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This article

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Abstract

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

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Kieran Jefferson[4] Prashant Patel[5] Ana Hughes[2]
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Background: Transurethral resection of bladder tumour has been the mainstay of bladder cancer staging for > 60 years. Staging inaccuracies are commonplace, leading to delayed treatment of muscle-invasive bladder cancer. Multiparametric magnetic resonance imaging offers rapid, accurate and non-invasive staging of muscle-invasive bladder cancer, potentially reducing delays to radical treatment.

Objectives: To assess the feasibility and efficacy of the introducing multiparametric magnetic resonance imaging ahead of transurethral resection of bladder tumour in the staging of suspected muscle-invasive bladder cancer.

Design: Open-label, multistage randomised controlled study in three parts: feasibility, intermediate and final clinical stages. The COVID pandemic prevented completion of the final stage.

Setting: Fifteen UK hospitals.

Participants: Newly diagnosed bladder cancer patients of age ≥ 18 years.

Interventions: Participants were randomised to Pathway 1 or 2 following visual assessment of the suspicion of non-muscle-invasive bladder cancer or muscle-invasive bladder cancer at the time of outpatient cystoscopy, based upon a 5-point Likert scale: Likert 1–2 tumours considered probable non-muscle-invasive bladder cancer; Likert 3–5 possible muscle-invasive bladder cancer. In Pathway 1, all participants underwent transurethral resection of bladder tumour. In Pathway 2, probable non-muscle-invasive bladder cancer participants underwent transurethral resection of bladder tumour, and possible muscle-invasive bladder cancer participants underwent initial multiparametric magnetic resonance imaging. Subsequent therapy was determined by the treating team and could include transurethral resection of bladder tumour.

Main outcome measures: Feasibility stage: proportion with possible muscle-invasive bladder cancer randomised to Pathway 2 which correctly followed the protocol.

Intermediate stage: time to correct treatment for muscle-invasive bladder cancer.

Results: Between 31 May 2018 and 31 December 2021, of 638 patients approached, 143 participants were randomised; 52.1% were deemed as possible muscle-invasive bladder cancer and 47.9% probable non-muscle-invasive bladder cancer. Feasibility stage: 36/39 [92% (95% confidence interval 79 to 98%)] muscle-invasive bladder cancer participants followed the correct treatment by pathway. Intermediate stage: median time to correct treatment was 98 (95% confidence interval 72 to 125) days for Pathway 1 versus 53 (95% confidence interval 20 to 89) days for Pathway 2 [hazard ratio 2.9 (95% confidence interval 1.0 to 8.1)], $p = 0.040$. Median time to correct treatment for all participants was 37 days for Pathway 1 and 25 days for Pathway 2 [hazard ratio 1.4 (95% confidence interval 0.9 to 2.0)].

Limitations: For participants who underwent chemotherapy, radiotherapy or palliation for multiparametric magnetic resonance imaging-diagnosed stage T2 or higher disease, it was impossible to conclusively know whether these were correct treatments due to the absence of histopathologically confirmed muscle invasion, this being confirmed radiologically in these cases. All patients had histological confirmation of their cancers.

Due to the COVID-19 pandemic, we were unable to realise the final stage.

Conclusion: The multiparametric magnetic resonance imaging-directed pathway led to a substantial 45-day reduction in time to correct treatment for muscle-invasive bladder cancer, without detriment to non-muscle-invasive bladder cancer participants. Consideration should be given to the incorporation of multiparametric magnetic resonance imaging ahead of transurethral resection of bladder tumour into the standard pathway for all patients with suspected muscle-invasive bladder cancer. The improved decision-making accelerated time to treatment, even though many patients subsequently needed transurethral resection of bladder tumour. A proportion of patients can avoid transurethral resection of bladder tumour completely, reducing costs and morbidity, given the much lower cost of magnetic resonance imaging and biopsy compared to transurethral resection of bladder tumour.

Future work: Further work to cross-correlate with the recently developed Vesical Imaging-Reporting and Data System will improve accuracy and aid dissemination. Longer follow-up to examine the effect of the pathway on outcomes is also required. Incorporation of liquid deoxyribonucleic acid-based biomarkers may further improve the quality of decision-making and should also be investigated further.

Study registration: This study is registered as ISRCTN 35296862.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 14/08/60) and is published in full in *Health Technology Assessment*; Vol. 28, No. 42. See the NIHR Funding and Awards website for further award information.

Contents

List of tables

List of figures

List of abbreviations

AE	adverse event
BAUS	British Association of Urological Surgeons
BC	bladder cancer
BCG	Bacillus Calmette–Guerin
CIS	carcinoma in situ
CTE	Commissioning through Evaluation
CONSORT	Consolidated Standards of Reporting Trials
cp	cell pellet
CRCTU	Cancer Research Clinical Trials Unit
CTE	Commissioning through Evaluation
DMC	Data Monitoring Committee
DTT	decision to treat
EAU	European Association of Urology
eGFR	estimated glomerular filtration rate
FBC	full blood count
GCP	good clinical practice
HBRC	Human Biomaterials Resource Centre
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trial Number
LFT	liver function test
MDT	multidisciplinary team
MIBC	muscle-invasive bladder cancer
mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
NIHR	National Institute for Health and Care Research
NMIBC	non-muscle-invasive bladder cancer
REC	Research Ethics Committee
SOC	standard of care
TMG	Trial Management Group
TSC	Trial Steering Committee
TTCT	time to correct treatment
TTDT	time to definitive treatment
TURBT	transurethral resection of bladder tumour
UCC	urothelial cell carcinoma
VI-RADS	Vesical Imaging-Reporting and Data System
WHO	World Health Organization

Plain language summary

The BladderPath trial explored how to accelerate diagnosis and avoid unnecessary surgery for patients with bladder cancer which had grown into the muscle wall of the bladder, referred to as muscle-invasive bladder cancer.

Following initial outpatient diagnosis, bladder cancer patients currently undergo inpatient or day-case surgical tumour removal using a telescope (transurethral resection of bladder tumour). This surgery is fundamental to the treatment of early bladder cancer (non-muscle-invasive). However, for muscle-invasive disease, the main role of transurethral resection of bladder tumour is to confirm that the tumour has grown into the bladder muscle, and this is often inaccurate; the actual correct treatment for muscle-invasive bladder cancer patients should include chemotherapy, radiotherapy and/or bladder removal. For these patients, having transurethral resection of bladder tumour may delay this correct treatment and impact survival. Additionally, for patients determined to need palliative care due to advanced disease, the transurethral resection of bladder tumour may represent over-treatment.

A magnetic resonance imaging scan with contrast agent (called multiparametric magnetic resonance imaging) gives a clearer picture of the bladder than normal scans, allowing distinction between invasive and non-invasive tumours. The BladderPath trial investigated adding multiparametric magnetic resonance imaging for patients with suspected muscle-invasive bladder cancer and the effect on treatment times. Subsequent therapy could include transurethral resection of bladder tumour if clinically determined as necessary by the treating team.

Trial participants were randomly allocated either to the standard pathway (Pathway 1: all underwent transurethral resection of bladder tumour) or to a new pathway (Pathway 2). In Pathway 2, urologists conducting the initial outpatient diagnostic bladder inspections used a scale to assess whether tumours appeared to be either probably non-muscle-invasive or possibly muscle-invasive. Participants whose tumours appeared possibly muscle-invasive had initial multiparametric magnetic resonance imaging as their next investigation instead of transurethral resection of bladder tumour. We then compared the duration of time from initial diagnosis to receiving the correct treatment for participants in each pathway.

Of the 143 participants, 75 (52.1%) were diagnosed as possibly muscle invasive. In Pathway 1, the duration for half of the participants in the group to have received their correct treatment for muscle-invasive bladder cancer was 98 days, which reduced to 53 days in Pathway 2. Furthermore, the duration for half of all the participants in the two groups to have received their correct treatment was 37 days for Pathway 1 and 31 days for Pathway 2.

In summary, use of initial multiparametric magnetic resonance imaging in suspected muscle-invasive bladder cancer participants substantially reduced the time to correct treatment (surgery, radiotherapy, chemotherapy or instigation of palliative care) and avoided unnecessary surgery. There was no negative impact on participants with non-invasive disease. Adopting multiparametric magnetic resonance imaging into the pathway ahead of transurethral resection of bladder tumour for patients with suspected muscle-invasive bladder cancer is recommended.

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 understages 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.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 14/08/60) and is published in full in *Health Technology Assessment*; Vol. 28, No. 42. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction and background literature

Bladder cancer (BC) is the fifth most common cancer in Western society. In the UK there are approximately 10,000 new cases and 5000 deaths attributed to BC annually.[1] In Western populations, over 90% of BCs are urothelial cell carcinoma (UCC). Standard management follows a pattern established during the 1950s with the development of the rigid cystoscope. Improvements in this pathway have high priority from patient Delphi consensus work.[2] Prognosis has not improved in the last 30 years.[3–5]

Standard management involves a pathway of diagnostic flexible cystoscopy followed by a transurethral resection of the bladder tumour (TURBT) with a rigid cystoscope.[6,7] TURBT has the multiple purposes of diagnosis, staging and treatment of non-muscle-invasive BC (NMIBC), that is removal of the tumour. Further treatments, such as neoadjuvant chemotherapy, radical cystectomy or chemoradiotherapy, are then necessary for muscle-invasive BC (MIBC).[8]

For MIBC, this initial TURBT often understages invasion (up to 30% of MIBCs are initially staged as high-grade NMIBC at first TURBT[5]) and may contribute to extravesical tumour dissemination through bladder perforation or venous emboli generated through the high-pressure resection process.[9] Cross-sectional pelvic imaging after TURBT impedes the accuracy of staging due to surgical artefacts (such as perivesical inflammation and reactive lymph nodes).[10–13]

Typically, the need for a TURBT, histopathological review and multidisciplinary team (MDT) decision-making adds at least 6–12 weeks to the pathway, prolonging the delay to commencing (the most appropriate) correct radical treatment for patients with MIBC.[5,14–17]

An ideal pathway would separate NMIBC patients from MIBC patients at the time of initial macroscopic diagnosis. Faster and more accurate application of established technologies would then streamline therapy, potentially improving outcomes and saving clinical costs.

For the 75–80% of BC patients who present with NMIBC, tumour recurrence and progression following TURBT are significant issues, compelling current guidelines to recommend intense long-term surveillance by cystoscopy and urine cytology. With the UK prevalence of BC estimated at 46,500, at any one time there will be 35,000–37,000 patients with NMIBC requiring such surveillance, performed as often as every 3–6 months at an estimated cost of at least £533 per flexible cystoscopy/cytology 'episode' (as costed in 2010[18]). Around 30% of NMIBC cases will progress to MIBC and require additional therapy.

Around 20–25% of new BC patients present with de novo MIBC.[19,20] Survival with MIBC remains poor (27–50% 5-year survival) and has not improved in the past 30 years.[1] The present pathway is largely geared to the treatment of NMIBC patients and actively delays effective MIBC treatment, which is often carried out in a different hospital to initial diagnosis and TURBT, increasing handovers and therefore delays. In Birmingham, for example, many NHS Trusts run haematuria clinics, a smaller number offer systemic chemotherapy, but only two carry out major pelvic surgery, and only one radiotherapy. Early clarity on staging and diagnosis would facilitate more coordinated planning and treatment delivery. Similar considerations exist in all major healthcare systems worldwide, especially in North America where BC patients are frequently diagnosed in an 'office urology' setting[21] and then need referral into the hospital setting for TURBT and definitive therapy.

This fragmented care with complicated staging and follow-up leads to the cumulative cost of treating BC exceeding all other forms of human cancer.

The current shared patient pathway thus delays therapy for MIBC patients. There is a growing body of opinion that such pathways should separate earlier in order to more appropriately and expeditiously treat MIBC patients,[3] and this is what we evaluated in BladderPath.

Staging and treatment

The pros and cons of staging and treatment techniques for BC are summarised in *Table 1*, including the aim of TURBT in the settings of NMIBC and MIBC.

From the above, it is clear that the main functions of TURBT in MIBC are histological diagnosis of cancer and staging. Diagnosis does not require large quantities of tissue – very small amounts are sufficient to confirm the presence of high-grade malignant cells to ascertain grade (as exemplified by the almost ubiquitous use of urine cytology). The main function of TURBT in MIBC therefore is to assess stage. Where muscle is adequately sampled and is found to contain tumour, a diagnosis of MIBC is correct by definition (although not a more comprehensive nodal or metastasis stage). The issue is the understaging of high-grade tumours due to inadequate sampling of muscle that subsequently turns out to be involved by tumour. As cystectomy is a recognised treatment for high-risk NMIBC,[12] either at diagnosis or after the failure of treatments such as bacillus Calmette–Guérin (BCG), the false-negative rate with respect to distinguishing NMIBC from MIBC in the highest risk cases can be estimated – this appears to be as high as 30%,[1,6] although will clearly vary depending upon the surgeon and referred case mix. Within this context, we can assess the accuracy of magnetic resonance imaging (MRI) for the same purpose. The key factor here is the split between tumours of stage pT1 and lower versus pT2 and higher.

Thus, the diagnostic function of TURBT can be substituted by a smaller biopsy obtained during outpatient flexible cystoscopy. For staging, multiparametric MRI (mpMRI) has performance characteristics that exceed those reported for TURBT, are less subject to operator variability and are amenable to external review.[22–24] Furthermore, in most cases, the therapeutic benefit for TURBT in MIBC patients remains unproven, particularly if cystectomy is the preferred definitive treatment option. The literature on staging BC has been recently reviewed by Bouchelouche and co-workers.[25–27]

A role for TURBT as palliation of severe symptoms from MIBC pending a definitive treatment decision will remain. Its precise magnitude will be quantified in this study but is likely to be limited as, in most cases, symptoms such as haematuria are intermittent (one of the factors leading to delayed presentation).

Hypothesis

The purpose of the BladderPath study is to evaluate a new pathway that would eliminate TURBT from the initial staging of MIBC patients. This allows more expeditious treatments for both MIBC (by eliminating delays and improved targeting of subsequent therapy) and NMIBC (by reducing demand for TURBT in the system). Our approach integrates flexible cystoscopy, urine cytology, biopsy and detailed imaging to confirm the diagnosis and stage of disease. Appropriate definitive radical therapy can then

TABLE 1 Aim of TURBT in NMIBC and MIBC

Aim of TURBT	NMIBC	MIBC
Diagnosis	✓	✓
Staging	✓	Sometimes – under-staging in up to 30%
Treatment	✓	No – may be harmful
Palliation of symptoms	Sometimes in cases of heavy bleeding	Sometimes in cases of heavy bleeding

be rapidly commenced. This could include TURBT if indicated for reasons such as diagnostic uncertainty, assessment of carcinoma in situ (CIS; e.g. for planning cystectomy) or debulking prior to radiotherapy. For the purposes of the trial, TURBT in patients with MIBC did not count as part of their definitive treatment. This is a paradigm shift in the context of BC but is standard practice in virtually every other solid tumour setting (e.g. prostate, breast, lung). Although TURBT is considered a standard part of care for NMIBC, for MIBC it is less obviously essential, particularly for patients undergoing subsequent radical surgery (cystectomy). This study tested the utility of TURBT and mpMRI as components of the initial care for MIBC patients in a randomised fashion.

Rationale

The prognosis for MIBC remains poor and has not changed for three decades.[1,3,4] Modern MRI approaches now have the ability to accurately stage bladder tumours[11,28,29] and experimental urinary biomarkers show great promise in identifying MIBC from a urine test.[30,31] The platforms therefore exist to improve patient pathways, potentially leading to improved outcomes.

In order to change the current pathway, we need to show that alternatives to TURBT exist for staging, and that faster treatment will improve outcomes:

1. Do we need TURBT for histology?
    a. Flexible cystoscopy and biopsy can give accurate tumour histological diagnosis and grading but does not assess stage or muscle invasion.
2. Can we replace TURBT for detailed assessment of the bladder tumour?
    a. TURBT is frequently inaccurate and operator dependent – up to 30% of tumours assessed as high-grade NMIBC at TURBT are subsequently diagnosed as invasive (MIBC) on repeat TURBT or at cystectomy.[5,32]
    b. Guidelines recommend repeat TURBT for patients staged G3pT1 because of the high incidence of understaging – further delaying correct treatment in some patients with MIBC.[5,32]
    c. Sensitivity and specificity of mpMRI for separating NMIBC from MIBC are 94% and 100%, respectively.[11,27–29,33,34]
    d. Introducing mpMRI ahead of TURBT (if indicated) should not compromise staging and may improve it.
3. Is TURBT an essential component of treatment?
    a. There are no randomised data on this topic – this is one of the aims of this study.
    b. Evidence exists that TURBT may increase local tumour dissemination[35] and lead to increases in circulating tumour cells.[9]
    c. In most other oncology settings, imaging and biopsy are sufficient for correct treatment; in some cases, imaging alone is sufficient (e.g. kidney cancer and upper tract urothelial cancer). Few tumour sites use an intermediate piecemeal debulking ahead of definitive therapy.[36]
4. Does delaying the correct definitive treatment affect prognosis?
    a. Typical duration from first clinic visit to correct definitive treatment within the NHS for MIBC is around 100 days.[6,20,37] Similar delays exist worldwide.[14]
    b. There is evidence that delay can affect prognosis for MIBC.[14,16,17]
    c. Hence, reducing delay should improve prognosis.

Aims and objectives

The aims of the BladderPath study are to evaluate whether it is possible to expedite radical treatment for patients with MIBC using MRI rather than TURBT to diagnose and more accurately and rapidly stage their cancer. We hypothesise this may improve outcomes from MIBC by reducing the time from diagnosis to radical treatment.

Outcome measures

The primary and secondary outcomes change as we go through the study. These are summarised in *Table 2*.

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 provided written informed consent for study participation. Ineligible patients were those who were unable or unwilling to undergo MRI, those with a previous BC diagnosis and those who had previously entered the study. Participants were randomised to the standard clinical pathway (Pathway 1: all patients undergo TURBT) or the investigational pathway (Pathway 2) whereby those participants with possible MIBC (Likert 3–5 as visually assessed on a 5-point Likert scale at flexible cystoscopy) undergo initial mpMRI-based assessment 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). 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.

Study design

The Image Directed Redesign of BC Treatment Pathways ('BladderPath') study was an open-label, multistage, randomised controlled study with three overlapping stages: feasibility, intermediate and final efficacy stage. BladderPath was conducted by the Urology units in 15 UK hospitals and was sponsored by the University of Birmingham, UK, with NHS Research ethics approval (17/LO/1819, ISRCTN 35296862), funded by the UK National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) scheme.[14,38] The study protocol is available online: www.birmingham.ac.uk/research/crctu/trials/bladder-path/index.aspx.

TABLE 2 Primary and secondary outcomes

	Primary outcomes	Secondary outcomes
Feasibility stage	The proportion of possible MIBC patients randomised to Pathway 2 who correctly follow pathway protocol	• Overall proportion of patients who correctly follow protocol on each pathway for all randomised patients • Recruitment and retention rates at each study site • Counts of each type of correct treatment
Intermediate stage	The TTCT for patients who were initially classified as possible MIBC and then were confirmed to have MIBC	• TTCT for all randomised patients • TTCT for probable NMIBC patients confirmed as NMIBC • TTDT for all randomised patients (this end point was subsequently dropped as changes in NHS definitions meant this was the same as TTCT) • All outcomes reported in the Feasibility Stage will be repeated if the first two stages are not conducted at the same time

TTCT, time to correct treatment; TTDT, time to definitive treatment.

Participants

Following the provision of dedicated patient information sheets, participants were recruited by Urology teams at hospital outpatient haematuria clinics.[39] A two-stage written informed consent process was adopted to allow prospective collection of urine samples before initial cystoscopy for a diagnostic urinary biomarker substudy (first stage),[35] with confirmatory written informed consent undertaken following cystoscopy (second stage). Hence, inclusion criteria were: patients attending clinic for the investigation of symptoms suspicious of BC (initial consent process), and patients given a diagnosis of suspected BC and requiring TURBT based on visual cystoscopic examination of the bladder (confirmatory consent process following outpatient flexible cystoscopy). Excluded patients were those unable or unwilling to undergo MRI, those with a previous diagnosis of BC and previous entry in the present study.

Randomisation and masking

Participants were randomised by computer using minimisation on a 1 : 1 basis to Pathway 1 (standard of care: TURBT) or Pathway 2 (investigational: mpMRI): minimisation factors used were patient sex (male/female), age (< 75/≥ 75 years old) and clinician assessment at outpatient flexible cystoscopy (probable NMIBC/possible MIBC). A random element was incorporated into the minimisation algorithm at 20% ensuring it was not predictable. Randomisation was not blinded, with both participants and healthcare teams knowing which pathway had been allocated to participants.

Procedures

The study compared TURBT with mpMRI for the initial assessment of possible MIBC. The current SOC pathway comprises flexible cystoscopy in outpatient clinics combined with upper urinary tract imaging and, potentially, cross-sectional imaging of the bladder/pelvis followed by TURBT for participants with lesions suspicious for BC.

Participants were randomised to either Pathway 1 or 2 following visual assessment of the suspicion of NMIBC or MIBC at the time of outpatient flexible cystoscopy. The definition of likelihood of MIBC was based on 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 and 2 were considered probable NMIBC and 3, 4 and 5 were considered possible MIBC.

