Title page

A randomised trial of PHOTOdynamic-surgery in non-muscle invasive bladder cancer

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Abstract

BACKGROUND

Recurrence of non-muscle invasive bladder cancer (NMIBC) is common after trans-urethral resection of bladder tumour (TURBT). Photodynamic diagnosis (PDD) provides better diagnostic accuracy, more complete tumour resection and may reduce recurrence. However, there is limited evidence on the longer term clinical and cost-effectiveness of PDD-guided resection.

METHODS

In this pragmatic open label parallel-group randomised trial conducted in 22 UK NHS hospitals, we rectuited participants with a suspected first diagnosis of NMIBC at intermediate or high-risk of recurrence based on routine visual assessment prior to being listed for TURBT. Participants were assigned (1:1) to PDD-guided TURBT or standard white light (WL)-guided TURBT. The primary clinical outcome was time to recurrence at three years of follow up, analysed by modified intention to treat.

RESULTS

A total of 538 participants were enrolled (269 in each group) and 112 participants without histological confirmation of NMIBC were excluded. After 22 months' median follow-up, 86/209 of the PDD group and 84/217 WL group had recurrences. Three year recurrence-free rates were 57.8% (95% confidence interval (CI) 50.7% to 64.2%) and 61.6% (95% CI 54.7% to 67.8%) in the PDD and WL groups respectively (hazard ratio 0.94 (0.69, 1.28), p=0.70)). Adverse events were rare and similar in both groups, as was health related quality of life. PDD-guided TURBT was £993 (95% CI: -£724 to £2,709) more costly than WL-guided TURBT over 3-year follow-up and there was no evidence of a difference in QALYs, -0.096 (95%CI: -0.34 to 0.15).

CONCLUSIONS

PDD-guided TURBT did not reduce recurrence rates, nor was it cost-effective compared with WL at three years. (Funded by the National Institute for Health Research Health Technology Assessment programme; Trial registration: ISRCTN84013636).

Introduction

Bladder cancer is the tenth commonest cancer worldwide, with 573,000 new diagnoses and over 200,000 deaths a year.[1] Most are non-muscle invasive bladder cancers (NMIBCs) routinely managed by endoscopic trans-urethral resection of the bladder tumour (TURBT). NMIBCs are highly recurrent, with recurrence probabilities related to tumour number, size, recurrence history, T-stage, grade, and presence of carcinoma in situ (CIS). Half of NMIBCs are intermediate (IR) or high-risk (HR) at diagnosis, with a combined 3-year recurrence rate >60% (40-75%).[2-5] In HR-NMIBC, 11-30% of cases progress into muscle invasive bladder cancers (MIBCs), with a 50% mortality rate at 5 years.[2,3] Recurrence reduction is a priority.

A number of strategies are established, including a single postoperative intravesical instillation of chemotherapy[6] and further courses of adjuvant intravesical chemotherapy or Bacillus Calmette-Guerin (BCG) immunotherapy. Nevertheless, recurrence rates remain high, with intensive post-treatment monitoring involving regular cystoscopy and imaging.[2,4,5] Consequently bladder cancer is one of the most expensive cancers to manage, with UK NHS costs estimated at >£210 million,[7,8] however cost-effectiveness has not been widely studied.[8] Health-related quality of life (HRQoL) is also affected in bladder cancer[9] and better strategies for reducing NMIBC recurrence to decrease both burdens for patients and NHS costs are urgently needed.

Failure to identify and treat satellite tumours and/or the full tumour extent may be a factor in 20-40% of recurrences.[10,11] Photodynamic diagnosis (PDD) uses an intravesical photosensitiser to cause tumours to fluoresce under blue light and guide TURBT. This offers better diagnostic accuracy therefore may reduce subsequent recurrence.[12]

This pragmatic trial compares the clinical and cost-effectiveness of PDD resection with conventional white light (WL) TURBT for newly diagnosed NMIBC at intermediate and high-risk of recurrence (the “PHOTO” trial).

Methods

TRIAL DESIGN AND OVERSIGHT

We conducted a Phase III pragmatic open label parallel-group randomised controlled trial conducted at 22 UK NHS hospitals following independent ethics committee approval (14/NE/1062). The trial is registered: ISRCTN84013636. The study was overseen by independent data monitoring and trial steering committees. The full study protocol has been previously published.[13] The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Investigators were responsible for data collection and analysis, and the sponsor also oversaw site monitoring and data collation (Newcastle upon Tyne NHS Trust). All authors were involved in drafting and approving submission for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

We enrolled eligible patients 16-years old or over with suspected first diagnosis of IR/HR NMIBC based on EORTC/EAU and NICE risk tables.[2,3,5]. Patients with low-risk NMIBC (solitary tumour <3cm), imaging evidence of MIBC, upper tract involvement, other life-threatening malignancy in the past two years, evidence of metastases, porphyria/known porphyrins hypersensitivity, pregnancy, or any other contraindications to PDD or WL surgery were excluded.

PROCEDURES

Following informed consent participants were centrally randomised by hospital clinical teams using the Centre for Healthcare Randomised Trials' web-based or interactive voice response randomisation system. Allocation (1:1) to control (WL) or experimental

(PDD) groups was by minimisation balanced by centre and sex and incorporating a random element. Treatment allocation was not masked. PDD group participants received preoperative intravesical hexaminolevulinate (85mg/50ml phosphate buffered saline). PDD-guided TURBT was conducted under blue light (wavelength 380-450nm) and fluorescent regions consistent with tumour were resected. The WL control group had standard tumour resection under white light.

Further treatment and follow-up was in accordance with standard guidelines: All participants received intravesical mitomycin C (40 mg in 40 ml saline) within six hours following TURBT or prior to discharge. A second TURBT conducted consistently with trial allocation was recommended for HR-NMIBC patients (high grade or histological stage pT1). Adjuvant intravesical therapy was prescribed according to relevant guidelines.[2] Cystoscopy was conducted three, six, nine, 12, 18, 24 and 36 months after initial TURBT (or second TURBT if required), in line with guidlelines for routine practice.

SAFETY

Adverse events were assessed post operatively, within 30 days of TURBT (Clavien Dindo)[14] and at three months using the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Serious adverse events (SAEs) related to study interventions were assessed throughout follow-up. HRQoL (EQ-5D-3L[15] EORTC-QLQ-C30 and EORTC QLQ-NMIBC-24) and health service utilisation questionnaires were completed by participants at baseline, following surgery and at three, six, 12, 18, 24 and 36 months after randomisation. After 36 months, data on disease status and survival were requested annually.

OUTCOME MEASURES

The primary clinical outcome measure was time to recurrence measured from randomisation to date of biopsy for pathologically proven first recurrence, progression, cystectomy or bladder cancer death. Secondary outcomes included self-reported HRQoL resulting from the effects of surgery and any subsequent cancer treatment. Health care utilisation and costs to the health service over the 36-month trial follow-up period were calculated. Quality adjusted life years (QALYs) were estimated from EQ-5D-3L and health care utilisation data. Other clinical outcomes included adverse events and complications up to three months from initial or second TURBT; disease progression (MIBC, development of nodal or distant metastatic disease or bladder cancer death), and overall and bladder cancer specific survival.

STATISTICAL ANALYSIS

Power calculations were based on log-rank analysis of time to recurrence and assumed three year recurrence-free rate of 60% in the control group (conservatively assuming all patients would have intermediate risk disease). The target hazard ratio (HR) was 0.64 (equivalent to PDD improving 3 year recurrence free rate to 72%). For 90% power and two-sided 5% significance 214 events were required; allowing for staggered recruitment over 2.5 years, minimum three years follow-up and 6.4% loss to follow-up at three years[16] the target sample size was 533 participants. Undertaking TURBT on visual characteristics is routine practice and it is only following resection that a formal histological NMIBC diagnosis can be confirmed. Accordingly, participants found to have MIBC or no tumour were planned to be excluded from the final analyses. Similarly, those participants with HR-NMIBC who underwent radical cystectomy in preference to cystoscopic surveillance, again in line with routine practice, were also

planned to be excluded. We refer to the resulting analysis population as the modified intention-to-treat (ITT) population.

The primary outcome was analysed using Cox proportional hazards models with patients censored at date of last follow-up or non-bladder cancer death. Unadjusted models, and models adjusting for minimisation factors gender and centre (random effects frailty model) and for known prognostic factors: smoking status, risk group, presence of CIS, and grade of surgeon (registrar, non-consultant career grade or consultant) were fitted. Proportional hazards were assessed visually using log (-log (survival)) versus log (analysis time) plots. Accelerated failure time models considering Weibull, exponential, log-logistics, log-normal and generalised gamma distributions were used to relax the proportional hazards assumption where required. Only the model with the smallest Akaike information criterion value is reported here. Time to progression and overall survival were analysed similarly to the primary outcome with Kaplan-Meier plots presented. A competing risk approach was used for bladder-cancer specific survival[17] with death from other causes considered a competing risk. A sensitivity analysis of the primary outcome treating non-bladder cancer deaths as a competing risk was also performed. Treatment effect estimates are presented with 95% confidence intervals. Two-sided p-values less than 0.05 were considered significant. Analyses were conducted in the modified ITT population by allocated treatment and in the per-protocol population restricted to participants who received the treatment to which they were allocated.

The proportion of participants experiencing adverse events (CTCAE grade 3 or above) was compared between groups using Poisson regression adjusting for minimisation covariates. The number of adverse events by Clavien-Dindo grade was tabulated.

Standard algorithms were used to derive HRQoL scores and handle missing data within each HRQoL outcome. A linear mixed model was used (random effect for centre and participant, fixed effect for nominal time, treatment, sex, smoking status, risk group, presence of CIS, and grade of surgeon) to analyse repeated measures. Treatment effects at each time were derived from the interaction term for time by treatment. To account for multiple HRQoL outcomes and time-points, we report 99% CIs.

