

## Comparing an imaging-guided pathway with the standard pathway for staging muscle-invasive bladder cancer

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1    **COMPARING AN IMAGING-GUIDED PATHWAY WITH THE STANDARD PATHWAY FOR**  
2    **STAGING MUSCLE-INVASIVE BLADDER CANCER: PRELIMINARY DATA FROM THE**  
3    **BLADDERPATH STUDY**

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40    **ABSTRACT**

41    Transurethral resection (TURBT) is central to the diagnosis of muscle-invasive bladder cancer (MIBC). With the  
42    oncological safety of TURBT unknown, staging inaccuracies commonplace, and correct treatment of MIBC  
43    potentially delayed, multiparametric (mp)MRI may offer rapid, accurate and non-invasive diagnosis of MIBC.  
44    BladderPath is a randomised trial comparing risk-stratified (5-point Likert scale) image-directed care with  
45    TURBT for patients with newly-diagnosed BC. To date, we have screened 279 patients and randomised 113.  
46    Here we report on the first 100 participants to complete staging: 48 in Pathway 1 (TURBT) and 52 in Pathway  
47    2 (mpMRI for possible MIBC, Likert 3-5). Fifty of 52 participants designated Likert 1-2 (probable NMIBC) from  
48    both pathways were confirmed as NMIBC (96%). Ten of 11 participants diagnosed NMIBC by mpMRI have  
49    been pathologically-confirmed as NMIBC, and 10/15 participants diagnosed MIBC by mpMRI have been  
50    treated as MIBC (5 participants underwent TURBT). The specificity of mpMRI for the identification of MIBC  
51    remains a limitation. These initial experiences indicate that it is feasible to direct possible MIBC patients to  
52    mpMRI for staging instead of TURBT. Furthermore, a 5-point Likert scale accurately identifies patients with a  
53    low risk of MIBC (Likert 1-2), and flexible cystoscopy biopsies appear sufficient for diagnosing BC.

54

## 55 BRIEF CORRESPONDENCE

56 Diagnostic pathways for bladder cancer (BC) patients have remained largely unchanged for >30-years, with  
57 transurethral resection of bladder tumour (TURBT) the initial diagnostic and staging tool [1;2]. Whilst TURBT  
58 is mostly well-tolerated and therapeutic for non-muscle-invasive BC (NMIBC), its role in muscle-invasive BC  
59 (MIBC) is predominantly diagnostic [1]. The shortcomings of TURBT are well-described [3], including  
60 hydrodistension and perforation (potentially facilitating extravesical tumour dissemination [4]), understaging  
61 [5], and post-TURBT artefacts which hinder timely accurate staging, all of which may delay radical treatment  
62 or lead to incorrect therapy choices, resulting in worse outcomes [6]. Imaging advances suggest  
63 multiparametric (mp)MRI may allow the accurate discrimination of NMIBC and MIBC [7-9], potentially offering  
64 a safer and faster route to radical treatment than TURBT. In order to test the hypothesis that MIBC patients  
65 can be expedited to radical treatment by using mpMRI rather than TURBT, we are undertaking the BladderPath  
66 randomised controlled trial (NHS Research Ethics Committee approval 17/LO/1819, ISRCTN 35296862,  
67 <https://www.birmingham.ac.uk/research/crcu/trials/bladder-path/index.aspx>, **Appendix 1: BladderPath**  
68 **protocol**).

69 Briefly, randomised patients are those diagnosed with BC following outpatient cystoscopy for relevant  
70 symptoms and without a prior history of urothelial cancer. Using endoscopic appearances, patients are  
71 stratified by a 5-point Likert scale: 1) strongly-agree or 2) agree that the lesion is NMIBC, or 3) equivocal, or 4)  
72 agree or 5) strongly-agree that the lesion is MIBC. Likert 1-2 patients are considered as 'probable NMIBC' and  
73 Likert 3-5 patients are considered as 'possible MIBC'. Provided illustrations facilitate the designation of Likert  
74 score (**Appendix 2**).

75 Consenting participants are randomised to standard-of-care (Pathway 1: TURBT) or risk-stratified mpMRI-  
76 directed care (Pathway 2: Likert 1-2 undergo TURBT, Likert 3-5 undergo flexible cystoscopy-guided tissue  
77 biopsy under local anaesthesia and mpMRI using the VI-RADS protocol, **Appendices 3 & 4**). TURBT is permitted  
78 for Likert 3-5 participants in Pathway 2 for the following indications:

- 79 • To ascertain the presence of histological variants;

- To debulk the tumour prior to radical therapy (e.g. prior to chemoradiotherapy);
- Lack of confidence that the MRI shows MIBC;
- To perform examination under anaesthesia in order to assess operability;
- To check for carcinoma in situ;
- To obtain prostatic urethral biopsies when considering neo-bladder;
- To re-stage after neoadjuvant chemotherapy; or
- For the management of symptoms, e.g. lower urinary tract symptoms, haematuria, etc.