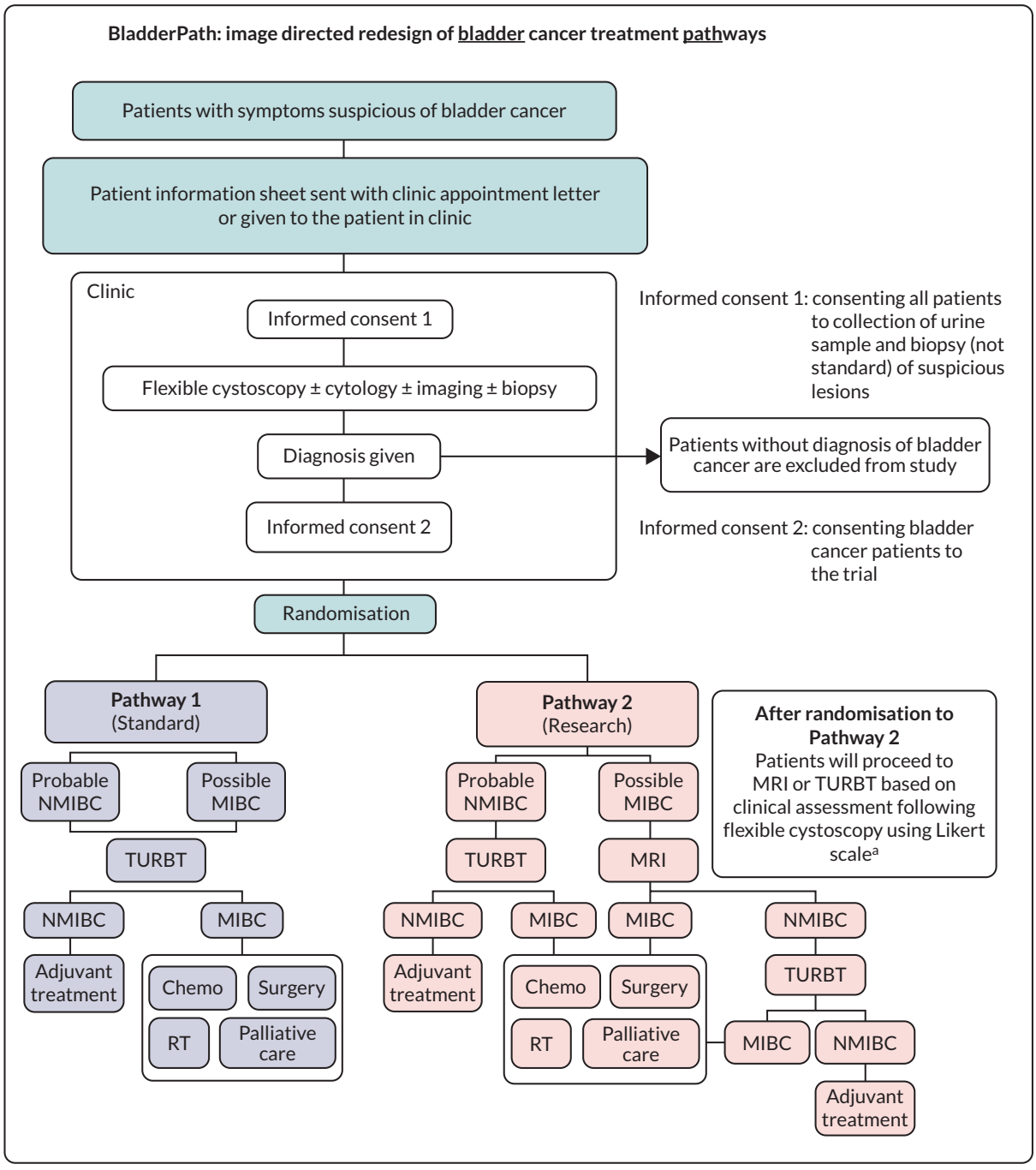
Pathway 1

For lesions suspicious for BC, inpatient TURBT was subsequently undertaken. TURBT was conducted as recommended by the European Association of Urology (EAU) and British Association of Urological Surgeons (BAUS):[6] resection of the exophytic component, sampling of underlying detrusor muscle, recording of clinical stage post TURBT (complete/incomplete resection, semi-fixed/fixed mass, etc.), bladder neck or urethral sampling for patients suitable for neobladder reconstruction, and sampling of areas suspicious of CIS. Separate biopsies of the tumour base were taken, with all samples sent for histopathological reporting and multidisciplinary review.

Pathway 2

In the investigational pathway, participants visually identified as probable NMIBC (Likert 1–2) underwent TURBT as SOC; participants identified as possible MIBC underwent mpMRI instead of TURBT. The criteria for diagnosing patients as possible MIBC were as follows: by appearance on flexible cystoscopy (Likert 3–5), by examination (the presence of a semi-fixed mass within the bladder before or after flexible cystoscopy), by cytology (the presence of high-grade urothelial cells in either urine or flexible cystoscopy biopsy) or by cross-sectional imaging when used [e.g. computerised tomography (CT)

urography]. Where possible, biopsy of suspicious lesions was carried out during initial outpatient flexible cystoscopy; if not achieved, then a confirmatory tissue sample was taken at a subsequent outpatient flexible cystoscopy.



[a] **Likert scale definition at flexible cystoscopy:**
1 = Strongly agree that the lesion is NMIBC
2 = Agree that the lesion is NMIBC
} Probable NMIBC (no MRI on either pathway)
3 = Equivocal (neither agree nor disagree) that the lesion is NMIBC or MIBC
4 = Agree that the lesion is MIBC
5 = Strongly agree that the lesion is MIBC
} Possible MIBC — if randomised to Pathway 2 patient to proceed to MRI

FIGURE 1 BladderPath Trial schema.

For possible MIBC participants, mpMRI was conducted and reported locally according to the BladderPath Imaging Manual. With the subsequent development of the 'Vesical Imaging-Reporting and Data System (VI-RADS)' protocol,[22] later patients were assessed using this system. Two of the VI-RADS authors are also part of the BladderPath team and hence both the systems were similar. Following mpMRI, TURBT was permitted for possible MIBC participants 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 showed MIBC; to perform examination under anaesthesia in order to assess operability; to assess for CIS; to obtain prostatic urethral biopsies when considering neobladder reconstruction; to re-stage after neo-adjuvant chemotherapy; or for the management of symptoms (e.g. haematuria).

All participants

Non-muscle-invasive bladder cancer participants underwent TURBT. In accordance with national and international guidelines, radical treatment with chemotherapy, surgery or (chemo) radiation was offered to all participants with MIBC where appropriate, based upon the results of either TURBT or mpMRI staging or both. For both groups, if unsuited to radical treatment, participants were referred for palliative care. All treatment decisions were made by the treating MDT. The study schema is shown in *Figure 1*.

Assessments

Initial clinical assessments (visit 1), potentially split over more than one visit depending on local practice) comprised: medical history (including concomitant medication), full blood count (FBC), liver function tests (LFTs), urea and electrolytes (U+Es), collection of urine samples for translational research, tumour biopsy (either via flexible cystoscopy at initial visit or at a subsequent visit if randomised to pathway 2 and considered possible MIBC) and completion of a participant reported outcomes quality of life booklet. At the time of the study procedure (visit 2, for either TURBT or mpMRI), a review of adverse events (AEs) was undertaken. At the decision to treat (DTT) (visit 3, following TURBT or mpMRI and multidisciplinary review), assessments comprised: medical history, FBC, LFTs, U+Es, and review of AEs. Adjuvant therapy and follow-up were according to SOC dependent upon NMIBC risk category[6] or MIBC treatment strategy.[14]

Outcomes

The aims of the BladderPath study were to evaluate whether it was possible to expedite radical treatment for participants with MIBC using mpMRI rather than TURBT to more accurately and rapidly stage their cancer. We hypothesised that this may improve outcomes from MIBC by reducing the time from diagnosis to the correct (radical) treatment. The study was conceived as three stages with the primary outcomes of feasibility, time to correct therapy (TTCT) for MIBC and clinical progression-free survival.

Feasibility stage

Primary outcome: the proportion of possible MIBC participants randomised to Pathway 2 who correctly follow pathway protocol. Secondary outcomes: overall proportion of participants who correctly follow protocol on each pathway for all randomised participants, recruitment and retention rates at each study site, counts of each type of correct treatment.

Intermediate stage

Primary outcome: TTCT for participants initially classified as possible MIBC and then confirmed to have MIBC. Secondary outcomes: TTCT for all randomised participants, TTCT for probable NMIBC participants confirmed as NMIBC, time to definitive treatment (TTDT) for all randomised participants.

Correct treatment was defined as TURBT for all confirmed NMIBC participants. For confirmed MIBC participants, the correct treatment may have included systemic chemotherapy, radiotherapy, cystectomy and/or palliative care. The final result of MIBC/NMIBC was based on cystectomy/TURBT pathological tumour staging. For participants who had MRI-diagnosed MIBC and were treated as MIBC (i.e. received at least one of the correct treatments for MIBC), their final result was MIBC. For participants who had MRI-diagnosed NMIBC, their correct treatment was TURBT.

Definitive treatment is defined under NHS guidelines, and the definitive treatment for BC was as TURBT at study inception. In this study, TURBT was used for diagnosis and treatment, and termed definitive treatment for all participants initially classified as probable NMIBC and for Pathway 1 participants classified as possible MIBC. For MIBC-classified participants randomised into Pathway 2, the definitive treatment at study inception included TURBT, systemic chemotherapy, radiotherapy, cystectomy and/or palliative care. Subsequently, NHS guidelines changed to align with our study definitions and TURBT was removed from the list of definitive treatments for MIBC and hence the TTDT end point became superfluous as it become identical to our TTCT end point and hence is not reported.

Final result of MIBC/NMIBC was based on cystectomy/TURBT pathological tumour staging if available. For participants who had MRI-staged MIBC and were treated as MIBC (i.e. received at least one of the correct treatments for MIBC), their final result was MIBC. Participants who were MRI-diagnosed NMIBC were to undergo TURBT as their correct treatment.

Sample size calculation

In the feasibility stage, the target sample size was 150 participants (approximately 38 possible MIBC participants in Pathway 2). If the proportion of possible MIBC participants randomised to Pathway 2 who correctly follow pathway protocol exceeded 80%, the image-directed Pathway 2 was considered feasible in clinical practice.[38]

For the Intermediate stage, the primary outcome was TTCT. We assumed that the TTCT in standard care had a median of 100 days and the effects of mpMRI would be to reduce the median TTCT to 70 days for MIBC participants. If the distribution of the TTCT for participants undergoing mpMRI followed a Weibull distribution with the same shape parameter as those receiving standard care, and that the usual proportional hazards assumption held, then a 'hazard ratio (HR)' of 3.6 was the effect size we wished to detect. More specifically, on average, it would be 3.6 times quicker to receive correct treatment for MIBC participants who underwent mpMRI compared to those underwent TURBT. To have 80% power to detect a HR of 3.6 using a Cox model required 20 MIBC participants. Around 20–25% of new BC participants present with de novo MIBC; hence, to recruit 20 MIBC participants, approximately 80–100 participants were required.

In the intermediate stage, the power was event driven and depended upon the number of observed events.

Due to slow recruitment (affected by COVID-19 the pandemic), it was unfeasible to reach the sample size required for a final clinical stage. A decision was made by the Trial Management Group (TMG), in discussion with the NIHR HTA, to close recruitment after sufficient participants for the first two stages had been recruited. The trial closed to recruitment on 31 December 2021. The database was locked on 20 September 2022 to allow a period of follow-up for the time-to-event outcomes. Longer-term follow-up to 2 years for all patients will be carried out via NHS digital records using methodology piloted during the study and will be reported once available in a separate publication.

Statistical analysis

The statistical analyses were carried out on an intention-to-treat basis, retaining patients in their randomised pathway groups and including patients who were protocol deviations and ineligible patients.

Proportions were calculated using the exact method and presented with 95% confidence intervals (CIs). Time-to-event estimates were assessed using Kaplan–Meier method and presented with 95% CIs. Time-to-event outcomes were analysed using a Cox regression model with stratification factors of age and sex included as covariates and study centre included as a random effect. Proportional hazards assumptions were investigated using Schoenfeld residuals and log–log plots. For instances when the Cox regression method was not appropriate due to small sample sizes, a mixed-effect Weibull survival model was utilised.

Health economics

Quality of life and health economics were outcomes for the final stage which was not completed. A basic health economic section has been added. Quality-of-life questionnaires from baseline assessment and subsequent follow-up time points were requested from consenting randomised participants. The returned data will be analysed and reported alongside the long-term follow-up data.

EuroQol-5 Dimensions data were collected but a formal health economic analysis was not carried out, as this would require the long-term outcomes data which are not yet available. We have however carried out some simple cost modelling using tariffs from NHS England[40] to estimate the crude cost impact of introducing MRI into the pathway for possible muscle-invasive disease.

Oversight

Trial Management Group: The TMG consisted of the Chief Investigator (Professor Nicholas James), Co-investigator Urology (Professor James Catto, Mr Prashant Patel and Mr Kieran Jefferson), Co-investigator Patient Involvement (Ms Jean Gallagher), Co-investigator Biomarker Research (Dr Richard Bryan), Co-investigator Qualitative substudy (Dr Veronica Nanton), Co-investigator Health Informatics (Ms Alicia Jakeman), Biology Systems Co-investigator, Statistics Co-investigator, Imaging Co-investigators, Medical Oncology Co-investigator, Trial Management Team Leader, Senior Trial Coordinator, Trial Coordinator/Administrator, Lead Statistician and Trial Statistician. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG were responsible for the day-to-day running and management of the trial.

Data analyses were supplied in confidence to an independent Data Monitoring Committee (DMC) who monitored patient safety and advised on whether the accumulated data justified continuation of recruitment. DMC meetings were scheduled at least annually until the study closed to recruitment.

Chapter 2 Results

Recruitment

Between 31 May 2018 and 31 December 2021, 15 of the 17 centres open to the BladderPath study recruited at least 1 participant; 638 patients were screened as potentially eligible, of which 309 were registered and 143 randomised (72 to Pathway 1, 71 to Pathway 2); 166 registered patients not randomised were not found to have BC during initial cystoscopy. *Figure 2* shows cumulative accrual versus target recruitment during the course of the study. The graph clearly shows the impact of the COVID-19 pandemic with cessation of recruitment for most of 2020, as required by the NHS pandemic response. Post pandemic, the recruitment rate was clearly much slower than prior to the event.

Recruitment targets were adjusted several times, initially aiming to improve recruitment (notably between June 2019 and February 2020) and, subsequently, to account for the devastating effect of the COVID-19 pandemic on recruitment from March 2020 onwards. The study eventually recruited 143 participants, summarised in the Consolidated Standards of Reporting Trials (CONSORT) diagram (*Figure 3*), close to the feasibility stage target of 150. Despite most sites having reopened to recruitment following the pandemic, fewer patients were able or willing to consider taking part in the study, and one site was unable to re-open.

Outcomes following randomisation are shown in a separate diagram (*Figure 4*).

Losses and exclusions

No patients were reported as being lost to follow-up during the study.

Ineligibilities

Three participants were subsequently found to be ineligible post randomisation: one in Pathway 1 and one in Pathway 2 due to estimated glomerular filtration rate (eGFR) below the accepted range and one participant in Pathway 2 due to ineligibility for MRI scanning.

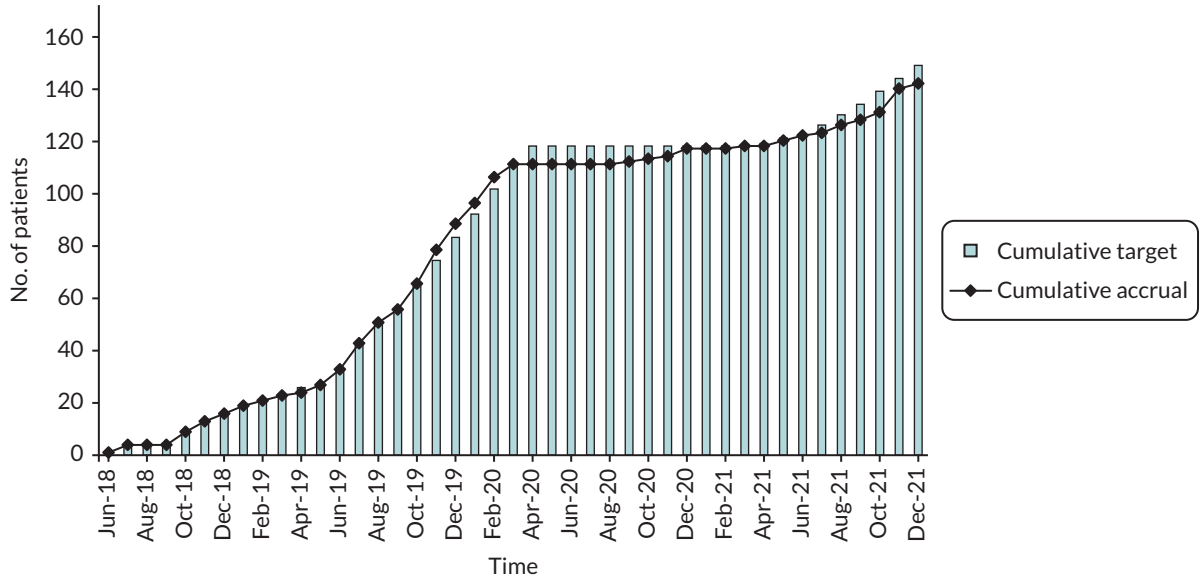


FIGURE 2 Recruitment between June 2018 and December 2021.

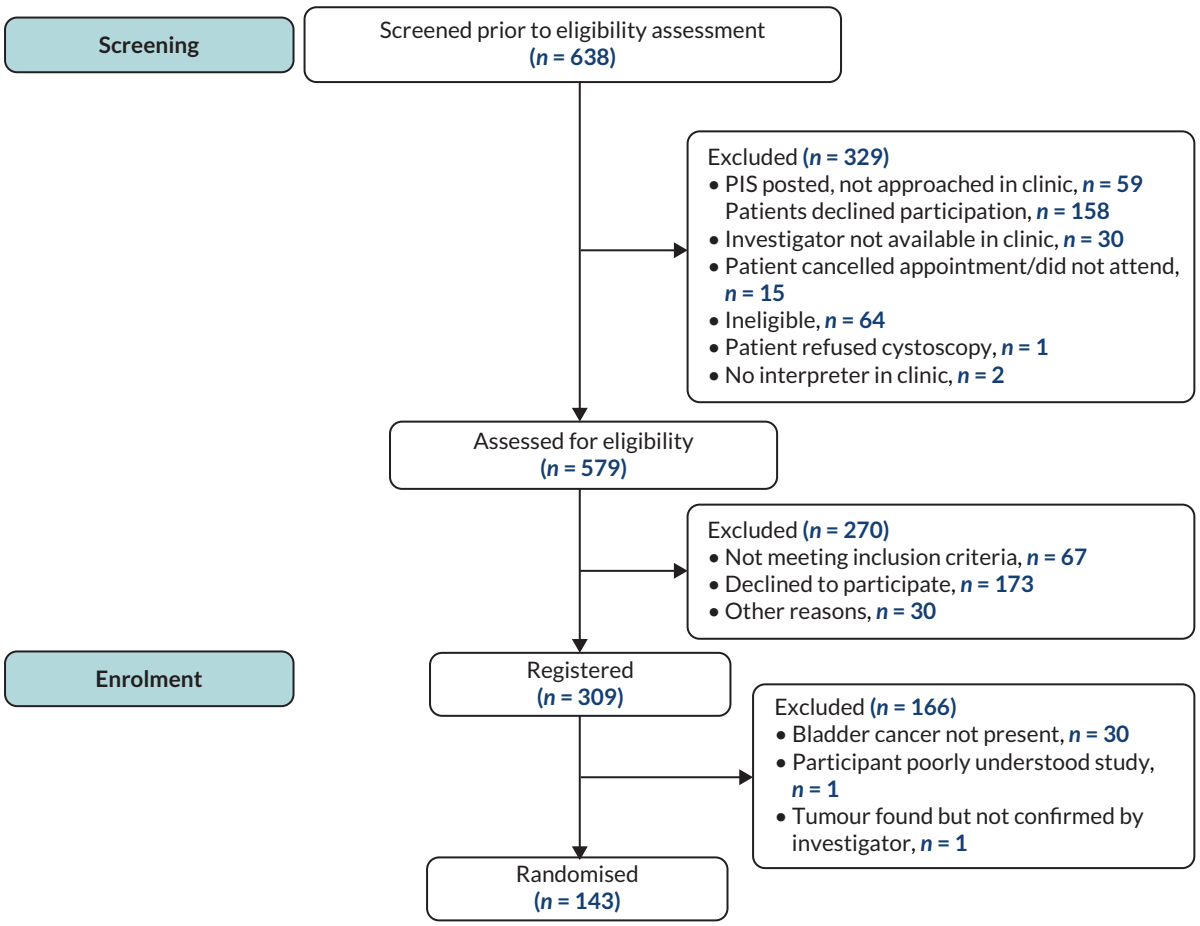


FIGURE 3 Consolidated Standards of Reporting Trials flow chart – showing recruitment through to randomised allocation.

