The Impacts of Bladder Cancer on Healthcare Costs and Patients' Health-Related Quality of Life: Evidence from the BOXIT Trial

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Abstract

Objectives: To estimate the cost and health-related quality of life (HRQoL) impact of non-muscle invasive bladder cancer (NMIBC) recurrence and progression to muscle invasive bladder cancer (MIBC) using evidence from a recent randomised control trial.

Materials and Methods: The costs and HRQoL associated with bladder cancer were assessed using data from the 472 NMIBC patients recruited to the Bladder COX-2 Inhibition Trial (BOXIT). Patient costs were aggregated annually and derived from the resource usage recorded over the first three years of the trial and relevant UK unit costs sourced from the literature. Patients' HRQoL was assessed using the EQ-5D-3L instrument and weighted using the UK 'tariff' onto the 0 (equivalent to dead) to 1 (equivalent to good health) scale. Marginal costs and HRQoL impacts from clinical events were estimated using generalised estimating equations. TMN tumour classification was used to categorise events by grade and stage.

Results: Evidence from the BOXIT trial suggests grade 3 recurrences and progressions are associated with a statistically significant -0.08 (95% confidence interval (CI) -0.13, -0.03) and -0.10 (95% CI -0.17, -0.03) HRQoL decrement, respectively. Grade 1 and grade 2 recurrences were associated with higher levels of HRQoL but were statistically insignificant predictors ($p>0.1$). Interactions between NMIBC recurrence and follow-up time indicated that a grade 3 recurrence within the first year may result in larger decrements in HRQoL (-0.11) compared with those in subsequent years (-0.04) ($p=0.102$). The average cost per NMIBC patient was estimated at £4,854 (95% CI £4,568, £5,140), £2,386 (£2,162, £2,610) and £1,496 (£1,306, £1,686) in the first, second and third years, respectively, amounting to a three-year total cost of £8,735 (£8,325, £9,145). The estimated marginal costs in a given year of grade 1, 2 and 3 recurrences of NMIBC were £1,218 (95% CI £403, £2033), £1,677 (£920, £2433) and £3,957 (£2,332, £5,583), respectively, and £5,407 (£2,663, £8,152) for a progression to muscle invasive bladder cancer. Estimated costs were significantly higher for high-risk bladder cancer patients during the first year of follow-up.

Conclusion: Evidence from the BOXIT trial suggests NMIBC patients will incur both decrements in HRQoL and significant costs, especially in the event of a grade 3 recurrence or a progression to MIBC. Study findings will inform the clinical community, those undertaking economic evaluations of interventions, patients and health service decision makers.

Key words: Bladder cancer, cost, HRQoL, QALY, non-muscle invasive bladder cancer, randomised controlled trial

Introduction

Bladder cancer is the ninth most common cancer and ranks 13th in terms of cancer associated mortality worldwide (1). In the UK, bladder cancer accounts for 3% of all new cancer cases with an estimated 10,171 new cases diagnosed in 2015 (2). Clinically, lesions are stratified using TMN classification, with non-muscle invasive bladder cancers (NMIBC) classified as Tis, Ta and T1, and muscle invasive bladder cancers (MIBC) classified as T2, T3 and T4. This distinction is important because the involvement of cancer invading muscle carries a significantly worse prognosis requiring either radical cystectomy, radical chemotherapy, or radical radiotherapy with or without neoadjuvant chemotherapy. NMIBC has more favourable survival rates but recurs frequently, being associated with repeated outpatient visits, cytologic and cystoscopic monitoring, as well as adjuvant intravesical treatment regimens following transurethral resection.

In the European Union, it has been estimated that bladder cancer costs €4.9 billion, representing 5% of total health care cancer cost (3). In the United States, bladder cancer is the most costly cancer to manage on a per patient basis (4, 5). Having estimates of the cost and health-related quality of life (HRQoL) impacts of clinical events relating to bladder cancer is important as a means of understanding its burden, informing resource allocation decisions and aiding further research. However, current evidence on such impacts is limited in several ways. Firstly, the distinction between NMIBC recurrences and progressions to MIBC are commonly overlooked (5-8). Secondly, HRQoL studies have predominantly focused on treatment-specific effects (6-9), and have not sought to understand the HRQoL impacts of specific clinical events such as recurrence and progression. Thirdly, systematic reviews repeatedly criticise the internal validity of HRQoL analyses, commonly citing retrospective or cross-sectional designs, non-validated instruments, short time horizons and failures in adjusting for confounders (7-11). Finally, there is a paucity of UK-specific cost analyses.

This paper aims to estimate the expected cost and HRQoL of patients diagnosed with NMIBC and to evaluate the impacts associated with NMIBC recurrence and progression to MIBC. It utilises evidence from a recent randomised controlled trial of intermediate and high-risk bladder cancer patients, the Bladder COX-2 Inhibition Trial (BOXIT).

Materials and Methods

The BOXIT trial

BOXIT (ISRCTN84681538, CRUK/07/004) is a randomised phase III placebo-controlled trial evaluating the addition of celecoxib to standard treatment for NMIBC patients with intermediate or high-risk of recurrence. Between 2007 and 2012 a total of 472 transitional cell carcinoma NMIBC patients were recruited, with a mean age of 65.9 years and the majority of whom were male (79%). Median follow-up at the point of analysis was 44 months (IQR: 36-57). The trial found no clear treatment benefit from celecoxib, with no significant differences in time to first recurrence of bladder cancer (NMIBC/MIBC) between patients randomised to either celecoxib or placebo for 2 years. Further details of the study design, treatment schedules, patients and clinical results from the trial have been published elsewhere (12).

Clinical events

At trial entry, intermediate and high-risk NMIBCs were defined according to clinical-pathological features outlined by the European Association of Urology (EAU) guidance (2002) (13). The clinical events of interest during the trial were NMIBC recurrence and progression to MIBC. Grade and stage of NMIBC and MIBC were classified according to the World Health Organisation (WHO) TNM classification (14). Patients could experience more than one recurrence episode of NMIBC during follow-up. Disease progression was defined as the development of MIBC (≥pT2). Intermediate and high-risk patients were recommended to have single adjuvant intravesical mitomycin C. Intermediate risk patients were recommended to have six once weekly adjuvant intravesical mitomycin C and high-risk patients were recommended to have induction Bacillus Calmette Guérin (BCG) with maintenance therapy for 3 years in accordance with international guidelines (15, 16). Surveillance cystoscopy was performed at 3-monthly intervals for the first two years and then 6-monthly for the third and fourth year. This paper focuses on the first 3 years of follow-up.

HRQoL, resource use and cost data

HRQoL was measured using the EQ-5D-3L, a generic preference-based measure encompassing five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and an overall health rating, measured using a visual analogue scale (17). HRQoL values were generated using published UK preference ‘tariffs’ for the 243 health states which are described by the EQ-5D-3L (18). Values range from 1.0 (perfect health status) to -0.594 with 0 indicating death and negative values reflecting health states

considered to be worse than death (19). High-risk individuals (n=346) in the trial undertook scheduled EQ-5D self-assessments at: baseline (trial entry), 2 months, 3 months, 6 months, 12 months, 24 months and 36 months. Intermediate risk patients (n=126) undertook scheduled EQ-5D self-assessments at: baseline, 12 months, 24 months and 36 months.

The cost analysis used resource use data from questionnaires collected from the trial and took the perspective of the NHS and personal social services. Relevant resources were those related to the diagnosis, treatment and three-year follow-up of patients in BOXIT. This included endoscopic investigations together with the primary, secondary and palliative care, alongside therapeutic procedures including radical cystectomy, chemotherapy, radical radiotherapy, immunotherapies and intravesical therapies. Missing information relating to the quantity or specific type of treatment administered following clinical events was assumed to follow usual practice. Unit costs were obtained from a variety of sources (see Table 1) and inflated to 2017 prices (20). Inpatient visits were costed based on a fixed component relating to the first two days of stay and a marginal component relating to any additional days. Care was assumed elective unless stated otherwise. Total costs were aggregated into years post-baseline, with each year estimated by multiplying the number of resources consumed over that period by their respective unit costs and summating.

The HRQoL analysis set consisted of high-risk patients who fully completed at least a single EQ-5D questionnaire during the trial (n=316). The focus on high-risk patients was to utilise the most EQ-5D data available and provide the most interpretable estimates of effect given the small number of MIBC and grade 3 NMIBC events in intermediate-risk patients and the different EQ-5D follow-up schedule between the risk groups. An analysis including both risk groups with annual EQ-5D follow-up is explored as a secondary analysis.

