Photodynamic versus white-light-guided resection of first-diagnosis non-muscle-invasive bladder cancer: PHOTO RCT

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Scientific summary

The PHOTO RCT

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Scientific summary

Background

Around 7500 people are diagnosed with non-muscle-invasive bladder cancer (NMIBC) in the UK each year. Recurrence is common following treatment with transurethral resection of bladder tumour (TURBT), and the intensive monitoring schedule required after initial treatment has associated costs for the patient and the NHS. Recurrence is thought to be partially related to incomplete resection of the tumour. Photodynamic diagnosis (PDD) involves the intravesical instillation of a photosensitiser, which is preferentially absorbed by cancerous cells and causes the tumour to fluoresce under blue light, helping to guide TURBT. This technique offers better diagnostic accuracy and, therefore, may reduce the chance of subsequent recurrence.

Objectives

To compare the clinical effectiveness and cost-effectiveness of PDD resection with conventional white-light-guided transurethral resection of bladder tumour (WL-TURBT) for patients with newly diagnosed NMIBC who are at intermediate or high risk of recurrence.

Methods

Design

The Photodynamic versus white-light-guided resection of first diagnosis non-muscle-invasive bladder cancer (PHOTO) trial was a multicentre, pragmatic, open-label, parallel-group, non-masked, superiority randomised controlled trial that recruited from 22 NHS hospitals. Patients aged > 16 years with a first suspected diagnosis of intermediate- to high-risk NMIBC were invited to participate. Patients were excluded if they met any of the following exclusion criteria: visual evidence of low-risk NMIBC (solitary tumour < 3 cm in diameter) or muscle-invasive bladder cancer (MIBC) on preliminary cystoscopy; imaging evidence of MIBC (including the presence of hydronephrosis); upper tract (kidney or ureteric) tumours on imaging; any other malignancy in the past 2 years [except (for patients who have a life-expectancy of > 5 years at trial entry) non-melanomatous skin cancer cured by excision, adequately treated carcinoma in situ of the cervix, ductal carcinoma in situ (DCIS)/lobular carcinoma in situ (LCIS) of the breast, or prostate cancer]; evidence of metastases; porphyria or known hypersensitivity to porphyrins; known pregnancy; any other contraindications to PDD or white-light (WL) surgery; and inability to provide informed consent or complete follow-up schedule [including health-related quality of life (HRQoL) questionnaires].

Interventions and randomisation

Eligible and consenting patients were allocated to receive either photodynamic diagnosis-guided transurethral resection of bladder tumour (PDD-TURBT) (i.e. the PDD group) or standard WL-TURBT (i.e. the WL group). All participants, unless there were clinical contraindications, received intravesical mitomycin C (40 mg in 40 ml of saline) after surgery and before discharge.

Treatment allocation used a 1 : 1 ratio and was conducted centrally by a remote web-based service, using a minimisation algorithm balanced by centre and sex.

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Main outcome measures

Primary outcome

The primary outcome was time to recurrence of bladder cancer measured in months from randomisation to recurrence, including recurrence associated with progression to MIBC, cystectomy or death due to bladder cancer. The principal time point of interest was 3 years.

The primary health economic outcomes were cost-effectiveness, as determined by the incremental cost per recurrence avoided, and cost–utility, measured as the incremental cost per quality-adjusted life-year (QALY) gained at 3 years.

