Image directed redesign of bladder cancer treatment pathways: the BladderPath RCT

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Scientific summary

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Scientific summary

Background

Bladder cancer (BC) is the fifth most common cancer in Western society. Standard management follows a pathway established > 60 years ago with the first description of transurethral resection of bladder tumour (TURBT), and prognosis has not improved for 30 years. Following visual diagnosis by outpatient flexible cystoscopy, TURBT is the subsequent diagnostic and staging tool for all patients. While TURBT is mostly well-tolerated and therapeutic for non-muscle-invasive BC (NMIBC), its role in muscle-invasive BC (MIBC) is predominantly diagnostic. Furthermore, for MIBC patients, initial TURBT often under-stages invasion (up to 30% of MIBCs are initially staged as high-grade NMIBC at first TURBT) and may contribute to extravesical tumour dissemination as a result of the piecemeal resection process. Subsequently, accurate staging by cross-sectional pelvic imaging post TURBT is impaired by post-surgical artefacts.

Moreover, internationally, TURBT followed by histopathological review and multidisciplinary team (MDT) decision-making typically adds a number of weeks to the pathway, creating a delay in commencing correct radical treatment for MIBC patients and potentially worse outcomes. Thus, an ideal pathway would separate NMIBC patients from MIBC patients at the time of diagnosis by the faster and more accurate application of established technologies to expedite therapy, potentially improving outcomes. Imaging advances suggesting multiparametric (mp) magnetic resonance imaging (MRI) may allow the accurate discrimination of NMIBC from MIBC, theoretically offering a safer and faster route to radical treatment than TURBT.

To test the hypothesis whether MIBC patients can be safely expedited to radical treatment by using initial mpMRI for local staging rather than TURBT, we undertook the BladderPath randomised controlled trial [NHS Research Ethics Committee (REC) approval 17/LO/1819, ISRCTN 35296862].

Objectives

To assess the feasibility and efficacy of the substitution of TURBT with mpMRI in the staging of patients with suspected MIBC, hypothesising that image-directed (mpMRI) staging would shorten the time period to correct treatment for MIBC patients compared to the standard TURBT-based pathway.

Methods

BladderPath is a randomised trial comparing risk-stratified image-directed (mpMRI) care with TURBT for patients with newly diagnosed BC. Patients with symptoms suspicious of a new diagnosis of BC were identified via haematuria clinics, and they provided written informed consent for study participation. Ineligible patients were those unable or unwilling to undergo MRI, those with a previous BC diagnosis and those who had previously entered the study. Participants with possible MIBC (Likert 3–5 as visually assessed on a 5-point Likert scale at flexible cystoscopy) were randomised to standard TURBT assessment (Pathway 1) or mpMRI-based assessment (Pathway 2) with flexible cystoscopy tumour biopsy Pathway 2 probable NMIBC (Likert 1–2) participants underwent TURBT.

Primary outcomes: Feasibility phase – proportion of Pathway 2 possible MIBC participants who correctly followed protocol (target: 80%); intermediate stage – time to first correct treatment (chemotherapy, radiotherapy, surgery, decision for palliative care) for participants with confirmed MIBC (target: 30-day improvement) and as time to TURBT or palliative care for NMIBC. Randomisation was achieved by using

a computerised allocation program; stratification variables included participants' sex, age and clinician's initial visual assessment of muscle invasiveness of the tumour. Blinding of participants, caregivers and outcome assessors was not possible.

Results

Between 31 May 2018 and 31 December 2021, recruitment took place in 15 UK urology centres; 638 patients were screened as potentially eligible, of which 309 were registered and 143 were randomised (72 to Pathway 1, 71 to Pathway 2). The 166 registered patients not randomised were not found to have BC during initial cystoscopy. Three participants were subsequently found to be ineligible post randomisation (one in Pathway 1, two in Pathway 2). Seven participants withdrew from the study (three in Pathway 1, four in Pathway 2), including three participants who were confirmed as not having cancer. Nine protocol deviations were reported by nine participants (five in Pathway 1, four in Pathway 2).

The primary outcome for the feasibility stage was the proportion of possible MIBC participants randomised to Pathway 2 who correctly followed the pathway protocol. In total, 36 of the 39 [92%; 95% confidence interval (CI) 79% to 98%] possible MIBC participants in Pathway 2 underwent mpMRI as per protocol. Three Pathway 2 possible MIBC participants did not undergo mpMRI post randomisation: one participant had metal in their eye, one patient withdrew (29 days post randomisation) and one underwent MRI prior to trial entry (scan was requested independently of the study). Of the 36 participants who underwent mpMRI, 17 were diagnosed as MIBC, 16 as NMIBC and 3 were inconclusive.