Methods of analysis

The standard approach to analysing HRQoL and cost data from clinical trials is to compare these between treatment arms over time to calculate quality-adjusted life-years (QALYs) and total cost for each patient in the trial (21). In trials showing no clinically or statistically significant benefit from a new treatment, this has little value. However, such trials offer a means of estimating the costs and HRQoL associated with a disease. This can include an exploration of how HRQoL and costs vary between patients, and of how patients' characteristics and the clinical events they experience may explain some of this variation (22, 23). This can provide valuable information for those assessing the potential value of other new treatments for similar patients (24).

Two forms of analysis were conducted for both costs and HRQoL. The first was descriptive, with mean EQ-5D scores calculated at each follow-up period of interest and mean costs calculated annually. Patients were grouped in accordance with types of events experienced over the 3-year follow-up. Costs were categorised into resource-related groups for comparison. The second established the effects of an event (NMIBC/MIBC) on each outcome measure. Patients' clinical events were linked to their closest post-event assessment. If multiple NMIBC recurrences occurred between EQ-5D or cost assessments, then the recurrence with the highest grade was recorded. The effects of events on HRQoL and costs were computed using repeated-measures regression controlling for relevant baseline covariates chosen on the basis of clinical relevance. These included baseline HRQoL, randomised treatment, history of bladder cancer, patients' characteristics (age, BMI, gender, diabetes), together with year of follow-up, risk group and interaction terms where appropriate.

To evaluate HRQoL and costs, separate generalised estimating equations (GEE) models were implemented in accordance with reporting guidelines (25, 26). Model fit, comparison and the selection of the working correlation structure was undertaken using quasi-likelihood information criterion (QIC) (27, 28). Dependent variables of annual cost and EQ-5D score were assumed to follow gamma and normal distributions, respectively.

Results

Patients' characteristics and events

Patients experiencing disease recurrence and progression had similar characteristics to those who did not, although modest differences in the rates of diabetes and prior history of NMIBC are noticeable (Table 2). We assessed whether systematic differences existed between patients with missing and non-missing EQ-5D data at different time points and found differences were small (Tables S1-S2). This supported the assumption in our complete case analysis of data being missing completely at random.

NMIBC recurrences were over 8 times more common than progression to MIBC. In total, 233 NMIBC recurrences in 138 patients (29.2%, total N=472) were recorded over the three-year follow-up compared to 29 patients (6.1%) experiencing progression to MIBC (62.1% receiving subsequent radical surgery). Of those events, 37 NMIBC recurrences were not graded, 46/472 patients (9.7%) experienced at least one grade 3 NMIBC recurrence (32.6% receiving subsequent radical surgery), while 62 (13.1%) and 36 (7.6%) patients, respectively, experienced one or more grade 2 and grade 1 recurrences (with jointly 4.1% receiving subsequent radical surgery). For further details on the clinical events in the trial, see Table S3.

HRQoL analysis

The completion rate of the EQ-5D over 3 years was 79% and ranged between 58% and 84% across the points of follow-up. The completion rates following a NMIBC recurrence and progression to MIBC were 60% and 38%, respectively. Figure 1 displays an overview of the observed mean EQ-5D index scores for high-risk patients and the proportion of events occurring between each EQ-5D follow-up period. For full details the HRQoL descriptive results see Table S4.

Figure 1 shows a set of sub-groups comprising patients who have incurred at least one of the specified clinical events over the 3-year follow-up or no event. The findings suggest NMIBC recurrence and MIBC progression may be associated with deteriorations in HRQoL at specific points in time. Variation in HRQoL at specific time-points is largely driven by the events experienced by patients. In contrast, variation in HRQoL between points of follow-up is related to the underlying within-patient variation, the non-uniform distribution of events over time and sampling error exacerbated by partitioning modestly sized sub-groups. A comparison of the EQ-5D dimensions by event-related sub-group found higher proportions of individuals reporting problems with pain/discomfort and undertaking usual activities when

experiencing a grade 3 recurrence or a MIBC progression compared with no event over the three year follow-up (see Figure S1).

Table 3 shows statistically significant clinical event effects on HRQoL in terms of estimated decrements, as well as mean health-state values. Progression to MIBC and NMIBC grade 3 recurrences were associated with predicted mean decrements in HRQoL of -0.10 (95% confidence interval (CI) -0.17, -0.03) and -0.08 (95% CI -0.13, -0.03), respectively, ($p<0.01$). In contrast, NMIBC grade 1 and grade 2 recurrences were associated with positive but statistically insignificant ($p>0.1$) increments in HRQoL compared to patients with no cancer.

Secondary analysis showed that introducing an interaction term into the regression revealed that NMIBC grade 3 recurrences in the first year incur larger decrements in HRQoL (-0.11) compared with those in subsequent years (-0.04) ($p=0.102$ – see Table S6). Small numbers precluded the same analysis for MIBC progression. Including both high- and intermediate-risk patients into the analysis based on only annual EQ-5D assessment generated NMIBC recurrence estimates closer to zero for all grades, with only MIBC events having a statistically significant decrement on HRQoL ($p<0.05$). Irrespective of bladder cancer grade or stage, radical cystectomy was associated with a -0.17 decrement in HRQoL (see Table S7). All regression results and primary variance-covariance matrices shown in Tables S5-S11.

Cost analysis

Figure 2 reports mean costs per patient for each type of care (Table 1), annually and in total. The mean cost of management for a NMIBC patient was £4,854 in the first year, with a total cost of £8,735 over 3 years. The results suggest costs decline over time, with mean costs of £1,496 in year 3. Endoscopic surveillance is the principal cost driver, accounting for over 52% of total costs and representing high proportions in years 2 (£1,384/£2,386) and 3 (£835/£1,496). These estimates put the three-year total cost for the UK NMIBC bladder cancer cohort diagnosed in 2015 at approximately £66.14 million, assuming 74.5% of the 10,171 UK bladder cancer cases were NMIBC (2, 29).

Figure 3 shows the impact of clinical events on annual costs, and indicates that MIBC progression and all grades of NMIBC recurrence lead to increased costs. Higher grades of NMIBC are associated with higher costs, with grade 3 recurrences necessitating more intensive therapy in addition to surveillance. Progression to MIBC is associated with the greatest cost increment with a £5,407 increase in the expected annual cost per patient, again reflecting more intensive therapy. Additionally, high-risk patients were associated with a £1,968 increase in mean costs in the first year, although this figure declined to £457 and

£74 in years 2 and 3, respectively. Table 4 presents predicted mean costs per patient by year, event status and risk group (variance-covariance matrix Table S10).

Discussion

Published economic evaluations of treatments for bladder cancer lack robust estimates of clinical effects on HRQoL and costs (30, 31). Furthermore, clinicians need to understand the consequences of clinical events for patients' well-being and health service costs. This study provides new evidence on the cost and HRQoL associated with NMIBC occurrence, recurrence and progression to MIBC, supporting future clinical and economic evaluations. Our findings suggest NMIBC has an average cost of £8,735 over a three year time horizon, with grade 1, 2 and 3 recurrences of NMIBC and progression to MIBC associated with £1,218, £1,677, £3,957, and £5,407 increases in annual costs respectively. In addition, grade 3 recurrences and progressions to MIBC were associated with statistically significant -0.08 and -0.10 decrements in HRQoL respectively.

Singer et al reported that patients with bladder cancer, muscle invasive or not, experience significant and clinically-relevant deteriorations in HRQoL (32). There is little evidence contradicting the notion that patients with MIBC bear a significant health burden; however, the same cannot necessarily be said for those with NMIBC. Commonly reported NMIBC morbidities include mental health impacts at diagnosis, physical discomfort, sexual problems and urinary symptoms (33-35), but these seem rarely to translate into reductions in longer term health outcomes and, in some cases, are not recorded at all (9, 36). It has been suggested that patients may become "accustomed" to NMIBC and its related management, accepting recurrences as a part of their lives (10). The evidence presented from the BOXIT trial offers some additional support to this view, but suggests that not all NMBIC recurrences should be considered equal. Based on recommended NMIBC surveillance guidelines, our results suggest that the negative impact of a NMIBC recurrence on HRQoL is concentrated within the high grade strata (G3), particularly at the first year following diagnosis. Further, no evidence of negative HRQoL outcomes from grade 1 or grade 2 NMIBC recurrences was found. This may be at least partially explained by the low rates of radical surgery observed following grade 1 and grade 2 NMIBC recurrences. Supplementary analyses support these findings, where cystectomy is a large and significant predictor of HRQoL status, and patient groups with the highest rates of radical surgery (grade 3 recurrences and progressions) are most likely to report relatable problems with pain/discomfort and undertaking usual activities. A fuller understanding of the mechanisms behind these findings requires further prospective research.