Secondary outcomes

Other clinical outcomes included adverse events (AEs) and complications up to 3 months from initial TURBT treatment. Direct, surgically related, postoperative events occurring within the 30 days following TURBT were assessed using the Clavien–Dindo classification for surgical complications [Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–13]. Events occurring up to 3 months after TURBT were assessed and recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 framework [National Cancer Institute. *CTCAEs* v4: *Common Terminology Criteria for Adverse Events* (*CTCAE*). Rockville, MD: National Cancer Institute; 2010. URL: https://ctep.cancer.gov/]. The relative changes in HRQoL resulting from the physical and psychological benefits, together with any harms associated with each strategy and subsequent necessary cancer treatment, were measured using the generic EuroQol-5 Dimensions, three-level version (EQ-5D-3L), questionnaire; the cancer-specific European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30 (EORTC-QLQ-C30); and the disease-specific European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Non-Muscle Invasive Bladder Cancer – 24 items (EORTC-QLQ-NMIBC-24). These were completed by the participant on paper at baseline (prior to knowledge of treatment allocation), following surgery and at 3, 6, 12, 18, 24 and 36 months after randomisation. Disease progression was defined as an increase in stage to MIBC or the development of nodal or metastatic disease. Rates of overall survival and bladder-cancer-specific survival were compared between the two treatment groups. Other cost-effectiveness outcomes included estimation of the incremental cost per recurrence avoided using the economic model over the patient's lifetime and estimation of the incremental cost per QALY gained using the economic model over the patient's lifetime.

Blinding

Surgeons and participants could not be blinded to the allocated procedure.

Sample size

The trial aimed to detect an absolute reduction in recurrence at 3 years of 12%, from 40% (under the conservative assumption that all the patients recruited are intermediate-risk patients with a probability of recurrence of 0.4 at 3 years) to 28% (similar effect sizes of photodynamic therapy are reported in both intermediate- and high-risk groups); this is equivalent to a relative reduction of 30%. Power calculations were based on log-rank analysis of time-to-event data, translating an improvement in fixed-time point recurrence-free rate from 60% to 72% into a target effect size hazard ratio (HR) of 0.64. The recruitment of 533 participants (214 recurrences) would enable the detection of a HR of 0.64 between the experimental and control strategies and provide, using the log-rank test, 90% power at a two-sided 5% significance level. This calculation assumed 2.5 years of staggered recruitment (with 6%, 13%, 21%, 29% and 31% of the total number of patients recruited in each successive 6-month period); a minimum of 3 years' follow-up; and cumulative follow-up attrition rates of 0.56% by the end of year 1, 1% at the end of year 2 and 6.4% at end of year 3, based on unpublished data from the Bladder cyclooxygenase 2 Inhibition Trial (BOXIT) (Professor Emma Hall, Insititute of Cancer Research, 2012, personal communication).

Statistical analysis

The primary outcome was analysed using Cox proportional hazards regression models in which deaths were treated as censored. Additional analysis used accelerated failure time models, relaxing the proportional hazards assumption. A sensitivity analysis of the primary outcome treating deaths from non-bladder-cancer causes as a competing risk, rather than non-informative censoring, was performed. Secondary outcomes were analysed using the appropriate generalised linear models. The proportion of participants experiencing AEs (CTCAE grade 3 or above) was compared between groups using chi-squared tests or Fisher's exact test if expected cell frequencies were less than five. The number of AEs by Clavien–Dindo grade was tabulated by group.

Economic evaluation

At 3 years, the mean differences in costs to the NHS Personal Social Services and QALYs were estimated. QALYs were based on self-reported responses to the EQ-5D-3L administered at baseline and discharge, and sent by post at 3, 6, 12, 18, 24 and 36 months post randomisation. Cost-effectiveness was expressed as an incremental cost per QALY gained, and the net monetary benefit approach was used to identify the optimal treatment when the value of a QALY to society was £30,000. Estimates of cost-effectiveness were extrapolated to a lifetime using a microsimulation model. Sensitivity analysis explored the imprecision in estimates of costs and QALYs, as well as costs falling on participants and their families, wider societal costs, alternative ways to handle missing data and the impact of changing the discount rate.

Results

Recruitment

Between 11 November 2014 and 6 February 2018, 538 participants were randomised. Five participants were excluded as they were found to be ineligible following randomisation (four because of signs of MIBC or upper tract involvement on subsequent imaging and one for an unknown reason). After the initial TURBT, 29 participants were found to have no histological evidence of tumour, 60 had MIBC and 18 had an early cystectomy. These 107 participants were excluded from further analysis. There were 426 participants (209 in the PDD group and 217 in the WL group) in the final analysis population.

Baseline and treatment received

The groups were well balanced at baseline: the mean age was 70, 80% were men and > 80% of participants in each group were classified as being at intermediate risk. Two participants in each group did not receive surgery. All participants in the WL group received WL-TURBT; in the PDD group, 13 (6.3%) received WL-TURBT.

