta/T1 from MIBC early on, for which a suggested feasible option is magnetic resonance imaging (MRI) with use of the Vesical Imaging-Reporting and Data System (VI-RADS) [4]. However, evaluation of this MRI-based pathway in the randomized BladderPath study revealed that one-third of patients diagnosed with MIBC according to MRI turned out to have NMIBC [5].

The aim of the current study was to assess flexible cystoscopy with MRI-directed biopsies to confirm MIBC with the novel Urodrill device, which improves endoscopic submucosal sampling of gastrointestinal tumors [6]. We also assessed the feasibility of molecular classification based on RNA sequencing to facilitate de-escalation of NAC in patients with the basal/squamous (Ba/Sq) subtype [7].

Ten consecutively identified patients with radiological suspicion on CT urography of MIBC were recruited between March 2021 and September 2022 in a tertiary referral center [4]. One additional patient was excluded, as benign prostatic enlargement was the cause of endoscopic and radiologic suspicion of MIBC. The primary outcome measure was confirmation of MIBC with the Urodrill device. Secondary outcomes were molecular classification, the presence of detrusor muscle in the Urodrill sample, and complications (Supplementary material).

The Urodrill instrument consists of a single-use handle with an electrically rotatable flexible sheath and a hollow cylinder tip for sampling (BiBBInstruments, Lund, Sweden). The instrument is used through the working channel of a flexible cystoscope (Olympus; Olympus Corporation, Shinjuku City, Japan). A sample is taken while the motor rotates the sheath and the distal hollow cylinder tip, resulting in cutting and collection of tissue. The direction and depth of the sampling cylinder are controlled by the examiner via the handle and an individually set depth, and bursts of cutting rotation are controlled with a pedal during sampling. Up to three consecutive biopsies are sampled in one session. The instrument is then removed from the endoscope and samples are pushed out and harvested by applying overpressure or a guide wire. After harvesting the first batch of biopsies, and additional one or two rounds were performed, depending on the previous yield.

The Urodrill was directed to the muscle-invasive portion of the tumor (Fig. 1A) under general anesthesia. TURB was subsequently performed through a 26 Ch resectoscope. A complete TURB was performed in two patients for whom curative radiotherapy was planned, whereas the TURB aim in the remaining eight patients was only to sample the tumor base to histologically confirm MIBC before preoperative NAC or induction chemotherapy and RC, even though a maximal TURB can improve pT0 rates in the cystectomy specimen.

One Urodrill biopsy was immediately transferred into AllProtect storage solution (Qiagen AB, Sollentuna, Sweden) and transported to the Center for Translational Genomics in Lund, Sweden for RNA extraction and sequencing. The protocol for sequencing and real-time single-sample molecular classification in the UROSCANSEQ pipeline [8] and the rationale behind the Lund taxonomy for classifying cancer cell phenotypes have previously been described [9].

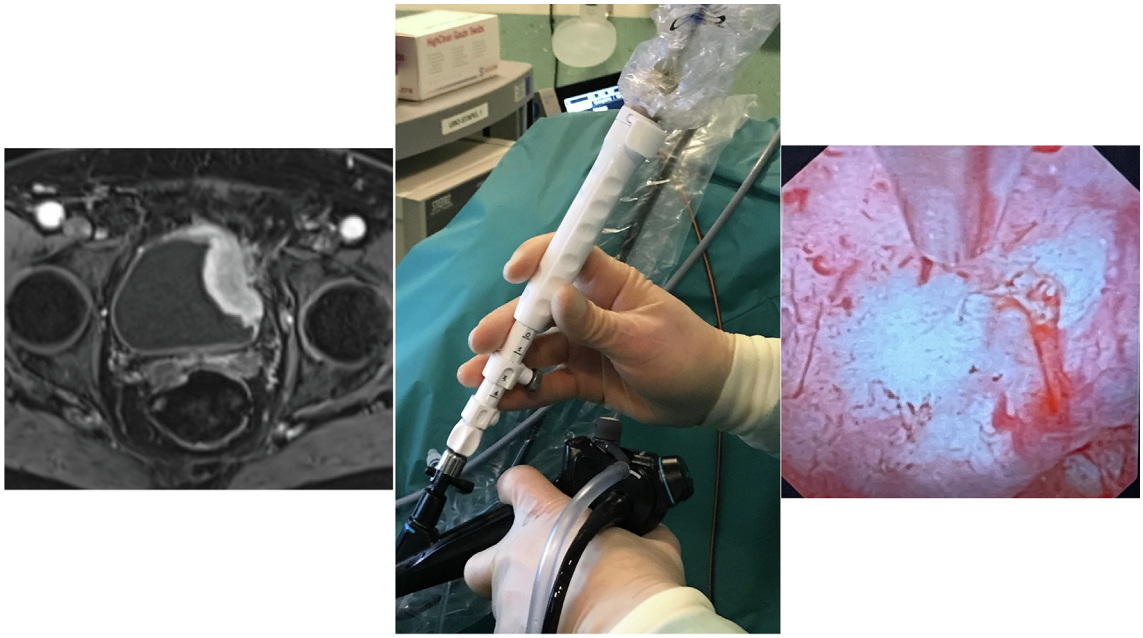
The ethics committee at Lund University (Lund, Sweden; EPN 2019-06537) and the Swedish Medical Products Agency (Uppsala, Sweden; reference 5.1-2020-40503) approved the study (ISRCTN80990426).