Sangar et al (2005) estimated that the UK cost in 2001-2002 for the diagnosis, treatment and 5 year follow-up of each bladder cancer case was £55.39 million, at a mean cost of £8,349.20 (37). Allowing for inflation and differing follow-up periods, these results are similar

to those reported here. To put this into context, it is less costly per patient to treat stage 2 colon, rectal and non-small cell lung cancers (38). Our analysis confirms the earlier study in showing the prominent role of endoscopic surveillance in driving costs, which remains the primary target for innovation in bladder cancer management (5, 39, 40), and optimising surveillance remains a research priority. Less costly and non-invasive urinary biomarkers represent an attractive option, but to date no commercially available test has the diagnostic accuracy to replace cystoscopy as patients demand a test with a high sensitivity before wide-spread acceptance (41-43). Similar to others, we report that progression to MIBC is associated with higher costs for intermediate- and high-risk patients (44).

This study's relatively large sample size, prospective design and use of a validated HRQoL instrument represents its strengths. To our knowledge, this is the first study to estimate both mean and marginal HRQoL and cost impacts across multiple grades and stages of bladder cancer. There are, however, several important limitations acknowledged. Despite BOXIT treatment protocol remaining representative of current UK guidelines, differences between BOXIT and current clinical practice are feasible (e.g. EAU now recommend BCG instillations for intermediate risk patients and have revised definitions of risk (45)). In addition, the trial's exclusion criteria may also limit the generalisability of this study, with results applicable to a cohort healthier than what might otherwise be observed in practice. With respect to HRQoL, the true negative repercussions of MIBC may be different to those reported because the number of patients who progressed to MIBC is relatively small as BOXIT was powered on time to first recurrence. This, coupled with a low post-progression EQ-5D response rate, results in uncertain estimates, and may lead to overestimates of HRQoL because patients with relatively poor health outcomes post-MIBC may be less likely to complete the EQ-5D. Moreover, increasingly protracted EQ-5D follow-ups meant clinical events in the study became progressively distant from EQ-5D collection. Whether improvements in reported post-event HRQoL outcomes over time stem from the true underlying dynamics of bladder cancer, or just time-related disparities between event and follow-up, remains to be seen. Finally, the EQ-5D is a generic measure and by design will neglect potentially relevant disease-specific dimensions of health (e.g. urinary, bowel and sexual function).

There may be underestimates in costs for several reasons. First, our analysis of the impact of events on annual costs neglects the potential dynamics and spill-over effects between time periods. Bladder cancer events inevitably prompt immediate resource use; however, the costs incurred from stricter surveillance and the greater risk of related events are realised further into the future. Understanding these dynamics requires more detailed collection of resource use data and remains a potential avenue for further research. Second, the assumption made that treatments were elective may again under-represent costs. Third, the

protracted and persistent nature of bladder cancer has far broader cost impacts than those incurred only by the NHS over three years. A wider perspective would give a more comprehensive account of the earnings, productivity and time forgone by bladder cancer patients and informal caregivers.

In conclusion, the results from this analysis of BOXIT trial data suggest that non-muscle invasive bladder cancer patients experience decrements in HRQoL and impose significant costs in the event of disease recurrence or progression, increasingly so with the abnormality and invasiveness of the lesion.

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Conflict of interests

ICMJE disclosure statements:

Dr Hall reports grants from Cancer Research UK, grants from Kyowa Hakko UK, grants from Alliance Pharma (previously Cambridge Laboratories), non-financial support from Pfizer, during the conduct of the study; grants from Pfizer Inc, grants and non-financial support from Merck Sharp & Dohm, grants and non-financial support from Astra Zeneca, grants from Janssen-Cilag, grants and non-financial support from Bayer, grants from Aventis Pharma Limited (Sanofi), grants from Accuray Inc.

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Tables and Figures

Table 1: Unit costs

Care	Unit Costs*	Source
Primary Care		*PSSRU Health and Social Care 2017* (20)
GP Home Visit	£86	
Specialist Nurse Home Visit	£57	
GP Surgery Visit (GP)	£32	
GP Surgery Visit (Nurse)	£10	
Secondary Care		*NHS Schedule Reference Costs 2016/17 (46)*
Outpatient Attendance	£108	TOA: Urology outpatient attendance [service code: 101]
Inpatient Attendance	£820	EL: Minor bladder procedures, 19 years and over [LB15E]
Inpatient Excess Days	£397	EL_XS: Intermediate open bladder procedures [LB12Z]
Palliative Care†		*NICE Technology Assessment Jan 2010* (47)
Palliative Care	£12,968	
Surveillance		*NICE Technology Assessment Jan 2010* (47)
Flexible Cystoscopy	£449	
Rigid Cystoscopy	£1,176	
Intravesical/Immuno-Therapies		
Mitomycin Instillation	£80	British National Formulary 2018
BCG Instillation	£101	NICE Technology Assessment Jan 2010 (47)
Radical Surgery		
Cystectomy	£9,973	Total_HRG's: Cystectomy with Urinary Diversion and Reconstruction [LB39C/ LB39D]
Lobectomy	£6,601	NICE clinical guideline 121 (2011) (48)
Nephroureterctomy	£6,471	Complex, Open or Laparoscopic, Kidney or Ureter Procedures, with CC Score 0-1 [LB60F]
Renogram	£256	Renogram, 19 years and over [RN25A]
Chemotherapy/Radiotherapy‡		
Radical Radiotherapy	£1,156	*NICE Technology Assessment Jan 2010 (47)*
Gemcitabine and Cisplatin	£169	*eMit drug unit costs & London Cancer Network administration schedules*
Gemcitabine-Carboplatin	£232	
5FU & MMC	£104	
Carboplatin-etoposide	£173	

*inflated to 2017 prices using PSSRU hospital and community health services index, costs presented are rounded up to nearest pound sterling.

† 135 days taken from reference material with per day NHS Schedule Reference 2016/2017 costs applied

‡ Specific chemotherapy unit costs were calculated as the product of the specific drug costs (taken from eMit), the dosage and the observed/recommended number of cycles (recommended schedules from the NHS Cancer Network used where trial information was missing).

Table 2: Patients' characteristics

	Total	High-Risk	Intermediate-Risk	No Event	Progression	Recurrence†	Recurrence (G1)	Recurrence (G2)	Recurrence (G3)
	(N=472)	(N=346)	(N=126)	(N=321)	(N=29)	(N=138)	(N=36)	(N=62)	(N=46)
EQ-5D Baseline – Mean (SD)	0.87 (0.15)	0.86 (0.17)	0.85 (0.22)	0.88 (0.15)	0.87 (0.13)	0.87 (0.16)	0.85 (0.20)	0.91 (0.11)	0.87 (0.14)
Age – Mean (SD)	65.9 (9.9)	65.8 (10.3)	66.2 (8.8)	65.7 (10.2)	67.8 (7.1)	66.2 (9.3)	65.9 (10.3)	66.1 (7.8)	68.0 (7.7)
BMI – Mean (SD)	27.8 (4.6)	27.9 (4.6)	27.7 (4.5)	27.8 (4.3)	27.0 (4.2)	28.1 (5.2)	27.8 (6.5)	28.7 (5.5)	27.9 (4.6)
Gender – Male N(%)	374 (79.2%)	278 (80.3%)	96 (76.2%)	262 (81.6%)	25 (86.2%)	102 (73.9%)	27 (75.0%)	45 (72.6%)	33 (71.7%)
Diabetes – N(%)	42 (8.9%)	30 (8.7%)	12 (9.6%)	23 (7.2%)	2 (6.9%)	19 (13.8%)	6 (16.7%)	8 (12.9%)	8 (17.4%)
NMIBC History – N(%)	159 (34.0%)	95 (27.8%)	64 (51.2%)	94 (29.7%)	14 (48.3%)	58 (42.3%)	17 (47.2%)	30 (48.4%)	16 (35.6%)
Celecoxib – N(%)	236 (50.0%)	167 (48.3%)	69 (54.8%)	164 (51.1%)	13 (44.8%)	65 (47.1%)	22 (61.1%)	30 (48.4%)	17 (37.0%)
Smoking Status – N(%)									
Never	145 (39.6%)	113 (33.0%)	32 (25.8%)	101 (31.8%)	8 (28.6%)	42 (30.9%)	10 (2.8%)	16 (26.2%)	18 (40.0%)
Previous	252 (54.1%)	187 (54.7%)	65 (52.4%)	173 (54.4%)	16 (57.1%)	70 (51.5%)	19 (52.8%)	34 (55.7%)	21 (46.7%)
Current	69 (14.8%)	42 (12.3%)	27 (21.8%)	44 (13.8%)	4 (14.3%)	24 (17.7%)	7 (19.4%)	11 (18.0%)	6 (13.3%)
ECG Result – N(%)									
Normal	370 (78.6%)	276 (79.8%)	94 (75.2%)	250 (78.1%)	24 (82.8%)	109 (79.0%)	8 (77.8%)	49 (79.0%)	37 (80.4%)
Abnormal	101 (21.4%)	70 (20.2%)	31 (24.8%)	70 (21.9%)	5 (17.2%)	29 (21.0%)	28 (77.8%)	13 (20.1%)	9 (19.6%)