The secondary outcome for the feasibility stage was the overall proportion of randomised participants who correctly followed the protocol in each pathway. For Pathway 1, this was defined as the number of probable NMIBC and possible MIBC participants randomly accrued who underwent TURBT at an appropriate stage, as a proportion of all participants randomised to that pathway. For Pathway 2, it was defined as the number of probable NMIBC participants who underwent TURBT plus the number of possible MIBC participants who underwent mpMRI, divided by all randomised to Pathway 2. The overall proportion of participants who correctly followed their respective protocol pathway was 96% (95% CI 88% to 99%) in each pathway. There was no statistical difference between the pathways.

For the Intermediate stage, the primary outcome was time to correct treatment (TTCT) for participants who were initially classified as possible MIBC and were then confirmed to have MIBC (by TURBT or mpMRI). For the 25 participants who were initially classified as possible MIBC and were then confirmed as MIBC (14 in Pathway 1; 11 in Pathway 2), 24 participants received a correct treatment (the remaining patients died 81 days post randomisation, before a correct treatment; date last seen is used in the time-to-event analysis). Median TTCT for all participants who were initially classified as possible MIBC and were then confirmed to have MIBC (N = 25) was 77 days (95% CI 54 to 98). Median TTCT for Pathway 1 (N = 14) was 98 days (95% CI 72 to 125). Median TTCT for Pathway 2 (N = 11) was 53 days (95% CI 20 to 81). The p-value of 0.0201 suggests a statistical difference in TTCT between the pathways. A Cox model adjusting for the stratification factors of sex and age, with study centre included as a random effect, showed that the hazard ratio (HR) of an event for Pathway 2 versus Pathway 1 was 2.9 (95% CI 1.0 to 8.1, p = 0.04). An event in this model indicates a patient receiving a correct treatment; therefore, the HR of 2.9 indicates that participants in Pathway 2 received correct treatment 2.9 times quicker than those in Pathway 1.

To assess the secondary outcome of TTCT for probable NMIBC participants confirmed as NMIBC, there were 58 participants initially classified as probable NMIBC and then confirmed as NMIBC (28 in Pathway 1 and 30 in Pathway 2), all of whom received correct treatment of TURBT. Median TTCT for probable NMIBC participants confirmed as NMIBC (N = 58) was 16 days (95% CI 11 to 23); median TTCT for Pathway 1 (N = 28) was 14 days (95% CI 10 to 29) and 17 days (95% CI 8 to 25) for Pathway 2

(*N* = 25), log-rank *p* = 0.6677. A Cox model adjusting for the stratification factors of sex and age showed that the HR for Pathway 2 versus Pathway 1 was 0.8 (95% CI 0.5 to 1.5).

For the secondary outcome of TTCT for all randomised participants, 131 of 143 randomised participants had received a correct treatment (72 in Pathway 1 and 71 in Pathway 2); participants who had not received a correct treatment were censored at their date last seen and included in the time-to-treatment analysis. Median TTCT for all randomised participants (*N* = 143) was 31 days (95% CI 22 to 37); median TTCT for Pathway 1 (*N* = 72) was 37 days (95% CI 23 to 47) and 25 days (95% CI 18 to 35) for Pathway 2 (*N* = 71), log-rank *p* = 0.0295. A Cox model adjusting for the stratification factors of sex and age showed that the HR for Pathway 2 versus Pathway 1 was 1.4 (95% CI 0.9 to 2.0).

To assess the secondary outcome of time to definitive treatment (TTDT) for all randomised participants, 137 randomised participants had received definitive treatment (6 participants did not receive definitive treatment and their date last seen was used in the time-to-event analysis). Median TTDT for all randomised participants (*N* = 143) was 23 days (95% CI 20 to 29); median TTDT for Pathway 1 (*N* = 72) was 23 days (95% CI 17 to 29) and for Pathway 2 (*N* = 71) was 22 days (95% CI 17 to 32), log-rank *p*-value of 0.9619. A Cox model adjusting for the stratification factors of sex and age showed that the HR for Pathway 2 versus Pathway 1 was 0.9 (95% CI 0.6 to 1.2).