Ten patients with clinical suspicion of MIBC were included, of whom four had lymph node metastases and one had a solitary bone metastasis in the right acetabulum (Table 1). In one patient with iliac vessels 10 mm from the muscle-invasive part of the tumor, the shallow setting for the Urodrill to avoid injury to the iliac-vessels did not allow retrieval of a sample. Among the other nine patients, MIBC was verified in six of nine patients and seven of nine samples contained detrusor muscle (Fig. 1B). In comparison to the TURB specimen, Urodrill biopsy failed to verify MIBC in three patients, instead showing T1 grade 3 (G3) with small cell/neuroendocrine (Sc/Ne) variant histology, pTx G2, and pT1 G2, respectively. For the latter two patients, the histological subtype was identified in the Urodrill biopsy sample. In one sample, RNA quality did not allow sequencing; thus seven

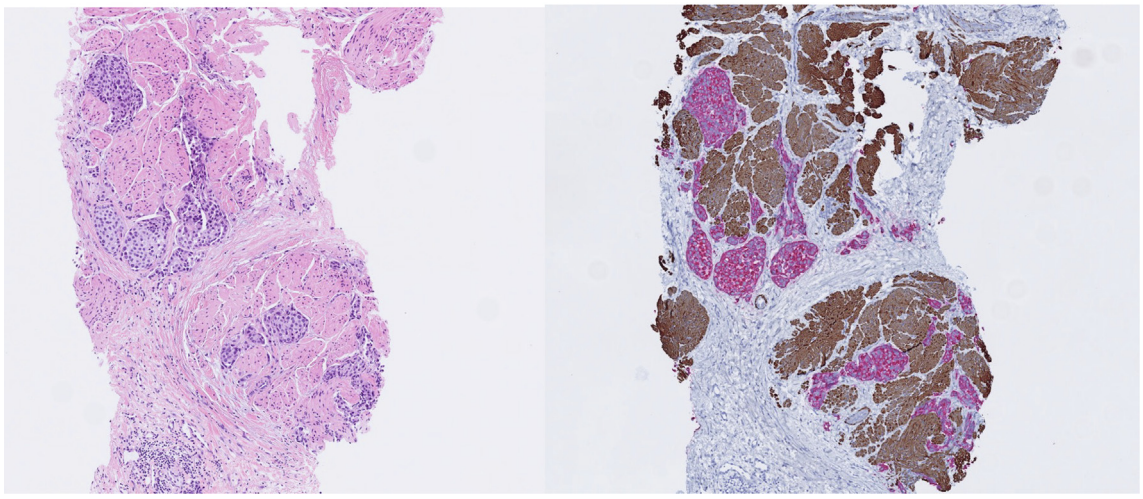
Table 1 – Patient and tumor characteristics

Case	Age (yr)	Sex	D_{max} (cm)	VI-RADS	T stage	N stage	M stage	Treatment intent	Oncological treatment
1	79	Male	5	5	T3b	N0	M0	Curative	NAC (MVAC × 2) + Cx
2	77	Male	3	4	T2	N0	M0	Curative	RT (55 Gy/20 fractions)
3	65	Female	7	6	T4b	N2	M0	BSC	NA
4	78	Male	6	– [a]	T2	N0	M0	Curative	RT (55Gy/20 fractions)
5	76	Male	4	5	T3b	N1	M0	Curative	ICT (Carb/Etop × 5) + Cx
6	67	Male	6	5	T3b	N1	M0	Curative	ICT (MVAC × 4) + Cx + aNivo
7	70	Male	5	5	T3b	N3	M0	Curative	ICT (MVAC × 3 + Carb/Gem × 2) + Cx
8	67	Male	3	4	T3b	N0	M1b	Curative	ICT (MVAC × 4) + Cx + consolidating RT to oligometastases + aNivo
9	68	Female	4.5	5	T3b	N0	M0	Curative	NAC (MVAC × 3) + Cx
10	72	Female	6	5	T4b	N0	M0	Curative	ICT (MVAC × 1+Carb/Gem × 4) + Cx

Dmax = maximum tumor diameter on magnetic resonance imaging; VI-RADS = Vesical Imaging-Reporting and Data System; NAC = neoadjuvant chemotherapy; MVAC = methotrexate, vinblastine, adriamycin, and cisplatin; Cx = cystectomy; RT = radiotherapy; BST = best supportive care; ICT = induction chemotherapy; Carb/Etop = carboplatin and etoposide; Carb/Gem = carboplatin and gemcitabine; NA = not applicable; aNivo = adjuvant nivolumab.
[a] Bilateral iliac stent grafts prevented VI-RADS interpretation.



