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DOI:
10.1016/j.eururo.2021.02.021

Document Version
Peer reviewed version

Citation for published version (Harvard):
Bryan, R, Liu, W, Pirrie, S, Amir, R, Gallagher, J, Hughes, A, Jefferson, K, Knight, A, Nanton, V, Mintz, H, Pope, A, Catto, J, Patel, P & James, N 2021, 'Comparing an imaging-guided pathway with the standard pathway for staging muscle-invasive bladder cancer: preliminary data from the BladderPath study', *European urology*, vol. 80, no. 1, pp. 12-15. https://doi.org/10.1016/j.eururo.2021.02.021

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

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Key words: Transurethral resection; TURBT; magnetic resonance imaging; MRI; bladder cancer; staging; clinical trial.

Word Count: **200** (Abstract) + **900** (Brief Correspondence) + **99** (Patient Summary) = **1199** (Total)

Funding: BladderPath is funded by the National Institute for Health Research (NIHR) [Health Technology Assessment Programme, project number 14/08/60]. JWFC is funded by a NIHR Research Professorship (2019-24). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Authorship: The authorship reflects members of the BladderPath trial management group. All authors had full access to all study data, helped in interpretation and analysis, and were involved in drafting and editing of the manuscript. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest: JWFC has received reimbursement for consultancy from Astra Zeneca and Janssen, speaker fees from BMS, MSD, Nucleix and Roche, and honoraria for membership of an advisory board for Ferring and Janssen. RTB has contributed to advisory boards for Olympus Medical Systems & Janssen, and undertakes research funded by UroGen Pharma and QED Therapeutics. NDJ has no relevant conflicts of interest for this work.

ABSTRACT

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

BRIEF CORRESPONDENCE

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

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

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

- 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 1st 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;

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

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

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

PATIENT SUMMARY

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

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169 **Table 1: Patient characteristics.**

		Pathway 1 (n=48) Standard of care		**Pathway 2 (n=52)** 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.