To establish within-trial cost-effectiveness over 36 months, we estimated the incremental cost per QALY gained for PDD relative to WL (see supplementary Appendix). Costs were assessed from health services perspective for the financial year 2018/19. Costs and QALYs were discounted at 3.5% per annum.[18] A micro-costing approach was used to estimate NHS and personal costs based on clinician reported data collected via the case report form and responses to the patient completed health service utilisation questionnaires. QALYs were estimated using responses to EQ-5D-3L scored using the UK value set[19] and the area under the curve approach.[20] The incremental cost per QALY was calculated from the coefficient of treatment effect on costs divided by the coefficient of treatment effect on QALYs from seemingly unrelated regression models.[21] The bootstrapped estimates of costs and QALYS were further used to produce cost-effectiveness acceptability curves.[22] See Supplementary Appendix 1 for further details of the cost-effectiveness analysis.

There was no formal interim analysis but an independent data monitoring committee reviewed the emerging safety and efficacy data. All analyses were conducted in Stata version 16.

Results

STUDY PARTICIPANTS

Twenty-two participating sites enrolled 538 participants between November 2014 and Feburuary 2018. Of these, 269 participants were allocated PDD and 269 WL (Figure 1). There were five post-randomisation exclusions. After initial TURBT 29 participants had no histological evidence of tumour, 60 had MIBC and 18 had early cystectomy, leaving 426 (209 PDD and 217 WL) in the modified ITT population (Supplementary Appendix 2).

Experimental and control groups were balanced on baseline characteristics (Table 1). Mean age was 70 years (SD 10) and most were men (339/426; 79.6%). Using EORTC categories, >85% (374/426) of participants in both treatment groups were intermediate risk. CIS was present in 13% (56/426) of participants. 207/209 participants (99.0%) in the PDD group and 215/217 (99.1%) in the WL group had TURBT. 194/207 (93.7%) participants in the PDD group had PDD, the rest received WL TURBT. All WL participants who had surgery had TURBT as allocated. Sixty-eight participants in both groups had a second resection (PDD: 68/209 (32.5%), WL: 68/217 (31.3%)).

Post-operative intravesical chemotherapy and adjuvant intravesical treatment rates were balanced in both groups (Supplementary Appendix Tables S3.1 & 3.2). 132/209 (63.2%) PDD and 143/217 (65.9%) WL participants received immediate post-operative intravesical MMC ($\chi 2=0.27$, $p=0.60$).

BLADDER CANCER RECURRENCE

Median follow-up was 21 months (IQR 6-42) for PDD and 22 months (IQR 5-44) for WL. There were 86 bladder cancer recurrences in the PDD group and 84 in WL. Time to recurrence is shown in Figure 2. Table 2 shows the results for the analyses of the primary and secondary clinical outcomes. The HR for recurrence was 0.94 (95% CI 0.69, 1.28), p=0.70. Relaxing the proportional hazards assumption using an accelerated failure time model based on log-normal distribution showed no evidence that the time ratio (TR) differed between groups (TR 1.12 (95% CI 0.78,1.60); p=0.55). Three-year recurrence free survival rates were 57.8% (95% CI 50.7%, 64.2%) for PDD and 61.6% (95% CI 54.7%, 67.8%) for WL: absolute difference -3.8% (95%CI -5.6%, 13.4%). There was no evidence that the sub hazard ratio (SHR) differed for either the PDD or WL group when considering competing risks of death (SHR 1.00 (95% CI 0.74,1.35); p=0.99) (Table 2). In those with recurrences, 30/86 (34.9%) in the PDD arm and 18/84 (21.4%) in the WL arm received BCG induction with or without maintenance.

There was no evidence of a difference in progression to invasive disease between PDD (n=19) and WL (n=12) groups (HR 1.41 (95% CI 0.67, 2.96); p=0.37). Nor was there evidence that bladder cancer specific survival differed between PDD (n=9 deaths) and WL (n=8 deaths) (sub HR 0.92 (95% CI 0.40, 2.14); p=0.85) or overall survival PDD (n=27 deaths), WL (n=30 deaths) (HR 0.83 (95% CI 0.49, 1.41); p=0.50). Of the 57 participants who died, 17 (29.8%) died of bladder cancer, nine (15.8%) of cardiovascular events, nine (15.8%) of other cancers and 22 (38.6%) of other causeSs.

ADVERSE EVENTS

Adverse events by Clavien-Dindo grade, SAEs and CTCAE >grade 3 events are reported in Table 3, with no significant difference between the groups.

PARTICIPANT-REPORTED OUTCOMES

The EQ-5D-3L, EORTC QLQ-30 and EORTC QLQ-NMIBC24 HRQoL responses were similar at all time points between PDD & WL (Supplementary Appendix Table S3.4 and Figures S3.3 & 3.4)

ECONOMIC EVALUATION

Full details of the economic evaluation are in supplementary Appendix. There was no evidence of differences between groups in terms of staff time and length of stay costs in the delivery of the intervention. Additional equipment cost caused the cost of PDD to be greater. There was no evidence of differences between groups in health service costs (mean difference: £876, 95% CI: -£776 to £2,518) over 36-months. QALYs at three years were 2.087 and 2.094 for PDD and WL respectively. There was no evidence of difference in QALYs gained between treatment groups at three years (mean difference: -0.007, 95% CI: -0.133 to 0.119). The probability that PDD was cost-effective was never above 30% over the range of society's cost-effectiveness thresholds considered.

Discussion

In this pragmatic trial comparing PDD and WL-guided TURBT in newly diagnosed IR and HR-NMIBC, no difference in bladder cancer recurrence was found over three years from initial treatment. In addition, cost-effectiveness analysis found PDD-guided TURBT in the management of primary IR and HR-NMIBC more costly than WL-guided TURBT over 3-years.

Previous studies and evidence syntheses showed increased sensitivity in the detection of NMIBC with PDD that translated into reduction of bladder cancer recurrence.[12,23-26] However these trials had differing protocols, including variable application of contemporary standards of care involving immediate post-operative intravessical chemotherapy, second resections and/or adjuvant intravesical treatments - limiting accurate meta-analysis and making it difficult to extrapolate these findings into current practice.[12] Nevertheless, these previous data led to uptake of PDD technology across the UK, Europe and the US, where expert recommendations were made on both reduction of recurrence and also health economic evaluations.[27-30] However, a longer-tem pragmatic randomised trial that overcomes limitations described above was required and is addressed by this PHOTO trial. In our study, recurrence rates appear to diverge over the first 12 months (Figure 2), supporting many preceding published data, but this emergent difference was not borne through to the longer term follow-up.

Other than surgical resection, we considered several established factors affect NMIBC recurrence, including (i) clinicopathological parameters that assign risk of recurrence, (ii) immediate post-operative single dose chemotherapy and (iii) adjuvant

chemotherapy or BCG. Taking each in turn, subgroup analyses for intermediate and high-risk cancers showed no difference in recurrence in the PDD and WL-guided TURBT participants, irrespective of variations in risk definitions using EORTC, NICE or EAU criteria. Use of immediate and adjuvant chemotherapies and BCG treatments were balanced across both groups.

A major strength of this effectiveness study is that the intervention was based in a pragmatic setting – embedding the assessment of the trial technology of PDD-guided TURBT in routine clinical management of a presumed new IR/HR-NMIBC following flexible cystoscopy. This ensured that only clinical parameters available at the point of diagnosis in the care pathway informed the risk category and although this included false positive diagnoses of higher-risk cancers, it represented the real-life decision making for when the technology would be used. Compared with prior analyses[12], integrated economic evaluation was a major strength as it obviated the need to extrapolate from surrogate end points to measure final outcomes of relevance to patients and health services. Although there were some missing data for cost and QALY outcomes the results remained unchanged over a range of plausible assumptions**.**

A recruitment of 533 participants was anticipated to provide 214 recurrences to detect a hazard ratio of 0.64 with a log-rank test (90% power, 2- sided 5% significance) but at the time of analysis, the study had accrued only 170 events. This reduction was related to (i) false positive visual diagnosis of IR/HR-NMIBC (14% MIBC and 7% benign) and (ii) early radical cystectomy for HR-NMIBC (8% of NICE high-risk or 36% of EORTC/EAU high-risk cancers). Despite this limitation, the PHOTO trial hazard ratio was 0.94 (95% CI 0.69, 1.28; p=0.7) comparing the two treatment

groups. Although the confidence interval is fairly wide, the estimate was precise enough to unequivocally rule out the difference pre-specified at the start of the trial.

Contributors

RH is the PHOTO trial Chief Investigator and GM and EH are the methodological leads.

RH, EH, LV and JN led study design and acquired funding for the trial.

GM and CR oversaw statistical analyses conducted by TV.

RL and CR contributed to study design and provided senior trial management oversight.

AD and SP conducted central study management at CHaRT and ICR-CTSU respectively.

LV oversaw the cost effectiveness study conducted and analysed by GY, MB, GO, SR.

AF, EC and LW were involved in translational sample collection.

PM, JC, JM, GN and HM were involved in recruitment and treatment of participants.

All authors are members of the PHOTO Trial Management Group which contributed to study design, was responsible for oversight throughout the trial and contributed to data interpretation and manuscript preparation.

Declaration of interests

RH is a member of the National Institute for Health Research (NIHR) Health Technology and Assessment (HTA) Commissioning committee (2017-ongoing), and declares receipt of NIHR funding for this project (HTA 11/142/02).

PM reports personal fees from Photocure, outside the submitted work.

CR reports and Member of the National Institutes for Health Research HTA Programme General Funding Committee (2017-present).

JN reports grants from University of Aberdeen, grants from University of Edinburgh, during the conduct of the study; and is a past and present member of the following: HTA Commissioning Sub-Board (Expressions of Interest), NIHR Clinical Trials Unit Standing Advisory Committee, NIHR HTA and EME Editorial Boards, Pre-Exposure Prophylaxis Impact Review Panel, EME Strategy Advisory Committee, EME – Funding Committee Members, EME Funding Committee Sub-Group Remit and Comp Check, HTA General Committee, HTA Funding Committee Policy Group (formerly CSG) and HTA Commissioning Committee.

LV reports grants from NIHR Health Technology Assessment Programme, during the conduct of the study; and Member of the NIHR Health Technology Assessment Programme Clinical Trials and Evaluation Panel 2015-2018.