Protocol deviations

Nine protocol deviations were reported by nine participants (five in Pathway 1, four in Pathway 2), mainly due to administrative error, summarised in *Table 3*.

Patient withdrawal of consent

Seven patients withdrew from the main trial (of which five also withdrew consent from all substudies). Of the seven withdrawals, three were found not to have cancer on histopathology, two participants felt unable to continue including one with severe dementia, one experienced delays in patient care timeline and one withdrew due to the complex nature of the diagnosis.

Six out of the seven participants who wished to withdraw from trial were not willing for further data to be supplied to the Trials Office (*Table 4*). One patient did not specify their wish to allow further data collection, not being able to remember consenting to take part – the clinical team withdrew the patient on discovering the participant had dementia.

Stratification factors

Participants were stratified by three factors at randomisation (*Table 5*).

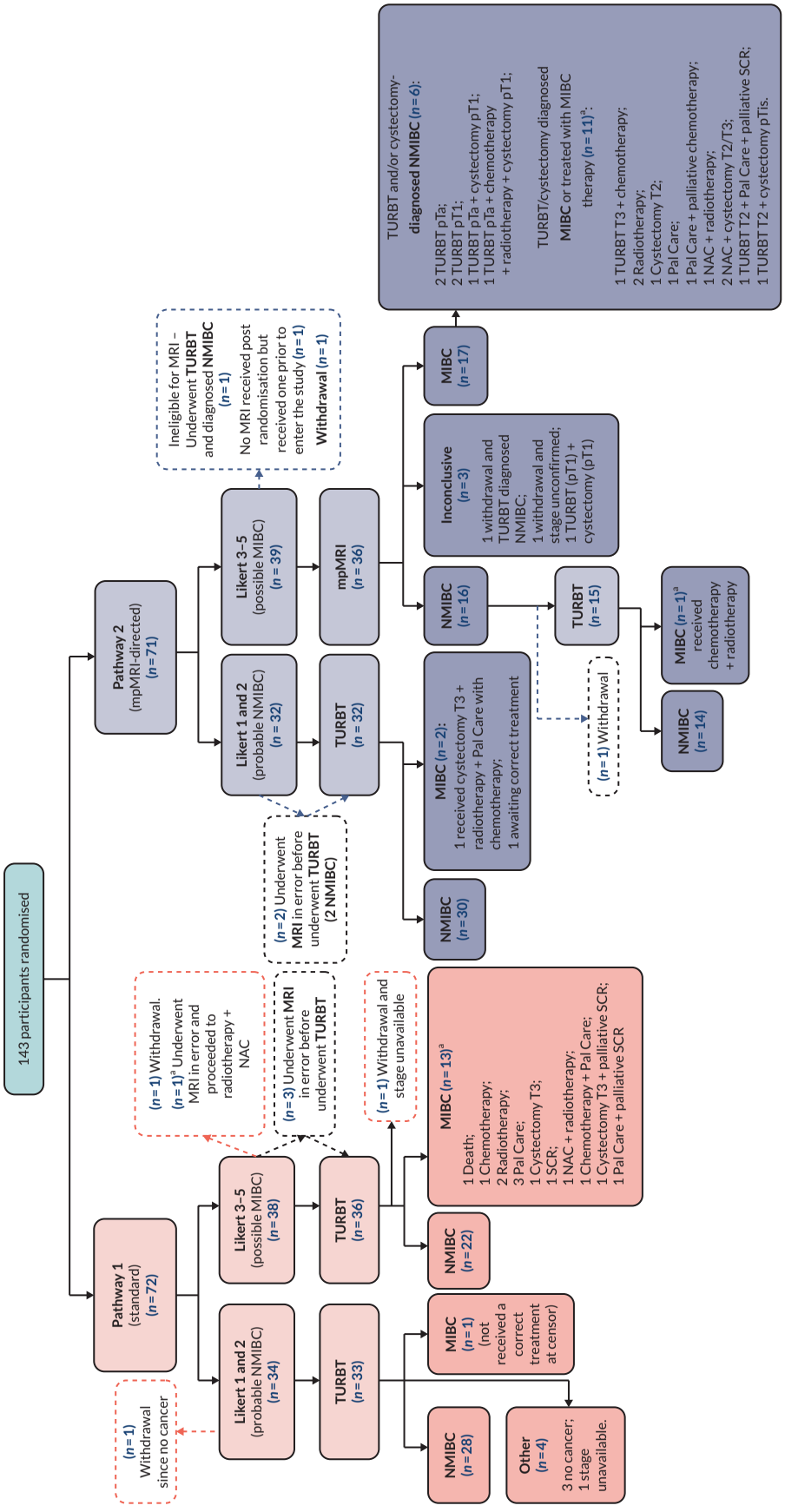


FIGURE 4 Illustration of the flow of participants through the study. [a]Population in primary outcome analysis (i.e. possible MIBC participants confirmed MIBC by TURBT/cystectomy or treated with MIBC therapy, 14 in Pathway 1 and 12 in Pathway 2). NAC, neo-adjuvant chemotherapy; Pal Care, Palliative care; SCR, synchronous chemo-radiotherapy.

TABLE 3 Summary of deviations

Category of deviation	Pathway 1	Pathway 2
Participant underwent MRI rather than TURBT due to an administrative error	1	2
Patient incorrectly randomised as possible MIBC instead of probably NMIBC as per initial flexible cystoscopy – clinician's error	1	0
Randomised after having had MRI	1	0
Participant had ad hoc mpMRI prior to protocol stipulated TURBT – clinician decision	1	0
MRI performed for superficial looking disease – misunderstanding of protocol	0	1
Initial flexible cystoscopy form returned Likert score of 2; however, at time of randomisation, clinician's assessment was possible MIBC based on available information at the time	0	2

TABLE 4 Withdrawal by randomisation arm

	Pathway 1 (*N* = 72)		Pathway 2 (*N* = 71)		Overall (*N* = 143)	
	N	%	*N*	%	*N*	%
Full withdrawal of consent	3	4.16	4	5.63	7	4.89
Withdrawal from:						
• Biomarker substudy	1		4		5	
• Imaging substudy	1		4		5	
• Qualitative substudy	1		4		5	

TABLE 5 Stratification factors

	Pathway 1 (*N* = 72)		Pathway 2 (*N* = 71)		Overall (*N* = 143)	
Stratifying variable	*N*	%	*N*	%	*N*	%
Sex						
• Male	55	76.4	53	74.6	108	75.5
• Female	17	23.6	18	25.4	35	24.5
Age						
• Less than 75	48	66.7	49	69.0	97	67.8
• 75 or over	24	33.3	22	31.0	46	32.2
Clinician's initial assessment						
• Probable NMIBC	34	47.2	32	45.1	66	46.2
• Possible MIBC	38	52.8	39	54.9	77	53.8

Participant characteristics

Characteristics of the 143 randomised participants are shown in *Table 6*.

Research sites were asked to provide baseline biochemistry and haematology results if tested as part of standard care at the time of screening, or within a short period prior to study entry. These results, as summarised in *Tables 7* and *8*, were only recorded at baseline with a view to forming a baseline picture. Blood tests were not repeated at subsequent time points for analysis purposes.

TABLE 6 Baseline characteristics

Pathway	Pathway 1 (*n* = 72)	Pathway 2 (*n* = 71)	Overall (*n* = 143)
Height (cm)			
N	66	60	126
Mean (SD)	171.2 (8.9)	171.5 (8.8)	171.3 (8.9)
Median	173.0	172.5	173.0
IQR	165.0–178.0	163.5–179.0	165.0–178.0
Range	147.0–187.0	152.0–191.0	147.0–191.0
Weight (kg)			
N	65	61	126
Mean (SD)	83.6 (16.2)	85.3 (17.8)	84.4 (16.9)
Median	82.0	82.0	82.0
IQR	71.8–91.4	72.0–97.8	72.0–96.0
Range	55.2–137.4	50.7–127.0	50.7–137.4
WHO performance status			
0	54 (79.4)	52 (78.8)	106 (79.1)
1	8 (11.8)	10 (15.2)	18 (13.4)
2	3 (4.4)	2 (3.0)	5 (3.7)
3	3 (4.4)	2 (3.0)	5 (3.7)
Not known	4	5	9
eGFR (value used for eligibility assessment ≥ 40 ml/minute/1.73 m^2)			
N	72	71	143
Mean (SD)	74.0 (16.2)	72.7 (16.2)	73.4 (16.1)
Median	79.0	78.0	78.0
IQR	60.5–89.0	60.0–88.0	60.0–88.0
Range	30.0–99.0	39.0–113.0	30.0–113.0
Smoking history			
Non-smoker	19 (27.1)	25 (37.3)	44 (32.1)
Ex-smoker	40 (57.1)	35 (52.2)	75 (54.7)
Smoker	11 (15.7)	7 (10.4)	18 (13.1)
Not known	2	4	6
Number of cigarettes per day			
N	34	28	62
Mean (SD)	17.5 (10.8)	15.5 (8.4)	16.6 (9.7)
Median	20.0	16.5	20.0
IQR	10.0–20.0	10.0–20.0	10.0–20.0
Range	1.0–40.0	1.0–40.0	1.0–40.0

IQR, interquartile range; SD, standard deviation; WHO, World Health Organization.

TABLE 7 Baseline blood biochemistry results summary

Pathway	Pathway 1 (*n* = 72)	Pathway 2 (*n* = 71)	Overall (*n* = 143)
Serum creatinine (μmol/L)			
N	71	68	139
Mean (SD)	85.8 (24.8)	87.3 (21.4)	86.6 (23.1)
Median	76.0	82.5	80.0
IQR	70.0–95.0	71.5–98.0	71.0–96.0
Range	57.0, 193.0	56.0–166.0	56.0–193.0
Urea (mmol/L)			
N	64	62	126
Mean (SD)	6.1 (2.0)	6.2 (2.0)	6.2 (2.0)
Median	5.8	5.9	5.8
IQR	5.2–7.0	5.0–6.9	5.0–6.9
Range	2.5–14.7	2.6–13.6	2.5–14.7
Albumin (g/L)			
N	40	38	78
Mean (SD)	40.7 (6.5)	43.8 (3.3)	42.2 (5.4)
Median	42.0	44.0	43.0
IQR	37.5–44.5	42.0–46.0	40.0–46.0
Range	14.0–51.0	33.0–50.0	14.0–51.0
Total protein (g/L)			
N	32	34	66
Mean (SD)	68.6 (4.4)	71.8 (5.0)	70.2 (4.9)
Median	68.0	71.5	70.0
IQR	65.5–71.0	69.0–75.0	67.0–73.0
Range	61.0–78.0	59.0–84.0	59.0–84.0
Bilirubin (μmol/L)			
N	40	37	77
Mean (SD)	8.3 (4.9)	8.5 (3.1)	8.4 (4.1)
Median	7.0	8.0	8.0
IQR	5.0–10.0	7.0–10.0	6.0–10.0
Range	3.0–29.0	4.0–21.0	3.0–29.0
AST or ALT (IU/L)			
N	41	36	77
Mean (SD)	22.5 (10.1)	22.8 (9.9)	22.6 (10.0)
Median	22.0	20.0	21.0
IQR	14.0–29.0	15.0–30.5	14.0–29.0
Range	5.0–43.0	7.0–48.0	5.0–48.0

TABLE 7 Baseline blood biochemistry results summary (*continued*)

Pathway	Pathway 1 (*n* = 72)	Pathway 2 (*n* = 71)	Overall (*n* = 143)
Alk phos (IU/L)			
N	43	35	78
Mean (SD)	93.4 (74.3)	77.1 (20.3)	86.1 (57.1)
Median	80.0	75.0	77.0
IQR	65.0–102.0	64.0–91.0	65.0–97.0
Range	38.0–543.0	36.0–119.0	36.0–543.0
Sodium (mmol/L)			
N	70	65	135
Mean (SD)	139.6 (4.1)	140.0 (2.6)	139.8 (3.4)
Median	140.5	140.0	140.0
IQR	137.0–142.0	139.0–142.0	138.0–142.0
Range	122.0–149.0	133.0–145.0	122.0–149.0
Potassium (mmol/L)			
N	67	64	131
Mean (SD)	4.5 (0.4)	4.4 (0.4)	4.5 (0.4)
Median	4.5	4.4	4.5
IQR	4.2, 4.8	4.2, 4.8	4.2, 4.8
Range	3.4, 5.7	3.4, 5.2	3.4, 5.7
PSA (males only) (ng/ml)			
N	26	34	60
Mean (SD)	6.6 (11.0)	8.8 (16.5)	7.9 (14.3)
Median	2.3	3.0	2.5
IQR	0.9–5.0	1.7–8.0	1.4–6.7
Range	0.0–43.0	0.1–79.0	0.0–79.0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; PSA, probabilistic sensitivity analysis; SD, standard deviation; WHO, World Health Organization.

Initial flexible cystoscopy

One hundred and forty-two participants underwent initial flexible cystoscopy; one participant underwent CT chest abdomen pelvis, so all flexible cystoscopy data for that patient are missing (*Table 9*).

Transurethral resection of bladder tumour

One hundred and thirty participants had 1 TURBT, 43 had 2, 7 had 3 and 2 had 4. In total, 182 TURBT procedures were carried out (*Table 10*).

Transurethral resection of bladder tumour pathology

Details from 172 TURBT histology reports were available (*Table 11*).

TABLE 8 Baseline haematology results summary

Pathway	Pathway 1 (*n* = 72)	Pathway 2 (*n* = 71)	Overall (*n* = 143)
Hb (g/L)			
N	65	68	133
Mean (SD)	138.5 (16.7)	142.2 (13.7)	140.4 (15.3)
Median	141.0	143.5	142.0
IQR	127.0–151.0	135.0–151.0	134.0–151.0
Range	101.0–172.0	104.0–173.0	101.0–173.0
WBC (x10^9/**L**)			
N	66	68	134
Mean (SD)	8.4 (3.5)	7.9 (2.5)	8.1 (3.0)
Median	8.0	7.5	7.6
IQR	6.3–9.3	6.2–8.4	6.3–8.9
Range	4.5–29.0	3.5–16.7	3.5–29.0
Neutrophils (× 10^9/L)			
N	66	68	134
Mean (SD)	5.6 (3.1)	4.9 (1.9)	5.3 (2.6)
Median	4.8	4.4	4.5
IQR	4.1–6.0	3.9–5.3	3.9–5.8
Range	2.4–24.0	1.8–11.4	1.8–24.0
Platelets (× 10^9/L)			
N	66	68	134
Mean (SD)	264.2 (78.7)	249.8 (74.5)	256.9 (76.7)
Median	250.0	247.5	250.0
IQR	221.0–298.0	200.0–281.5	213.0–293.0
Range	117.0–667.0	113.0–528.0	113.0–667.0

IQR, interquartile range; SD, standard deviation; WBC, white blood cell.

TABLE 9 Initial flexible cystoscopy results

Allocation	Pathway 1 (72)	Pathway 2 (71)	Overall (143)
Number of lesions			
N	61	63	124
Mean (SD)	1.8 (1.8)	1.7 (1.6)	1.8 (1.7)
Median	1.0	1.0	1.0
IQR	1.0–2.0	1.0–2.0	1.0–2.0
Range	1.0–10.0	1.0–10.0	1.0–10.0

TABLE 9 Initial flexible cystoscopy results (*continued*)

Allocation	Pathway 1 (72)	Pathway 2 (71)	Overall (143)
Largest dimension			
N	55	59	114
Mean (SD)	2.9 (1.9)	3.2 (1.7)	3.0 (1.8)
Median	2.5	3.0	3.0
IQR	1.5–3.0	2.0–4.0	2.0–4.0
Range	0.2–10.0	0.5–10.0	0.2–10.0
Random biopsies			
No	53 (76.8)	54 (78.3)	107 (77.5)
Yes	16 (23.2)	15 (21.7)	31 (22.5)
Unknown	3	2	5
Poor views			
No	57 (83.8)	60 (88.2)	117 (86.0)
Yes	11 (16.2)	8 (11.8)	19 (14.0)
Unknown	4	3	7
Describe the significant lesion			
Flat and solid	1 (1.6)	0 (0.0)	1 (0.8)
Papillary	32 (50.0)	41 (64.1)	73 (57.0)
Papillary and solid	9 (14.1)	9 (14.1)	18 (14.1)
Solid	22 (34.4)	14 (21.9)	36 (28.1)
Not reported	8	7	15
Estimated bladder capacity (ml)			
N	27	23	50
Mean (SD)	422.2 (118.8)	434.8 (110.2)	428.0 (113.9)
Median	400.0	450.0	400.0
IQR	400.0–500.0	400.0–500.0	400.0–500.0
Range	200.0–700.0	200.0–700.0	200.0–700.0

IQR, interquartile range; SD, standard deviation.

TABLE 10 Transurethral resection of bladder tumour by pathway

Pathway	Pathway 1 (97)	Pathway 2 (85)	Overall (182)
Number of tumours visible			
N	77	73	150
Mean (SD)	1.8 (1.8)	1.6 (1.4)	1.7 (1.6)
Median	1.0	1.0	1.0
IQR	1.0–2.0	1.0–1.0	1.0–2.0
Range	0.0–10.0	0.0–7.0	0.0–10.0

continued

TABLE 10 Transurethral resection of bladder tumour by pathway (*continued*)

Pathway	Pathway 1 (97)	Pathway 2 (85)	Overall (182)
Size of largest tumour (cm)			
N	65	59	124
Mean (SD)	3.4 (2.6)	2.6 (1.8)	3.0 (2.3)
Median	3.0	2.0	2.9
IQR	1.9–4.0	1.0–4.0	1.5–4.0
Range	0.4–12.0	0.0–10.0	0.0–12.0
Random biopsies			
No	73 (79.3)	65 (84.4)	138 (81.7)
Yes	19 (20.7)	12 (15.6)	31 (18.3)
Not known	5	8	13
Location of tumour(s) present			
Anterior	4 (4.1)	1 (1.2)	5 (2.7)
Dome	4 (4.1)	2 (2.4)	6 (3.3)
Dome, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral	13 (13.4)	17 (20.0)	30 (16.5)
Left lateral, anterior	2 (2.1)	2 (2.4)	4 (2.2)
Left lateral, anterior, dome	0 (0.0)	1 (1.2)	1 (0.5)
Left lateral, dome	1 (1.0)	1 (1.2)	2 (1.1)
Left lateral, posterior	4 (4.1)	1 (1.2)	5 (2.7)
Left lateral, posterior, anterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral, posterior, dome	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral, posterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral, prostatic urethra	0 (0.0)	1 (1.2)	1 (0.5)
Left lateral, trigone	2 (2.1)	4 (4.7)	6 (3.3)
Left lateral, trigone, prostatic urethra	1 (1.0)	0 (0.0)	1 (0.5)
N/A	11 (11.3)	13 (15.3)	24 (13.2)
Posterior	8 (8.2)	4 (4.7)	12 (6.6)
Posterior, anterior	0 (0.0)	1 (1.2)	1 (0.5)
Posterior, dome	0 (0.0)	1 (1.2)	1 (0.5)
Posterior, trigone, prostatic urethra	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral	21 (21.6)	22 (25.9)	43 (23.6)
Right lateral, anterior	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral, anterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral, dome, trigone	1 (1.0)	1 (1.2)	2 (1.1)
Right lateral, left lateral	2 (2.1)	0 (0.0)	2 (1.1)
Right lateral, left lateral, anterior, dome	1 (1.0)	0 (0.0)	1 (0.5)

TABLE 10 Transurethral resection of bladder tumour by pathway (*continued*)

Pathway	Pathway 1 (97)	Pathway 2 (85)	Overall (182)
Right lateral, left lateral, posterior, anterior	2 (2.1)	1 (1.2)	3 (1.6)
Right lateral, left lateral, posterior, anterior, dome	2 (2.1)	0 (0.0)	2 (1.1)
Right lateral, left lateral, posterior, anterior, dome, trigone	0 (0.0)	1 (1.2)	1 (0.5)
Right lateral, left lateral, posterior, anterior, trigone	0 (0.0)	1 (1.2)	1 (0.5)
Right lateral, posterior	4 (4.1)	1 (1.2)	5 (2.7)
Right lateral, posterior, dome	1 (1.0)	1 (1.2)	2 (1.1)
Right lateral, posterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral, prostatic urethra	0 (0.0)	1 (1.2)	1 (0.5)
Right lateral, trigone	1 (1.0)	3 (3.5)	4 (2.2)
Trigone	4 (4.1)	4 (4.7)	8 (4.4)
Initial clinician assessment			
Probable NMIBC	50 (51.5)	41 (48.2)	91 (50.0)
Possible MIBC	47 (48.5)	44 (51.8)	91 (50.0)
Location(s) of tumour resected/diathermied			
Anterior	3 (3.1)	1 (1.2)	4 (2.2)
Dome	4 (4.1)	1 (1.2)	5 (2.7)
Dome, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral	10 (10.3)	17 (20.0)	27 (14.8)
Left lateral, anterior	2 (2.1)	2 (2.4)	4 (2.2)
Left lateral, anterior, dome	0 (0.0)	1 (1.2)	1 (0.5)
Left lateral, dome	1 (1.0)	1 (1.2)	2 (1.1)
Left lateral, posterior	3 (3.1)	1 (1.2)	4 (2.2)
Left lateral, posterior, anterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral, posterior, dome	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral, posterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Left lateral, prostatic urethra	0 (0.0)	1 (1.2)	1 (0.5)
Left lateral, trigone	1 (1.0)	2 (2.4)	3 (1.6)
N/A	24 (24.7)	22 (25.9)	46 (25.3)
Posterior	7 (7.2)	4 (4.7)	11 (6.0)
Posterior, anterior	0 (0.0)	1 (1.2)	1 (0.5)
Posterior, dome	0 (0.0)	1 (1.2)	1 (0.5)
Posterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Posterior, trigone, prostatic urethra	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral	21 (21.6)	19 (22.4)	40 (22.0)
Right lateral, anterior	1 (1.0)	0 (0.0)	1 (0.5)

continued

TABLE 10 Transurethral resection of bladder tumour by pathway (*continued*)

Pathway	Pathway 1 (97)	Pathway 2 (85)	Overall (182)
Right lateral, anterior, trigone	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral, dome, trigone	1 (1.0)	1 (1.2)	2 (1.1)
Right lateral, left lateral	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral, left lateral, anterior, dome	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral, left lateral, anterior, trigone	0 (0.0)	1 (1.2)	1 (0.5)
Right lateral, left lateral, posterior, anterior	2 (2.1)	0 (0.0)	2 (1.1)
Right lateral, left lateral, posterior, anterior, dome	1 (1.0)	0 (0.0)	1 (0.5)
Right lateral, left lateral, posterior, anterior, trigone	0 (0.0)	1 (1.2)	1 (0.5)
Right lateral, posterior	3 (3.1)	1 (1.2)	4 (2.2)
Right lateral, posterior, dome	1 (1.0)	1 (1.2)	2 (1.1)
Right lateral, prostatic urethra	0 (0.0)	1 (1.2)	1 (0.5)
Right lateral, trigone	1 (1.0)	3 (3.5)	4 (2.2)
Trigone	2 (2.1)	2 (2.4)	4 (2.2)
Post-resection examination under anaesthetic			
No mass	40 (60.6)	32 (56.1)	72 (58.5)
Mobile mass	5 (7.6)	4 (7.0)	9 (7.3)
Fixed mass	3 (4.5)	4 (7.0)	7 (5.7)
Uncertain	7 (10.6)	7 (12.3)	14 (11.4)
Not done	11 (16.7)	10 (17.5)	21 (17.1)
N/A	31 (32.0)	28 (32.9)	59 (32.4)

IQR, interquartile range; N/A, not available; SD, standard deviation.