SD: Standard Deviation, ECG: Electrocardiogram, N: Number

† The number of patients who experienced a recurrence exceeds the sum of the graded recurrences on account of missing grading data and patients experiencing multiple recurrences of different grade

Table 3: Estimated statistically significant effects on HRQoL, and associated health state values, from clinical events (high-risk patients only)

	Estimated HRQoL decrements (mean, 95% CI)[a]	Estimated health state value (mean, 95% CI)[a]
No event	-	0.84606 (0.83292, 0.85921)
NMIBC Recurrence (G3)	-0.08306** (-0.13379, -0.03233,)	0.76300 (0.71178, 0.81422)
MIBC Progression	-0.09909** (-0.17256, -0.02561)	0.74698 (0.67309, 0.82087)

[a] Multivariate HRQoL longitudinal model controlling for: baseline EQ-5D score, treatment (celecoxib), patient characteristics, bladder cancer history, annual time dummies and events.

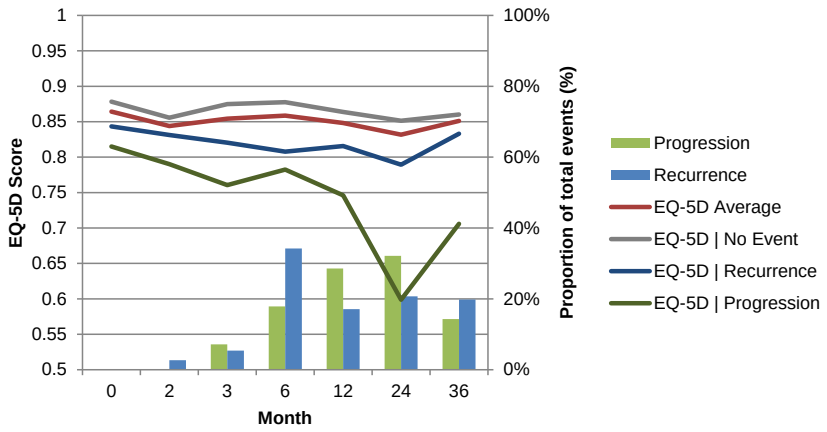
**p<0.05, **p<0.01*

Table 4: Estimated patient costs across time, risk group and event status

Risk Group	Year	No bladder cancer	NMIBC recurrence			MIBC progression
			Grade 1	Grade 2	Grade 3	
High-risk	Year 1	£4,796	£6,014	£6,472	£8,753	£10,374
	Year 2	£2,363	£3,581	£4,039	£6,320	£7,940
	Year 3	£1,387	£2,605	£3,063	£5,344	£6,964
Intermediate-risk	Year 1	£2,828	£4,046	£4,505	£6,785	£8,406
	Year 2	£1,907	£3,125	£3,583	£5,864	£7,484
	Year 3	£1,314	£2,532	£2,990	£5,271	£6,891

Predicted values from a multivariate longitudinal panel cost-related analysis controlling for: treatment, patient characteristics, risk group, annual time dummies, bladder cancer events and interactions.

Figure 1: EQ-5D scores in high-risk patients for each event-related sub-group and the associated proportion of events in each follow-up period over three years follow-up



The x-axis represents time in months post-baseline with categories and their distance solely indicative of trial follow-up, and not equating to the length of time between intervals.

Figure 2: Mean costs per patient over time by resource category (intermediate and high-risk patients)

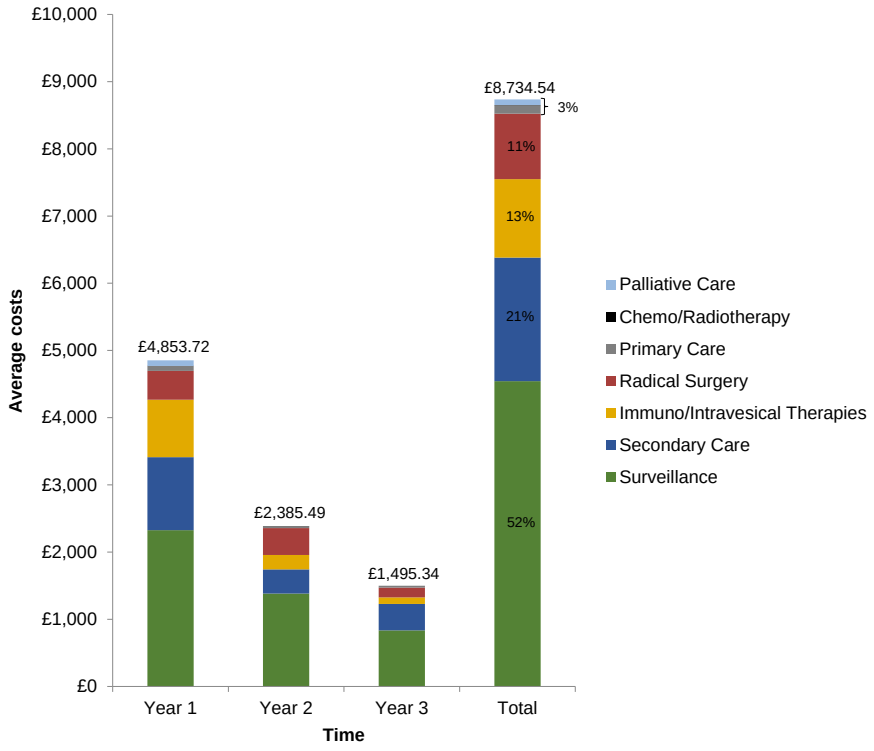
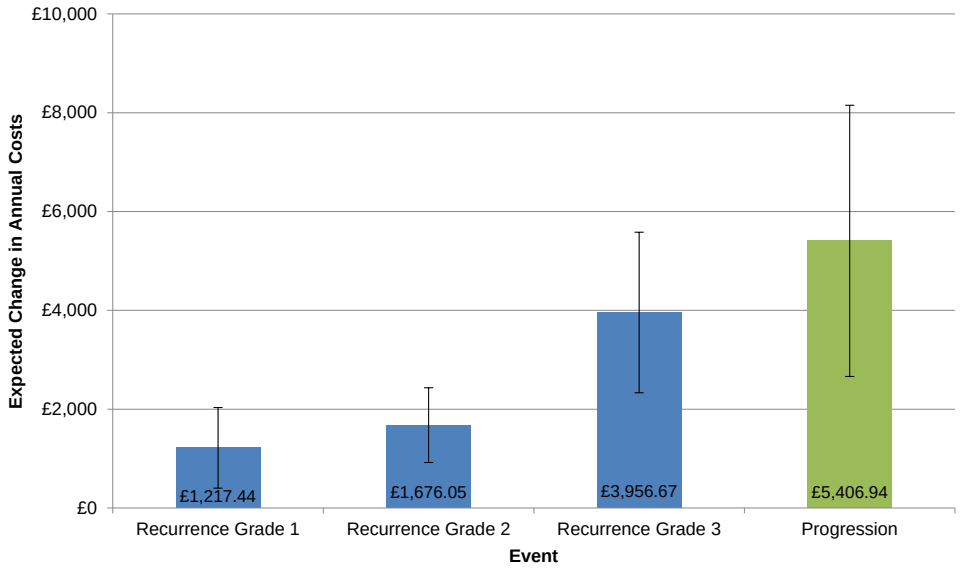


Figure 3: Estimated mean change in annual cost per patient associated with clinical events (95% confidence intervals shown by the vertical bars)



Multivariate longitudinal panel cost-related analysis controlling for: treatment, patient characteristics, risk group, annual time dummies, bladder cancer events and interactions.