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All other authors declare no other interests.

Data sharing

Deidentified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request. The investigators support wider dissemination of information from the research they conduct and increased cooperation between researchers. Trial data are obtained, managed, stored, shared, and archived according to CHaRT standard operating procedures to ensure the enduring quality, integrity, and utility of the data. Formal requests for data sharing are considered in line with CHaRT procedures, with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the investigators in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale. Restrictions relating to patients' confidentiality and consent will be limited by aggregating and anonymising identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed.

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Figure 1 CONSORT flow diagram

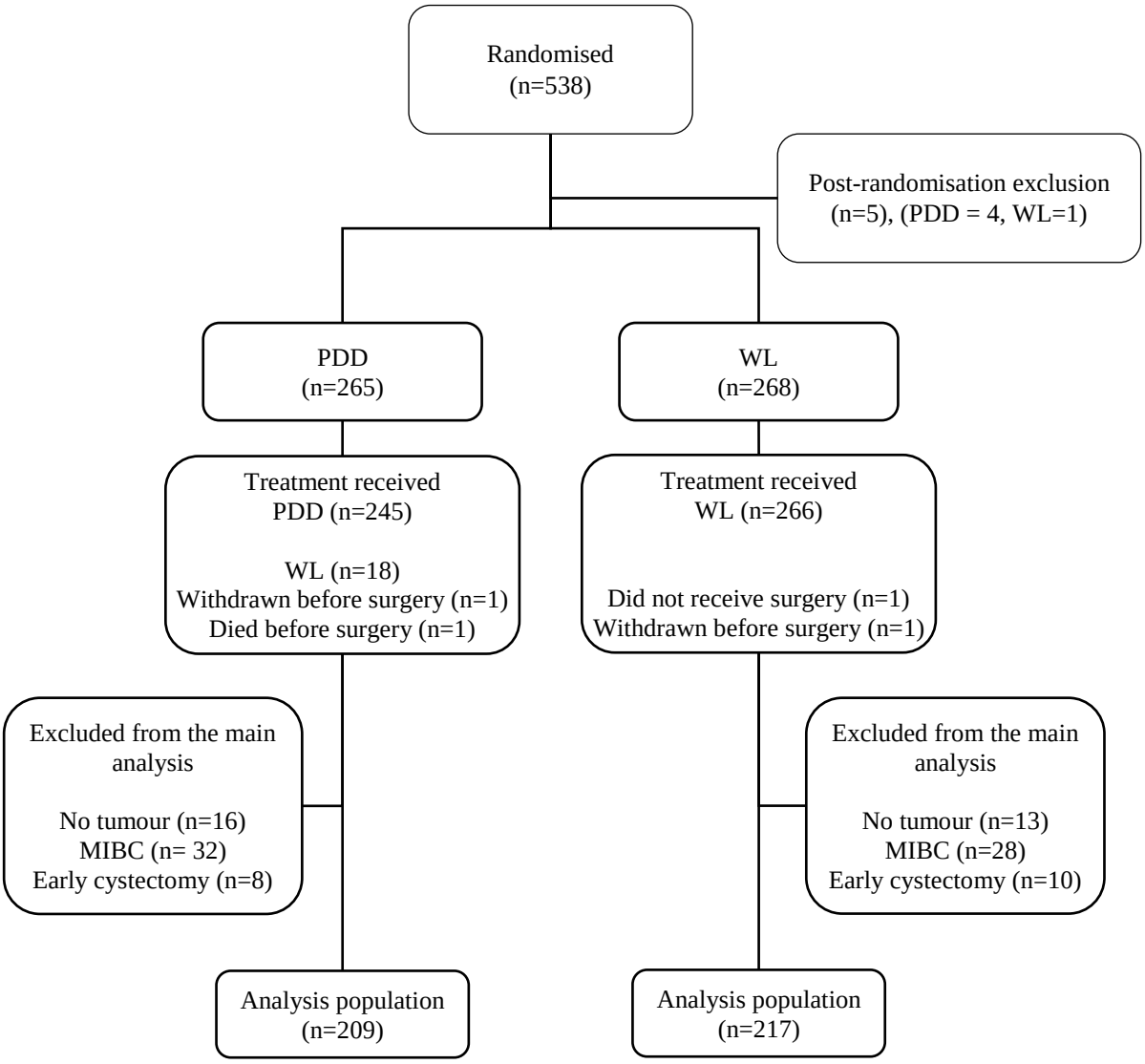


Figure 2 survival curves for recurrence free survival

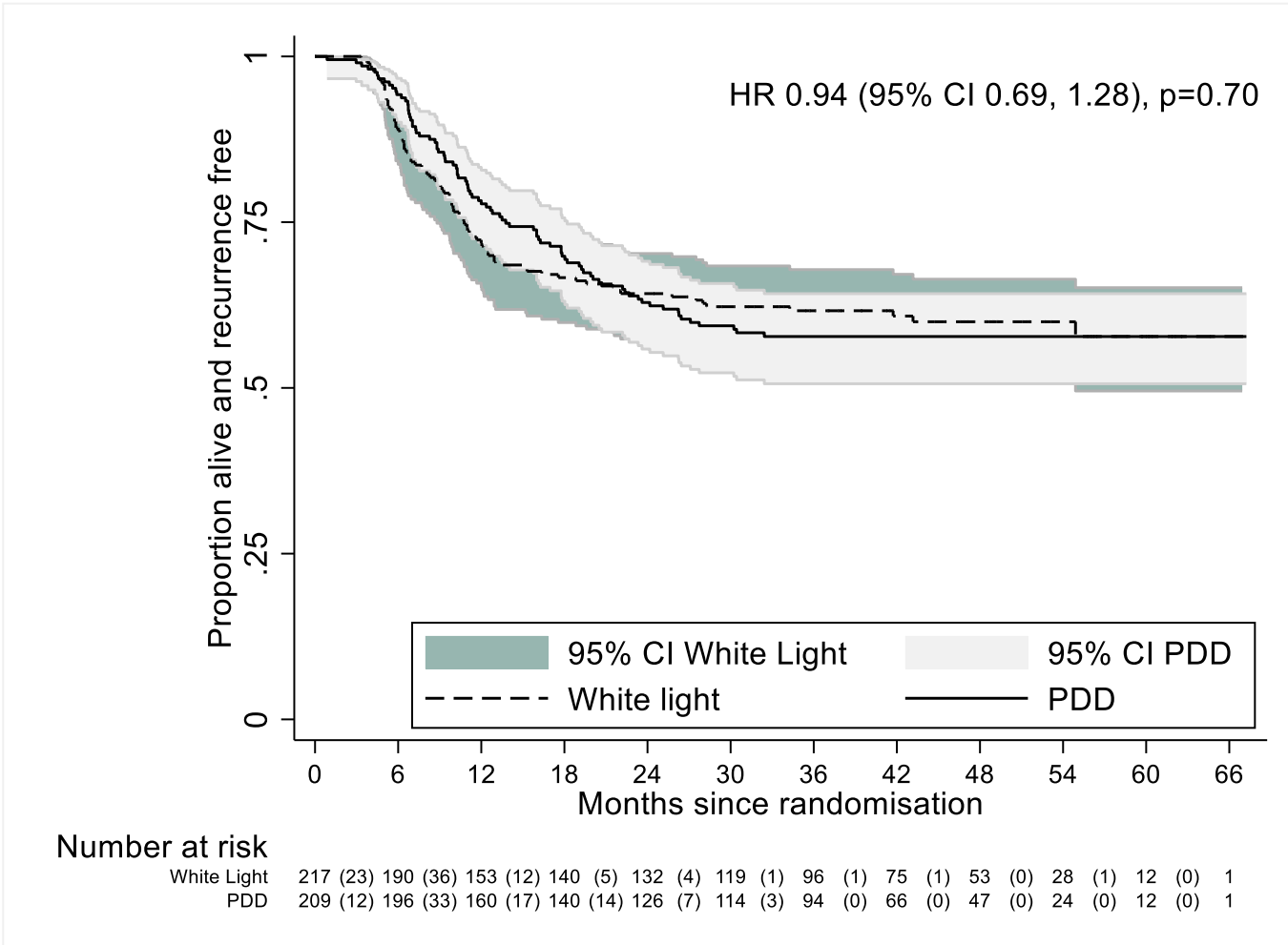


Table 1 Baseline characteristics of the analysis population

	PDD	White Light
	N=209	N=217
Age; mean,(SD)	71,(11)	70,(10)
Smoking Status		
Current Smoker	33(15·8%)	30(13·8%)
Previous Smoker	117(56·0%)	123(56·7%)
Never	57(27·3%)	60(27·6%)
Unknown	1(0·5%)	3(1·4%)
Missing	1(0·5%)	1(0·5%)
Number of tumours		
Single	66(31·6%)	81(37·3%)
2-7	122(58·4%)	113(52·1%)
>=8	17(8·1%)	21(9·7%)
Missing	4(1·9%)	2(0·9%)
Tumour size at baseline (cm)		
<3	69(33·0%)	81(37·3%)
>=3	133(63·6%)	129(59·4%)
Missing	7(3·3%)	7(3·2%)
Histological grade at baseline		
G1	17(8·1%)	16(7·4%)
G2	116(55·5%)	112(51·6%)
G3	72(34·4%)	86(39·6%)
Missing	4(1·9%)	3(1·4%)
Histological stage at baseline		
pTa	150(71·8%)	160(73·7%)
pT1	64(30·6%)	66(30·4%)

Carcinoma-in-situ		
Present	27(12·9%)	24(11·1%)
Absent	180(86·1%)	190(87·6%)
Missing	2(1·0%)	3(1·4%)
EORTC Risk Group (score)		
Low risk (0)	0	2(0·9%)
Intermediate risk (1-9)	184(88·0%)	190(87·6%)
High risk (10-17)	17(8·1%)	15(6·9%)
Not calculable	8(3·8%)	10(4·6%)
NICE Risk Group		
Low risk	10(4·8%)	8(3·7%)
Intermediate risk	100(47·8%)	96(44·2%)
High risk	96(45·9%)	107(49·3%)
Not calculable	3(1·4%)	6(2·8%)