TABLE 11 Transurethral resection of bladder tumour histology results

Pathway	Pathway 1 (90)	Pathway 2 (82)	Overall (172)
Histological composition			
Adenocarcinomatous elements	0 (0.0)	1 (1.2)	1 (0.6)
None	1 (1.1)	1 (1.2)	2 (1.2)
Other	10 (11.1)	6 (7.3)	16 (9.3)
Squamous elements	1 (1.1)	1 (1.2)	2 (1.2)
Squamous elements, other	1 (1.1)	0 (0.0)	1 (0.6)
Transitional cell carcinoma	71 (78.9)	68 (82.9)	139 (80.8)
Transitional cell carcinoma, other	1 (1.1)	1 (1.2)	2 (1.2)
Transitional cell carcinoma, sarcomatous elements	0 (0.0)	1 (1.2)	1 (0.6)
Transitional cell carcinoma, squamous elements	3 (3.3)	3 (3.7)	6 (3.5)
Transitional cell carcinoma, squamous elements, sarcomatous elements	2 (2.2)	0 (0.0)	2 (1.2)

TABLE 11 Transurethral resection of bladder tumour histology results (*continued*)

Pathway	Pathway 1 (90)	Pathway 2 (82)	Overall (172)
Detrusor muscle (tumour base)			
No	36 (41.4)	42 (51.9)	78 (46.4)
Yes	51 (58.6)	39 (48.1)	90 (53.6)
Not known	3	1	4
Tumour present in muscle			
No	40 (80.0)	30 (81.1)	70 (80.5)
Yes	10 (20.0)	7 (18.9)	17 (19.5)
Not known	40	45	85
Random bladder biopsy			
No	79 (89.8)	73 (91.3)	152 (90.5)
Yes	9 (10.2)	7 (8.8)	16 (9.5)
Not known	2	2	4
Cytology			
No	82 (95.3)	78 (97.5)	160 (96.4)
Yes	4 (4.7)	2 (2.5)	6 (3.6)
Not known	4	2	6
Other sampling			
Adjacent flat urothelium sampled no cancer found	1 (1.1)	0 (0.0)	1 (0.6)
Cystitis glandularis sighted in the background	1 (1.1)	0 (0.0)	1 (0.6)
Left ureteric biopsy	0 (0.0)	1 (1.2)	1 (0.6)
N/A	87 (96.7)	81 (98.8)	168 (97.7)
Ureteric biopsy grade 2 pTa	1 (1.1)	0 (0.0)	1 (0.6)
Bladder carcinoma			
No	10 (11.1)	7 (8.5)	17 (9.9)
Yes	80 (88.9)	75 (91.5)	155 (90.1)
Grade (WHO 1973)			
Grade 1	3 (3.9)	4 (5.9)	7 (4.9)
Grade 2	25 (32.9)	34 (50.0)	59 (41.0)
Grade 3	47 (61.8)	27 (39.7)	74 (51.4)
Unable to determine	1 (1.3)	3 (4.4)	4 (2.8)
Not known	14	14	28
Grade (WHO 2004)			
High	53 (69.7)	33 (47.1)	86 (58.9)
Low	23 (30.3)	37 (52.9)	60 (41.1)
Not known	14	12	26

continued

TABLE 11 Transurethral resection of bladder tumour histology results (*continued*)

Pathway	Pathway 1 (90)	Pathway 2 (82)	Overall (172)
pT stage			
Ptx	2 (2.4)	4 (5.0)	6 (3.7)
T2	9 (11.0)	5 (6.3)	14 (8.6)
T2 or higher	2 (2.4)	0 (0.0)	2 (1.2)
T3	0 (0.0)	2 (2.5)	2 (1.2)
Unable to specify	3 (3.7)	0 (0.0)	3 (1.9)
pT1	21 (25.6)	20 (25.0)	41 (25.3)
pTa	45 (54.9)	45 (56.3)	90 (55.6)
pTis	0 (0.0)	4 (5.0)	4 (2.5)
Not known	8	2	10
Concomitant flat in situ carcinoma			
No	40 (51.3)	50 (64.9)	90 (58.1)
Yes	18 (23.1)	7 (9.1)	25 (16.1)
Not known	20 (25.6)	20 (26.0)	40 (25.8)
Not known (missing)	12	5	17
Total tumour volume (cm^3)			
N	10	9	19
Mean (SD)	3.8 (3.0)	11.0 (17.9)	7.2 (12.7)
Median	3.0	2.5	2.7
IQR	1.5–5.0	0.5–14.0	1.3–8.0
Range	0.7–10.0	0.2–54.0	0.2–54.0
Total biopsy or tumour dimension (mm)			
N	36	30	66
Mean (SD)	21.7 (20.1)	20.1 (21.2)	21.0 (20.5)
Median	17.0	12.0	14.5
IQR	8.5–25.5	8.0–25.0	8.0–25.0
Range	0.7–85.0	0.5–104.0	0.5–104.0

IQR, interquartile range; N/A, not available; SD, standard deviation; WHO, World Health Organization.

The number (and proportion) of participants in Pathway 2 who underwent TURBT after MRI-diagnosed MIBC was also monitored. (Note: participants who were diagnosed NMIBC by MRI and then underwent TURBT as the correct treatment, or where MRI diagnosis was considered inconclusive, were excluded.) Seventeen participants were diagnosed MIBC by MRI, of which eight had TURBT afterwards; two had TURBT procedures twice (including one for TURBT biopsy only). Clinician intention for carrying out TURBT following MRI for Pathway 2 participants with confirmed MIBC is summarised in *Table 12* for each procedure.

TABLE 12 Intentions of TURBT after MRI

Procedure and intention	Number of participants
Formal TURBT	13
Lack of confidence that the MRI shows MIBC	3
To ascertain presence of histological variants	4
To check for CIS	1
To debulk the tumour prior to radical therapy	4
To perform examination under anaesthesia in order to assess resectability	1
TURBT biopsy	1
To ascertain presence of histological variants	1
Grand total	14

TABLE 13 Magnetic resonance imaging data results

Pathway	Pathway 1 (*n* = 4)	Pathway 2 (*n* = 38)
Number of tumours visible		
0	1 (33.3)	1 (3.0)
1	1 (33.3)	30 (90.9)
2	1 (33.3)	0 (0.0)
3	0 (0.0)	1 (3.0)
10	0 (0.0)	1 (3.0)
Not reported	1	5
Size of largest tumour (cm)		
N	4	33
Mean (SD)	4.0 (3.3)	3.2 (1.6)
Median	4.0	3.5
IQR	1.6–6.4	1.8–4.4
Range	0.0–8.0	0.0–6.3
Location of tumour(s)		
Anterior	1 (25.0)	2 (5.3)
Anterior, dome	0 (0.0)	1 (2.6)
Dome	0 (0.0)	1 (2.6)
Left lateral	1 (25.0)	7 (18.4)
Left lateral, posterior	0 (0.0)	1 (2.6)
Left lateral, trigone	0 (0.0)	1 (2.6)
N/A	1 (25.0)	2 (5.3)

continued

TABLE 13 Magnetic resonance imaging data results (*continued*)

Pathway	Pathway 1 (*n* = 4)	Pathway 2 (*n* = 38)
Posterior	0 (0.0)	2 (5.3)
Posterior and trigone	0 (0.0)	2 (5.3)
Right lateral	1 (25.0)	11 (28.9)
Right lateral, dome	0 (0.0)	1 (2.6)
Right lateral, left lateral, posterior, anterior	0 (0.0)	1 (2.6)
Right lateral, left lateral, posterior, anterior	0 (0.0)	1 (2.6)
Dome, trigone, prostatic urethra		
Right lateral, posterior	0 (0.0)	2 (5.3)
Trigone	0 (0.0)	3 (7.9)
VI-RADS score		
1	1 (50.0)	2 (10.5)
2	0 (0.0)	7 (36.8)
3	0 (0.0)	3 (15.8)
4	1 (50.0)	5 (26.3)
5	0 (0.0)	2 (10.5)
Not reported	2	19
Diagnosis		
MIBC	3 (75.0)	17 (44.7)
NMIBC	1 (25.0)	18 (47.4)
Inconclusive	0 (0.0)	3 (7.9)
Lymph node involvement		
No	3 (100.0)	34 (89.5)
Yes	0 (0.0)	3 (7.9)
Unclear	0 (0.0)	1 (2.6)
Not reported	1	0

IQR, interquartile range; N/A, not available; SD, standard deviation.

Magnetic resonance imaging

Table 13 summarises the numbers of participants who underwent MRI. In all, 42 participants underwent MRI, including 6 in error (4 in Pathway 1 who were possible MIBC; 2 in Pathway 2 who were probable NMIBC).

Definitive and correct treatments

Overall, 137 (95.8%) patients received their definitive treatment. Of the six participants who did not receive definitive treatment, one did not have cancer, four were early withdrawals and one was due to an administrative error in which a Pathway 1 participant underwent MRI (but not TURBT) with MRI confirming MIBC.

As summarised in *Table 14*, 130 (90.9%) participants received correct treatment. Of the 13 participants who did not, 3 did not have cancer, 3 withdrew early (< 100 days), 1 died, 2 were probable NMIBC who had TURBT-diagnosed MIBC and were awaiting a correct treatment, and 4 were probable NMIBC participants who had no confirmed MIBC, NMIBC or were awaiting a correct treatment.

Swimmer plots: initial clinical assessment of probable non-muscle-invasive bladder cancer and possible muscle-invasive bladder cancer across arms

Four swimmer plots sorted by TTDT: 34 Pathway 1 probable NMIBC participants *Figure 5*), 38 Pathway 1 possible MIBC (*Figure 6*), 32 Pathway 2 probable NMIBC (*Figure 7*) and 39 Pathway 2 possible MIBC (*Figure 8*). Two participants in *Figure 6* and four participants in *Figure 7* received MRI in error.

Swimmer plots: final assessment of non-muscle-invasive bladder cancer and muscle-invasive bladder cancer

Four swimmer plots sorted by TTCT. Of the 143 participants, 133 (93.0%) had a confirmed NMIBC/MIBC, including 51 NMIBC in Pathway 1 (*Figure 9*), 55 NMIBC in Pathway 2 (*Figure 10*), 14 MIBC in Pathway 1 (*Figure 11*) and 13 MIBC in Pathway 2 (*Figure 12*). Of note, 7/14 MIBC patients on Pathway 2 avoided the need for TURBT.

TABLE 14 Definitive and correct treatment received split by pathway

Arm	Pathway 1 (*n* = 72)	Pathway 2 (*n* = 71)	Overall (*n* = 143)
Was definitive treatment received			
No	3 (4.2)	3 (4.2)	6 (4.2)
Yes	69 (95.8)	68 (95.8)	137 (95.8)
Definitive treatment			
Chemotherapy	0 (0.0)	3 (4.4)	3 (2.2)
Cystectomy	0 (0.0)	1 (1.5)	1 (0.7)
Palliative care	0 (0.0)	1 (1.5)	1 (0.7)
Radiotherapy	0 (0.0)	2 (2.9)	2 (1.5)
TURBT	69 (100.0)	61 (89.7)	130 (94.9)
Not known	3	3	6
Was correct treatment received			
No	9 (12.5)	4 (5.6)	13 (9.1)
Yes	63 (87.5)	67 (94.4)	130 (90.9)
First correct treatment			
Chemotherapy	4 (6.3)	5 (7.5)	9 (6.9)
Cystectomy	2 (3.2)	3 (4.5)	5 (3.8)
Palliative care	4 (6.3)	3 (4.5)	7 (5.4)
Radiotherapy	3 (4.8)	2 (3.0)	5 (3.8)
TURBT	50 (79.4)	54 (80.6)	104 (80.0)
Not known	9	4	13

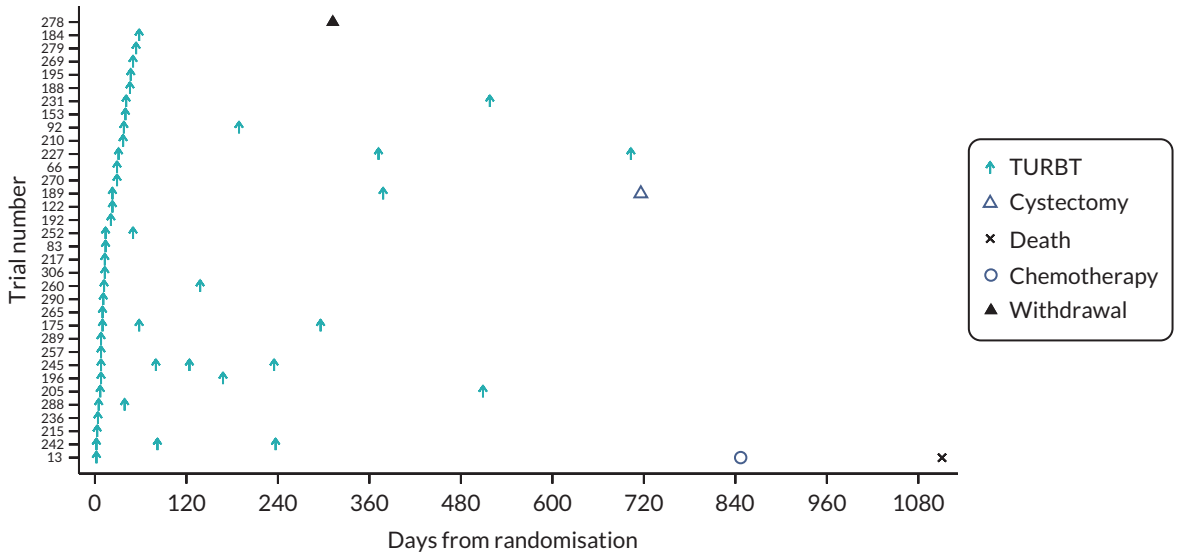


FIGURE 5 Swimmer plot for pathway 1 probable NMIBC participants.

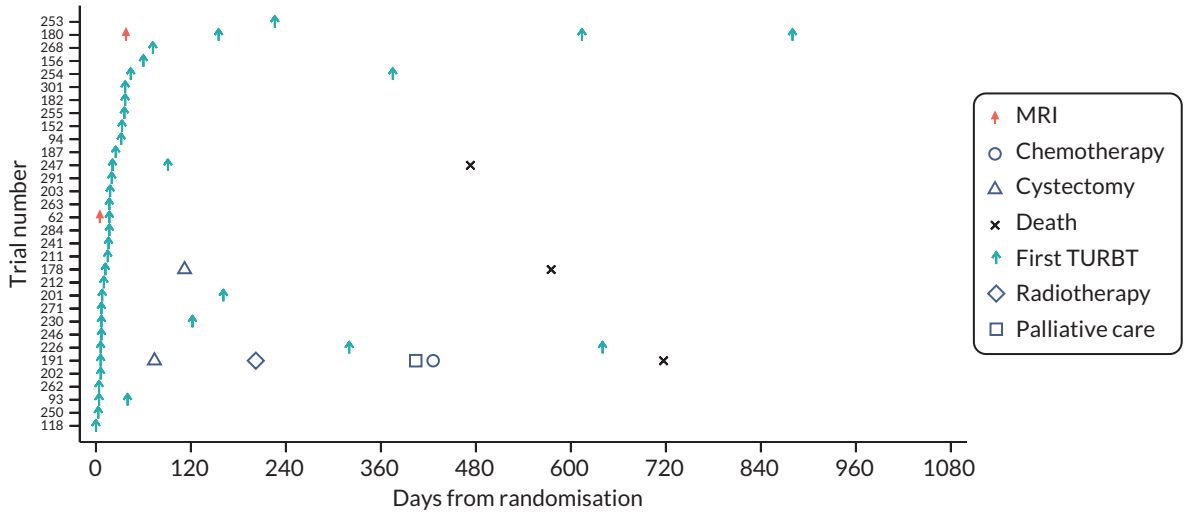


FIGURE 6 Swimmer plot for Pathway 2 probable NMIBC participants.

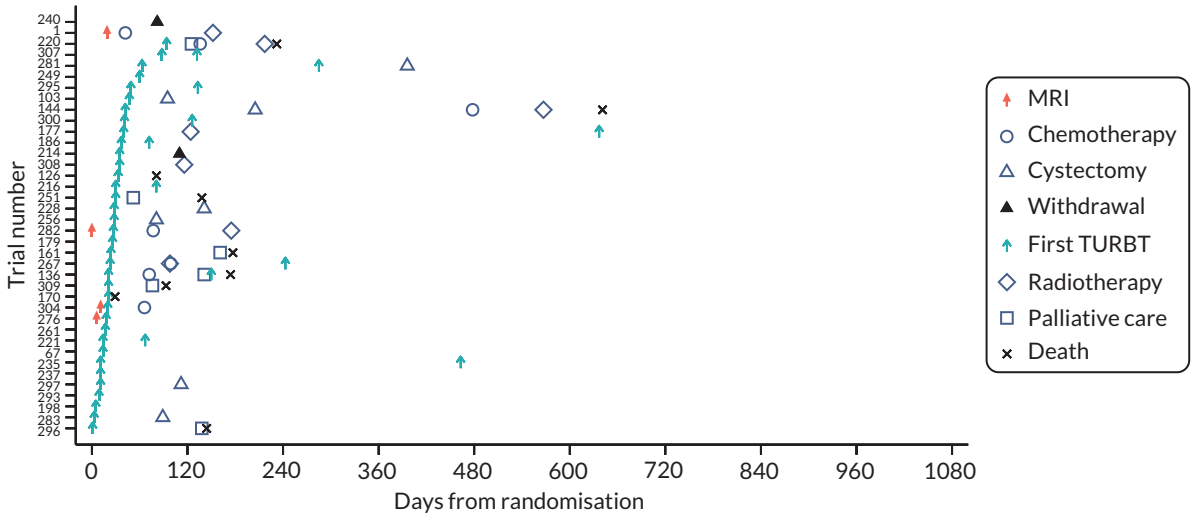


FIGURE 7 Swimmer plot for Pathway 1 possible MIBC participants.