(a)



(b)

Fig. 1 – (A) Visualization of T1-weighted magnetic resonance imaging in patient number 1, insertion of the Urodrill device via a flexible cystoscope before sampling, and the Urodrill device entering the tumor (endoscopic view). (B) Corresponding sections from a biopsy obtained in patient number 1 with hematoxylin-eosin and cytokeratin-desmin staining. Desmin staining of detrusor muscle appears brown, and cytokeratin staining of tumor cells appears pink.

of eight Urodrill samples could be molecularly classified (Table 2). No complications related to the Urodrill sampling occurred (Supplementary material).

The current proof-of-concept study demonstrates that the Urodrill instrument can facilitate both histological confirmation of MIBC based on MRI findings and molecular classification. Two relevant issues emerged during the study: interindividual complexity related to tumor location and a need for assistant support of the flexible cystoscope when sampling in female patients. Limitations related to the specificity of MRI for identification of MIBC suggest a remaining need for biopsies [4], which is exemplified by the patient excluded from the present series because of benign histology. Furthermore, urine cytology cannot identify histological subtypes and thus cannot guide changes in chemotherapy, such as for patient 5 in this study (Sc/Ne histology), for whom combinations with etoposide would be more suitable than standard platinum-based regimens [10]. The Ba/Sq Lund subtype determined via gene expression is independently associated with lower response to NAC, suggesting that patients with this subtype can be directly referred for RC without NAC [7].

Table 2 – Urodrill biopsy outcomes in comparison to pathology for corresponding TURB samples [a]

Case	Urodrill biopsies			pT stage		Molecular subtype (Lund taxonomy)	
	Total length (mm)	Cancer length (mm)	DM present	Urodrill biopsies	TURB specimen	Urodrill biopsies	TURB specimen
1	61	54	Yes	pT2 G2 + LVI	pT2 G2 + LVI	UroC	NS
2	35	23	Yes	pT2	pT2 G3	Uro	NS
3	26	24	Yes	pT2 G3 + SCC	pT2 G3 + SCC	Ba/Sq	Ba/Sq
4	19	16	Yes	pT2 G3	pT2 G3 + LVI	NS	NS
5	17	7	Yes	pT1 G3 + Sc/Ne	pT2 G3 + Sc/Ne	Sc/NE-like	NS
6	n/a	n/a	No	n/a	pT1 G2	Not obtained	UroA
7	66	46	Yes	pT2 G3	pT2 G3	Ba/Sq	Ba/Sq
8	2.1	2.1	No	pTx G2	pT2 G3 + LVI	Not obtained	UroA
9	41	25	Yes	pT2 G3	pT2 G3	Ba/Sq and Mes-like	Ba/Sq
10	28	25	No	pT1 G2	pT2 G2 + LVI	Ba/Sq and UroB	Uro

TURB = transurethral resection of bladder; DM = detrusor muscle; LVI = lymphovascular invasion; SCC = squamous cell carcinoma; Sc/Ne = small cell/neuroendocrine; NS = not sequenced because of low RNA content; UroA = urothelial-like A; UroB = urothelial-like B; UroC = urothelial-like C; Uro = urothelial-like without further subclassification possible; Ba/Sq = basal/squamous-like; Sc/NE-like = small cell/neuroendocrine-like; Mes-like = mesenchymal-like

[a] Comparisons with pathological tumor stage in cystectomy specimens were not possible because of stage regression related to preoperatively administered chemotherapy.

Use of the Urodrill instrument via a flexible cystoscope opens the possibility of exploratory biopsies under local anasthesia, obviating the need for TURB under general anesthesia and compensating for the additional cost of the single-use Urodrill instrument (€700 for a CE-approved endodrill device for gastrointestinal use). Shortening the current pathway to the use of MRI and Urodrill biopsies has potential to de-escalate the use of NAC in patients with the Ba/Sq subtype, adjust the type of NAC by histological subtypes, and decrease delays to definitive treatment with NAC and RC.

Histological verification and molecular classification of MIBC are possible for samples collected with the Urodrill device. Further evaluation of sampling under local anesthesia and a definition of the optimal biopsy depth in a larger and randomized context are warranted.

Author contributions: Fredrik Liedberg 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: Eriksson, Berg, Bernardo, Bobjer, Brändstedt, Löfgren, Simoulis, Sjödahl, Sundén, Wokander, Zackrisson, Liedberg.
Acquisition of data: Eriksson, Berg, Löfgren, Simoulis, Sjödahl, Zackrisson, Liedberg.
Analysis and interpretation of data: Eriksson, Bobjer, Bernardo, Löfgren, Simoulis, Sjödahl, Zackrisson, Liedberg.
Drafting of the manuscript: Eriksson, Berg, Bernardo, Bobjer, Brändstedt, Löfgren, Simoulis, Sjödahl, Sundén, Wokander, Zackrisson, Liedberg.
Critical revision of the manuscript for important intellectual content: Eriksson, Berg, Bernardo, Bobjer, Brändstedt, Löfgren, Simoulis, Sjödahl, Sundén, Wokander, Zackrisson, Liedberg.
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Appendix A. Supplementary data

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