Table 2 Primary and secondary efficacy outcomes

Outcomes	Effect estimates (95% CI); p-value
Recurrence of bladder cancer	
Intention to treat [b]	
Unadjusted	1·01 (0·75,1·36); 0·95
Adjusted for minimisation variables	0·95 (0·70,1·28); 0·73
Adjusted for pre-specified baseline variables [a]	0·94 (0·69,1·28); 0·70
Progression of bladder cancer[b]	
Unadjusted	1·64(0·80,3·38); 0·18
Adjusted for minimisation variables	1·63(0·79,3·37); 0·19
Adjusted for pre-specified baseline variables[a]	1·41(0·67,2·96); 0·37
Overall survival[b]	
Unadjusted	0·91(0·54,1·54); 0·73
Adjusted for minimisation variables	0·91(0·54,1·53); 0·72
Adjusted for pre-specified baseline variables[a]	0·83(0·49,1·41); 0·50
Bladder cancer specific death	Sub Hazard ratios (95% CI); p-value
Unadjusted	1.14(0.44, 2.91); 0.79
Adjusted for minimisation variables	1.13(0.46, 2.78); 0.78
Adjusted for pre-specified baseline variables[a]	0.92 (0.40, 2.14);0.85

[a] Adjusted for gender, centre, smoking status, risk group, presence/absence of CIS and grade of surgeon.
[b]Frailty model with centre as random effect, hazard ratio

Table 3 Safety data

	PDD N=209	White Light N=217
Clavien Dindo grade		
Clavien I	28	31
Clavien II	16	20
Clavien IIIa	2	3
Clavien IIIb	2	0
Clavien IVa	0	0
Clavien IVb	0	0
Clavien V	0	0
Number of participants	34 (16·3%)	31 (14·3%)
Serious adverse event		
Number of participants	12 (5·7%)	12 (5·5%)
Number of events	13	13
Event related to TURBT*	13	13
Expected events	13	13
Type of SAE[#]		
Prolongation of existing hospitalisation	6	2
Requires re-hospitalisation after medical discharge	6	11
Considered medically significant by the investigator	1	.
AEs[$] (CTCAE grade 3 or above)		
Number of participants who had AEs (CTCAE[£] Grade 3 and above)	3 (1·4%)	5 (2·3%)

***** Transurethral resection of bladder tumour (TURBT), [#] Serious adverse events (SAE), [$] Adverse events (AE), [£] Common Terminology Criteria for Adverse Events

Supplementary materials

Contents

1 Appendix 1: Within-Trial Cost-Effectiveness Analysis

1.1 Economic analysis

Intervention costs: The resources associated with the initial procedure included all the resources incurred until discharge. These data were collected prospectively for each participant. The operative details were recorded at the time of surgery (e.g. time in theatre, grade of operator) on the operation details case report form (CRF). Use of service (cost) incurred after the TURBT but before discharge were collected via the initial resection CRF and post-treatment participant questionnaire. These forms contained information on the length of hospital stay for the initial TURBT (based on admission and discharge dates), medical procedures and medical events that could occur during the treatment phase.

Non-intervention NHS costs: After participants were discharged, their resource use was captured using the health service utilisation questionnaire (HSUQ) completed by participants at three, six, 12, 18, 24, and 36 months.

The sources of unit costs were the British National Formulary and the NHS reference costs for secondary care resource-use data, and Personal and Social Services Research Unit (PSSRU) unit costs of health and social care for primary care resource-use data.[1-3] Price year for costs is 2018/19.

Quality-adjusted life years

Utility value data derived from the EQ-5D-3L. Following standard methods, assuming from the point of death a utility value of 0 was assigned. QALYs were calculated using area under curve approach.

Handling missing data

To account for missing data, multiple imputations were used to impute missing EQ-5D-3L utility values and cost values for individuals with data for baseline or at least one follow-up visit. Missing values of total follow-up cost and EQ-5D-3L utility values at each time point were imputed using predictive mean matching by treatment allocation group, accounting for the three closest estimates in terms of baseline EORTC recurrence risk group, age at randomisation, and sex.

Estimation of cost-effectiveness

Costs and QALYs for each year beyond the first year were discounted at a rate of 3.5% per annum. The total discounted costs and QALYs for each participant was then calculated by summing costs and QALYs over the trial follow-up period.

The primary cost-effectiveness analysis of the trial data was conducted under the missing at random (MAR) assumption. A seemingly unrelated regression (SUR) approach was used to simultaneously estimate total discounted costs at three years and total discounted QALYs at three years, allowing for the likely correlation of costs and effects.[4] For the QALY outcome variables, baseline EORTC recurrence risk group, age at randomisation, gender and baseline EQ-5D-3L utility value were included as covariates. For the cost outcome variables, baseline EORTC recurrence risk group was included as a covariate. Results are reported as incremental cost per QALY gained for PDD-TURBT relative to WLC-TURBT. Non-parametric bootstrapping methods was used to estimate 95% CIs for the incremental costs and QALYs, using 2000 repetitions.[5] This was presented as a cost-effectiveness plane and for cost-effectiveness as a cost-effectiveness acceptability curve (CEAC).[6]

Sensitivity analysis was used to explore alternative assumptions about missing data and variations to the discount rate used for costs and QALYs between from 0% to 6% per annum.

1.2 Results

Cost analysis

There was no evidence of differences between groups in terms of staff time and length of stay costs in the initial procedure. The additional equipment cost for PDD-TURBT is the cost of the photosensitiser (Hexvix), which results in the differences in total intervention costs between groups, £669 (95% CI: £31 to £1,308). Health care resource use per participant was broadly similar between groups throughout follow-up (Table A1.1).

EQ-5D scores and quality-adjusted life-years (QALYs)

Results for incremental QALYs gained are presented comparing PDD-TURBT with WL-TURBT for raw differences between QALY estimates. There was no evidence of differences in QALYs gained between treatment groups at three years (mean difference -0.096, 95%CI: -0.342 to 0.151).

Base case analysis

The upper section of Table A1.2 presents the results of the base-case analysis from an NHS and PSS perspective over the three-year time horizon. On average PDD-TURBT is more costly and less effective. Therefore, an incremental cost-effectiveness ratio (ICER) is not presented. Figure A1 illustrates the scatterplot of incremental costs and incremental QALYs for this analysis. It shows that there is substantial uncertainty in QALYs gained, but also that PDD-TURBT is more costly than WL-TURBT. The cost-effectiveness acceptability curve (CEAC, Figure A2) shows that PDD-TURBT has a 23% and 26% chance of being considered cost-effectiveness at threshold ICERs of £20,000 per QALY gained and £30,000 per QALY gained, respectively.

Sensitivity analysis

The results under the different missing data scenarios and the complete case analysis are reported in the lower section of Table A1.2. ***Error! Reference source not found.*** It shows that the alternative departures from MAR had little effect on the incremental costs and QALYs in these scenarios when MAR departures in total costs and HRQoL are assumed to be the same in each group. This will usually be the case when the missing data pattern is broadly similar across treatment groups, as the MNAR bias applies roughly equally to each group and cancels out in the treatment comparison. Our results were also consistent across alternative discount rates applied to costs and QALYs (see Table A1.3). The conclusions based on the net benefit statistics (at a threshold value of £30,000 per QALY gained) remained unchanged for the exploration of alternative discount rates.

1.3 Tables

Table S1.1: Average health-care costs by treatment group over 3 years

	Costs (£)								
	PDD-TURBT			WL-TURBT					
	n	mean	SD	n	mean	SD	Mean difference (95% CI)		p-value
Total NHS costs	**244**	**12,927**	**10,994**	249	**11,934**	**8,235**	**993**	**(-724 to 2,709)**	**0.0.256**
Intervention									
1st TURBT	244	3,850	4,153	249	3,185	2,964	665	(28 to 1,303)	0.041
2nd TURBT	78	89	53	79	77	51	11	(-5 to 28)	0.172
Total intervention costs	**244**	**3,879**	**4,157**	**249**	**3,210**	**2,967**	**669**	**(31 to 1,308)**	**0.040**
Follow up management (1 year)									
Secondary care	244	5,804	6,649	249	5,920	6,323	-116	(-1,264 to 1,032)	0.843
Primary care	244	116	195	249	114	228	2	(-36 to 40)	0.916
Follow up management (2-3 years)									
Secondary care	244	1,852	6,760	249	1,331	2,064	521	(-359 to 1,402)	0.245
Primary care	244	20	59	249	22	133	-3	(-21 to 15)	0.751
Total follow-up costs	**244**	**9,048**	**10,071**	249	**8,724**	**7,677**	**323**	**(-1,259 to 1,906)**	**0.688**

Table S1.2 Trial-based cost-effectiveness analysis results of PDD-TURBT vs. WL-TURBT (NHS/PSS perspective)

	Adjusted, mean (95% CI)						Incremental, mean (95% CI)							Probability that intervention is cost-effective for different threshold values for society's WTP for an additional QALY			
	Costs (£)			QALYs			Costs (£)			QALYs			ICER (£/QALY)	£0	£20,000	£30,000	£50,000
Base case																	
Imputed data analysis (3 years), MAR																	
WL-TURBT	12,005	(10,845 to	13,166)	2.094	(2.010 to	2.178)							WL-TURBT dominates PDD-TURBT	21%	23%	26%	30%
PDD-TURBT	12,881	(11,713 to	14,049)	2.087	(1.996 to	2.179)	876	-(766 to	2,518)	-0.007	-(0.133 to	0.119)					
Scenario analyses																	
Imputed data analysis (3 years), same MNAR parameters in both groups (-10% QoL)																	
WL-TURBT	12,005	(10,845 to	13,166)	1.956	(1.877 to	2.035)							WL-TURBT dominates PDD-TURBT	21%	21%	24%	27%
PDD-TURBT	12,881	(11,713 to	14,049)	1.948	(1.861 to	2.034)	876	-(766 to	2,518)	-0.008	-(0.127 to	0.110)					
Imputed data analysis (3 years), same MNAR parameters in both groups (+10% cost)																	
WL-TURBT	12,075	(10,899 to	13,251)	2.094	(2.010 to	2.178)							WL-TURBT dominates PDD-TURBT	21%	24%	27%	30%
PDD-TURBT	12,948	(11,765 to	14,132)	2.087	(1.996 to	2.179)	873	-(791 to	2,538)	-0.007	-(0.133 to	0.119)					
Imputed data analysis (3 years), different MNAR parameters in both groups (-10% QoL in WL-TURBT group)																	
WL-TURBT	12,005	(10,845 to	13,166)	1.956	(1.877 to	2.035)											
PDD-TURBT	12,881	(11,713 to	14,049)	2.087	(1.996 to	2.179)	876	-(766 to	2,518)	0.131	(0.009 to	0.254)	6,664	21%	85%	90%	93%
Complete case analysis (3 years)																	
WL-TURBT	12,265	(10,131 to	14,399)	2.146	(2.030 to	2.261)											
PDD-TURBT	15,089	(12,577 to	17,602)	2.168	(2.032 to	2.305)	3,236	-(081 to	6,554)	0.034	-(0.146 to	0.213)	95,606	2%	16%	26%	38%

