Supplement

Contents

Appendix A. Late Genitourinary Endpoint Amalgamation Process

Note on RTOG Scoring:
In the trial follow-up forms, rather than an overall RTOG score, the possible contributory components were requested separately:

- Cystitis
- Haematuria
- Stricture

Note on baseline scores
The baseline score is generated as the WORST score of the baseline assessment and the pre-RT assessment. Patients would not be assigned a baseline score without the relevant endpoint being scored at one or both of those visits (and thus would be excluded from that endpoint). Only RMH and LENTSOM were collected at those timepoints, so RTOG scores are not considered in the adjudication of zero baseline toxicity.

Endpoint generation
The composite individual endpoints generated are listed, along with subdomain scores that would generate an event score in the composite endpoint. Exclusion criteria are explained.

Dysuria G1+

- Exclude unless:
    - Baseline LENT-SOM Subjective dysuria = G0 **AND**
    - Baseline LENT-SOM Management dysuria = G0
- Toxicity scored if:
    - Any ≥6 month f/u LENT-SOM Subjective dysuria (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Management dysuria (G1+)
- Exclude if missing >50% follow-up scores for any of:
    - LENT-SOM Subjective dysuria **OR**
    - LENT-SOM Management dysuria
- Otherwise score as No Toxicity

Dysuria G2+

- Exclude unless:
    - Baseline LENT-SOM Subjective dysuria = G0 **AND**
    - Baseline LENT-SOM Management dysuria = G0
- Toxicity scored if:
    - Any ≥6 month f/u LENT-SOM Subjective dysuria (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Management dysuria (G1+)
- Exclude if missing >50% follow-up scores for any of:
    - LENT-SOM Subjective dysuria **OR**
    - LENT-SOM Management dysuria
- Otherwise score as No Toxicity

Haematuria G1+

- Exclude unless:
    - Baseline LENT-SOM Subjective Haematuria = G0 **AND**
    - Baseline LENT-SOM Objective Haematuria = G0 **AND**
    - Baseline LENT-SOM Objective Endoscopy = G0 **AND**
    - Baseline LENT-SOM Management Haematuria = G0
- Toxicity scored if:
    - Any ≥6 month f/u RTOG Haematuria (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective Haematuria (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Objective Haematuria (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Objective Endoscopy (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Management Haematuria (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - RTOG Haematuria **OR**
    - LENT-SOM Subjective Haematuria **OR**
    - Baseline LENT-SOM Objective Haematuria **OR**
    - Baseline LENT-SOM Objective Endoscopy **OR**
    - Baseline LENT-SOM Management Haematuria
- Otherwise score as No Toxicity

Haematuria G2+

- Exclude unless:
    - Baseline LENT-SOM Subjective Haematuria = G0 **AND**
    - Baseline LENT-SOM Objective Haematuria = G0 **AND**
    - Baseline LENT-SOM Objective Endoscopy = G0 **AND**
    - Baseline LENT-SOM Management Haematuria = G0
- Toxicity scored if:
    - Any ≥6 month f/u RTOG Haematuria (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective Haematuria (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Objective Haematuria (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Objective Endoscopy (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Management Haematuria (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - RTOG Haematuria **OR**
    - LENT-SOM Subjective Haematuria **OR**
    - Baseline LENT-SOM Objective Haematuria **OR**
    - Baseline LENT-SOM Objective Endoscopy **OR**
    - Baseline LENT-SOM Management Haematuria
- Otherwise score as No Toxicity

Urinary Incontinence G1+

- Exclude unless:
    - Baseline RMH Urinary Incontinence = G0 **AND**
    - Baseline LENT-SOM Subjective Urinary Incontinence = G0 **AND**
    - Baseline LENT-SOM Management pain Urinary Incontinence = G0
- Toxicity scored if:
    - Any ≥6 month f/u RMH Urinary Incontinence (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective Urinary Incontinence (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Management pain Urinary Incontinence (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - LENT-SOM RMH Urinary Incontinence **OR**
    - LENT-SOM Subjective Urinary Incontinence **OR**
    - LENT-SOM Management pain Urinary Incontinence
- Otherwise score as No Toxicity

Urinary Incontinence G2+

- Exclude unless:
    - Baseline RMH Urinary Incontinence = G0 **AND**
    - Baseline LENT-SOM Subjective Urinary Incontinence = G0 **AND**
    - Baseline LENT-SOM Management pain Urinary Incontinence = G0
- Toxicity scored if:
    - Any ≥6 month f/u RMH Urinary Incontinence (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective Urinary Incontinence (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Management pain Urinary Incontinence (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - LENT-SOM RMH Urinary Incontinence **OR**
    - LENT-SOM Subjective Urinary Incontinence **OR**
    - LENT-SOM Management pain Urinary Incontinence
- Otherwise score as No Toxicity

