

# A multidisciplinary discussion of BladderPath

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**B**ladderPath is a randomized clinical trial that explores an innovative approach to investigate newly diagnosed bladder tumors. The trial aimed to determine the feasibility of replacing the current standard procedure, transurethral resection of bladder tumor (TURBT), with cystoscopic biopsy and magnetic resonance imaging (MRI). The primary objective of the efficacy phase was to reduce the time to correct treatment (TTCT) for muscle-invasive bladder cancer (MIBC) by at least 30 days.<sup>1</sup> Expediting care in MIBC is key to improving outcomes.

Preliminary results pertaining to the performance of MRI in the trial were published in 2021,<sup>2</sup> and the primary outcome was presented at the annual meeting of the European Society of Medical Oncology (ESMO) in 2022.<sup>1</sup> This commentary is based on a multidisciplinary discussion of the trial and its impact on clinical practice at the Canadian Bladder Cancer Forum (“the Forum”; <https://www.cua.org/program/16937>) on March 31, 2023.

The premise underlying BladderPath is that TURBT does not adhere to oncologic principles. TURBT involves piecemeal resection, which may result in the dispersion of cancer cells and tumor seeding. Incomplete staging and the need for re-resection can lead to treatment delays, and there are complications associated with TURBT. Incorporating MRI after cystoscopic biopsy could address the limitations associated with TURBT. The hypothesis being tested is that substituting TURBT with MRI will avoid unnecessary surgery, reduce the TTCT for MIBC, and ultimately improve clinical outcomes.

In the trial, patients presenting with suspected bladder cancer were randomized before cystoscopy to undergo routine cystoscopy followed by subsequent TURBT (standard of care) or to undergo cystoscopy, assessment by the urologist of the likelihood that the tumor is MIBC using a Likert scale ranging from 1–5, and concurrent office biopsy of the tumor. The method or extent of biopsy was not mandated in the study protocol beyond the suggestion that it be performed at the time of flexible cystoscopy. In this investigational arm, if the tumor was suspected to be MIBC based on clinical evaluation, an MRI was performed. If the MRI confirmed MIBC, the patient was treated accordingly with systemic therapy, radical cystectomy, radiation, or palliative care. For cases classified as non-MIBC (NMIBC), TURBT was subsequently performed, followed by standard adjuvant treatment, as per the guidelines.

One of the main concerns raised by the expert panel at the Forum regarding this MRI pathway was the poor specificity of MRI to stage MIBC accurately. According to the published results, 14 of the first 100 randomized patients were diagnosed with MIBC based on MRI; however, five of these 14 patients underwent TURBT and all were found to have NMIBC. It is not clear why these five patients underwent TURBT. One could speculate that they had lower tumor burden so that there was clinical uncertainty about the determination of muscle invasion on MRI. One could similarly speculate that large bulky tumors do not need an MRI to verify muscle invasion.

MIBC could only be confirmed by cystectomy in three of the remaining nine patients. The panelists considered the 35% rate of overstaging based on MRI as unacceptable due to the associated risk of overtreatment with resultant toxicity. Furthermore, since only a small proportion of patients in the trial ended up with MIBC, the panelists were concerned about the small sample size. Although the accrued sample size corresponded to the power calculations for the trial based on the endpoint of TTCT (<https://www.birmingham.ac.uk/research/crcut/trials/bladder-path/index.aspx>), the final determination of the impact of the novel diagnostic pathway was dependent on a comparison of only 12 MIBC patients managed without TURBT to 14 patients who were managed according to the current standard

of care with TURBT.<sup>1</sup> A larger cohort with MIBC would certainly have added more robustness to the analysis.

While the investigators highlighted in their ESMO presentation the limitations of TURBT, the panel at the Forum focused also on the potential benefits of TURBT that are lost in the MRI pathway. Previous trials have shown that a small percentage (6–15%) of MIBC cases achieve a complete response with TURBT alone.<sup>3–6</sup> Studies also suggest that complete TURBT may improve outcomes after trimodal therapy<sup>7,8</sup> and neoadjuvant chemotherapy with cystectomy.<sup>9</sup> This is relatively low-quality evidence. Future studies will need to determine if TURBT plays a role beyond staging and whether the residual tumor left behind in the absence of TURBT impacts treatment outcomes.

The panelists highlighted that insufficient tissue obtained through the MRI pathway may impact downstream assessment and treatment. Tumor sequencing and custom circulating tumor DNA tests, which may guide future systemic treatment decisions, may not be possible if biopsy tissue is too scant. Additionally, a simple office biopsy to confirm urothelial carcinoma may not adequately identify histologic subtypes. This may impact the counselling and selection of appropriate treatment, such as the need for and type of neoadjuvant chemotherapy, and the selection of cystectomy vs. chemoradiation.

Finally, the primary outcome, TTCT, may have limited clinical significance. The trial demonstrated that obtaining an MRI is faster than accessing operating room time for a TURBT in the U.K., which may have limited applicability in some countries, especially in those where bladder MRI is infrequently performed due to long waiting lists or limited experience of radiologists. The VI-RADS system is not without pitfalls. For instance, assigning a VI-RADS score to lesions in the ureteric orifices and bladder neck is difficult and interobserver variation is high.<sup>10</sup> There is a potential oncologic benefit of reducing TTCT by 30 days, although this has not been substantiated to date, particularly if definitive treatment can still be performed within an appropriate timeframe of less than three months.<sup>11</sup> If TTCT is an important parameter, other system measures could be introduced to ensure more timely delivery of care while retaining the advantages of TURBT.

The authors of BladderPath are to be applauded for their efforts to “think outside the box” in an attempt to improve what is an imperfect practice. Although the TURBT is generally a safe procedure, it is associated with complications, especially in older and frailer patients, and there is a theoretical risk that the procedure itself could lead to locoregional or distant tumor dissemination. These outcomes have not (yet) been

addressed by the trial, and the small sample size will preclude any definitive conclusions. While acknowledging the need to reconsider the current diagnostic pathway in patients with suspected MIBC, the panel at the Forum concluded that BladderPath did not yield results that should change current clinical practice; however, further interventional studies like BladderPath should be encouraged and will hopefully lead to improved management pathways in the future.

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