MAR: missing at random; MNAR: missing not at random

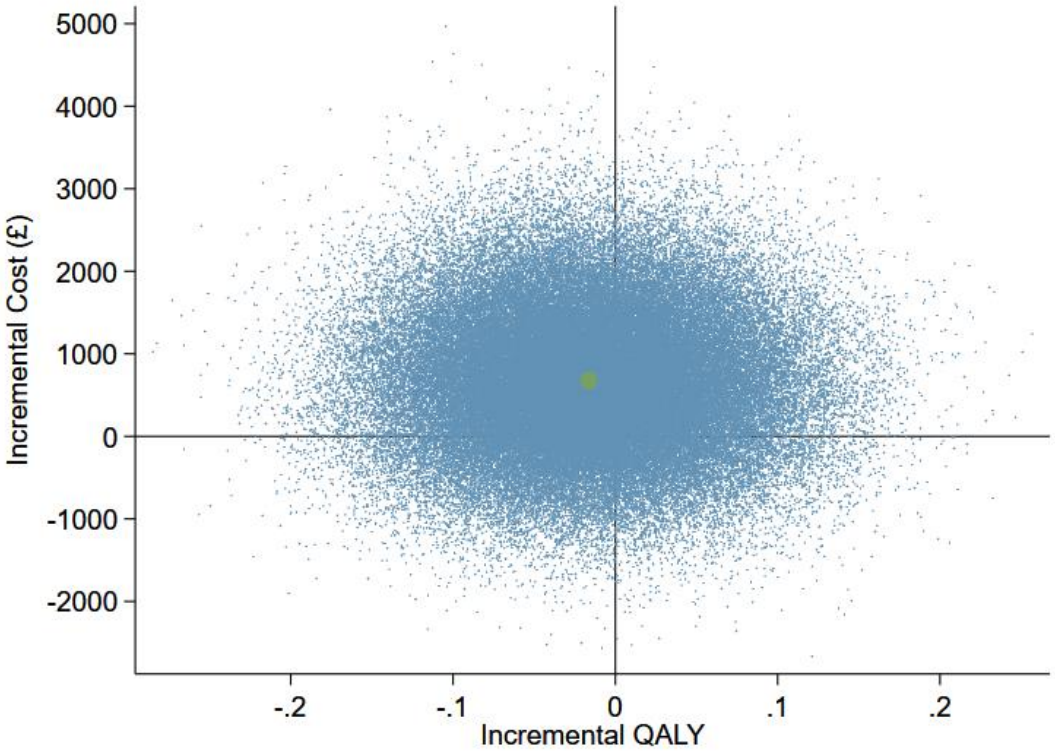
Table S1.3 Trial-based cost-effectiveness analysis results of PDD-TURBT vs. WL-TURBT with varying discount rates

	Adjusted, mean (95% CI)						Incremental, mean (95% CI)							Probability that intervention is cost-effective for different threshold values for society's WTP for an additional QALY			
	Costs (£)			QALYs			Costs (£)			QALYs			ICER (£/QALY)	£0	£20,000	£30,000	£50,000
Base case																	
Imputed data analysis (3 years), MAR, 3.5% discount rate																	
WL-TURBT	12,005	(10,845 to	13,166)	2.094	(2.010 to	2.178)							WL-TURBT dominates PDD-TURBT	21%	23%	26%	30%
PDD-TURBT	12,881	(11,713 to	14,049)	2.087	(1.996 to	2.179)	876	-(766 to	2,518)	-0.007	-(0.133 to	0.119)					
Scenario analyses																	
Imputed data analysis (3 years), MAR, 0% discount rate																	
WL-TURBT	12165	(10,975 to	13,356)	2.169	(2.083 to	2.255)							WL-TURBT dominates PDD-TURBT	21%	26%	29%	33%
PDD-TURBT	13055	(11,843 to	14,266)	2.168	(2.072 to	2.264)	889	-(787 to	2,566)	-0.001	-(0.130 to	0.127)					
Imputed data analysis (3 years), MAR, 6% discount rate																	
WL-TURBT	11,879	(10,739 to	13,019)	2.047	(1.969 to	2.126)							WL-TURBT dominates PDD-TURBT	20%	24%	27%	31%
PDD-TURBT	12,745	(11,603 to	13,887)	2.044	(1.958 to	2.131)	866	-(733 to	2,465)	-0.003	-(0.119 to	0.113)					

MAR: missing at random

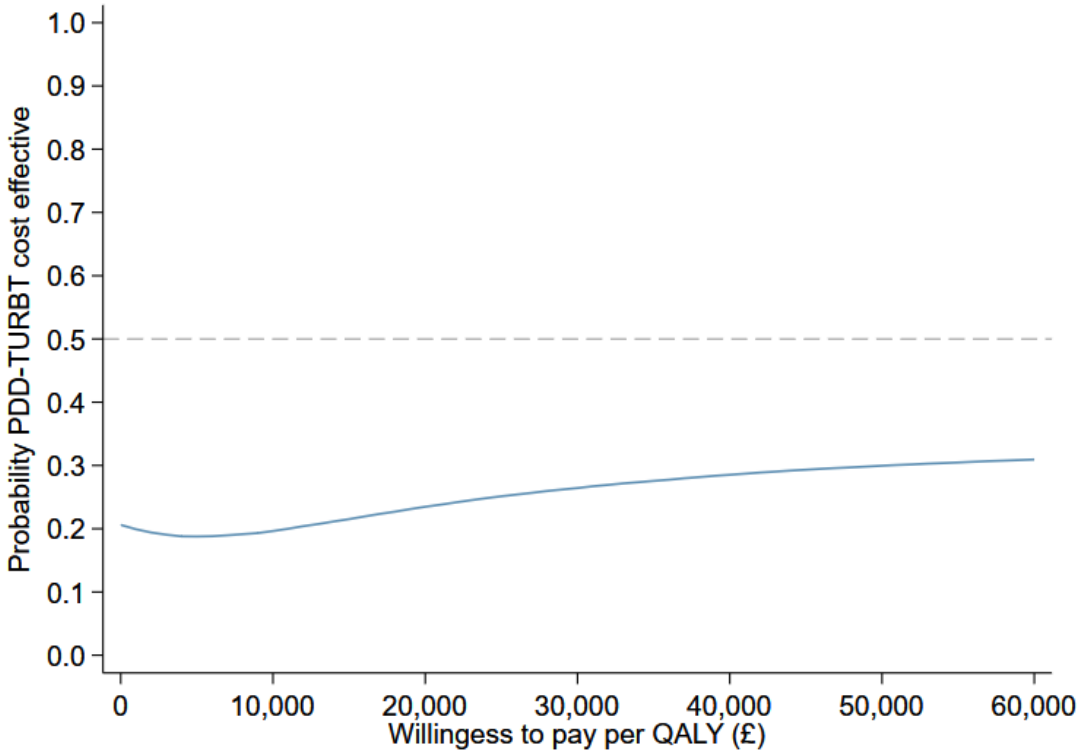
1.4 Figures

Figure S1.1 Scatterplot of incremental costs and QALYs for PDD-TURBT compared with WL-TURBT: base case



The estimated incremental cost-effectiveness ratio (ICER) fell in the northwest quadrant, with positive costs and negative effects, meaning that PDD-TURBT is more costly but less effective than WL-TURBT.

Figure S1.2 Cost-effectiveness acceptability curves: base case



1.5 References

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2 Appendix 2: PHOTO centres and recruitment

Table S2.1 PHOTO trial recruitment by centre

Centre	Principal Investigator	Total participants recruited
NHS Lothian	Mr Param Mariappan	84
Dartford and Gravesham NHS Trust	Professor Sanjeev Madaan	57
South Tees Hospitals NHS Foundation Trust	Miss Joanne Cresswell	53
Newcastle Hospitals NHS Foundation Trust	Mr Andrew Thorpe	52
Royal Devon and Exeter NHS Foundation Trust	Mr John McGrath	49
Leeds Teaching Hospitals NHS Trust	Mr Sunjay Jain	35
Oxford University Hospitals NHS Foundation Trust	Mr Jeremy Crew	30
Swansea Bay University Health Board	Mr Pradeep Bose	26
University Hospitals of North Midlands NHS Trust	Mr Lyndon Gommersall	24
Salisbury NHS Foundation Trust	Miss Melissa Davies	21
NHS Grampian	Mr Sarfraz Ahmad	20
Hull University Teaching Hospitals NHS Trust	Mr Matthew Simms	18
Imperial College Healthcare NHS Trust	Ms Norma Gibbons	12
University Hospitals of Derby and Burton NHS Foundation Trust	Mr Amjad Peracha	11
NHS Tayside	Professor Ghulam Nabi	10
University Hospital Southampton NHS Foundation Trust	Professor Bhaskar Somani	10
Ashford and St Peter's Hospitals NHS Foundation Trust	Mr Sachin Agrawal	8
East and North Hertfordshire NHS Trust	Mr Nikhil Vasdev	7
Hampshire Hospitals NHS Foundation Trust	Mr Hugh Mostafid	6
University College London Hospitals NHS Foundation Trust	Mr Mark Feneley	3
Cwm Taf Morgannwg University Health Board	Mr Rhidian Hurle	1
Royal Free London NHS Foundation Trust	Mr Paras Singh	1
NHS Greater Glasgow and Clyde	Mr Omar Aboumarzouk	0