Clinical analysis

Delays in administering the correct treatment for MIBC patients after initial urological consultation and disease diagnosis are internationally widespread [Russell B, Liedberg F, Khan MS, Nair R, Thurairaja R, Malde S, *et al*. A systematic review and meta-analysis of delay in radical cystectomy and the effect on survival in bladder cancer patients. *Eur Urol Oncol* 2020;**3**(2):239–49]. Prolonged delays contribute to poor prognosis, and so attempts to improve and refine the diagnostic and treatment pathways for BC patients are of international importance and a priority for patients and healthcare professionals alike [Russell *et al*. 2020; Bessa A, Maclennan S, Enting D, Bryan R, Josephs D, Hughes S, *et al*. Consensus in bladder cancer research priorities between patients and healthcare professionals using a four-stage modified Delphi method. *Eur Urol* 2019;**76**(2):258–9]. Although first described over 60 years ago, the piecemeal resection of bladder tumour(s), TURBT, remains the initial diagnostic and staging tool for all patients. The shortcomings of TURBT are well-reported [Bessa *et al*. 2019; Del Giudice F, Flammia RS, Pecoraro M, Moschini M, D'Andrea D, Messina E, *et al*. The accuracy of Vesical Imaging-Reporting and Data System (VI-RADS): an updated comprehensive multi-institutional, multi-readers systematic review and meta-analysis from diagnostic evidence into future clinical recommendations. *World J Urol* 2022;**40**(7):1617–28; Wallace DM, Bryan RT, Dunn JA, Begum G, Bathers S; West Midlands Urological Research Group. Delay and survival in bladder cancer. *BJU Int* 2002;**89**(9):868–78; Bryan RT, Collins SI, Daykin MC, Zeegers MP, Cheng KK, Wallace DMA, *et al*. Mechanisms of recurrence of Ta/T1 bladder cancer. *Ann R Coll Surg Engl* 2010;**92**(6):519–24], all of which may delay the correct radical treatment for MIBC patients or lead to incorrect therapy choices. Over the course of the last decade, data suggest that mpMRI may allow the accurate discrimination of NMIBC and MIBC, and so potentially offering a safer and faster route to radical treatment than TURBT (Panebianco *et al*. 2018; Del Giudice *et al*. 2022).

We have shown that it is feasible to introduce mpMRI for initial staging into the pathway for those patients visually diagnosed with possible MIBC at outpatient diagnostic flexible cystoscopy. Moreover, we have demonstrated that by doing so, possible MIBC patients receive their correct therapy significantly quicker – 45 days quicker, even if some of these MIBC patients still require TURBT either to resolve diagnostic uncertainty or as part of their planned care (e.g. to debulk tumour prior to radiotherapy).

Although the relationship between delay and survival in BC is complex (Wallace *et al*. 2002), it is reasonable to contemplate that administering correct treatment to MIBC patients more than 6 weeks earlier than the current standard of care can only be beneficial. Several studies report adverse outcomes

associated with delays of over 3 months between bladder cancer diagnosis and radical cystectomy (Russell *et al*. 2020); the mpMRI-guided BladderPath pathway (Pathway 2) undercut this TTCT by a considerable margin (median TTCT 53 days), whereas the standard pathway did not (median TTCT 98 days). Unfortunately, with substantial interruptions to recruitment due to the COVID-19 pandemic, we have been unable to recruit sufficient patients to evaluate our a priori survival outcomes.

Further limitations to the study are that, for patients who underwent systemic chemotherapy, radiotherapy or palliation for mpMRI-diagnosed MIBC, it is impossible to conclusively know whether these were 'correct' treatments in the sense that staging was radiological not pathological, that is by histological confirmation of muscle invasion. This is however the norm for staging of most cancers. All patients had histological confirmation of their cancers and all treatments were approved via the relevant MDT.

An important component of this new pathway is the ability of urologists to accurately triage patients as probable NMIBC or possible MIBC at the time of outpatient diagnostic flexible cystoscopy based upon the macroscopic appearances of suspicious bladder lesions. Building upon previous evidence (Bryan *et al*. 2010), we have shown that 89% of visually diagnosed probable NMIBCs were pathologically confirmed as NMIBCs, demonstrating that urologists can reliably identify such tumours. Hence, the simple patient pathway change suggested by the BladderPath data described here is universally applicable and is easy to implement.

Conclusions

The mpMRI-directed pathway led to a substantial reduction in TTCT for MIBC participants without detriment to the TTCT for NMIBC participants. Consideration should be given to the incorporation of mpMRI ahead of TURBT in the standard pathway for all patients with suspected MIBC. A proportion of patients were able to avoid TURBT completely and the improved decision-making accelerated time to treatment, even though many patients subsequently needed TURBT as part of their treatment plan.

Trial registration

This trial is registered as ISRCTN 35296862.

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