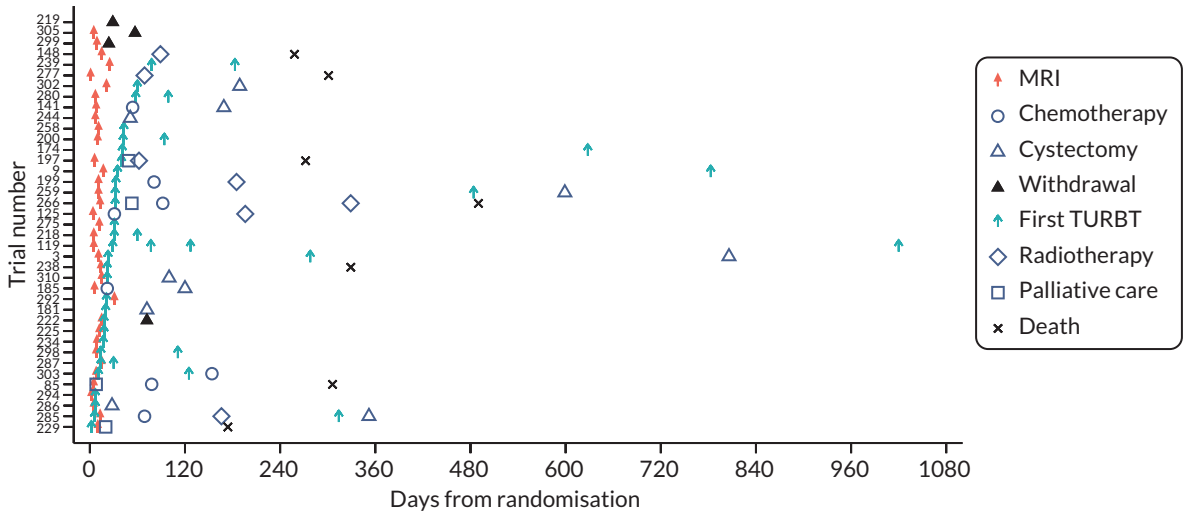


FIGURE 8 Swimmer plot for Pathway 2 possible MIBC participants.

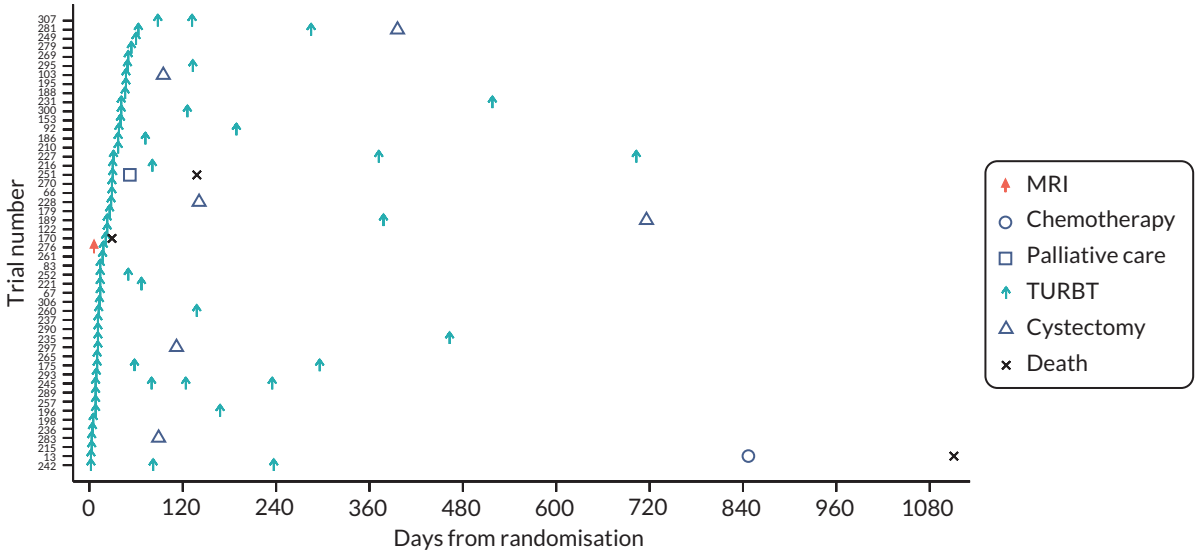


FIGURE 9 Swimmer plot for Pathway 1 NMIBC participants.

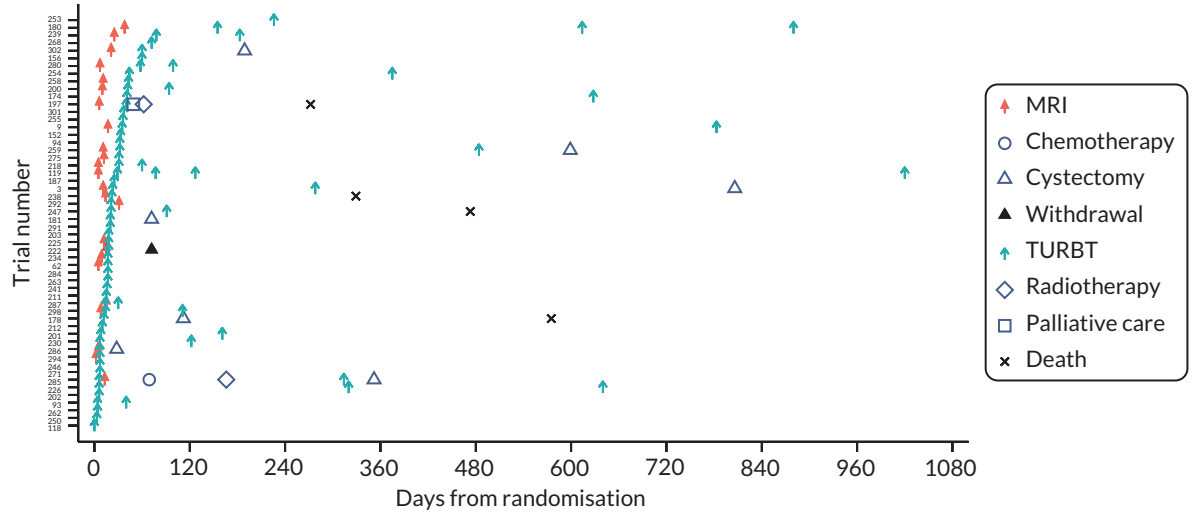


FIGURE 10 Swimmer plot for Pathway 2 NMIBC participants.

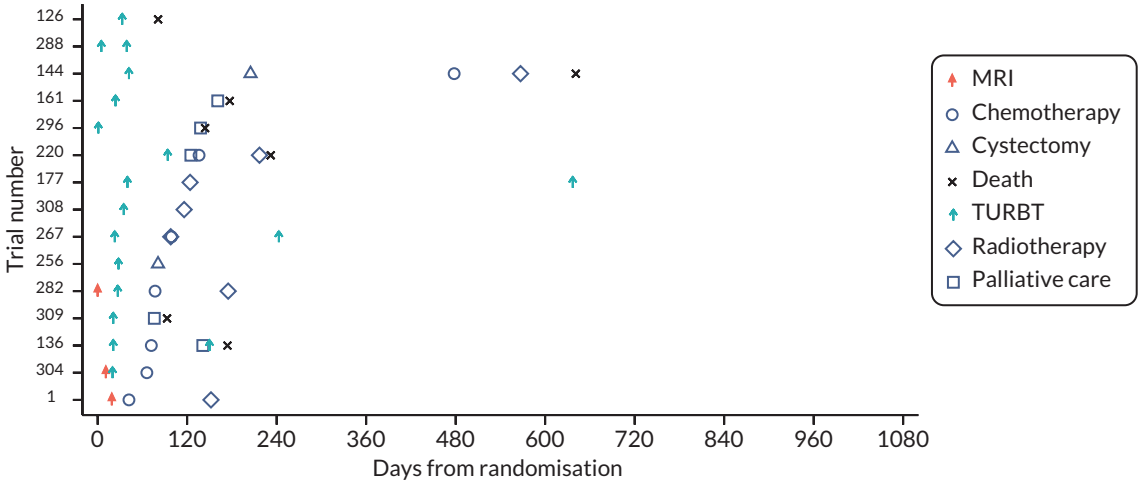


FIGURE 11 Swimmer plot for Pathway 1 MIBC participants.

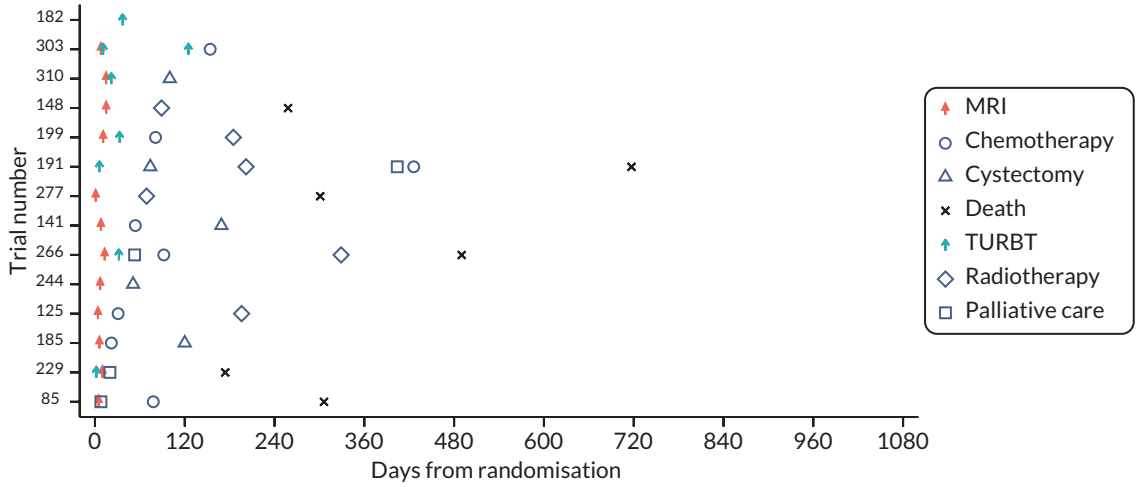


FIGURE 12 Swimmer plot for Pathway 2 MIBC participants.

Summaries of types of treatment received

Intravesical therapy

Thirty-four participants received at least one intravesical BCG (*Table 15*); 11 participants received intravesical chemotherapy (*Table 16*).

Chemotherapy

Eighteen chemotherapy treatments were received by 17 participants (one received both neo-adjuvant and synchronous chemotherapy with radiotherapy; *Table 17*).

Radiotherapy

Fifteen participants received radiotherapy (*Table 18*).

Cystectomy

Twenty participants underwent cystectomy (*Table 19*). One participant underwent surgery which was immediately abandoned upon anaesthetic induction due to the participant experiencing heart arrhythmia.

TABLE 15 Summary of participants who underwent intravesical BCG

Pathway	Pathway 1 (20)	Pathway 2 (14)	Overall (34)
Induction course			
Yes	20 (100.0)	14 (100.0)	34 (100.0)
Number of induction doses			
N	20	14	34
Mean (SD)	6.2 (1.1)	6.0 (0.0)	6.1 (0.8)
Median	6.0	6.0	6.0
IQR	6.0–6.0	6.0–6.0	6.0–6.0
Range	4.0–9.0	6.0–6.0	4.0–9.0
Maintenance course			
No	8 (40.0)	5 (35.7)	13 (38.2)
Yes	12 (60.0)	9 (64.3)	21 (61.8)
Number of maintenance doses			
N	12	9	21
Mean (SD)	4.8 (4.6)	7.7 (7.8)	6.0 (6.2)
Median	3.0	3.0	3.0
IQR	3.0–5.0	3.0–9.0	3.0–6.0
Range	1.0–18.0	3.0–21.0	1.0–21.0

IQR, interquartile range; SD, standard deviation.

TABLE 16 Summary of participants who received intravesical chemotherapy

Pathway[a]	Initial clinician assessment	Within 24 hours, single dose	Single drug used	Chemotherapy course of intravesical	Course drug used	Number of cycles
Pathway 1	Probable NMIBC	–	–	Yes	Mitomycin C	6
Pathway 1	Probable NMIBC	–	–	Yes	Mitomycin C	7
Pathway 1	Probable NMIBC	Yes	Mitomycin C	Yes	Mitomycin C	12
Pathway 1	Possible MIBC	Yes	Epirubicin	–	–	–
Pathway 2	Possible MIBC	Yes	Mitomycin C	Yes	Mitomycin C	6
Pathway 2	Possible MIBC	–	–	Yes	Epirubicin	8
Pathway 2	Probable NMIBC	Yes	Mitomycin C	Yes	Mitomycin C	6
Pathway 2	Possible MIBC	–	–	Yes	Epirubicin	6
Pathway 2	Probable NMIBC	–	–	Yes	Epirubicin	8
Pathway 2	Probable NMIBC	Yes	Epirubicin	–	–	–
Pathway 2	Possible MIBC	–	–	Yes	Other	6

a Each row represents one participant.

TABLE 17 Summary of participants who received systemic chemotherapy

Pathway	Pathway 1 (*n* = 8)	Pathway 2 (*n* = 10)	Overall (*n* = 18)
Type			
Neoadjuvant	4 (50.0)	5 (50.0)	9 (50.0)
Synchronous with radiotherapy	1 (12.5)	2 (20.0)	3 (16.7)
Palliative chemotherapy	3 (37.5)	3 (30.0)	6 (33.3)
Regimen			
Fluorouracil and mitomycin	0 (0.0)	1 (10.0)	1 (5.6)
Gemcitabine Carboplatin	2 (25.0)	2 (20.0)	4 (22.2)
Gemcitabine Cisplatinum	4 (50.0)	7 (70.0)	11 (61.1)
Gemcitabine	1 (12.5)	0 (0.0)	1 (5.6)
Pembrolizumab flat dose 6 weekly	1 (12.5)	0 (0.0)	1 (5.6)
Number of cycles			
N	8	9	17
Mean (SD)	2.9 (1.0)	5.3 (3.2)	4.2 (2.7)
Median	3.0	4.0	4.0
IQR	2.5–3.5	4.0–6.0	3.0–4.0
Range	1.0–4.0	1.0–12.0	1.0–12.0

IQR, interquartile range; SD, standard deviation.

TABLE 18 Summary of participants who received radiotherapy

Pathway	Initial clinician assessment	Intention of treatment	Intention of treatment field	Number of fractions given	Total dose given (Gy)	Radiotherapy completed as planned	Was chemotherapy given synchronously	Synchronous chemotherapy
Pathway 1	Possible MIBC	Radical	Bladder	20	55	Yes	Yes	Mitomycin
Pathway 2	Possible MIBC	Radical	Bladder	–	–	Yes	No	N/A
Pathway 1	Possible MIBC	Palliative	Metastatic state	5	20	Yes	–	N/A
Pathway 2	Possible MIBC	Radical	Bladder	20	55	Yes	No	N/A
Pathway 1	Possible MIBC	Radical	Bladder	20	50	Yes	No	N/A
Pathway 2	Probable NMIBC	–	Bladder, upper renal tract	27	55	Yes	No	N/A
Pathway 2	Possible MIBC	–	Metastatic site	5	20	Yes	No	N/A
Pathway 2	Possible MIBC	Radical	Bladder	55	20	Yes	Yes	Cisplatin, gemcitabine

TABLE 18 Summary of participants who received radiotherapy (*continued*)

Pathway	Initial clinician assessment	Intention of treatment	Intention of treatment field	Number of fractions given	Total dose given (Gy)	Radiotherapy completed as planned	Was chemotherapy given synchronously	Synchronous chemotherapy
Pathway 1	Possible MIBC	Palliative	Bladder	1	8	Yes	No	N/A
Pathway 2	Possible MIBC	Palliative	Metastatic site	5	30	Yes	No	N/A
Pathway 1	Possible MIBC	Radical	Bladder	20	55	Yes	Yes	Gemcitabine
Pathway 2	Possible MIBC	Radical	Bladder	20	55	Yes	Yes	Other
Pathway 1	Possible MIBC	Radical	Bladder	20	55	Yes	Yes	5-Fluorouracil, mitomycin
Pathway 2	Possible MIBC	Radical	Bladder	20	55	Yes	Yes	Mitomycin, other
Pathway 1	Possible MIBC	Radical	Bladder	20	55	Yes	Yes	Mitomycin, capecitabine

N/A, not available.
Note
Each row represents a participant.

TABLE 19 Summary of participants who underwent cystectomy

Pathway	Pathway 1 (*n* = 8)	Pathway 2 (*n* = 12)	Overall (*n* = 20)
Treatment intent			
Curative	8 (100.0)	12 (100.0)	20 (100.0)
Resection type			
Radical cystectomy	7 (100.0)	10 (83.3)	17 (89.5)
Partial cystectomy	0 (0.0)	2 (16.7)	2 (10.5)
Not known	1	0	1
Technique			
Pure open	5 (62.5)	9 (90.0)	14 (77.8)
Pure robotic	2 (25.0)	1 (10.0)	3 (16.7)
Mixed	1 (12.5)	0 (0.0)	1 (5.6)
Not known	0	2	2
Lymph nodes			
Sampled	5 (62.5)	3 (25.0)	8 (40.0)
Clearance	3 (37.5)	9 (75.0)	12 (60.0)
Lymph nodes clinically suspicious			
No	3 (50.0)	7 (58.3)	10 (55.6)
Yes	3 (50.0)	5 (41.7)	8 (44.4)
Not known	2	0	2

continued

TABLE 19 Summary of participants who underwent cystectomy (*continued*)

Pathway	Pathway 1 (*n* = 8)	Pathway 2 (*n* = 12)	Overall (*n* = 20)
Other viscera removed			
None	1 (12.5)	0 (0.0)	1 (5.0)
Other	0 (0.0)	2 (16.7)	2 (10.0)
Ovaries	0 (0.0)	1 (8.3)	1 (5.0)
Prostate	2 (25.0)	4 (33.3)	6 (30.0)
Prostate, other	0 (0.0)	3 (25.0)	3 (15.0)
Prostate, urethra	1 (12.5)	0 (0.0)	1 (5.0)
Urethra, uterus	1 (12.5)	0 (0.0)	1 (5.0)
Urethra, vagina	1 (12.5)	0 (0.0)	1 (5.0)
Urethra, vagina, uterus, ovaries	2 (25.0)	0 (0.0)	2 (10.0)
Uterus, ovaries	0 (0.0)	1 (8.3)	1 (5.0)
Vagina, uterus, other	0 (0.0)	1 (8.3)	1 (5.0)
Reconstruction			
Conduit and urostomy	8 (100.0)	8 (100.0)	16 (100.0)
Not known	0	4	4

Cystectomy histology

Histopathology reports were provided for all participants who underwent cystectomy. *Table 20* summarises the findings. The commonest histological tumour type in this subset was transitional cell carcinoma (50%). One participant's pathology report related to a colorectal resection involving partial cystectomy of the bladder; however, the report stated 'no evidence of malignant neoplasm' in the bladder.

A total of nine patients had prostate cancer diagnosed upon pathological examination of the cystoprostatectomy specimen, three in pathway 1 and six in Pathway 2, as summarised in *Table 21*.

Participants whose cystectomy specimens showed non-muscle-invasive bladder cancer

Thirteen participants were confirmed as NMIBC (and not MIBC) by pathological examination of the cystectomy specimen, summarised in *Table 22*. There was no statistical difference in the number of cystectomies undertaken for NMIBC between the two pathways, Fisher's exact test ($p = 0.337$). One participant experienced two recurrences of locoregional disease (on 15 April 2019 and 21 December 2019) and a new primary tumour site (prostate) confirmed (on 9 October 2020). All patients who had no invasive disease at cystectomy had prior TURBT in addition, so no patient had cystectomy due to incorrect MRI staging. It should be noted that it is well documented that post TURBT with MIBC, around 10–15% of cystectomy specimens will then show no invasive disease, presumably due to the prior endoscopic resection.

Accuracy of magnetic resonance imaging

Nine Pathway 2 participants underwent both MRI diagnosis and subsequent cystectomy with available histology (*Table 23*).

Accuracy of transurethral resection of bladder tumour

Eight participants in each pathway had both TURBT and cystectomy tumour staging available (see *Tables 24* and *25*).