3 Appendix 3: Additional statistical analyses

Table S3.1: Adjuvant therapy – Immediate post-operative mitomycin-C (MMC)

	Low Risk		Intermediate Risk		High Risk		Not calculable	
	PDD	**WL**	**PDD**	**WL**	**PDD**	**WL**	**PDD**	**WL**
	N=0	**N=2**	**N=184**	**N=190**	**N=17**	**N=15**	**N=8**	**N=10**
Administered			122/184(66.3%)	130/190(68.4%)	7/17(41.2%)	6/15(40.0%)	3/8(37.5%)	7/10(70.0%)
Not administered		2/2(100.0%)	57/184(31.0%)	56/190(29.5%)	10/17(58.8%)	9/15(60.0%)	3/8(37.5%)	1/10(10.0%)
Missing			5/184(2.7%)	4/190(2.1%)			2/8(25.0%)	2/10(20.0%)
Reason for not administering MMC								
Deep resection			24/57(42.1%)	28/56(50.0%)	5/10(50.0%)	4/9(44.4%)	1/3(33.3%)	1/1(100.0%)
Perforation			7/57(12.3%)	3/56(5.4%)	2/10(20.0%)	1/9(11.1%)		
Uncontrollable bleeding			1/57(1.8%)	1/56(1.8%)				
Irritation		1/2(50.0%)		1/56(1.8%)				
Physicians choice		1/2(50.0%)	14/57(24.6%)	15/56(26.8%)	3/10(30.0%)	3/9(33.3%)	1/3(33.3%)	
Other			7/57(12.3%)	6/56(10.7%)		1/9(11.1%)		
Missing			4/57(7.0%)	2/56(3.6%)			1/3(33.3%)	
Timing for MMC								
< 6 hours after TURBT			86/122(70.5%)	86/130(66.2%)	5/7(71.4%)	4/6(66.7%)	2/3(66.7%)	7/7(100.0%)
6-24 hours after TURBT			27/122(22.1%)	33/130(25.4%)	1/7(14.3%)	1/6(16.7%)		
>24 hours after TURBT			5/122(4.1%)	2/130(1.5%)	1/7(14.3%)		1/3(33.3%)	
Missing			4/122(3.3%)	9/130(6.9%)		1/6(16.7%)		

Table S3.2: Adjuvant therapy – for those who recurred and those who did not recur up to 36 months after operation

	Low Risk		Intermediate Risk		High Risk		Not calculable	
	PDD	**WL**	**PDD**	**WL**	**PDD**	**WL**	**PDD**	**WL**
	N=0	**N=2**	**N=184**	**N=190**	**N=17**	**N=15**	**N=8**	**N=10**
Adjuvant intravesical treatment in those who recurred								
BCG Induction			12/74(16.2%)	11/74(14.9%)	4/9(44.4%)	2/7(28.6%)	1/3(33.3%)	
BCG Induction and maintenance			11/74(14.9%)	5/74(6.8%)	2/9(22.2%)			
MMC weekly (6 weeks)			10/74(13.5%)	6/74(8.1%)		2/7(28.6%)		
None		1/1(100.0%)	33/74(44.6%)	45/74(60.8%)	2/9(22.2%)	2/7(28.6%)		1/2(50.0%)
Other			4/74(5.4%)	3/74(4.1%)	1/9(11.1%)	1/7(14.3%)	1/3(33.3%)	1/2(50.0%)
Missing			4/74(5.4%)	4/74(5.4%)			1/3(33.3%)	
Duration of BCG maintenance (months)								
12			1/23(4.3%)	1/16(6.3%)				
36				1/16(6.3%)				
Adjuvant intravesical treatment for those who did not have recurrence up to 36 months after operation								
BCG Induction			1/60(1.7%)	3/67(4.5%)		1/5(20.0%)		
BCG Induction and maintenance			16/60(26.7%)	27/67(40.3%)	3/4(75.0%)	2/5(40.0%)	1/2(50.0%)	1/2(50.0%)
MMC weekly (6 weeks)			14/60(23.3%)	11/67(16.4%)		2/5(40.0%)	1/2(50.0%)	
None			23/60(38.3%)	15/67(22.4%)				
Other			5/60(8.3%)	11/67(16.4%)	1/4(25.0%)			1/2(50.0%)
Missing			1/60(1.7%)					
Duration of BCG maintenance (months)								
12			1/17(5.9%)					
36			2/17(11.8%)	3/30(10.0%)				

Table S3.3: Sensitivity analysis for primary and secondary outcomes

Outcomes	**Effect estimates (95% CI); p-value**
Recurrence	
Per-protocol[b]	
Unadjusted	1·01 (0·74,1·37); 0·95
Adjusted for minimisation variables	0·95 (0·70,1·30); 0·76
Adjusted for pre-specified baseline variables [a]	0·97 (0·71,1·32); 0·82
Accelerated failure time[c]	
Adjusted for minimisation variables	1·10 (0·76,1·59); 0·61
Adjusted for pre-specified baseline variables [a]	1·12 (0·78,1·60); 0·55
Recurrence with death as competing risk	Sub hazard ratios (95%CI); p-value
Unadjusted	1·02 (0·75,1·38); 0·90

Adjusted for minimisation variables	1·02 (0·73,1·42); 0·91
Adjusted for pre-specified baseline variables[a]	1·00 (0·74,1·35); 0·99
Progression of bladder cancer	Effect estimates (95% CI); p-value
Accelerated failure time[d]	
Adjusted for minimisation variables	0·61(0·29,1·25); 0·18
Adjusted for pre-specified baseline variables[e]	0·69(0·33,1·46); 0·33
Overall survival	Effect estimates (95% CI); p-value
Accelerated failure time[c]	
Adjusted for minimisation variables	1·09(0·61,1·93); 0·77
Adjusted for pre-specified baseline variables[a]	1·19(0·70,2·02); 0·51

[a] Adjusted for gender, centre, smoking status, risk group, presence/absence of CIS and grade of surgeon.
[b]Frailty model with centre as random effect, hazard ratio
[c] Frailty model with centre as random effect, log-normal distribution, time ratio
[d] Frailty model with centre as random effect, exponential distribution, time ratio
[e] Adjusted for gender, centre, smoking status, presence/absence of CIS and grade of surgeon. Risk group was not included because model failed to converge.

