Intravesical Bacillus Calmette-Guérin versus radical cystectomy in high-risk non-muscle-invasive bladder cancer: a cost-utility analysis

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Background

- Approximately two-thirds to three-quarters of bladder cancer (BC) cases present as non-muscle-invasive BC (NMIBC) [1]. NMIBC can be further classified into low-, intermediate-, high-, or very high-risk disease [2].
- Patients classified as having high-risk NMIBC under the European Association of Urology risk stratification system, are usually treated with either intravesical Bacillus Calmette-Guérin (BCG), but immediate radical cystectomy (RC) can also be considered.
- Although it is a frequently used treatment option [2,3,4], the evidence base supporting intravesical BCG is often inconsistent, and of a mixed quality.
- Differences in treatment schedules, high discontinuation rates, and suboptimal transurethral resection of bladder tumour (TURBT) before BCG use make it difficult to identify the causes behind failures of BCG therapy.
- Definitions for "adequate" BCG therapy have recently been outlined [5,6], and adequate BCG therapy has been shown to have excellent real-world outcomes [7]. However, these definitions are too recent to have found widespread use in the literature.
- Given the challenges concerning the evidence base for BCG and an ongoing worldwide shortage of BCG, demonstrating the value of BCG is crucial for healthcare payers and decision-makers.

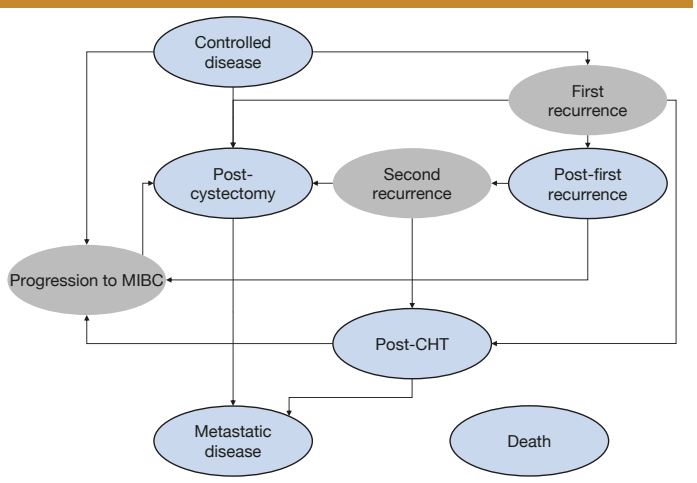
Objectives

The aim of the present study was to develop a cost-utility model for the evaluation of the clinical, cost, and quality of life effects of adequate BCG therapy in the treatment of high-risk NMIBC.

Methods

- An English National Health Service (NHS) perspective was adopted for our analysis.
- A six-state Markov model was developed covering controlled disease, post-cystectomy, post-first recurrence, post-chemohyperthermia, metastatic disease, and death (Figure 1).
- BCG-medac, over a 3-year time horizon and at full dose, was the intervention of interest. Immediate RC was the comparator. Chemohyperthermia served as a treatment option for patients unwilling to undergo RC.
- The model incorporated three "tunnel" states: first recurrence, second recurrence, and progression to muscle-invasive BC.
- Drug costs were obtained from the British National Formulary, while costs of RC were obtained from the National Tariff Payment System [8]. For BCG-medac, a per-vial cost of GBP 150 was assumed. Utilities and dis-utilities were obtained primarily from the BOXIT trial [9].
- Analyses were run over a 30-year time horizon, with future costs and effects discounted at 3.5% per annum. Net monetary benefit (NMB) was calculated using willingness-to-pay (WTP) thresholds of GBP 20,000 and 30,000 per QALY gained, respectively.
- One-way and probabilistic sensitivity analyses (PSA) were performed to evaluate the robustness of the model and the base-case results.

Figure 1 Markov model schematic



Note: Regular Markov states are coloured in blue and tunnel states in grey. The "Death" state is accessible from every other state in the model and is itself an absorbing state.
Abbreviations: CHT, chemohyperthermia; MIBC, muscle-invasive bladder cancer.

Results: Base case

- The base case results are summarised in Table 1. The analysis comparing BCG with RC showed that BCG would result in an increase in life expectancy of 0.29 life years (LYs) versus RC, from 8.48 to 8.77 LYs.
- Patients treated with BCG incurred lower costs than those treated with RC, with costs decreasing from GBP 81,158 to GBP 66,201 over patient lifetimes. Cost savings were driven by the lower cost of BCG versus RC, reductions in costs of chemotherapy for metastatic disease, and neoadjuvant chemotherapy.
- BCG also resulted in an increase of 0.42 quality-adjusted life years (QALYs) versus RC, from 6.13 to 6.65 QALYs. This in turn yielded an NMB of GBP 23,274 for a WTP threshold of GBP 20,000 and of GBP 27,432 for a WTP of GBP 30,000 per QALY gained
- Based on these results, BCG was the dominant intervention, improving QALYs and reducing costs when compared to RC.

Table 1 Base case results

Intervention	Life expectancy (years)	QALE (QALYs)	Cost (GBP)	ICUR (GBP) per QALY gained	NMB (GBP)
RC	8.48	6.13	81,158		
BCG	8.77	6.55	66,201	BCG more effective, less costly than RC	23,274
Incremental	**0.29**	**0.42**	**-14,958**		

Abbreviations: BCG, Bacillus Calmette-Guérin; GBP, pounds sterling; ICUR, incremental cost-utility ratio; NMB, net monetary benefit; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life years; RC, radical cystectomy.