Reduced Flow / Stricture G1+

- Exclude unless:
    - Baseline LENT-SOM Subjective decreased stream = G0 **AND**
    - Baseline LENT-SOM Management decreased stream = G0
- Toxicity scored if:
    - Any ≥6 month f/u RTOG Urethral Stricture (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective decreased stream (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Management decreased stream (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - RTOG Urethral Stricture **OR**
    - LENT-SOM Subjective decreased stream **OR**
    - LENT- SOM Management decreased stream
- Otherwise score as No Toxicity

Reduced Flow / Stricture G2+

- Exclude unless:
    - Baseline LENT-SOM Subjective decreased stream = G0 **AND**
    - Baseline LENT-SOM Management decreased stream = G0
- Toxicity scored if:
    - Any ≥6 month f/u RTOG Urethral Stricture (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective decreased stream (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Management decreased stream (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - RTOG Urethral Stricture **OR**
    - LENT-SOM Subjective decreased stream **OR**
    - LENT- SOM Management decreased stream
- Otherwise score as No Toxicity

Urine Frequency G1+

- Exclude unless:
    - Baseline RMH Urine Daytime Frequency = G0 **AND**
    - Baseline RMH Nocturia = G0 AND
    - Baseline LENT-SOM Subjective urinary frequency = G0 **AND**
    - Baseline LENT-SOM Management urinary frequency = G0
- Toxicity scored if:
    - Any ≥6 month f/u RTOG Cystitis (G1+) **OR**
    - Any ≥6 month f/u RMH Urine Daytime Frequency (G1+) **OR**
    - Any ≥6 month f/u RMH Nocturia (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective urinary frequency (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Management urinary frequency (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - RTOG Cystitis **OR**
    - RMH Urine Daytime Frequency **OR**
    - RMH Nocturia **OR**
    - LENT-SOM Subjective urinary frequency **OR**
    - LENT-SOM Management urinary frequency
- Otherwise score as No Toxicity

Urine Frequency G2+

- Exclude unless:
    - Baseline RMH Urine Daytime Frequency = G0 **AND**
    - Baseline RMH Nocturia = G0 AND
    - Baseline LENT-SOM Subjective urinary frequency = G0 **AND**
    - Baseline LENT-SOM Management urinary frequency = G0
- Toxicity scored if:
    - Any ≥6 month f/u RTOG Cystitis (G2+) **OR**
    - Any ≥6 month f/u RMH Urine Daytime Frequency (G2+) **OR**

    - Any ≥6 month f/u RMH Nocturia (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Subjective urinary frequency (G2+) **OR**
    - Any ≥6 month f/u LENT-SOM Management urinary frequency (G1+)
- Exclude if missing >50% (4/7) follow-up scores for any of:
    - RTOG Cystitis **OR**
    - RMH Urine Daytime Frequency **OR**
    - RMH Nocturia **OR**
    - LENT-SOM Subjective urinary frequency **OR**
    - LENT-SOM Management urinary frequency
- Otherwise score as No Toxicity

Supplementary Table A. Toxicity Rates and Missing Data by Endpoint

Patients excluded for any of: missing baseline data; baseline toxicity above grade 0; missing >50% of follow-up forms. Presented percentages are calculated without the inclusion of patients excluded for each endpoint, so that event rates in modelled patients can be seen. Abbreviations: GX+ = Grade X or more.

GU Endpoints & Grades of Interest	Dose-Fractionation Regimen						Total	
	57 Gy in 19 fractions		60 Gy in 20 fractions		74 Gy in 37 fractions			
	No.	%	No.	%	No.	%	No.	%
Dysuria G1+								
No	639	89.4%	612	85.8%	595	87.1%	1,846	87.4%
Yes	76	10.6%	101	14.2%	88	12.9%	265	12.6%
Excluded	33	N/A	35	N/A	27	N/A	95	N/A
Dysuria G2+								
No	674	94.3%	668	93.7%	644	94.3%	1,986	94.1%
Yes	41	5.7%	45	6.3%	39	5.7%	125	5.9%
Excluded	33	N/A	35	N/A	27	N/A	95	N/A
Haematuria G1+								
No	615	89.5%	623	88.7%	606	91.3%	1,844	89.8%
Yes	72	10.5%	79	11.3%	58	8.7%	209	10.2%
Excluded	61	N/A	46	N/A	46	N/A	153	N/A
Haematuria G2+								
No	652	95.2%	655	93.4%	641	96.5%	1,948	95.0%
Yes	33	4.8%	46	6.6%	23	3.5%	102	5.0%
Excluded	63	N/A	47	N/A	46	N/A	156	N/A
Incontinence G1+								
No	499	76.8%	486	74.9%	489	77.9%	1,474	76.5%
Yes	151	23.2%	163	25.1%	139	22.1%	453	23.5%
Excluded	98	N/A	99	N/A	82	N/A	279	N/A
Incontinence G2+								
No	604	93.1%	597	92.1%	585	93.5%	1,786	92.9%
Yes	45	6.9%	51	7.9%	41	6.5%	137	7.1%
Excluded	99	N/A	100	N/A	84	N/A	283	N/A
Reduced Flow / Stricture G1+								
No	442	73.7%	445	74.7%	405	74.0%	1,292	74.1%
Yes	158	26.3%	151	25.3%	142	26.0%	451	25.9%
Missing	148	N/A	152	N/A	163	N/A	463	N/A
Reduced Flow / Stricture G2+								
No	520	86.7%	523	87.8%	483	88.3%	1,526	87.6%
Yes	80	13.3%	73	12.2%	64	11.7%	217	12.4%
Excluded	148	N/A	152	N/A	163	N/A	463	N/A
Urine Frequency G1+								
No	105	44.9%	98	42.8%	80	41.9%	283	43.3%
Yes	129	55.1%	131	57.2%	111	58.1%	371	56.7%
Excluded	514	N/A	519	N/A	519	N/A	1,552	N/A