Figure S3.1: Survival curves – Overall survival

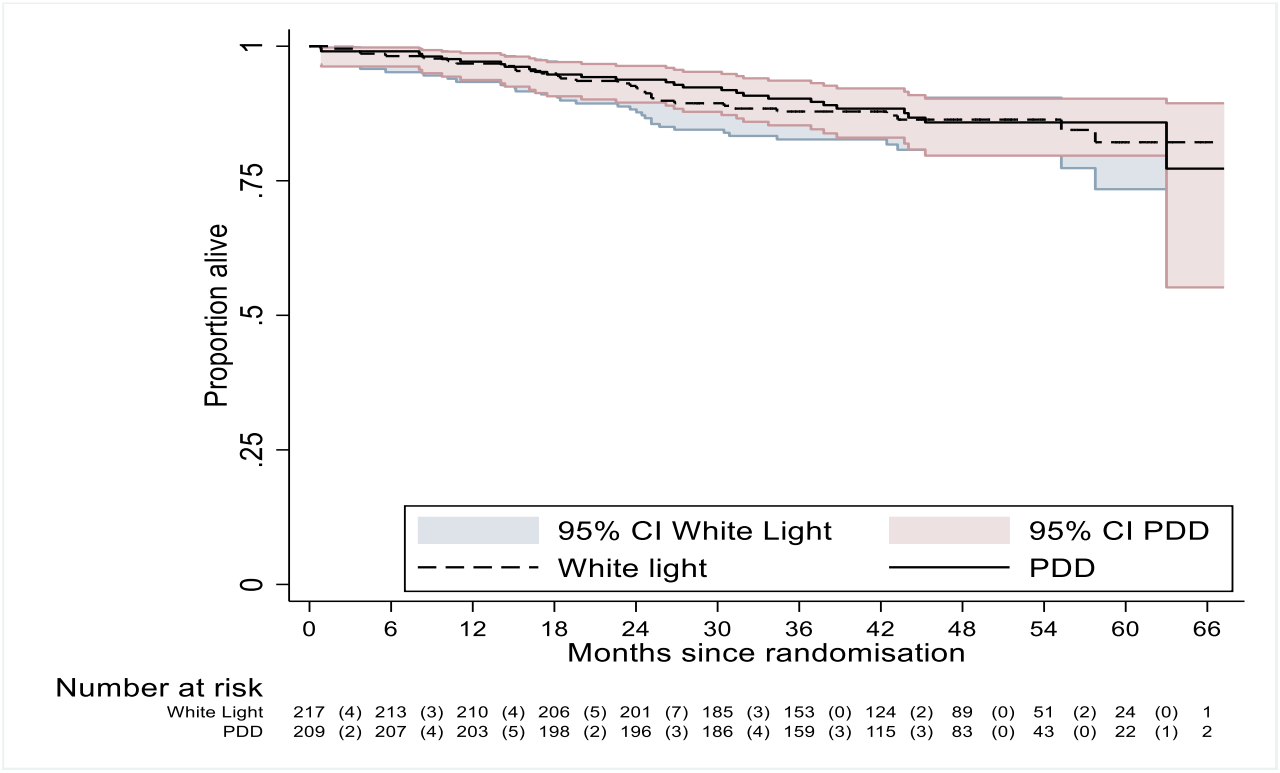

Figure S3.2: Survival curves – Progression free survival

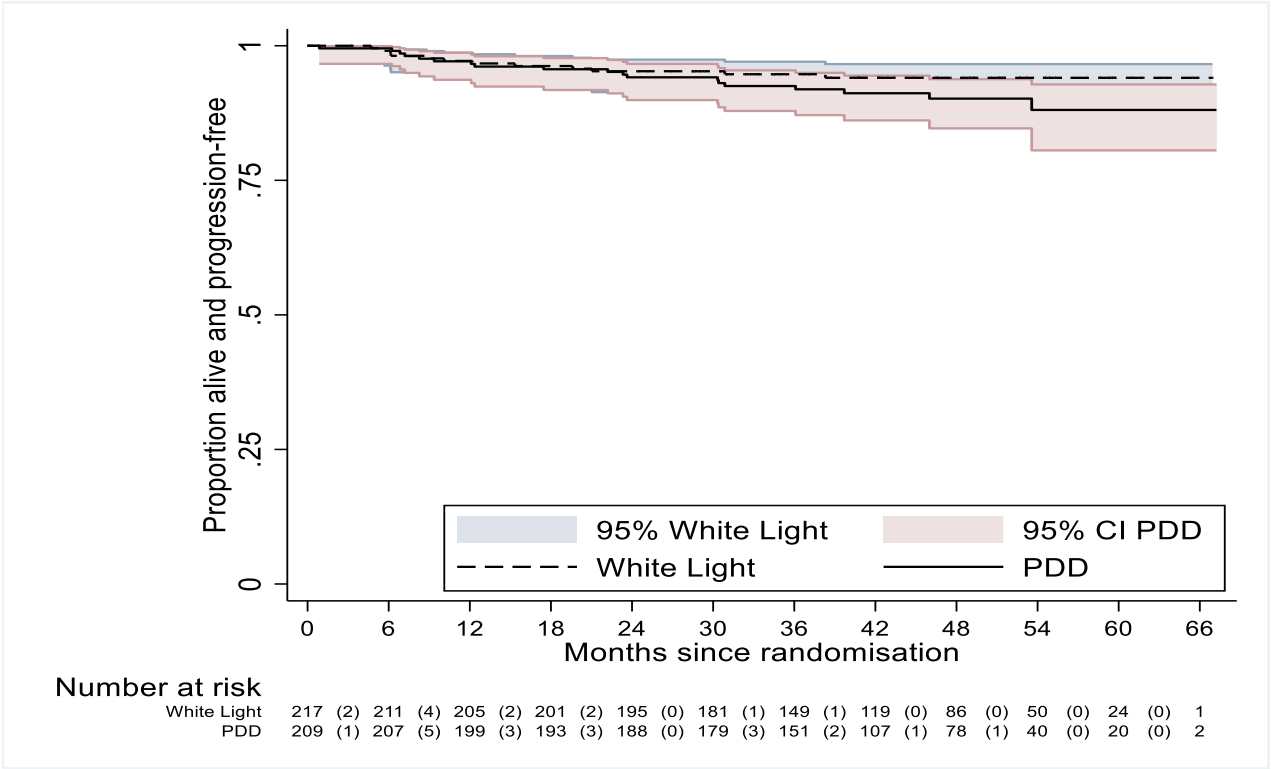

Table S3.4: Health related quality of life outcome – EQ-5D and EORTC QLQ-30

		PDD	White Light	Estimate (99% CI); p-value
		N=209	N=217	
EQ-5D	**Baseline**	0.834 (0.205); 187	0.838 (0.223); 188	
	PT	0.706 (0.265); 170	0.717 (0.279); 174	-0.000(-0.058, 0.058);0.995
	3 months	0.793 (0.242); 178	0.806 (0.226); 190	-0.005(-0.063, 0.054);0.842
	6 months	0.806 (0.237); 176	0.817 (0.223); 179	-0.001(-0.060, 0.057);0.950
	12 months	0.796 (0.263); 161	0.819 (0.243); 170	-0.018(-0.078, 0.042);0.449
	18 months	0.802 (0.242); 161	0.831 (0.219); 166	-0.019(-0.080, 0.041);0.412
	24 months	0.762 (0.284); 148	0.827 (0.241); 151	-0.064(-0.126, -0.001);0.009
	36 months	0.797 (0.251); 95	0.825 (0.238); 94	-0.013(-0.086, 0.061);0.660
EORTC QLQ-C30				
Functioning scales*				
Physical	**Baseline**	83.6(20.3);189	85.8(17.7);195	
	PT	76.0(24.5);167	78.6(23.2);177	0.3(-3.7, 4.4);0.829
	3 months	79.5(22.5);183	82.4(20.9);196	-1.3(-5.4, 2.7);0.390
	6 months	79.6(22.9);183	81.9(20.8);187	-1.1(-5.1, 3.0);0.495
	12 months	78.7(24.1);166	82.4(21.1);174	-2.1(-6.2, 2.1);0.203
	18 months	79.6(22.2);164	83.0(20.5);166	-2.1(-6.3, 2.2);0.209
	24 months	79.1(22.9);154	80.9(22.1);156	-0.9(-5.1, 3.4);0.609
	36 months	80.6(22.6);100	81.8(21.4);96	0.5(-4.6, 5.5);0.813
Role	**Baseline**	85.7(24.8);188	87.7(22.0);195	
	PT	75.0(31.3);171	74.5(32.4);178	2.5(-4.0, 9.1);0.320
	3 months	75.2(30.1);183	81.4(27.1);196	-4.4(-10.9, 2.1);0.084
	6 months	79.0(29.0);183	83.2(25.1);186	-2.5(-9.0, 4.1);0.337
	12 months	79.8(30.9);166	83.4(25.1);174	-1.9(-8.6, 4.9);0.473
	18 months	80.1(28.1);164	84.0(25.9);166	-2.2(-9.0, 4.7);0.415
	24 months	76.5(29.4);155	82.8(27.0);156	-5.0(-11.9, 2.0);0.066
	36 months	78.7(30.3);100	84.0(27.4);96	-2.7(-10.9, 5.6);0.404
Cognitive	**Baseline**	85.7(18.3);188	87.5(18.1);195	
	PT	82.2(20.3);173	84.4(20.3);181	-1.6(-6.1, 2.8);0.343
	3 months	82.1(20.4);185	84.8(19.0);198	-1.7(-6.1, 2.8);0.335
	6 months	81.4(22.1);184	84.5(17.3);189	-1.6(-6.1, 2.9);0.354
	12 months	83.4(19.4);166	82.5(19.7);174	2.2(-2.4, 6.8);0.214
	18 months	82.2(20.8);164	83.1(20.0);167	0.0(-4.6, 4.6);0.993
	24 months	80.8(20.1);154	80.4(22.8);157	2.0(-2.7, 6.7);0.278
	36 months	80.2(19.8);100	83.7(20.4);96	-1.0(-6.5, 4.5);0.630
Emotional	**Baseline**	80.4(20.8);186	81.5(19.2);192	
	PT	80.0(20.5);172	77.5(22.9);180	3.3(-1.2, 7.9);0.061
	3 months	81.8(20.7);185	80.5(20.8);196	2.3(-2.3, 6.8);0.195
	6 months	80.3(22.2);183	82.0(19.1);188	-0.5(-5.0, 4.1);0.790
	12 months	81.7(22.7);164	81.3(21.4);174	1.2(-3.5, 5.9);0.499
	18 months	84.0(22.4);164	82.1(21.7);166	2.5(-2.2, 7.2);0.173
	24 months	80.1(24.2);151	83.0(20.6);155	-1.8(-6.7, 3.1);0.341
	36 months	81.2(21.9);100	83.0(22.4);96	-0.4(-6.0, 5.3);0.872
Social	**Baseline**	87.0(22.0);186	88.6(21.2);193	
	PT	78.4(25.0);172	77.3(28.1);179	3.0(-3.1, 9.2);0.198
	3 months	79.9(25.7);185	83.3(23.9);197	-1.0(-7.0, 5.0);0.673
	6 months	81.0(27.4);182	83.6(24.8);189	-0.6(-6.6, 5.5);0.813