Supplementary Appendix

Key	
Label	**Definition**
Patient Gender	Female = 0
	Male = 1
ECG Result	Normal result = 0
	Abnormal result = 1
Celecoxib	Placebo arm = 0
	Treatment arm = 1
History	No prior history of NMIBC = 0
	Prior history of NMIBC = 1
Diabetes	No diabetes = 0
	Diabetes = 1

Tables S1: Summary statistics comparison: missing and non-missing EQ-5D collection

	Month 2			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	187	65.19	285	66.38
BMI	180	27.71	266	27.89
Gender	187	75%	285	82%
“Never Smoked”	48	26%	97	34%
“Previous Smoker”	97	53%	155	55%
“Current Smoker”	39	21%	30	11%
ECG Result	186	23%	285	21%
Celecoxib	187	52%	285	48%
Diabetes	186	11%	285	8%
History	183	44%	284	27%

	Month 3			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	185	65.41	287	66.26
BMI	179	27.77	267	27.85
Gender	185	75%	287	82%
“Never Smoked”	44	24%	101	35%
“Previous Smoker”	97	53%	155	55%
“Current Smoker”	41	23%	28	10%
ECG Result	184	21%	287	22%
Celecoxib	185	54%	287	47%
Diabetes	184	11%	287	8%
History	181	46%	286	27%

	Month 6			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	196	65.27	276	66.40
BMI	189	27.66	257	27.93
Gender	196	74%	276	83%
“Never Smoked”	50	26%	95	35%
“Previous Smoker”	103	53%	149	55%
“Current Smoker”	40	21%	29	10%
ECG Result	195	21%	276	22%
Celecoxib	196	53%	276	48%
Diabetes	195	12%	276	7%
History	192	46%	275	26%

	Month 12			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	125	65.67	347	66.02
BMI	120	27.91	326	27.78
Gender	125	78%	347	80%
“Never Smoked”	31	25%	114	33%
“Previous Smoker”	66	54%	186	54%
“Current Smoker”	25	21%	44	13%
ECG Result	124	19%	347	22%
Celecoxib	125	52%	347	49%
Diabetes	124	9%	347	9%
History	122	34%	345	34%

	Month 24			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	163	66%	309	66.03
BMI	155	27.65	291	27.91
Gender	163	79%	309	80%
“Never Smoked”	42	26%	103	34%
“Previous Smoker”	90	56%	162	53%
“Current Smoker”	28	18%	41	13%
ECG Result	162	16%	309	24%
Celecoxib	163	52%	309	49%
Diabetes	162	10%	309	8%
History	160	36%	307	33%

	Month 36			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	191	66.21	281	65.73
BMI	183	27.62	263	27.95
Gender	191	79%	281	79%
“Never Smoked”	47	25%	98	35%
“Previous Smoker”	100	53%	152	55%
“Current Smoker”	41	22%	28	10%
ECG Result	190	20%	281	22%
Celecoxib	191	53%	281	48%
Diabetes	190	9%	281	9%
History	188	36%	279	33%

Tables S2: Summary statistics comparison: missing and non-missing costs

	Year 1			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	25	69.16	447	65.75
BMI	23	27.29	423	27.85
Gender	25	80%	447	79%
“Never Smoked”	6	24%	145	32%
“Previous Smoker”	13	52%	239	53%
“Current Smoker”	6	24%	63	14%
ECG Result	24	8%	447	22%
Celecoxib	25	52%	447	50%
Diabetes	24	13%	442	9%
History	23	52%	444	33%

	Year 2			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	30	68.57	442	65.75
BMI	28	26.91	418	27.88
Gender	30	80%	442	79%
“Never Smoked”	7	23%	144	33%
“Previous Smoker”	19	63%	223	53%
“Current Smoker”	4	13%	65	15%
ECG Result	29	14%	442	22%
Celecoxib	30	47%	442	50%
Diabetes	29	10%	442	9%
History	28	39%	439	34%

	Year 3			
	Missing Values		Non Missing Values	
	N	Mean	N	Mean
Age	47	68.09	425	65.69
BMI	45	27.15	401	27.89
Gender	47	74%	425	80%
“Never Smoked”	11	23%	140	33%
“Previous Smoker”	26	55%	226	53%
“Current Smoker”	10	21%	59	14%
ECG Result	46	11%	425	23%
Celecoxib	47	43%	425	50%
Diabetes	46	7%	425	9%
History	45	42%	422	33%

Table S3: Trial events

	Trial events													
	Month 2		Month 3		Month 6		Month 12		Month 24		Month 36		Total Events	Total Patients
	HR	IR	HR	IR	HR	IR	HR	IR	HR	IR	HR	IR		
MIBC Progressions	0	0	2	0	5	0	8	0	9	1	4	0	29	29
NMIBC Recurrences	3	2	6	6	38	20	19	32	23	44	22	18	233	138
Graded Recurrences	2	2	6	4	35	14	16	29	17	37	17	17	196	121
Unknown	0	0	0	0	0	0	2	0	0	0	1	0	3	3
Grade 1	0	1	0	0	4	7	3	11	5	14	0	9	54	36
Grade 2	1	0	3	4	9	7	4	15	7	21	7	7	85	62
Grade 3	1	1	3	0	22	0	7	3	5	2	9	1	54	46

HR: High-risk patients; IR: Intermediate-risk patients

In instances when multiple NMIBC recurrences occur between EQ-5D/annual cost assessments then the analysis set applies the recurrence with the highest grade recorded (see methods)

Table S4: Observed EQ-5D scores from the BOXIT trial

High-risk patients

		EQ-5D Event-Specific Scores						
		Baseline	Month 2	Month 3	Month 6	Month 12	Month 24	Month 36
EQ-5D Average	Mean (SD)	0.86 (0.17)	0.84 (0.20)	0.85 (0.18)	0.86 (0.18)	0.85 (0.19)	0.83 (0.19)	0.85 (0.19)
	N	309	284	286	274	250	223	205
EQ-5D | No Event	Mean (SD)	0.88 (0.15)	0.86 (0.20)	0.87 (0.15)	0.88 (0.16)	0.86 (0.17)	0.85 (0.16)	0.86 (0.18)
	N	224	210	209	209	297	181	168
EQ-5D | Progression	Mean (SD)	0.82 (0.23)	0.79 (0.23)	0.76 (0.22)	0.78 (0.26)	0.75 (0.26)	0.60 (0.30)	0.71 (0.35)
	N	28	26	28	19	15	10	7
EQ-5D | Recurrence	Mean (SD)	0.84 (0.20)	0.83 (0.20)	0.82 (0.21)	0.81 (0.21)	0.82 (0.21)	0.79 (0.25)	0.83 (0.20)
	N	71	62	64	56	45	35	33
EQ-5D | Recurrence Grade 1	Mean (SD)	0.90 (0.11)	0.85 (0.12)	0.88 (0.14)	0.86 (0.11)	0.93 (0.20)	0.81 (0.21)	0.83 (0.33)
	N	8	7	8	7	4	4	4
EQ-5D | Recurrence Grade 2	Mean (SD)	0.88 (0.14)	0.90 (0.10)	0.89 (0.13)	0.86 (0.20)	0.84 (0.14)	0.70 (0.32)	0.78 (0.78)
	N	23	21	21	20	17	14	10
EQ-5D | Recurrence Grade 3	Mean (SD)	0.85 (0.17)	0.82 (0.21)	0.79 (0.23)	0.75 (0.22)	0.79 (0.26)	0.77 (0.27)	0.80 (0.22)
	N	36	31	33	27	20	16	6

Intermediate- and high-risk patients

		EQ-5D Event-Specific Scores			
		Baseline	Month 12	Month 24	Month 36
EQ-5D Average	Mean (SD)	0.86 (0.19)	0.85 (0.20)	0.83 (0.20)	0.85 (0.20)
	N	410	347	309	281
EQ-5D | No Event	Mean (SD)	0.87 (0.16)	0.86 (0.18)	0.84 (0.18)	0.85 (0.20)
	N	275	244	224	209
EQ-5D | Progression	Mean (SD)	0.82 (0.23)	0.71 (0.28)	0.66 (0.55)	0.71 (0.35)
	N	29	16	11	7
EQ-5D | Recurrence	Mean (SD)	0.85 (0.21)	0.84 (0.23)	0.84 (0.24)	0.87 (0.19)
	N	121	95	78	68
EQ-5D | Recurrence Grade 1	Mean (SD)	0.81 (0.29)	0.77 (0.31)	0.80 (0.30)	0.87 (0.26)
	N	28	24	21	18
EQ-5D | Recurrence Grade 2	Mean (SD)	0.91 (0.12)	0.88 (0.16)	0.84 (0.26)	0.88 (0.19)
	N	54	48	41	33
EQ-5D | Recurrence Grade 3	Mean (SD)	0.86 (0.17)	0.80 (0.27)	0.77 (0.29)	0.83 (0.21)
	N	41	26	21	20