Radical treatment with neoadjuvant chemotherapy (where safe and appropriate) is offered to all participants with MIBC, using the results of either TURBT or mpMRI staging.

The study is being conducted in three stages with primary outcomes of feasibility, time to correct therapy for MIBC, and clinical progression-free survival, respectively. Primary/secondary outcomes, definitions, accrual targets and statistical considerations are detailed in **Appendix 1: BladderPath protocol**. To 1<sup>st</sup> October 2020, 15 centres have opened BladderPath, 279 patients have been screened as potentially eligible, and 113 have been randomised. Here we report data from the first 100 randomised patients (88%) who have completed staging and/or have commenced treatment as we feel that there are important take home messages for the urological community, especially within the context of the COVID-19 pandemic. See **Table 1 & Figure 1**.

For 5 recruiting units, taking pinch biopsies during flexible cystoscopy was compatible with local protocols; all 30 biopsies confirmed BC - see inset panel of **Figure 1** (stage classification not definitive). As can also be seen from **Figure 1**, 52 participants designated as Likert 1-2 have undergone TURBT, with NMIBC confirmed in 50 (96%). A total of 42 participants designated as Likert 3-5 have undergone TURBT or cystectomy with pathological staging available (22 in Pathway 1, 20 in Pathway 2), confirming MIBC in 13 (8 in Pathway 1, 5 in Pathway 2); considering these participants, and all those treated clinically as MIBC by bladder-preservation or palliation, then stage T2+ disease was diagnosed in 19/48 participants designated as Likert 3-5 (40%).

Of 11 participants diagnosed with NMIBC based upon mpMRI, 10 (91%) were pathologically confirmed as NMIBC by TURBT. Of 15 patients diagnosed with MIBC based upon mpMRI, 10 (67%) were treated as MIBC;

105 the remaining 5 patients underwent TURBT which demonstrated 5 NMIBCs (two pT1 tumours and three pTa  
106 tumours), thus highlighting the limitations in the specificity of mpMRI for diagnosing MIBC. For patients who  
107 underwent systemic chemotherapy, radiotherapy or palliation for mpMRI-diagnosed MIBC it is impossible to  
108 conclusively know whether these were correct treatments, and this is a limitation of the study design.

109 Our initial experience indicates that it is feasible to direct possible MIBC patients (Likert 3-5) to mpMRI instead  
110 of TURBT for staging, with clinicians accepting a tumour biopsy and imaging approach for diagnosing MIBC.  
111 Furthermore, based upon TURBT, a 5-point Likert scale accurately identifies patients with a low risk of MIBC,  
112 i.e. those designated as Likert 1-2 (albeit, only cystectomy can be considered as providing definitive staging).  
113 Likert scales have been used effectively in a variety of urological settings, including cystoscopy [10], and so  
114 wider use of our Likert scale may be appropriate for determining and expediting subsequent management  
115 following visual diagnosis in the outpatient setting. Finally, flexible cystoscopy biopsies appear sufficient for  
116 diagnosing BC.

117 A qualitative substudy is underway to understand the impact of the study and the new pathway on patients,  
118 their partners, relatives or friends, and healthcare professionals. The main study continues to investigate the  
119 intermediate outcome of time to correct therapy for MIBC and NMIBC, and the final outcome of clinical  
120 progression-free survival. Notwithstanding, in the COVID-19 environment, aspects of the mpMRI-directed  
121 pathway (Pathway 2) could be perceived as beneficial.

122

## 123 **PATIENT SUMMARY**

124 We are conducting a clinical trial to assess whether some bladder tumour resections (TURBTs) can be replaced  
125 by MRI scanning to determine the stage of the tumour in patients whose tumours appear to be invasive. The  
126 early data shown here suggest that this approach is feasible. The data also show that using a special score  
127 (Likert scale) can help to visually identify bladder tumours that are very unlikely to be invasive, and that taking  
128 a biopsy in the outpatient clinic at the time of initial camera inspection of the bladder (diagnostic flexible  
129 cystoscopy) is useful for confirming bladder cancer.

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169     **Table 1: Patient characteristics.**

		Pathway 1 (n=48)		Pathway 2 (n=52)	
		Standard of care		mpMRI-directed care	
		N	(%)	N	%
Age	Median (yrs)	73		72	
Gender	Male	36	(75)	38	(73)
	Female	12	(25)	14	(27)
Cystoscopic appearance	Likert 1-2	25	(52)	27	(52)
	Likert 3-5	23	(48)	25	(48)
Final stage	Ta/T1	39	(81)	39	(75)
	T2 or above	9	(19)	13	(25)

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**Figure 1: Flow of patients through the study.** NAC = neoadjuvant chemotherapy, Pal = palliative, chemo = chemotherapy, RT = radiotherapy, \*denotes cystectomy abandoned due to unresectable disease. **Inset:** histopathology results from the 30 pinch biopsies taken at outpatient flexible cystoscopy.