	12 months	82.2(27.5);164	85.4(22.8);174	-1.7(-7.9, 4.6);0.492
	18 months	82.2(25.4);164	84.6(24.9);166	-1.4(-7.7, 4.9);0.577
	24 months	81.8(26.4);151	84.9(25.6);155	-2.1(-8.6, 4.4);0.412
	36 months	83.0(25.3);100	86.6(22.9);96	-2.4(-10.0, 5.3);0.423
Global QoL	**Baseline**	73.7(19.0);186	73.8(20.4);193	
	PT	68.9(21.3);172	67.9(21.1);180	1.8(-2.5, 6.1);0.276
	3 months	71.8(18.7);185	71.2(19.4);196	0.7(-3.6, 4.9);0.685
	6 months	74.0(20.2);183	72.9(18.6);189	0.8(-3.5, 5.1);0.634
	12 months	72.5(19.3);164	74.0(20.0);174	-1.0(-5.4, 3.4);0.546
	18 months	73.7(19.2);165	73.7(20.3);166	-0.2(-4.6, 4.2);0.900
	24 months	70.9(20.3);152	72.5(20.3);156	-0.7(-5.2, 3.9);0.704
	36 months	73.4(19.3);100	76.2(19.2);96	-2.3(-7.6, 3.0);0.265
Symptom scales and/or items+				
Fatigue	**Baseline**	21.7(22.9);187	19.4(20.3);195	
	PT	28.7(25.0);172	27.3(24.9);180	-1.8(-7.0, 3.3);0.361
	3 months	27.4(24.5);184	26.6(23.8);197	-1.0(-6.1, 4.1);0.616
	6 months	27.9(25.0);182	26.8(23.8);187	-0.7(-5.9, 4.5);0.733
	12 months	27.4(25.8);166	25.2(23.4);174	-0.4(-5.8, 4.9);0.831
	18 months	25.5(23.6);164	25.0(24.2);166	-0.9(-6.3, 4.4);0.659
	24 months	27.5(24.3);153	25.9(24.8);156	-0.2(-5.7, 5.3);0.928
	36 months	25.3(22.7);100	24.2(21.3);96	-0.5(-7.0, 5.9);0.827
Nausea and	**Baseline**	3.9(12.0);187	3.2(9.3);195	
Vomiting	**PT**	5.0(13.0);172	5.2(12.9);180	-0.8(-4.0, 2.3);0.494
	3 months	4.5(12.0);184	4.8(13.1);198	-0.8(-3.9, 2.3);0.494
	6 months	5.4(12.3);182	3.9(11.7);187	0.1(-3.1, 3.2);0.952
	12 months	4.9(13.8);165	3.4(10.5);174	-0.3(-3.5, 2.9);0.805
	18 months	4.9(12.2);164	4.8(13.7);166	-1.6(-4.9, 1.7);0.209
	24 months	5.7(13.1);154	5.9(16.9);156	-1.7(-5.0, 1.7);0.204
	36 months	6.0(15.6);100	3.3(10.2);96	0.1(-4.0, 4.1);0.962
Pain	**Baseline**	18.7(25.2);189	17.4(25.2);195	
	PT	26.4(29.7);172	23.2(27.1);180	1.4(-4.4, 7.3);0.523
	3 months	21.9(27.6);184	18.9(25.5);198	1.3(-4.5, 7.0);0.569
	6 months	19.8(25.2);183	16.7(23.4);187	1.8(-4.0, 7.6);0.428
	12 months	21.6(28.0);166	15.8(25.0);174	3.9(-2.1, 9.9);0.090
	18 months	21.2(26.1);164	16.4(24.1);166	3.1(-2.9, 9.2);0.186
	24 months	22.3(27.2);154	16.6(24.9);156	4.1(-2.1, 10.3);0.088
	36 months	23.5(27.0);100	14.1(23.7);96	6.1(-1.2, 13.5);0.031
Dyspnoea	**Baseline**	14.3(22.9);187	14.0(21.6);195	
	PT	14.3(24.5);170	12.8(22.5);177	0.9(-4.7, 6.5);0.667
	3 months	17.8(26.5);184	17.7(25.5);198	-1.0(-6.6, 4.5);0.635
	6 months	18.7(27.9);182	18.4(26.1);187	-0.8(-6.4, 4.8);0.704
	12 months	17.7(26.5);164	17.4(26.0);174	-0.9(-6.7, 4.8);0.681
	18 months	17.1(26.1);162	17.8(25.4);165	-3.1(-8.9, 2.7);0.169
	24 months	18.6(26.7);154	18.2(26.1);156	-1.6(-7.5, 4.3);0.479
	36 months	17.2(26.7);99	17.7(24.6);96	-2.7(-9.6, 4.2);0.307
Sleep disturbance	**Baseline**	22.0(29.5);188	23.1(27.2);195	
	PT	28.3(30.7);171	28.9(29.9);181	1.5(-5.6, 8.6);0.592
	3 months	29.3(31.2);183	26.0(30.0);195	3.9(-3.1, 11.0);0.153
	6 months	29.3(32.0);183	25.3(27.5);187	4.6(-2.5, 11.7);0.098
	12 months	27.6(31.1);163	23.3(27.9);173	4.2(-3.1, 11.6);0.140

	18 months	26.2(28.1);164	22.6(28.5);165	2.9(-4.5, 10.3);0.309
	24 months	29.2(30.7);155	26.9(29.8);156	2.7(-4.9, 10.3);0.358
	36 months	29.0(30.6);100	25.3(29.9);95	3.7(-5.3, 12.7);0.292
Appetite loss	**Baseline**	12.1(23.6);187	8.7(20.0);195	
	PT	15.7(24.3);172	12.0(20.7);181	1.6(-3.7, 7.0);0.425
	3 months	11.7(22.9);183	9.8(21.9);198	0.7(-4.6, 5.9);0.750
	6 months	12.3(21.9);182	8.4(19.1);187	2.5(-2.8, 7.8);0.228
	12 months	11.4(22.5);166	9.8(21.8);174	-0.3(-5.8, 5.2);0.892
	18 months	10.5(20.2);162	10.4(22.9);166	-0.9(-6.5, 4.6);0.665
	24 months	14.5(23.2);154	10.6(22.1);154	1.6(-4.1, 7.3);0.478
	36 months	11.0(20.7);100	9.4(19.2);96	-1.1(-7.9, 5.7);0.682
Constipation	**Baseline**	12.7(23.4);187	8.7(19.4);195	
	PT	18.1(27.3);171	18.2(26.2);179	-2.6(-8.6, 3.5);0.275
	3 months	16.0(25.0);181	15.5(23.7);198	-2.1(-8.1, 3.9);0.362
	6 months	16.4(24.5);181	12.4(20.1);186	1.3(-4.7, 7.4);0.573
	12 months	16.4(25.7);165	13.9(24.4);173	-0.0(-6.3, 6.2);0.984
	18 months	15.7(23.5);163	16.6(24.6);165	-2.8(-9.1, 3.5);0.253
	24 months	13.7(23.5);151	14.7(22.8);156	-2.5(-8.9, 3.9);0.316
	36 months	13.8(23.3);99	7.4(17.0);95	3.0(-4.7, 10.7);0.315
Diarrhoea	**Baseline**	7.1(18.6);184	5.2(14.7);194	
	PT	5.6(15.7);173	5.4(15.4);180	-2.0(-6.4, 2.4);0.240
	3 months	6.3(16.0);181	6.4(17.3);197	-1.1(-5.4, 3.3);0.526
	6 months	6.8(17.4);182	6.6(15.8);186	-0.6(-5.0, 3.8);0.721
	12 months	9.1(18.2);165	7.1(17.8);174	1.3(-3.2, 5.9);0.444
	18 months	7.7(18.0);160	6.6(16.1);166	0.7(-3.9, 5.3);0.707
	24 months	7.8(20.2);150	6.9(17.3);154	0.8(-3.9, 5.5);0.660
	36 months	10.8(22.8);99	5.2(12.2);96	2.7(-3.0, 8.5);0.218
Financial	**Baseline**	4.5(15.5);185	4.3(14.0);193	
difficulties	**PT**	6.8(19.4);171	5.8(15.8);178	0.7(-3.7, 5.2);0.663
	3 months	7.4(20.9);184	7.0(20.9);196	0.4(-4.0, 4.7);0.833
	6 months	8.3(21.7);180	6.6(18.5);188	2.2(-2.2, 6.6);0.201
	12 months	6.5(17.7);163	6.2(17.7);172	-1.4(-5.9, 3.1);0.426
	18 months	6.3(20.1);164	6.2(18.6);166	-0.4(-5.0, 4.1);0.808
	24 months	5.8(19.6);150	6.2(18.9);156	-1.6(-6.2, 3.1);0.390
	36 months	6.7(18.3);100	4.9(16.7);96	0.7(-4.8, 6.2);0.732

Figure S3.3: EQ-5D and NMIBC24 score at each timepoint

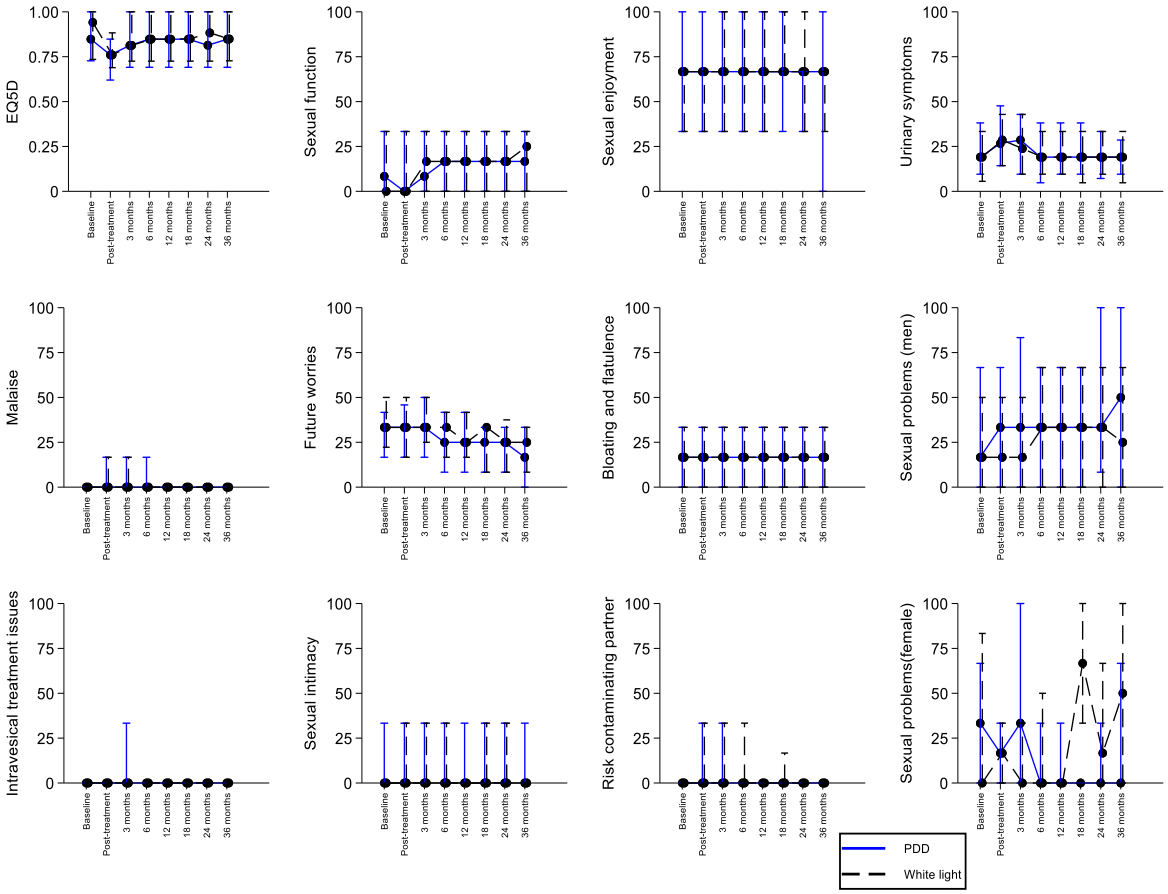

Figure S3.4: EORTC QLQ-30 score at each timepoint