TABLE 20 Cystectomy histology

Pathway	Pathway 1 (*n* = 8)	Pathway 2 (*n* = 12)	Overall (*n* = 20)
Histological composition			
Adenocarcinomatous elements	0 (0.0)	2 (16.7)	2 (10.0)
None	0 (0.0)	1 (8.3)	1 (5.0)
Squamous elements, other	0 (0.0)	1 (8.3)	1 (5.0)
Transitional cell carcinoma	4 (50.0)	6 (50.0)	10 (50.0)
Transitional cell carcinoma, adenocarcinomatous elements	0 (0.0)	1 (8.3)	1 (5.0)
Transitional cell carcinoma, other	2 (25.0)	0 (0.0)	2 (10.0)
Transitional cell carcinoma, squamous elements	2 (25.0)	1 (8.3)	3 (15.0)
Detrusor muscle (tumour base)			
No	3 (60.0)	5 (50.0)	8 (53.3)
Yes	2 (40.0)	5 (50.0)	7 (46.7)
Not known	3	2	5
Tumour present in muscle			
Yes	2 (100.0)	5 (100.0)	7 (100.0)
Not known	6	7	13
Random bladder biopsy			
No	6 (100.0)	11 (100.0)	17 (100.0)
Not known	2	1	3
Cytology			
No	6 (100.0)	11 (100.0)	17 (100.0)
Not known	2	1	3
Other sampling			
Abdominoperineal resection (APER)	0 (0.0)	1 (8.3)	1 (5.0)
N/A	8 (100.0)	10 (83.3)	18 (90.0)
Uterus, cervix, adnexa	0 (0.0)	1 (8.3)	1 (5.0)
Bladder carcinoma			
No	0 (0.0)	2 (16.7)	2 (10.0)
Yes	8 (100.0)	10 (83.3)	18 (90.0)
Grade (WHO 1973)			
Grade 2	0 (0.0)	1 (11.1)	1 (6.3)
Grade 3	5 (71.4)	7 (77.8)	12 (75.0)
Unable to determine	2 (28.6)	1 (11.1)	3 (18.8)
Not known	1	3	4
Grade (WHO 2004)			
High	4 (100.0)	8 (88.9)	12 (92.3)
Low	0 (0.0)	1 (11.1)	1 (7.7)
Not known	4	3	7

continued

TABLE 20 Cystectomy histology (*continued*)

Pathway	Pathway 1 (*n* = 8)	Pathway 2 (*n* = 12)	Overall (*n* = 20)
pT stage			
T2	0 (0.0)	2 (18.2)	2 (10.5)
pT0	1 (12.5)	1 (9.1)	2 (10.5)
pT1	1 (12.5)	0 (0.0)	1 (5.3)
pT1a (pCIS)	3 (37.5)	1 (9.1)	4 (21.1)
pT1b (pCIS)	0 (0.0)	2 (18.2)	2 (10.5)
pT3a	0 (0.0)	1 (9.1)	1 (5.3)
pT3b	1 (12.5)	1 (9.1)	2 (10.5)
pT4a	1 (12.5)	0 (0.0)	1 (5.3)
pTa	0 (0.0)	2 (18.2)	2 (10.5)
pTis	1 (12.5)	1 (9.1)	2 (10.5)
Not known	0	1	1
pN stage			
N0	6 (85.7)	10 (100.0)	16 (94.1)
N2	1 (14.3)	0 (0.0)	1 (5.9)
Not known	1	2	3
Margins/status			
Positive	0 (0.0)	1 (9.1)	1 (5.6)
Negative	7 (100.0)	7 (63.6)	14 (77.8)
Unknown	0 (0.0)	3 (27.3)	3 (16.7)
Not known	1	1	2
Concomitant flat in situ carcinoma			
No	2 (25.0)	5 (50.0)	7 (38.9)
Yes	6 (75.0)	5 (50.0)	11 (61.1)
Not known	0	2	2
Total tumour volume (cm^3)			
N	0	1	1
Mean (SD)		1.5 (.)	1.5 (.)
Median		1.5	1.5
IQR		1.5–1.5	1.5–1.5
Range		1.5–1.5	1.5–1.5
Total biopsy or tumour dimension (mm)			
N	3	6	9
Mean (SD)	164.3 (120.2)	111.8 (122.0)	129.3 (116.6)
Median	100.0	64.5	90.0
IQR	90.0–303.0	40.0–125.0	54.0–125.0
Range	90.0–303.0	26.0–350.6	26.0–350.6

IQR, interquartile range; N/A, not available; SD, standard deviation; World Health Organization.

TABLE 21 Cystectomy histology–associated prostate cancer

Pathway	Pathway 1 (3)	Pathway 2 (6)	Overall (9)
pT			
TX	1 (50.0)	0 (0.0)	1 (16.7)
T2	1 (50.0)	4 (100.0)	5 (83.3)
Not known	1	2	3
pN			
NX	1 (50.0)	0 (0.0)	1 (16.7)
N0	1 (50.0)	4 (100.0)	5 (83.3)
Not known	1	2	3
pM			
MX	1 (100.0)	1 (33.3)	2 (50.0)
M0	0 (0.0)	2 (66.7)	2 (50.0)
Not known	2	3	5
Margin positive			
No	1 (50.0)	5 (100.0)	6 (85.7)
Yes	1 (50.0)	0 (0.0)	1 (14.3)
Not known	1	1	2
Gleason sum score			
N	1	5	6
Mean (SD)	7.0 (.)	6.2 (0.4)	6.3 (0.5)
Median	7.0	6.0	6.0
IQR	7.0–7.0	6.0–6.0	6.0–7.0
Range	7.0–7.0	6.0–7.0	6.0–7.0

IQR, interquartile range; SD, standard deviation.

TABLE 22 Treatment pathway for participants who did not have MIBC confirmed by cystectomy

Pathway	Initial assessment	MRI diagnosis	First TURBT stage	Second TURBT stage	Chemotherapy Y/N	Radiotherapy Y/N	Cystectomy stage
2	Possible MIBC	NMIBC	pT1	pTa			pTa
1	Possible MIBC		pT1				pT1
2	Possible MIBC		pT1				pTa
1	Probable NMIBC		pT1				pT0
1	Possible MIBC		pT1				pTa

continued

TABLE 22 Treatment pathway for participants who did not have MIBC confirmed by cystectomy (*continued*)

Pathway	Initial assessment	MRI diagnosis	First TURBT stage	Second TURBT stage	Chemotherapy Y/N	Radiotherapy Y/N	Cystectomy stage
2	Possible MIBC	NMIBC	pT1				pT0
1	Possible MIBC		pTa				pTa
1	Possible MIBC		pT1				pTis
2	Possible MIBC	MIBC	pTa	pTa	Y	Y	pTis
2	Possible MIBC	MIBC	pTa				pT1
1	Possible MIBC		pT1				pTis
2	Possible MIBC	Inconclusive	pT1				pT1
2	Possible MIBC	MIBC	T2				pTis

Note
Each row represents a participant assessment comparison.
Accuracy of MRI/TURBT by comparison with histological confirmed diagnosis.

TABLE 23 Comparison of MRI diagnosis with cystectomy histological tumour staging

MRI diagnosis	MIBC (*n* = 6)	NMIBC (*n* = 2)	Inconclusive (*n* = 1)	Overall (*n* = 9)
Tumour stage based on cystectomy pathology				
pT0	0 (0.0)	1 (50.0)	0 (0.0)	1 (11.1)
pTa	0 (0.0)	1 (50.0)	0 (0.0)	1 (11.1)
pTis	2 (33.3)	0 (0.0)	0 (0.0)	2 (22.2)
pT1	1 (16.7)	0 (0.0)	1 (100.0)	2 (22.2)
T2	2 (33.3)	0 (0.0)	0 (0.0)	2 (22.2)
T3	1 (16.7)	0 (0.0)	0 (0.0)	1 (11.1)
Total	6 (100.0)	2 (100.0)	1 (100.0)	9 (100.0)

TABLE 24 Comparison of TURBT tumour staging with cystectomy for Pathway 1

Tumour stage based on TURBT pathology	pTa (1)	pT1 (5)	T2 (1)	T2 or higher (1)	Overall (8)
Tumour stage based on cystectomy pathology					
pT0	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (12.5)
pTa	1 (100.0)	1 (20.0)	0 (0.0)	0 (0.0)	2 (25.0)
pTis	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	2 (25.0)
pT1	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (12.5)
T3	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	2 (25.0)
Total	1 (100.0)	5 (100.0)	1 (100.0)	1 (100.0)	8 (100.0)

TABLE 25 Comparison of TURBT tumour staging with cystectomy for Pathway 2

Tumour stage based on TURBT pathology	pTa (2)	pT1 (4)	T2 (2)	Overall (8)
Tumour stage based on cystectomy pathology				
pT0	0 (0.0)	1 (25.0)	0 (0.0)	1 (12.5)
pTa	0 (0.0)	2 (50.0)	0 (0.0)	2 (25.0)
pTis	1 (50.0)	0 (0.0)	1 (50.0)	2 (25.0)
pT1	1 (50.0)	1 (25.0)	0 (0.0)	2 (25.0)
T3	0 (0.0)	0 (0.0)	1 (50.0)	1 (12.5)
Total	2 (100.0)	4 (100.0)	2 (100.0)	8 (100.0)

Outcomes

Feasibility stage

Primary outcome: proportion of possible muscle-invasive bladder cancer participants randomised to Pathway 2 who correctly followed the protocol pathway

In total, there were 39 possible MIBC participants in Pathway 2, of which 36 (92%, 95% CI 79% to 98%) received MRI as per protocol. Three Pathway 2 possible MIBC participants did not undergo MRI after randomisation, including one who was found to have a metal fragment in his eye prior to undergoing the MRI examination, one who cancelled their MRI as the participant withdrew from the trial (29 days post randomisation) and one who underwent MRI prior to being entered into the trial (the scan was requested by the surgeon independently of the study). Of the 36 participants who underwent MRI, 17 were diagnosed as having MIBC, 16 were NMIBC and for 3 the mpMRI images were inconclusive.

Secondary outcome: overall proportion of all randomised participants who correctly followed the protocol pathway in their respective pathways

For Pathway 1, this was defined as the number of probable NMIBC and possible MIBC participants randomised to the pathway who received a TURBT at the appropriate pathway stage as a proportion of all participants randomised to Pathway 1.

For Pathway 2, it was defined as the number of probable NMIBC participants in the pathway who had a TURBT plus the number of possible MIBC participants in the pathway who underwent MRI as a proportion of all participants randomised to Pathway 2.

The overall proportion of participants who correctly followed their respective pathway protocol was 96% CI (88% to 99%) in each pathway. No statistical difference between the pathways was found.

Intermediate stage

Primary outcome: time to correct treatment for participants who were initially classified as possible muscle-invasive bladder cancer and then were confirmed to have muscle-invasive bladder cancer

Of the 26 participants who were initially classified as possible MIBC and then were confirmed MIBC (14 in Pathway 1 and 12 in Pathway 2; *Figure 13*), 25 received a correct treatment and 1 participant did not due to death 81 days post randomisation. For this latter participant, the date last seen was used in the time-to-event analysis to account for the length of time they had waited to start treatment. Median TTCT for all participants who were initially classified as possible MIBC and then were confirmed to have MIBC (N = 26) was 77 days (95% CI 54 to 100). Median TTCT for Pathway 1 (N = 14) was 98 days (95% CI 72 to 125). Median TTCT for Pathway 2 (N = 12) was 53 days (95% CI 20 to 89, p = 0.0201),

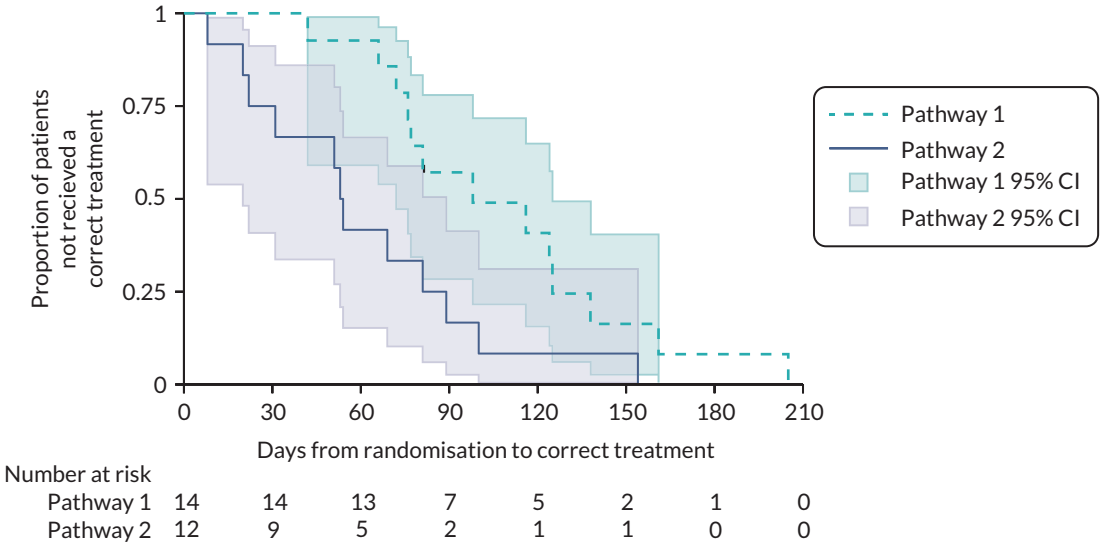


FIGURE 13 Kaplan–Meier curves of TTCT by pathway for possible MIBC participants who were confirmed MIBC and received a correct treatment.

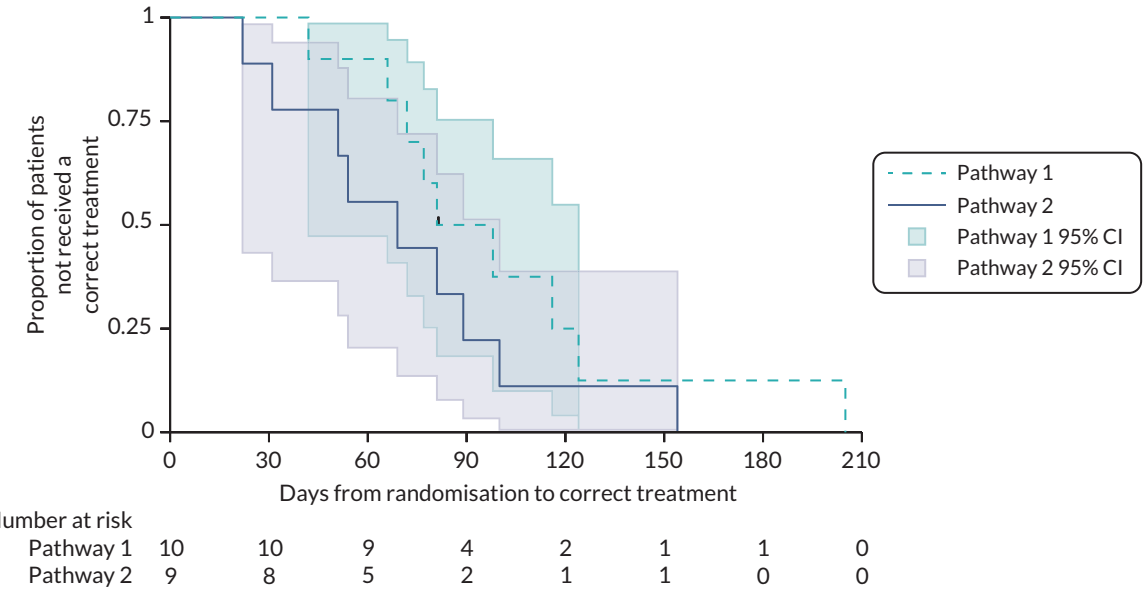


FIGURE 14 Kaplan–Meier curves of TTCT by pathway for possible MIBC participants with confirmed MIBC and received correct treatment, excluding participants who received palliative care as their correct treatment.

suggesting a statistical difference in TTCT between the two pathways. A Cox model, adjusted for the stratification factors of sex and age with study centre included as a random effect in the model, showed that the 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 relates to a participant receiving a correct treatment; therefore, a HR of 2.9 indicates that participants in Pathway 2 received correct treatment 2.9 times quicker than those in Pathway 1.

Exploratory sensitivity analysis: the primary outcome in the intermediate stage but excluding participants whose correct treatment was palliative care

Some participants were declared as requiring palliative care, but the date of that decision depended upon on the sites' clinical teams. Hence, careful consideration was made to account for these participants appropriately within the time-to-treatment analysis, while avoiding misleading results. This section shows a sensitivity analysis for the primary outcome, excluding participants with palliative care as their correct treatment.

There were 19 participants who were initially classified and then confirmed as having MIBC, where their correct treatment was not palliative care alone (10 in Pathway 1, and 9 in Pathway 2; *Figure 14*). Median TTCT for this subset of participants (*N* = 19) was 81 days (95% CI 54 to 100). Median TTCT for Pathway 1 (*N* = 10) was 81 days (95% CI 42 to 124) and median TTCT for Pathway 2 (*N* = 9) was 54 days (95% CI 22 to 100), log-rank *p* = 0.2366. Hence, the difference in TTCT between pathways became smaller when excluding participants whose correct treatment was palliative care only. In this post hoc subgroup analysis, a Cox model adjusted for the stratification factors of sex and age shows that the HR for Pathway 2 versus Pathway 1 was 1.9 (95% CI 0.6 to 5.9).

It should be noted in this context that the decision to offer palliative care was made often very early in the MRI pathway, whereas it was often made very late in the standard pathway (in one case after the patient had died). This should be viewed as a very positive advantage for early MRI as patients will have likely been offered more appropriate palliative care support and are potentially spared the morbidity of a diagnostic TURBT if, for example, they are found to have locally advanced or metastatic disease.

Secondary outcome: TTCT for probable non-muscle-invasive bladder cancer participants confirmed as non-muscle-invasive bladder cancer

There were 58 participants who were initially classified as having probable NMIBC which was then confirmed (28 in Pathway 1 and 30 in Pathway 2; *Figure 15*); all such participants received their 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 median TTCT for Pathway 2 (*N* = 30) was 17 days (95% CI 8 to 25, *p* = 0.6677). A Cox model adjusted 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).

Secondary outcome: TTCT for all randomised participants

Of the 143 randomised participants (72 in Pathway 1 and 71 in Pathway 2; *Figure 16*), 131 received a correct treatment. Participants who did not receive a correct treatment were censored at their date last seen and were 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 median TTCT for Pathway 2 (*N* = 71) was 25 days (95% CI 18 to 35, *p* = 0.0295). A Cox model

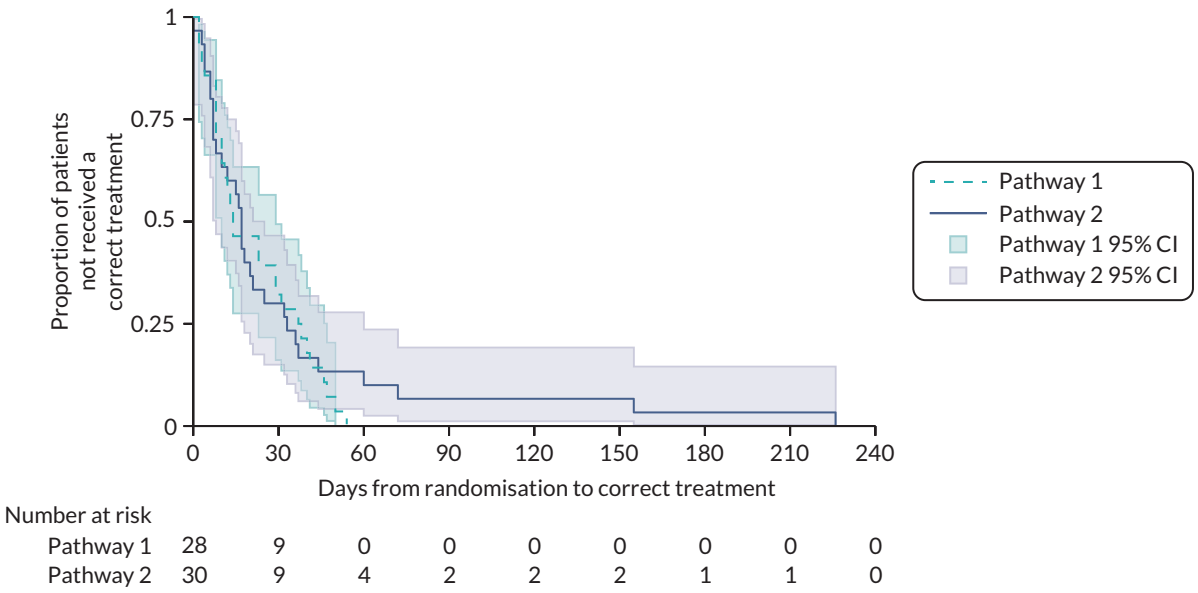


FIGURE 15 Kaplan–Meier curves of TTCT by pathway for probable NMIBC participants who were confirmed NMIBC and received a correct treatment.

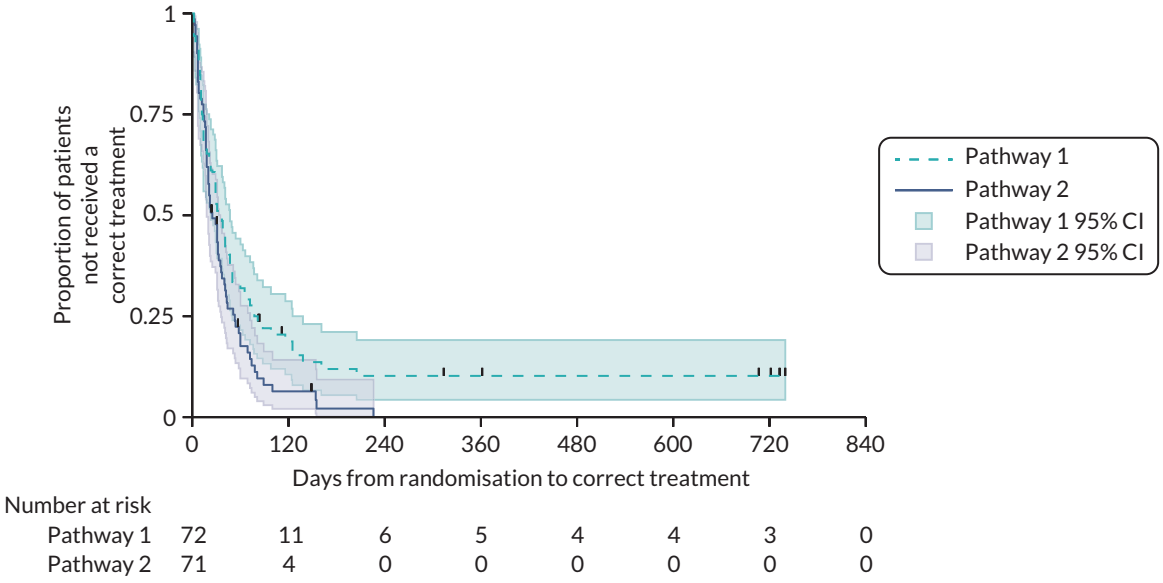


FIGURE 16 Kaplan–Meier curves of TTCT by pathway for all randomised participants.

adjusted 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).

