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)(9). 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:*

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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)

13%

11%

3%

21%

**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



**Table S6:** Primary HRQoL regression including time and event interaction



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

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

**Table S9:** Costing regression

**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).