Table S5: Primary HRQoL regression

EQ5D_Score_Month	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
EQ5D_Score_Baseline	.5967924	.0406532	14.68	0.000	.5171136	.6764713
Patient_Gender	.0521357	.0179587	2.90	0.004	.0169372	.0873341
Age_Category						
50-59 yr_old	-.0187366	.0338184	-0.55	0.580	-.0850194	.0475462
60-69yr_old	-.0039931	.0318242	-0.13	0.900	-.0663674	.0583812
70-79yr_old	-.0108462	.0331665	-0.33	0.744	-.0758513	.0541589
>80 yr_old	-.0243156	.0396575	-0.61	0.540	-.1020428	.0534116
BMI_Category						
Overweight	-.0100358	.0166613	-0.60	0.547	-.0426913	.0226198
Obese	-.0069584	.0182376	-0.38	0.703	-.0427036	.0287867
Morbidly Obese	-.0652968	.0651534	-1.00	0.316	-.1929952	.0624015
Smoking_Status						
Previous	-.0033888	.0148166	-0.23	0.819	-.0324288	.0256512
Current	-.0069576	.0239007	-0.29	0.771	-.0538022	.039887
ECG_Result	-.0057031	.016846	-0.34	0.735	-.0387207	.0273145
Celecoxib_Treatment_Consumption	-.0010674	.0136832	-0.08	0.938	-.0278859	.0257511
Diabetes	-.0989409	.0252237	-3.92	0.000	-.1483784	-.0495034
TCC_History	-.015477	.0155777	-0.99	0.320	-.0460086	.0150547
Year						
Year 2	-.0250881	.0103193	-2.43	0.015	-.0453134	-.0048627
Year 3	-.0107493	.0102873	-1.04	0.296	-.0309119	.0094134
Tumour_Recurrence_Month						
Unknown	.0334809	.0823301	0.41	0.684	-.1278831	.1948449
Grade 1	.0620308	.0555815	1.12	0.264	-.046907	.1709685
Grade 2	.0518003	.0339202	1.53	0.127	-.014682	.1182826
Grade 3	-.0830612	.0258832	-3.21	0.001	-.1337914	-.0323311
Progression_Month	-.0990853	.037488	-2.64	0.008	-.1725605	-.0256102
Progression_History_Month	.0043892	.0516379	0.08	0.932	-.0968193	.1055976
_cons	.3218822	.0489321	6.58	0.000	.225977	.4177873

Table S6: Primary HRQoL regression including time and event interaction

EQ5D_Score_Month	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
EQ5D_Score_Baseline	.5973907	.0407683	14.65	0.000	.5174862	.6772952
Patient_Gender	.0530437	.0180207	2.94	0.003	.0177238	.0883636
Age_Category						
50-59 yr_old	-.020057	.0339243	-0.59	0.554	-.0865473	.0464333
60-69yr_old	-.0060109	.0319299	-0.19	0.851	-.0685923	.0565705
70-79yr_old	-.0113383	.0332657	-0.34	0.733	-.0765379	.0538613
>80 yr_old	-.0274407	.0397877	-0.69	0.490	-.1054232	.0505419
BMI_Category						
Overweight	-.01043	.0167119	-0.62	0.533	-.0431847	.0223247
Obese	-.0073803	.0183151	-0.40	0.687	-.0432771	.0285166
Morbidly Obese	-.0629669	.0653087	-0.96	0.335	-.1909695	.0650357
Smoking_Status						
Previous	-.0029297	.0148631	-0.20	0.844	-.0320609	.0262014
Current	-.0080374	.0239813	-0.34	0.738	-.05504	.0389651
ECG_Result	-.0052007	.0168996	-0.31	0.758	-.0383233	.0279219
Celecoxib_Treatment_Consumption	-.0004786	.0137258	-0.03	0.972	-.0273807	.0264235
Diabetes	-.1000132	.0253062	-3.95	0.000	-.1496125	-.0504139
TCC_History	-.0157322	.0156268	-1.01	0.314	-.0463602	.0148957
Tumour_Recurrence_Month#Yearint						
No Cancer#>Year 1	-.0209844	.0089722	-2.34	0.019	-.0385696	-.0033992
Unknown#Year 1	.0506889	.1156377	0.44	0.661	-.1759568	.2773346
Unknown#>Year 1	.0038289	.1159498	0.03	0.974	-.2234286	.2310864
Grade 1#Year 1	-.028671	.0896046	-0.32	0.749	-.2042929	.1469509
Grade 1#>Year 1	.0907741	.0706822	1.28	0.199	-.0477605	.2293087
Grade 2#Year 1	.0284185	.0468997	0.61	0.545	-.0635031	.1203402
Grade 2#>Year 1	.0690765	.0486986	1.42	0.156	-.026371	.1645239
Grade 3#Year 1	-.1096423	.0317785	-3.45	0.001	-.171927	-.0473577
Grade 3#>Year 1	-.0429308	.0428694	-1.00	0.317	-.1269532	.0410917
Progression_Month	-.0937818	.0373684	-2.51	0.012	-.1670225	-.0205412
Progression_History_Month	.0053212	.051364	0.10	0.917	-.0953503	.1059927
_cons	.3228122	.0490795	6.58	0.000	.2266181	.4190063

Table S7: HRQoL regression with intermediate- and high-risk patients and annual EQ-5D

EQ5D_Score_Month	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
EQ5D_Score_Baseline	.6222412	.0440824	14.12	0.000	.5358413	.7086411
Risk_Group	-.0221777	.0181653	-1.22	0.222	-.0577811	.0134256
Patient_Gender	.0344006	.0192668	1.79	0.074	-.0033617	.0721629
Age_Category						
50-59 yr_old	-.0421994	.0414963	-1.02	0.309	-.1235307	.039132
60-69yr_old	-.051239	.0393116	-1.30	0.192	-.1282882	.0258103
70-79yr_old	-.0600482	.0411742	-1.46	0.145	-.1407482	.0206518
>80 yr_old	-.0726505	.0482603	-1.51	0.132	-.1672389	.0219379
BMI_Category						
Overweight	-.0221557	.018897	-1.17	0.241	-.0591931	.0148818
Obese	-.0381121	.0206114	-1.85	0.064	-.0785097	.0022855
Morbidly Obese	-.10648	.0743021	-1.43	0.152	-.2521095	.0391495
Smoking_Status						
Previous	.0102264	.0171481	0.60	0.551	-.0233833	.0438361
Current	-.0547593	.0252457	-2.17	0.030	-.1042399	-.0052786
ECG_Result	-.0382036	.0187138	-2.04	0.041	-.074882	-.0015251
Celecoxib_Treatment_Consumption	-.0081224	.0155085	-0.52	0.600	-.0385186	.0222737
Diabetes	-.0627696	.027287	-2.30	0.021	-.116251	-.0092881
TCC_History	-.0177708	.016869	-1.05	0.292	-.0508335	.0152919
Year						
Year 2	-.0205743	.009907	-2.08	0.038	-.0399916	-.001157
Year 3	-.0187082	.0106461	-1.76	0.079	-.0395742	.0021579
Tumour_Recurrence_Month						
Unknown	.0616068	.0957521	0.64	0.520	-.1260638	.2492774
Grade 1	-.005975	.0317292	-0.19	0.851	-.068163	.056213
Grade 2	.0019765	.0221878	0.09	0.929	-.0415108	.0454638
Grade 3	-.0434608	.0277767	-1.56	0.118	-.0979022	.0109806
Progression_Month	-.1020626	.0428498	-2.38	0.017	-.1860467	-.0180785
Progression_History_Month	-.0434159	.0623099	-0.70	0.486	-.1655411	.0787093
_cons	.4007673	.0596421	6.72	0.000	.2838709	.5176637