Health economics

Pre-trial costing suggested that the pathway may be cost-saving depending on the numbers of TURBT procedures that were removed by the earlier use of MRI and biopsy. The NHSE (NHS England) tariff cost of TURBT is £2183 (LB13D) and the tariff cost of mpMRI is £200 (RD05Z). There may be a small additional charge if biopsy is carried out during flexible cystoscopy but pre trial we ascertained that in many sites this was already common standard practice.

Based on these tariffs, we can estimate that bypassing TURBT in cases where it is not required is likely to be cost saving if only > 1 : 10 MRI scans lead to this outcome. Our data show that 7/36 patients had either definitive therapy or palliative care that did not require TURBT, a saving of approximately £8000–9000 on the £78,000 that would have been spent had all these patients had a TURBT. There are thus unlikely to be significant cost barriers to implementing the pathway. Separate issues apply within trusts concerning the relative availability of scanning capacity and operating theatre or surgical capacity which are likely to vary from hospital to hospital.

Follow-up

Length of follow-up

Overall, the median length of follow-up was 23.7 months (95% CI 23.7 to 24.0), 23.7 months (95% CI 23.7 to 24.0) for Pathway 1 (*N* = 72) and 24.0 months (95% CI 23.7 to 24.1) for Pathway 2 (*N* = 71), illustrated in *Figure 17*.

Follow-up cystoscopy results are summarised in *Table 26*.

Follow-up data reporting cytology and imaging results on suspicion of recurrence are summarised in *Table 27*.

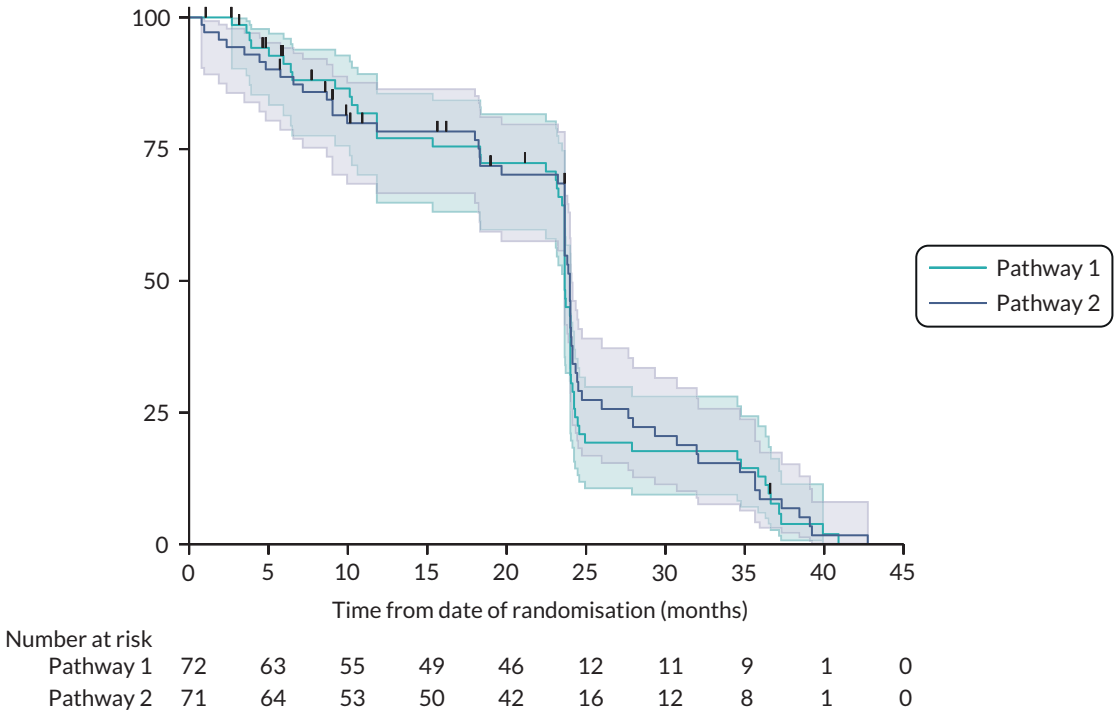


FIGURE 17 Proportion of participants followed up.

Recurrence/progression/new primary/death

There were 70 recurrence, progression or new primary events from 47 participants (26 in Pathway 1 and 21 in Pathway 2), summarised in *Table 28*.

Twenty participant deaths were reported (10 in each pathway), summarised in *Table 29*.

Substudies

Urinary DNA substudy

The trial included a translational study evaluating the use of a urinary DNA test in the haematuria clinic. The aim was to test the ability of mutational analysis of urinary DNA to non-invasively detect BC within the context of haematuria investigations and NMIBC surveillance. The initial BladderPath screening patients were offered entry into this biomarker study which had separate funding and eventually 176 participants were recruited. It should be noted that these patients only partially overlap with the main trial patients as most did not have BC and hence did not proceed to the main study. The DNA substudy was also supplemented with other patients from haematuria clinics, separate from BladderPath recruitment. The results summarised below have been separately published.[30]

In brief, pre-cystoscopy mid-stream urine specimens (up to 50 ml) were collected in Norgen Urine Collection and Preservation Tubes (Norgen Biotek, Thorold, ON, Canada) on the day of clinic attendance and transferred to the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham at ambient temperature by post (in UN3373 packaging). On receipt at HBRC, samples were centrifuged at 1000 *g* for 10 minutes; cell pellets and supernatants were then separated and frozen at −80 °C. The non-BC patients were determined to be 'normal' or with diagnoses including calculi, benign prostatic hyperplasia, cystitis, inflammation, urinary tract infection, prostate cancer and kidney cancer. A 'panel of normals' and 'confirmatory controls' were randomly selected from this cohort.

Deoxyribonucleic acid was extracted from cell pellets (cp) using Quick-DNA Urine Kits (Zymo Research, Irving, CA, USA) and quantitated using high-sensitivity double-stranded DNA Qubit kits (Thermo Fisher, Waltham, MA, USA). Laboratory staff were unaware of patient diagnoses. Libraries were prepared from

TABLE 26 Summarised data from follow-up cystoscopy

Follow-up (month)	3 (131)	6 (123)	9 (115)	12 (105)	18 (97)	24 (90)	36 (22)	Overall (683)
Has the participant had a cystoscopy as part of their follow-up								
No	107 (82.9)	73 (60.8)	61 (55.5)	56 (57.1)	28 (31.5)	35 (40.7)	7 (33.3)	367 (56.2)
Yes	22 (17.1)	47 (39.2)	49 (44.5)	42 (42.9)	61 (68.5)	51 (59.3)	14 (66.7)	286 (43.8)
Not known	2	3	5	7	8	4	1	30
Cystoscopy type								
Flexible cystoscopy	14 (66.7)	41 (87.2)	45 (91.8)	35 (83.3)	55 (91.7)	50 (98.0)	13 (92.9)	253 (89.1)
Rigid cystoscopy	7 (33.3)	6 (12.8)	4 (8.2)	7 (16.7)	5 (8.3)	1 (2.0)	1 (7.1)	31 (10.9)
Not known	110	76	66	63	37	39	8	399
Tumour biopsies taken at the time of cystoscopy								
No	13 (59.1)	41 (87.2)	43 (87.8)	33 (78.6)	45 (73.8)	40 (78.4)	9 (75.0)	224 (78.9)
Yes	9 (40.9)	6 (12.8)	6 (12.2)	9 (21.4)	16 (26.2)	11 (21.6)	3 (25.0)	60 (21.1)
Not known	109	76	66	63	36	39	10	399
Random biopsies of mucosa taken at the time of cystoscopy								
No	15 (78.9)	41 (91.1)	43 (95.6)	36 (90.0)	49 (86.0)	44 (88.0)	12 (92.3)	240 (89.2)
Yes	4 (21.1)	4 (8.9)	2 (4.4)	4 (10.0)	8 (14.0)	6 (12.0)	1 (7.7)	29 (10.8)
Not known	112	78	70	65	40	40	9	414
Cystoscopy findings								
No evidence of disease	14 (66.7)	36 (76.6)	32 (65.3)	31 (73.8)	41 (67.2)	33 (64.7)	10 (71.4)	197 (69.1)
No tumour seen but suggestive of CIS	2 (9.5)	1 (2.1)	0 (0.0)	1 (2.4)	3 (4.9)	3 (5.9)	0 (0.0)	10 (3.5)
Evidence of tumour	5 (23.8)	8 (17.0)	10 (20.4)	9 (21.4)	12 (19.7)	12 (23.5)	3 (21.4)	59 (20.7)
Equivocal (tumour suspected but not confirmed)	0 (0.0)	2 (4.3)	7 (14.3)	1 (2.4)	5 (8.2)	3 (5.9)	1 (7.1)	19 (6.7)
Not known	110	76	66	63	36	39	8	398

TABLE 27 Summarised data from follow-up further cytology and imaging

Follow-up (month)	3 (131)	6 (123)	9 (115)	12 (105)	18 (97)	24 (90)	36 (22)	Overall (683)
Clinical examination findings suspicious of recurrence								
No	95 (93.1)	87 (91.6)	64 (83.1)	58 (82.9)	61 (82.4)	65 (86.7)	18 (94.7)	448 (87.5)
Yes	7 (6.9)	8 (8.4)	13 (16.9)	12 (17.1)	13 (17.6)	10 (13.3)	1 (5.3)	64 (12.5)
Not known	29	28	38	35	23	15	3	171
Cytology								
No	99 (96.1)	90 (92.8)	71 (94.7)	63 (91.3)	67 (90.5)	67 (89.3)	15 (78.9)	472 (92.2)
Yes	4 (3.9)	7 (7.2)	4 (5.3)	6 (8.7)	7 (9.5)	8 (10.7)	4 (21.1)	40 (7.8)
Not known	28	26	40	36	23	15	3	171
Cytology result								
Abnormal cells suspicious	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.3)	1 (5.3)	3 (0.6)
Malignant cells present	2 (1.9)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (1.3)	0 (0.0)	4 (0.8)
N/A	99 (96.1)	90 (92.8)	71 (95.9)	63 (91.3)	67 (90.5)	67 (89.3)	15 (78.9)	472 (92.4)
No malignant cells	2 (1.9)	6 (6.2)	3 (4.1)	4 (5.8)	7 (9.5)	6 (8.0)	3 (15.8)	31 (6.1)
Not done	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Not known	28	26	41	36	23	15	3	172
Further imaging								
No	82 (71.3)	90 (81.1)	79 (84.9)	71 (84.5)	68 (77.3)	59 (72.8)	16 (76.2)	465 (78.4)
Yes	33 (28.7)	21 (18.9)	14 (15.1)	13 (15.5)	20 (22.7)	22 (27.2)	5 (23.8)	128 (21.6)
Not known	16	12	22	21	9	9	1	90
Further imaging detail								
CT scan	28 (24.3)	19 (17.1)	13 (14.0)	12 (14.3)	16 (18.2)	19 (23.5)	5 (23.8)	112 (18.9)
MRI scan	2 (1.7)	2 (1.8)	0 (0.0)	1 (1.2)	2 (2.3)	1 (1.2)	0 (0.0)	8 (1.3)

continued

TABLE 27 Summarised data from follow-up further cytology and imaging (*continued*)

Follow-up (month)	3 (131)	6 (123)	9 (115)	12 (105)	18 (97)	24 (90)	36 (22)	Overall (683)
N/A	82 (71.3)	90 (81.1)	79 (84.9)	71 (84.5)	68 (77.3)	59 (72.8)	16 (76.2)	465 (78.4)
Ultrasound	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	3 (0.5)
X-ray	1 (0.9)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	2 (2.5)	0 (0.0)	5 (0.8)
Not known	16	12	22	21	9	9	1	90
Disease recurrence/progression								
N/A	82 (71.9)	90 (81.8)	79 (84.9)	71 (84.5)	68 (77.3)	59 (72.8)	16 (76.2)	465 (78.7)
No	26 (22.8)	15 (13.6)	11 (11.8)	8 (9.5)	15 (17.0)	18 (22.2)	2 (9.5)	95 (16.1)
Yes	6 (5.3)	5 (4.5)	3 (3.2)	5 (6.0)	5 (5.7)	4 (4.9)	3 (14.3)	31 (5.2)
Not known	17	13	22	21	9	9	1	92

N/A, not available.

TABLE 28 Recurrence, metastatic disease and new primary cancer

Pathway	Pathway 1 (*n* = 39)	Pathway 2 (*n* = 31)	Overall (*n* = 70)
Locoregional disease			
No	7 (18.4)	4 (13.3)	11 (16.2)
Yes	31 (81.6)	26 (86.7)	57 (83.8)
Not known	1	1	2
Upper tract urothelial cancer or urethra			
N/A	7 (18.9)	4 (13.8)	11 (16.7)
No	26 (70.3)	23 (79.3)	49 (74.2)
Yes	4 (10.8)	2 (6.9)	6 (9.1)
Not known	2	2	4
Was the recurrence in the same location as the primary tumour			
N/A	7 (20.0)	4 (14.8)	11 (17.7)
No	7 (20.0)	9 (33.3)	16 (25.8)
Yes	21 (60.0)	14 (51.9)	35 (56.5)
Not known	4	4	8
Metastatic disease			
No	27 (73.0)	25 (89.3)	52 (80.0)
Yes	10 (27.0)	3 (10.7)	13 (20.0)
Not known	2	3	5
Metastatic site			
Brain	1 (2.6)	0 (0.0)	1 (1.4)
Liver	1 (2.6)	0 (0.0)	1 (1.4)
Lung	3 (7.7)	2 (6.5)	5 (7.1)
Lung, bone	1 (2.6)	0 (0.0)	1 (1.4)
Lung, pelvic nodal, metastatic nodal	1 (2.6)	0 (0.0)	1 (1.4)
N/A	27 (69.2)	25 (80.6)	52 (74.3)
Not known	2 (5.1)	3 (9.7)	5 (7.1)
Other	1 (2.6)	1 (3.2)	2 (2.9)
Pelvic nodal	1 (2.6)	0 (0.0)	1 (1.4)
Pelvic nodal, metastatic nodal	1 (2.6)	0 (0.0)	1 (1.4)
New primary tumour			
No	37 (97.4)	25 (86.2)	62 (92.5)
Yes	1 (2.6)	4 (13.8)	5 (7.5)
Not known	1	2	3
Site of new primary tumour			
N/A	37 (94.9)	25 (80.6)	62 (88.6)
Not known	1 (2.6)	5 (16.1)	6 (8.6)
Other	0 (0.0)	1 (3.2)	1 (1.4)
Renal	1 (2.6)	0 (0.0)	1 (1.4)

N/A, not available.

TABLE 29 Summary of causes of death

Pathway	Pathway 1 (*n* = 10)	Pathway 2 (*n* = 10)	Overall (*n* = 20)
Cause of death			
Disease related	7 (70.0)	3 (30.0)	10 (50.0)
Not known	1 (10.0)	3 (30.0)	4 (20.0)
Other cancer – metastatic prostate Ca + metastatic oropharyngeal Ca	1 (10.0)	0 (0.0)	1 (5.0)
Other cancer – leukaemia	0 (0.0)	1 (10.0)	1 (5.0)
Other non-cancer – COVID-19	0 (0.0)	1 (10.0)	1 (5.0)
Other non-cancer – COVID-19 pneumonitis	1 (10.0)	0 (0.0)	1 (5.0)
Other non-cancer – multiorgan failure	0 (0.0)	1 (10.0)	1 (5.0)
Other non-cancer – pulmonary thromboembolism	0 (0.0)	1 (10.0)	1 (5.0)

25 ng urine cell pellet DNA (cpDNA; extracted from an average of 23 ml of urine) using Nonacus Cell3 Target enrichment. DNA was enzymatically sheared, end-repaired and A-tailed, and adapters (including Unique Molecular Identifiers) ligated to the fragments. Libraries were amplified and pooled in batches of 12 prior to overnight hybridisation with biotinylated probes and subsequent capture and final amplification of the next generation sequencing libraries. The probes targeted hotspots or regions of 23 genes. All libraries were 2 × 150 bp sequenced on a NovaSeq (Illumina, San Diego, CA, USA).

Sequencing data were demultiplexed and aligned to hg19 using bwa (version 0.7.15-r1140). Consensus reads were built using fgbio (version 1.1.0) requiring ≥ 3 reads to produce a consensus as described previously[36] and re-aligned to the reference. Average raw and consensus read depths were 27,100 × and 3000 ×, respectively. Samples with consensus read depth < 500 at ≥ 10 loci were excluded (35 out of 919, 3.8%). Base calls with quality ≥ 30 were extracted using bam-readcount and used to calculate VAFs at 443 predefined genomic coordinates (a refined set of single nucleotide variants from our study of 956 BCs[36]). An optimal variant calling strategy was developed based on the maximum variant allele frequencies observed in a panel of 100 BC-negative haematuria patients and confirmed on a further 62 BC-negative haematuria patients.

A 'positive test' was defined as detection of any one of the 443 mutations in a cpDNA sample at > 0.9% VAF for chr5:129528A/G or > 0.5% VAF at all other coordinates. This combination provided 89.9% specificity in the 'panel of normals' and 91.2% specificity in a further 62 'confirmatory controls' (non-BC haematuria clinic cpDNAs).

Applying the assay to the prospectively collected haematuria clinic cohort, including BladderPath patients, achieved 86.8% sensitivity at 81.0% specificity.[30] Combining two haematuria clinic cohorts to derive test positivity and VAFs across grades and stages of disease, 144/165 BCs tested positive [87.3% (95% CI 81.2 to 92.0) sensitivity] and 223/264 non-BCs tested negative [84.8% (95% CI 79.9 to 89.0) specificity].[30] Mutations were detected significantly more commonly (and with higher VAFs) in cpDNA from patients with all stages and grades of BC compared with non-BC patients ($p < 0.001$). Sensitivity was 97.4% (95% CI 91.4 to 99.7) for grade 3 BC, 86.5% (95% CI 74.2 to 94.4) for grade 2 BC and 70.8% (95% CI 48.9 to 87.4) for grade 1 BC. Sensitivity was 79.3% (95% CI 69.3 to 87.2) for pTa, 100% (95% CI 90.0 to 100.0) for pT1 and 91.7% (95% CI 78.1 to 98.3) for MIBC; all three cases of solitary CIS were detected. The median maximum VAF in incident BCs was 18.7%, versus 0.28% in non-BC patients ($p < 0.001$), with a median of three mutations per BC cpDNA. The most commonly detected mutations were *TERT*, *TP53*, *FGFR3*, *PIK3CA*, *ERCC2*, *ERBB2* and *RHOB*, mirroring previous tumour tissue data.[36,41,42]

The study concluded that ultra-deep sequencing of somatic mutations in a 23 gene panel in urinary DNA had the potential to detect new cases of BC with high sensitivity and specificity and could reduce reliance on cystoscopy in the haematuria clinic setting. The test also has a potential role in post-diagnosis surveillance, and this is being evaluated further.[35]

Routine data use

The trial initially intended to use access to routine data to reduce the need for conventional data collection via case record forms. The methodology was developed as part of a PhD thesis and the findings have been separately published.[43] This data model could be used as part of a future Commissioning through Evaluation (CTE)-based evaluation. It was not unfortunately possible to use the data collected in this way for the primary trial analysis as NHS Digital wished to charge around £3000 for each data extraction, even though these data extractions were multiple repeats of the same query, rather than each being a new bespoke query. As this was potentially monthly for up to 5 years, these costs were prohibitive.[44] The Chief Investigator met with the Chair of NHS Digital to explore ways of reducing these costs. While he agreed that it made no sense to levy these high charges for simple repeat queries, there did not seem to be any mechanism to waive them. In the end, we were forced to collect data the 'traditional' way via local case record forms, research nurses and data managers, thereby depleting valuable local trial resources within trusts. A positive end note to this is that the HTA have agreed to fund a one-off NHS Digital data sweep to correspond with the last entered patient completing 2 years of follow-up. This has allowed us to close all the trial sites to further follow-up and still to perform an event-driven and survival analysis using this methodology as a future analysis.

Conclusions

The mpMRI-directed pathway (Pathway 2) led to a substantial reduction in TTCT for MIBC participants without detriment to the TTCT for NMIBC participants. The initial Likert scale assessment at flexible cystoscopy accurately identified lower-risk NMIBC who all required TURBT and suggest no benefit from MRI in this lower-risk setting. Higher-risk patients identified at flexible cystoscopy benefited from MRI prior to any further intervention. Consideration should be given to the incorporation of mpMRI ahead of TURBT in the standard pathway for all patients with suspected MIBC. The improved decision-making accelerated time to treatment, even though many patients subsequently needed TURBT as part of their treatment plan. It also allowed around half of the MIBC patients to avoid TURBT completely and to proceed, with combined histological (for tissue diagnosis) and radiological confirmation of invasion or metastasis, to correct treatment for their MIBC, saving resources and reducing patient morbidity.