Primary outcome

The median follow-up time was 21 months for PDD and 22 months for WL group. Overall, there were 86 recurrences of bladder cancer in the PDD group and 84 in the WL group. The intention-to-treat (ITT) analysis of the primary outcome estimated a HR of 0.94 [95% confidence interval (CI) 0.69 to 1.28; $p = 0.70$]. The prespecified important difference, HR 0.64, was incompatible with the data. Relaxing the proportional hazards assumption using an accelerated failure time model based on log-normal distribution showed no evidence that the time ratio (TR) for trial participants differed between groups (TR 1.12, 95% CI 0.78 to 1.60; $p = 0.550$). The 3-year recurrence-free survival rates were 57.8% (95% CI 50.7% to 64.2%) in the PDD group and 61.6% (95% CI 54.7% to 67.8%) in the WL group, with an absolute difference of 3.8% (95% CI −5.59% to 13.37%).

Secondary outcomes

There were 19 bladder cancer progressions in the PDD group and 12 in the WL group (HR 1.41, 95% CI 0.67 to 2.96; $p = 0.369$). There were 16 deaths due to bladder cancer: eight in each group. There was no evidence that bladder-cancer-specific survival differed between the PDD and WL groups (subhazard ratio 0.80, 95% CI 0.37 to 1.72; $p = 0.56$).

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There were 57 deaths: 27 in the PDD group and 30 in the WL group. Of the 57 participants who died, 16 (28.1%) died from bladder cancer, nine (15.8%) from cardiovascular events, nine (15.8%) from other cancers and 23 (40.4%) died of other causes. There was no difference in overall survival between the PDD and WL groups (HR 0.83, 95% CI 0.49 to 1.41; $p = 0.496$). At 36 months, the mean score difference between the groups in EQ-5D-3L, was −0.013 (99% CI −0.086 to 0.061; $p = 0.660$).

All the domains of the EORTC-QLQ-C30 and EORTC-QLQ-NMIBC-24 were similar over time. At 36 months, there was no evidence of a difference between the PDD and WL groups across all domains.

Eight participants had AEs (CTCAE grade 3 and above). There was no significant difference between the groups in the number of participants who experienced an AE: the number of participants who experienced an AE (CTCAE grade 3 and above) was 3 (1.4%) in the PDD group and 5 (2.3%) in the WL group [rate ratio (RR) 0.62, 95% CI 0.24 to 1.60; $p = 0.33$].

Economic evaluation

At 3 years, on average, the total cost of PDD-TURBT was £12,881 per participant and the total cost of WL-TURBT was £12,005 per participant. There was no evidence of a statistically significant difference between the groups in the total NHS cost or the use of health services at 3 years. The incremental total NHS cost of PDD-TURBT compared with WL-TURBT was £876 (95% CI −£766 to £2518). Widening the perspective of costs to include those falling on participants and families and wider societal costs reduced the incremental cost to £763 (95% CI £1048 to £2574), although there were no differences between treatment groups.

The average QALY gain at 3 years was 2.094 in the PDD group and 2.087 in the WL group (mean difference −0.007, 95% CI −0.133 to 0.119). The probability of PDD-TURBT being considered cost-effective never exceeded 30% over the range of society's cost-effectiveness thresholds for a QALY considered from either an NHS/Personal Social Services perspective or a wider economic perspective. The results did not alter over the range of sensitivity analyses considered, except when it was assumed that the patient's quality of life (QoL) for WL was 10% lower than the value for QoL used in the missing at random setting.

Conclusions

The PHOTO trial found no evidence of an improvement in clinical effectiveness associated with PDD. The cost-effective analysis demonstrated that PDD was not more cost-effective than WL at 3 years. Overall, the use of PDD-TURBT is not supported in the management of primary intermediate- to high-risk NMIBC.

Future work

Further work should include modelling appropriate surveillance schedules and exploring predictive and prognostic biomarkers.

Trial registration

This trial is registered as ISRCTN84013636.

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