Table S8: Base case HRQoL regression including cystectomy as a covariate

EQ5D_Score_Month	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
EQ5D_Score_Baseline	.636108	.0377744	16.84	0.000	.5620715	.7101444
Patient_Gender	.0477877	.0163828	2.92	0.004	.0156781	.0798973
Age_Category						
50-59 yr_old	-.0288782	.0346037	-0.83	0.404	-.0967001	.0389438
60-69yr_old	-.037565	.0327225	-1.15	0.251	-.1016999	.0265698
70-79yr_old	-.0464312	.0342036	-1.36	0.175	-.1134689	.0206066
>80 yr_old	-.052182	.0399786	-1.31	0.192	-.1305387	.0261747
BMI_Category						
Overweight	-.0177077	.0156904	-1.13	0.259	-.0484604	.0130449
Obese	-.0150946	.0172463	-0.88	0.381	-.0488967	.0187074
Morbidly Obese	-.0273359	.0608352	-0.45	0.653	-.1465707	.0918989
Smoking_Status						
Previous	.0064122	.0142637	0.45	0.653	-.0215443	.0343686
Current	-.0295427	.0214073	-1.38	0.168	-.0715001	.0124148
ECG_Result	-.0215747	.0157273	-1.37	0.170	-.0523997	.0092503
Celecoxib_Treatment_Consumption	-.0081632	.0129252	-0.63	0.528	-.0334961	.0171696
Diabetes	-.0881547	.0233651	-3.77	0.000	-.1339494	-.0423601
TCC_History	-.022155	.0137706	-1.61	0.108	-.049145	.0048349
Year						
Year 2	-.0174281	.0085872	-2.03	0.042	-.0342587	-.0005975
Year 3	-.0161801	.0090078	-1.80	0.072	-.033835	.0014749
Cystectomy_Month	-.1676828	.0382576	-4.38	0.000	-.2426664	-.0926992
_cons	.3340947	.0476971	7.00	0.000	.24061	.4275793

Table S9: Costing regression

TOTAL_COSTS_Month	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Tumour_Recurrence_Month						
Unknown	1517.223	1729.041	0.88	0.380	-1871.636	4906.082
Grade 1	1217.438	415.9633	2.93	0.003	402.1653	2032.711
Grade 2	1676.051	385.9831	4.34	0.000	919.5377	2432.564
Grade 3	3956.667	829.3751	4.77	0.000	2331.122	5582.212
Risk_Group						
High Risk	1967.914	311.494	6.32	0.000	1357.397	2578.431
Year						
Year 2	-921.3536	251.7046	-3.66	0.000	-1414.686	-428.0217
Year 3	-1514.189	233.9928	-6.47	0.000	-1972.806	-1055.571
Risk_Group#Year						
High Risk#Year 2	-1511.85	343.8087	-4.40	0.000	-2185.702	-837.997
High Risk#Year 3	-1894.898	319.9745	-5.92	0.000	-2522.036	-1267.759
Progression_Month	5406.938	1400.335	3.86	0.000	2662.332	8151.544
Progression_History_M~h	2269.138	806.8528	2.81	0.005	687.7356	3850.54
TCC_History	91.53518	91.50393	1.00	0.317	-87.80923	270.8796
Patient_Gender	162.3912	104.348	1.56	0.120	-42.12716	366.9096
Diabetes	-67.09895	147.0358	-0.46	0.648	-355.2838	221.0859
1.Celecoxib_Treatment~n	-103.1504	90.55783	-1.14	0.255	-280.6405	74.33965
Toxicity_Month						
Mild Condition	190.4007	173.7812	1.10	0.273	-150.2041	531.0055
Moderate Condition	171.735	300.5923	0.57	0.568	-417.415	760.885
Celecoxib_Treatment_C~n#						
Toxicity_Month						
1#Mild Condition	153.2397	242.295	0.63	0.527	-321.6498	628.1292
1#Moderate Condition	390.0575	387.7738	1.01	0.314	-369.9651	1150.08
Age						
50-59 yrs old	36.85634	193.8437	0.19	0.849	-343.0704	416.7831
60-69 yrs old	62.7073	177.3931	0.35	0.724	-284.9767	410.3913
70-79 yrs old	-78.92821	182.5277	-0.43	0.665	-436.676	278.8195
>80 yrs old	59.02592	226.9982	0.26	0.795	-385.8824	503.9342
BMI						
Overweight	207.6795	95.78029	2.17	0.030	19.95362	395.4054
Obese	258.0722	113.3226	2.28	0.023	35.96402	480.1804
Morbidly Obese	1257.968	623.3053	2.02	0.044	36.31178	2479.624
Smoking_Status						
Previous	-57.20011	97.19538	-0.59	0.556	-247.6996	133.2993
Current	-241.9663	122.4042	-1.98	0.048	-481.8741	-2.058529
_cons	2348.796	305.0676	7.70	0.000	1750.875	2946.718

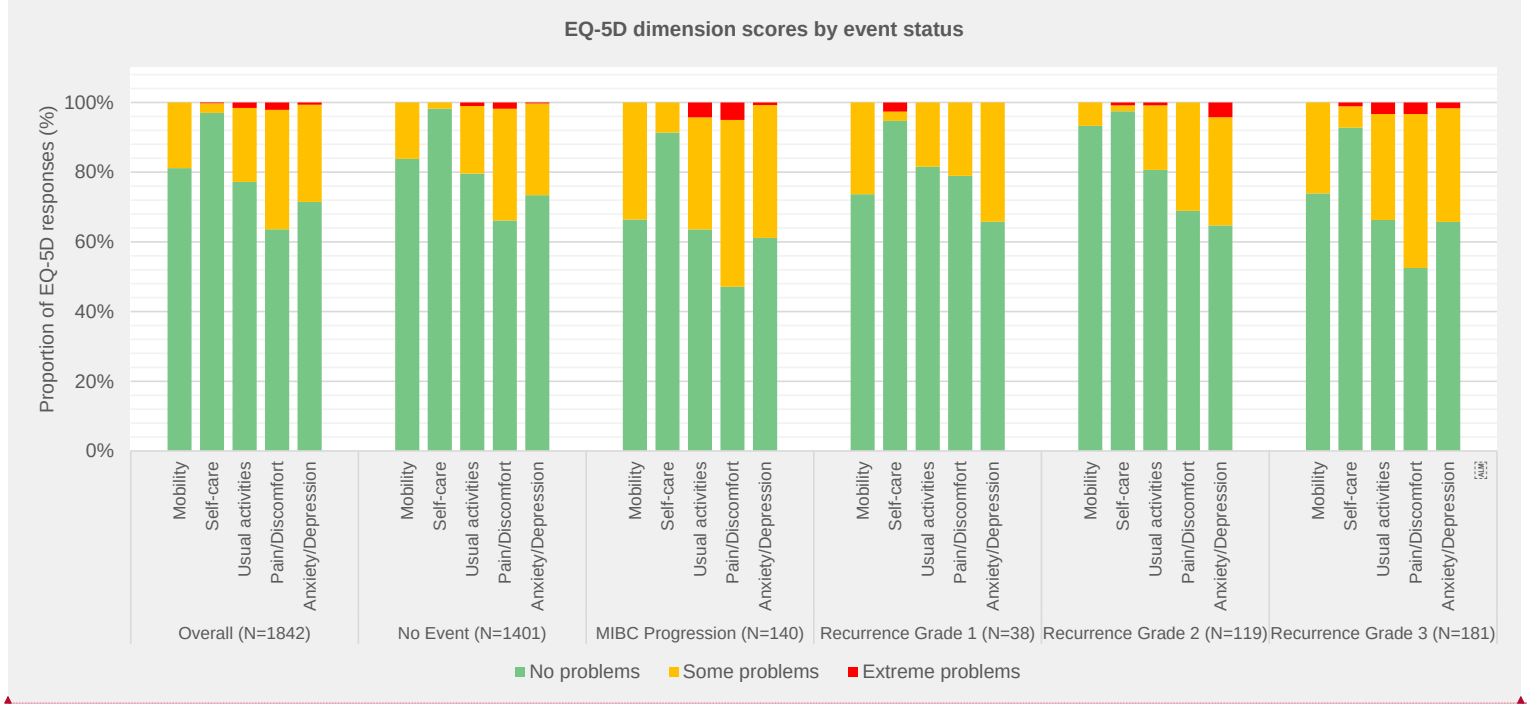
Table S10: Variance-covariance matrix base case HRQoL regression analysis