Discussion

We undertook the BladderPath study to investigate whether suspected MIBC participants may be safely expedited to correct treatment using initial mpMRI for initial local staging rather than TURBT. We have shown that it is feasible to introduce mpMRI for a proportion of participants visually diagnosed with possible MIBC at outpatient diagnostic flexible cystoscopy[45] and, in doing so, MIBC participants receive their correct treatment significantly (over 6 weeks) quicker. We also show that deploying mpMRI in this way also allowed NMIBC participants to receive their correct treatment (TURBT) more rapidly, perhaps by reducing operating theatre demand through avoiding inappropriate TURBT for MIBC. As noted, many of these higher-risk patients also required TURBT, for example to resolve diagnostic uncertainty, to debulk patients prior to chemoradiation or to assess factors such as CIS or variant histology. Despite this, the Pathway 2 patients still received their definitive treatment faster than those assessed solely with TURBT.

Delays in administering the correct treatment for MIBC participants are internationally widespread and contribute to worsening prognosis.[14,21,45–47] The shortcomings of TURBT are well-reported and delay

the correct treatment for MIBC participants by radical therapies, lead to incorrect therapy choices and possibly contribute to tumour spread.[45] Over the last decade, multiple studies have confirmed that mpMRI has higher sensitivity and specificity for more accurate discrimination of NMIBC and MIBC than TURBT,[22,23] and so potentially offering a safer and faster route to staging and hence correct treatment. Although the relationship between delay and survival in BC is complex,[48] it is reasonable to suggest that administering correct treatment to MIBC participants more than 6 weeks earlier than the current SOC can only be beneficial. Several studies report adverse outcomes associated with delays of over 3 months between BC diagnosis and RC;[49,50] the mpMRI-guided pathway (Pathway 2) undercut this by a considerable margin (median TTCT 53 days), whereas the standard pathway did not (median TTCT 98 days).

Transurethral resection of bladder tumour has been the cornerstone of the MIBC pathway for nearly 100 years.[51] Advocates suggest it is important to resect the luminal BC component to allow full histological categorisation (including the identification of variant histology) to obtain pathological proof of muscle invasion prior to commencing systemic chemotherapy/radical treatment and for reduction in tumour volume (perhaps to facilitate bladder sparing radical treatment).[52] However, the literature clearly shows that TURBT and cystectomy histology are often discordant with respect to variant and subtyping,[53,54] understaging of muscle invasion in TURBT samples is common,[11,55] and there are few data to suggest that tumour debulking is a necessary component of radiotherapy regimens. It should be noted that debulking is prognostic in many series, with incomplete debulking being associated with worse outcomes. However, this is likely to reflect completeness of debulking as being a surrogate for stage rather than a direct therapeutic effect. Indeed, the operator dependency of TURBT[56] may confuse the identification of complete chemotherapy response (stage ypT0) and so mean that cystectomy is used in many participants where bladder sparing would be possible.[57] Although not yet routine, modern technologies allow complex RNA expression profiling and DNA mutation analysis to be undertaken on small biopsies or on tumour DNA from urine.[35,58] There is thus no need for large excision biopsies for detailed molecular subtyping. Small tumour biopsies obtained during flexible cystoscopy yield enough material to permit both histopathological diagnosis of cancer and molecular subtyping (cf. prostate cancer[59]); liquid biopsy approaches may contribute additional risk stratification.[35,60,61]

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,[62] we have shown that such initial triage is accurate, demonstrating that 89% of lesions where the initial cystoscopic assessor strongly agreed or agreed the likely diagnosis was NMIBC were subsequently confirmed as NMIBC and accounted for around 50% of all cases. For the remaining 50%, where the initial urological assessment was less certain, the addition of mpMRI provided rapid, accurate triage with an approximately equal split between NMIBC and MIBC. Such an approach dovetails neatly with standard practice for prostate cancer diagnostics in the same units.[63] With initial outpatient cystoscopic triage, plus the lower numbers of cases of BC versus prostate cancer, any impact on departmental MRI workload would be relatively modest. Notwithstanding, it should be noted that a proportion of participants in Pathway 2 underwent TURBT for a range of reasons post MRI (e.g. to ascertain presence of histological variants, debulking pre-radiotherapy) without compromising TTCT. Of 14 TURBTs undertaken after mpMRI scanning in Pathway 2, only 3 (21%) were undertaken due to 'lack of confidence that the MRI shows MIBC', all from the same hospital. Hence, for the majority of patients, mpMRI provided staging information such that these TURBT procedures could be assigned to the correct surgeon for the correct indication (e.g. to debulk tumour prior to radical therapy) and be given high priority to reflect the needs of MIBC participants.

Thirteen participants underwent cystectomy but were later diagnosed with NMIBC after histopathological examination of the cystectomy specimen (six in Pathway 1 and seven in Pathway 2); there was no significant difference in the number of cystectomies undertaken for NMIBC between

the two pathways. All 13 of these participants underwent TURBT prior to cystectomy, with TURBT diagnosing NMIBC in all but 1 participant. This latter participant (Pathway 2, possible MIBC) had MIBC confirmed at TURBT and then pTis in the cystectomy specimen, indicating a complete resection of tumour at the initial TURBT. Hence, there was no evidence that early use of MRI for staging led to NMIBC patients undergoing 'unnecessary' cystectomy. As detailed in the introduction, cystectomy is a potentially appropriate treatment for high-grade or extensive NMIBC and the similar numbers in both pathways reflect this. We were unable to determine in more detail the decision-making process at the MDT meeting following first TURBT. We suggest that future studies in this setting should set out to capture such data.

Experience with the introduction of MRI into the prostate cancer pathway has been that, after initial scepticism, there has been widespread acceptance of the paradigm that more accurate imaging can improve clinical decision-making.[64] Notably, this adoption has occurred in the absence of randomised studies linked to clinical outcomes beyond the initial biopsy findings. To apply similar considerations to the BC pathway, generally managed via the same teams, is likely to be potentially more straightforward. Experience with setting up BladderPath suggests that clinicians rapidly become comfortable with using MRI to guide downstream decisions.

Regarding the cost associated with Pathway 2, a simple analysis demonstrates that saving 1 : 10 patients from needing a TURBT pays the crude costs of the additional nine MRI scans. Around 1 : 6 patients avoided a MRI scan in BladderPath making it likely that the pathway can be self-funding at the very least. The faster time to definitive therapy for NMIBC, but also for MIBC, is likely to improve outcomes which in itself may be cost saving. A full health economic analysis to examine these effects will require access to the long-term follow-up data which will become available in around 18 months' time and will be analysed separately. We conclude that it is feasible to add mpMRI for those participants visually diagnosed with possible MIBC at outpatient diagnostic cystoscopy. By doing so, possible MIBC participants receive their correct therapy significantly quicker, potentially leading to improved long-term outcomes, even if these patients require TURBT as part of their further assessments prior to definitive treatment. The initial radiological staging data which MRI adds over and above the urinary tract imaging that is routinely carried out in haematuria clinics thus leads to accelerated access to correct treatment. Anecdotally, where patients are undergoing TURBT post MRI, the procedure may be different and more targeted than the standard full diagnostic procedure on Pathway 1. Additionally, separating the lower-risk NMIBC from the higher-risk NMIBC and MIBC allows triage of cases to appropriate levels of surgical expertise. This is more difficult on the standard pathway where all patients need to have a TURBT for staging in order to plan further therapy.

The BC diagnostic and staging pathway has followed a largely unchanged pattern for nearly a century with rigid cystoscopy forming the mainstay of both histological diagnosis and initial staging. For patients with NMIBC, TURBT is also the mainstay of treatment. Unfortunately, TURBT is not the main treatment for the most lethal form of BC and may even be pro-metastatic. In the main, most cancers are staged with a biopsy to confirm histology and imaging to determine stage ahead of definitive treatment. For patients with MIBC, the TURBT pathway is frequently inaccurate with the need for repeat TURBT to assess muscle invasion with consequent delay – a minimum delay of 6 weeks between initial and re-do TURBT is standard.

Interpretation

A modified pathway with initial triage based on appearance at flexible cystoscopy correctly identified lower-risk NMIBC patients requiring TURBT. For higher-risk patients, use of a MRI scan allowed identification of NMIBC patients for TURBT while accelerating the identification of very high-risk patients requiring more complex therapy, which may include TURBT but equally allowed some patients to bypass this stage and proceed to definitive treatment more rapidly. The impact of the MRI on TTCT for these patients is substantial with no evidence of a detrimental effect on NMIBC care.

Limitations

There are various limitations to the current study. Unfortunately, there were substantial interruptions to recruitment due to COVID-19 and so we were unable to enrol sufficient participants to evaluate our a priori progression free survival-based outcomes.

Secondly, the exact pathological stage in participants who underwent systemic chemotherapy, radiotherapy or palliation for mpMRI-diagnosed MIBC was unknown and so it is impossible to conclusively know whether these were correct treatments. However, TURBT has been shown to have substantial error rates, with many NMIBC patients upstaged to MIBC at subsequent cystectomy.[11,65] Hence, there is no perfect 'ground truth' on either side of the randomisation – this would require a trial in which all participants undergo cystectomy. Thirdly, the development of a mpMRI grading system, VI-RADS,[22] occurred during the conduct of our study (two of the trial team were part of the VI-RADS group) and provides a separate, peer-reviewed classification system for implementation. Work to validate the VI-RADS system with the BladderPath images is ongoing. Notwithstanding, the VI-RADS mpMRI sequences are analogous to those in widespread use for prostate cancer diagnosis by the same clinical teams. Hence, roll-out of a mpMRI-based pathway incorporating VI-RADS should be straightforward.

Further work to cross-correlate with the VI-RADS system[22] will improve accuracy and aid dissemination. Longer follow-up to examine the effect of the pathway on outcomes is also required.

A comprehensive health economic analysis was not feasible in the absence of longer-term outcomes data. However, a simple cost: consequence analysis shows that the MRI-based pathway is likely to be cost saving.

Generalisability

The MRI sequences used are similar to those in widespread use for prostate cancer diagnosis by the same teams and hence roll out should be relatively straightforward. The trial was carried out in a range of NHS units and thus broader roll out should be feasible.

Overall evidence

The trial was carried out at a time when image-directed treatment decisions have become standard practice in prostate cancer. The development of a MRI grading system, VI-RADS,[22] occurred during the conduct of the trial and provides a separate, peer-reviewed, classification system for implementation. Taken with the work on VI-RADS, a move to the pathway examined in the BladderPath trial appears to be both feasible and desirable.

Research recommendations

Key areas for further research:

1. A large, randomised trial to look at failure-free survival is unlikely to be feasible given the issues faced by BladderPath and the current very difficult research and broader NHS environment. However, part of the BladderPath programme included the development of tools to extract the key end points of interest from NHS Digital records. This would allow broader evaluation of a MRI-based pathway via the CTE programme. As our costings indicate, this is likely to be cost saving and will free up around 10% of TURBT slots, participation in such a programme may be attractive to Trusts.
2. A CTE programme looking at MRI should also evaluate the role of VI-RADS specifically as a decision-making tool. Studies examining the role of biomarkers, particularly liquid DNA biomarkers in blood and urine, are required. These may further improve the diagnostic accuracy and therapeutic decision-making provided by MRI (± TURBT) as well as providing non-invasive tools for follow-up and response assessment reducing the need for invasive check cystoscopy.

Patient participation and involvement

Patient participation and involvement in this study are summarised in *Table 30*.

Equality, diversity and inclusion

Registration into the study was open to any adult patient of 18 years or more attending haematuria clinic for investigation of blood in their urine. If initial examination found evidence of potential BC, then randomised entry into the main study was offered to the patient. During the course of the trial only one registered participant was under the age of 20 years, and they were not found to have cancer during initial examination. Lowering the age of entry to 16 years was considered in 2020, but with the approaching end of recruitment and the unlikely prospect of a 16- to 17-year-old presenting with BC, this was decided against.

One recruiting site reported that sending out the invitation letter and participant information sheet to patients due to attend the haematuria clinic for initial investigation was found to be upsetting to some of the patients, which also upset the research staff. The site's research team explained that the biggest barrier and upset for potential patients was the term 'Cancer' in the information sent to them prior to clinic, when approximately 80% of patients attending for investigation of their haematuria do not typically have cancer. At the same time, an investigator at another recruiting site pointed out that eligible patients might be discovered through alternative routes, such as inpatient investigations. Further to these early comments from sites, the protocol was amended to allow sites to approach patients about the study after their being given an initial diagnosis of suspicious tumours suitable for TURBT, which would in turn permit other patients found to be eligible for TURBT and treatment of BC to be recruited.

TABLE 30 Guidance for Reporting Involvement of Patients and the Public 2 short form

Section and topic	Item
1: Aim	To work with clinicians and researchers to ensure that the study remained patient-centred, had public accountability and the findings are shared with the general public in appropriate and accessible ways
2: Methods	The BladderPath study has had strong patient representative involvement from the protocol development and grant application stages, through to active engagement as members of both the TMG (two members, male and female) and Trial Steering Committee (one member) As members of the TMG, patient representative members have regularly attended TMG meetings throughout the duration of the study, ensuring the patient perspective was properly considered
3: Study results	The lived experience of patients as active contributors supported the development and delivery of the study. In particular: • Development of patient-facing materials • Input into relevant protocol amendments (see *Appendix 1*) • Input into regular progress reports to be submitted to the funding body • Influential in writing letters of support to the funding body at times of submitting applications to extend the study recruitment period • Utilising existing networks and resources known to the contributors to promote the study • Patient contributor attended a site initiation meeting and later provided a slide used at all subsequent site initiation meetings that presented their thoughts on how research nurses may answer questions from potential patients
4: Discussion and conclusions	It was helpful to have more than one patient representative member at the TMG – where one might not be able to attend, the other usually did. However, having only three contributors may have limited the breadth and diversity of public perspective into the study
5: Reflections/critical perspective	The strong collaboration with patient/public contributors has added relevance and value to the study and highlights the importance of collaboration throughout the trial cycle

The difference between participants being registered prior to their initial bladder examination or registered and randomised into the study after the examination was that a biopsy of any tumour found might be obtained. Most of the sites were not able to obtain a biopsy during the initial examination (flexible cystoscopy) due to the procedure being carried out by a clinical nurse specialist rather than a urologist or that the surgical kit required to obtain the biopsy was not available. Participants who were both registered and randomised after flexible cystoscopy and found to have possible MIBC and randomised to Pathway 2 had to return for a repeat cystoscopy with biopsy in order that a histological diagnosis could be made.

These changes made it easier both for the recruiting sites to recruit, and reduced some of the stress experienced by patients awaiting examination.

Pictures and diagrams used in the participant information sheet were of body parts common to all, rather than having any link to a particular part of society.

The study management group is composed of clinicians, academics and academic and support research staff and patient representatives of various ethnicities, ages and abilities – as is the University of Birmingham in general.

Additional information

Contributions of authors

Nicholas James (https://orcid.org/0000-0002-7314-8204) [Chief Investigator, Institute of Cancer Research (ICR) and Principal Investigator (PI) at The Royal Marsden Hospital, London] substantially contributed to the conception and design of the work, revising this report critically for important intellectual content and had final approval of the version to be published. NDJ is also accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sarah Pirrie (https://orcid.org/0000-0002-2894-2230) [Principal Statistician at the Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, University of Birmingham] substantially contributed to the design of the work and analysis of trial data.

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James Catto (https://orcid.org/0000-0003-2787-8828) (Co-investigator, Consultant Urological Surgeon and PI at Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, UK) substantially contributed to the conception and design of the work, drafting and revising this report critically for important intellectual content.

Kieran Jefferson (https://orcid.org/0000-0002-0029-8359) (Co-investigator, Consultant Urological Surgeon and PI at Department of Urology, University Hospitals Coventry and Warwickshire NHS Trust, UK) substantially contributed to the conception and design of the work, drafting and revising this report critically for important intellectual content.

Prashant Patel (https://orcid.org/0000-0002-2882-5990) (Co-investigator, Consultant Urological Surgeon and PI at University Hospitals Birmingham recruiting site) substantially contributed to the conception and design of the work, drafting and revising this report critically for important intellectual content.

Ana Hughes (https://orcid.org/0000-0001-7274-9422) (Senior Trial Coordinator at CRCTU, Institute of Cancer & Genomic Sciences, University of Birmingham) contributed to the drafting and revising this report critically for important intellectual content.

Ann Pope (https://orcid.org/0000-0001-7458-3294) (Trial Coordinator at CRCTU, Institute of Cancer & Genomic Sciences, University of Birmingham) contributed to the drafting and revising this report critically for important intellectual content.

Veronica Nanton (https://orcid.org/0000-0002-9553-822X) (Co-investigator, based at the Medical School, University of Warwick) contributed to the qualitative research section.

Harriet P Mintz (https://orcid.org/0000-0003-1583-6268) (Research Associate) contributed to the design of the work.

Allen Knight (https://orcid.org/0000-0001-8123-9547) (Patient and Public Involvement Representative on the Trial Management Group) contributed to the design and concept and has been involved in drafting the report.

Jean Gallagher (https://orcid.org/0009-0007-6308-2292) (Patient and Public Involvement Representative on the Trial Management Group) contributed to the design and concept and has been involved in drafting the report.

Richard T Bryan (https://orcid.org/0000-0003-2853-4293) (Co-investigator and Director of the Bladder Cancer Research Centre, Institute of Cancer & Genomic Sciences, University of Birmingham) substantially contributed to the conception and design of the work, drafting and revising this report critically for important intellectual content. He also obtained funding for and led the diagnostic urinary biomarker sub-study of BladderPath.

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Other contributors

Sophia Magwaro, Trial Management Team Leader, CRCTU.

Hiede Doyle, Trial Data Manager, CRCTU.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

Participant data and the associated supporting documentation will be available within 6 months after the publication of the study results in a peer-reviewed journal. Details of our data request process are available on the CRCTU website. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. All data requests should be submitted to the corresponding author for consideration.

Ethics statement

The BladderPath study was conducted in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 [World Medical Association. *WMA Declaration of Helsinki: Ethical Principles for*

Medical Research Involving Human Subjects. 6 September 2022. URL: www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed 14 July 2023)]. The study was also conducted in accordance with applicable UK Statutory Instruments (including the Data Protection Act 1998 and Human Tissue Act 2004 and Good Clinical Practice (GCP). The study protocol and patient information and consent documents were peer reviewed and ethically approved prior to the study opening (NIHR London Bridge Research Ethics Committee, UK project reference 17/LO/1819; approval date 4 December 2017). It was the responsibility of Principal Investigators at the recruiting sites that local approvals were in place and maintained, and to take immediate clinical action if thought necessary to protect the health and interest of individual patients.

Information governance statement

The University of Birmingham is the data controller and its Cancer Research Clinical Trials Unit (CRCTU) the data processor of all study participants' personal data handled throughout the BladderPath study. As per the EU General Data Protection Regulation and the UK Data Protection Act 2018, all trial/study participants were provided with additional details regarding the legal basis that allows us to hold and process their personal data, available on the study's web page [bladderpath-patient-info-sheet-v5.0a-10-sep-2020.pdf (birmingham.ac.uk)].

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR journals Library report publication page at https://doi.org/10.3310/DEHT5407.

Primary conflicts of interest: Nicholas James received funding for this project from the National Institute of Health and Care Research (NIHR) Health Technology Assessment programme and was a member of HTA General Committee. He is also a NIHR Senior Investigator. Richard T Bryan received research funding for this project from the National Institute of Health and Care Research Health Technology Assessment program. His research is also funded by grants from Cancer Research UK (Early Detection & Diagnosis), Cancer Research UK (Data Innovation Award), Janssen, University Hospitals Birmingham Charity (UK), Cancer Research UK (Biospecimen Collection), UroGen Pharma (USA). He receives consulting fees from Cystotech (Denmark) and is an unpaid charity trustee for Action Bladder Cancer UK. James Catto receives consulting fees from Astra Zeneca, BMS, Gilead, QED Therapeutics, Roche, Ferring, Steba biotech, UroGen, Jansenn, Photocure, and also received honoraria payments from BMS, Astra Zeneca and Roche. He is an unpaid trustee for Fight Bladder Cancer UK and member of BMS advisory board. Allen Knight was a member of EME Strategy Group, PHR Research Funding Board and EME Funding Committee Member, he is an unpaid Trustee of Action Bladder Cancer UK, unpaid Director of the World Bladder Cancer Patient Coalition and unpaid Birmingham Bladder Cancer Research Centre advisory board member.

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Articles

Mintz HP. *Can Routinely Collected Data be Used to Inform Randomised Controlled Trial Outcomes in Oncology?* PhD thesis. Coventry: University of Warwick; 2019.

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Meetings

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Nick James presented a poster entitled: Replacing TURBT with mpMRI for Staging MIBC: Pilot Data from the BladderPath study (source: www.urotoday.com/conference-highlights/asco-gu-2020/asco-gu-2020-bladder-cancer/119353-asco-gu-2020-replacing-turbt-with-mpmri-for-staging-mibc-pilot-data-from-the-bladderpath-study.html) EAU March 2020.

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Appendix 1 Protocol amendments

Amendment	Amendment date	Description	Documents approved
SA1	19 February 2019	Clarification of different methods of referral and communication between hospitals and patients, sources of referral and order of consent/initial investigation process	Protocol, V3.0, 19 February 2019
SA2	17 September 2019	Addition of qualitative substudy details.	Protocol, V4.0, 17 September 2019

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