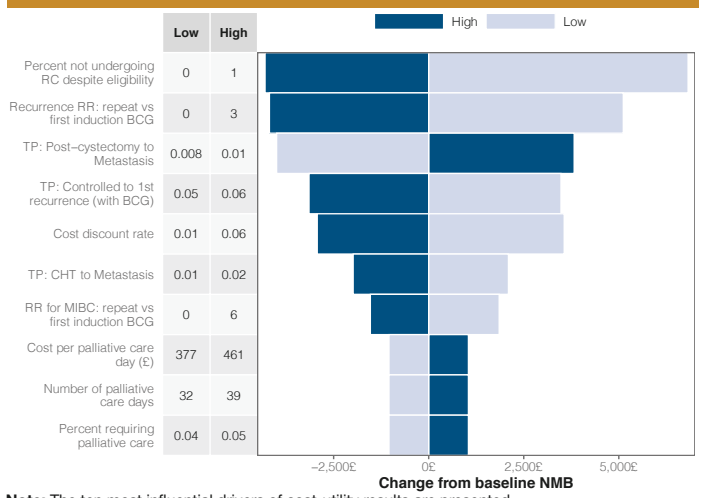
Results: One-way sensitivity analyses

- For the one-way sensitivity analyses (OWSA), the ten parameters with the largest comparative impact on the final NMB are presented in Figure 2.
- The proportion of patients not undergoing RC despite their eligibility was associated with the greatest variation in NMB compared to the base case results.
- When all patients eligible for RC did not receive the procedure, the final NMB decreased by over GBP 4,000.
- When all patients eligible for RC did receive the procedure, the final NMB increased by over GBP 6,000, for a WTP threshold of GBP 20,000 per QALY gained.
- The corresponding estimates for a WTP threshold of GBP 30,000 per QALY gained were a decrease by GBP 6,090 and an increase by GBP 9,666, respectively.
- Notably, the cost of BCG vials was not among the ten parameters that had the most impact on NMB.
- Shorter maintenance periods with BCG, of 12, 18, 24 months, and 30 months, were also associated with increased cost savings relative to RC versus the base case.

Results: Probabilistic sensitivity analyses

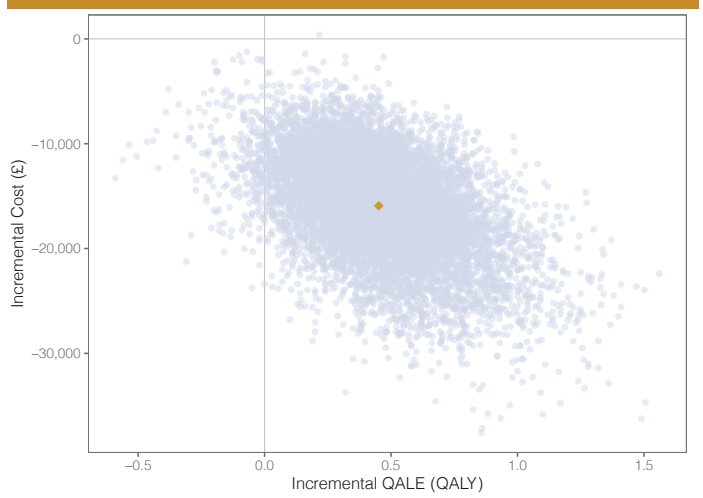
- For the PSA, key model parameters were sampled during the analysis to investigate the effects of uncertainty surrounding the chosen model inputs.
- For this study, the PSA consisted of 10,000 Monte Carlo iterations.
- In most PSA iterations, ICURs fell within the south-eastern quadrant of the cost-utility plane, indicating that BCG was associated with QALY gains and cost savings (Figure 3).
- At all WTP thresholds between GPB 20,000 and GBP 100,000, there was a 100% likelihood of adequate BCG therapy being considered a cost-effective strategy.

Figure 2 Tornado diagram of one-way sensitivity analysis



Note: The ten most influential drivers of cost-utility results are presented.
Abbreviations: BCG, Bacillus Calmette-Guérin; CHT, chemohyperthermia; NMB, net monetary benefit; RC, radical cystectomy; RR, risk ratio; TP, transition probability.

Figure 3 Cost-utility scatterplot showing results from PSA



Note: Blue circles represent incremental cost-QALY combinations from 10,000 Monte Carlo iterations. The orange diamond represents the mean value across these 10,000 iterations.
Abbreviations: QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year.

Discussion

- The main limitation of this study was the sparse health outcomes data available in the literature, specifically regarding adequate BCG therapy. Given this limitation, assumptions were made concerning the applicability of similar data, with considerations being given to factors such as the treatment setting and the risk group of patients used in available studies.
- Therefore, whilst the study demonstrates that adequate BCG therapy is a cost-effective treatment option relative to RC for NMIBC in the United Kingdom (UK), current real-world clinical practice shows that inconsistent use of BCG, non-adherence to treatment guidelines, and the shortage of BCG remain important barriers to effective therapy.
- For the NHS to see maximal utility gains from adequate BCG therapy, more work is required to ensure uniformity of dosing and scheduling, and to improve patient compliance.

Conclusions

- Treating high-risk NMIBC patients with intravesical BCG was found to improve quality-adjusted life expectancy and reduce costs from the healthcare payer perspective in the UK.
- Further work investigating the effects of adequate BCG treatment on patient health outcomes could be beneficial in strengthening the evidence base for future cost-effectiveness studies.

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