	EQ5D_Base	Gender	Age 50-60	Age 60-70	Age 70-80	Age 80+	BMI1	BMI2	BMI3	Smoke1	Smoke2	ECG	Celecoxib	Diabetes	History	Year2	Year3	Unk	G1	G2	G3	Prog	Proghistory	_cons
EQ5D_Baseline	0.00165																							
Gender	0.0000	0.0003																						
Age 50-60	0.0000	-0.0001	0.0011																					
Age 60-70	-0.0001	-0.0001	0.0009	0.0010																				
Age 70-80	0.0000	-0.0001	0.0009	0.0009	0.0011																			
Age 80+	-0.0001	-0.0001	0.0009	0.0009	0.0010	0.0016																		
BMI overweight	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0003																	
BMI obese	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0003																
BMI morbidly obese	-0.0001	0.0000	-0.0001	-0.0001	0.0000	0.0000	0.0002	0.0002	0.0042															
Smoking previous	0.0000	0.0000	-0.0001	-0.0001	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0002														
Smoking current	0.0001	-0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	-0.0001	0.0001	0.0006													
ECG_Result	0.0000	0.0000	0.0000	-0.0001	-0.0001	-0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0003												
Celecoxib	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0002											
Diabetes	0.0001	0.0000	0.0000	-0.0001	-0.0001	-0.0001	0.0000	0.0000	-0.0002	0.0000	0.0000	0.0000	0.0000	0.0006										
TCC_History	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002									
2.Year	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001								
3.Year	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001							
Tumour_Unk	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0068						
Tumour G1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0031					
Tumour G2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0012				
Tumour G3	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0007			
Progression	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0014		
Proghistory	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0004	0.0027	
_cons	-0.0014	-0.0002	-0.0008	-0.0008	-0.0008	-0.0008	-0.0001	-0.0002	0.0000	0.0000	-0.0001	0.0000	-0.0001	-0.0001	-0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0024

Table S11: Variance-covariance matrix base case cost regression analysis

	Tumour_U	Tumour G1	Tumour G2	Tumour G3	HR	Year 2	Year 3	#Year 2	#Year 3	Prog	Prog Hist	TCC hist	Gender	Diabetes	Celecoxib	Tox Mild	Tox Mod	#mild	#mod	Age 50-60	Age 60-70	Age 70-80	Age 80+	BMI 1	BMI 2	BMI 3	Smoking 1	Smoking 2	constant
Tumour_Unk	2989584																												
Tumour G1	3197.897	173025.4																											
Tumour G2	455.0007	5153.004	148982.9																										
Tumour G3	4751.888	1440.31	5766.639	687863.1																									
High Risk	-12708.1	7947.394	6233.751	-12978.7	97028.53																								
Year 2	128.5532	2513.226	5118.316	2360.683	45236.91	63355.2																							
Year 3	417.7922	6185.773	9399.375	3398.295	46386.92	47142.29	54752.65																						
High Risk#Year 2	12903.19	-2631.28	-1898.03	13670.3	-92607.2	-61490.2	-44871.9	118204.4																					
High Risk#Year 3	10099.37	-5412.12	-5798.32	12242.9	-94413.4	-44807.9	-51859.6	91808.03	102383.7																				
Prog Month	3772.371	67.20135	-12774.8	-87906.4	-11840.8	-1096.95	-1184.22	6543.22	10696.11	1960938																			
Prog HistMonth	3597.378	131.9645	1131.308	3651.328	-756.922	429.5359	37.94244	-3169.66	-1512.31	47298.56	651011.4																		
TCC_History	-3973.36	177.3514	-249.955	-618.622	1794.413	201.794	446.6992	-80.3491	-176.578	-1414.4	-2551.17	8372.969																	
Patient_Gender	-2929.97	-77.8528	500.8079	550.0644	-184.652	924.8961	1028.345	-228.396	-256.491	-934.697	-1450.44	634.9075	10888.51																
Diabetes	174.1897	458.7002	-786.564	-1579.5	61.53177	93.05056	-59.2129	-127.267	-313.961	1281.531	-1474.4	518.0848	588.3711	21619.53															
Celecoxib	2048.935	402.4205	-98.0007	920.2471	216.8488	-36.8882	-714.756	81.53749	647.6306	231.6324	515.0038	-10.0378	-759.794	-1101.22	8200.721														
Toxicity Mild	-600.194	429.0679	321.6055	-73.1877	630.1364	4588.025	5054.176	-527.603	-608.46	713.4595	1786.313	298.7808	2207.895	-454.888	3779.813	30199.89													
Toxicity Moderate	2383.184	-2263.53	1663.632	2924.52	-1789.75	6931.381	6671.093	103.2672	3430.716	4155.016	1639.651	135.8265	1061.755	-97.2649	3874.048	6976.896	90355.71												
Celecoxib#mild	438.1648	-1952.97	601.5322	-1065.34	-393.143	-880.25	427.7197	-287.85	-203.163	-1276.02	-266.424	226.7488	-1008.46	427.0523	-7417.36	-29182.4	-5234.27	58706.88											
Celecoxib#moderate	-578.645	204.5142	-1252.18	-3234.89	3614.205	-463.231	1200.66	-1325.14	-5724.77	-4619.99	-150.712	-435.541	-60.541	550.1123	-7471.91	-5457.64	-88242.4	9219.409	150368.5										
Age 50-60	-461.326	-1297.4	-2167.35	-219.887	877.5002	-383.189	-780.626	-62.6462	536.8991	1446.35	-632.307	54.15569	-388.29	-844.322	1911.414	-315.633	-16.8047	-1357.87	-284.003	37575.4									
Age 60-70	-760.247	-565.579	-1189.19	-1265.14	1569.057	-532.382	-836.337	80.84493	565.3626	-535.485	-3198.85	294.7149	-1511.36	-2402.45	2058.851	-920.176	-519.123	-1076.13	-61.9788	27048.9	31468.3								
Age 70-80	-3417.03	-643.19	-422.365	-493.563	1144.489	-680.322	-1062.53	32.89036	515.9473	-632.644	-2133.45	-233.831	-1363.8	-2793.31	1804.646	-1484.46	-1129.18	375.9521	-995.23	26940.94	27342.93	33316.37							
Age 80+	-2210.66	-1113.08	-169.061	-1806.11	892.5153	-297.992	-451.897	16.11853	386.4642	1645.557	-342.335	140.223	-925.094	-1278.83	2066.425	-156.349	460.59	-827.155	-2429.76	27010.24	27247.6	27388.06	51528.18						
BMI Overweight	3529.466	573.0519	-339.4	-552.401	250.3219	24.09107	739.0862	109.069	-443.283	491.4164	290.0057	-150.674	-73.1737	-792.842	-161.863	724.8933	-623.956	-1356.18	1204.683	-556.359	-313.425	38.44737	-1558.25	9173.863					
BMI Obese	3521.786	400.006	-595.534	-726.146	-612.32	-32.3199	604.3832	90.40263	-260.271	-246.015	1816.794	-373.677	-373.834	-3086.28	-306.06	117.209	-1073.1	28.07319	1280.047	-2138.66	-816.066	193.7971	-609.137	5204.197	12842.01				
BMI morbidly obese	-118.211	-9986.43	-9469.14	-2409.75	-2017.09	40.76192	1044.331	456.362	986.1302	3133.209	1577.672	33.32034	4273.654	-6030.72	-2071.96	2339.3	19.31831	-1655.31	1015.499	4159.043	3032.126	6170.16	5360.11	5745.526	6500.394	388509.5			
Smoking previous	3051.792	-192.533	-525.105	735.3619	147.8917	-410.739	-357.737	167.0641	-65.6603	-492.734	1603.186	-316.844	-1847.56	-829.911	91.54407	-1454.3	-945.744	1053.433	-61.0395	-905.897	-1423.65	-677.65	-1246.05	-968.874	-696.796	-4306.3	9446.943		
Smoking current	3021.291	1286.492	-351.976	619.1337	1659.942	-449.125	-294.024	231.7881	-115.202	-93.4865	785.4893	216.0982	-2526.05	-1053.26	-581.953	-978.082	-1439.44	1179.949	787.8671	1593.945	1184.458	2831.625	2421.957	409.944	639.0463	-575.662	5894.281	14982.78	
constant	-650.554	-8561.44	-9019.26	-3331.26	-50134.5	-48152.1	-49973.6	45313.96	46188.36	2439.925	2001.973	-4320.44	-6659.01	1944.855	-5262.25	-9175.75	-10217.5	5459.517	3663.643	-26755.5	-26623.3	-26969.7	-26842.4	-4592.3	-3397.78	-9238.54	-2227.81	-6309.84	93066.23

Figure S1: EQ-5D responses in high-risk patients for each event-related sub-group, EQ-5D dimension and EQ-5D level over three years follow-up



The number (N) is indicative of the maximum number of observations recorded of an EQ-5D dimension for a given event-related sub-group (e.g. up to 119 recording were made of an EQ-5D dimension for patients who experienced a Grade 2 recurrence during the three years follow-up).

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