Table continues overleaf…

Urine Frequency G2+								
No	195	84.1%	170	75.6%	145	76.3%	510	78.8%
Yes	37	15.9%	55	24.4%	45	23.7%	137	21.2%
Excluded	516	N/A	523	N/A	520	N/A	1,559	N/A
Total	**748**	**100.0%**	**748**	**100.0%**	**710**	**100.0%**	**2,206**	**100.0%**

Appendix B. Detailed description of the modelling methodology

The LKB-NoEQD2 Model

Fitting the simple LKB model without EQD2 correction of dose

Step 1

For each patient, the first step is calculation of DEff:

$$D_{Eff} = \left(\sum_{i=1}^{z} (D_i)^{\frac{1}{n}} \cdot v_i \right)^n \quad (1)$$

Where:

n = relatively organ seriality: closer to zero is more serial, closer to ≥1 is more parallel (fitted model parameter)

z = number of dose bins in DVH, iterated by *i*

v_i = relative volume of DVH dose bin *i*

D_i = dose of DVH dose bin *i*

Step 2

This is then used to calculate *t:*

$$t = \frac{D_{Eff} - TD_{50}}{m \cdot TD_{50}} \quad (2)$$

Where:

TD_{50} = Toxic dose 50% (fitted model parameter)

m = Constant inversely proportional to dose response steepness (fitted model parameter)

Step 3

The value of *t* defines the normal tissue complication probability from:

$$NTCP = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^{t} e^{-0.5 \cdot x^2} \, dx \quad (3)$$

Where:

NTCP = Normal Tissue Complication Probability. The predicted probability of toxicity

Step 4

The likelihood contribution for each patient is then calculated by comparing their predicted to true toxicity status:

$$Likelihood = f(toxicity) = \begin{cases} NTCP & toxicity = 1 \\ 1 - NTCP & toxicity = 0 \end{cases} \quad (4)$$

Step 5

Having undertaken each of the above steps for each patient, the naïve model performance is then calculated as the sum of the log likelihoods. The negative value of this (a positive number) is then maximised (fitting *n, m, TD50*) to obtain the best model fit for the endpoint population.

$$Naive\ Performance = Summed\ Log\ Likelihood = \sum_{j=1}^{c} \ln Likelihood_j \tag{5}$$

Where:

c = total number of patients, iterated by j

Step 6

2000 bootstraps for that endpoint of interest (stratified by toxicity status, with replacement) are then refitted for steps 1-5. The performance was then assessed on patients not included in that bootstrap, then averaged across bootstraps:

$$Out\ of\ the\ bag\ (OOB)\ performance = \sum_{j=1}^{c}\left(\frac{1}{z} \times \sum_{b=1}^{z} \ln \widehat{likelihood}_{j,b}\right) \tag{7}$$

Where:

z = total number of bootstraps not containing patient *j*, iterated by *b*

Step 7

The 632 estimator (explained in main body) was then used to provide an estimate of model test performance. This is a method used to modulate the naïve performance (overly optimistic, overfitted) and OOB performance (overly pessimistic). This was preferred over the 632+ method due to ease of calculation and very low risk of near perfect performance (where 632+ is strongly preferred).

$$632\ Estimator = 0.368 \cdot Naive\ Performance + \ 0.632 \cdot OOB\ Performance \tag{8}$$

This could then be used to compare different nested models by means of the likelihood ratio test. The differing methodologies for the other more complicated models follows.

The LKB-EQD2 Model

The model replaces step 1 in the above model with:

$$D_{Eff} = \left(\sum_{i=1}^{z} (\ EQD2_i\ )^{\frac{1}{n}} \cdot v_i\right)^n \tag{9}$$

Where $EQD2_i$ is defined as:

$$EQD2_i = D_i \cdot \left(\frac{d_i + \alpha/\beta}{2\ Gy + \alpha/\beta}\right) \tag{10}$$

Where:

D_i = Total dose to dose bin *i*

d_i = Dose per fraction to dose bin *i*

α/β = The α/β ratio for that toxicity endpoint (fitted model parameter)

The LKB-EQD2 model therefore fits: *n, m, TD50,* α/β

The LKB-EQD2-DMF Model

This model keeps the modification to step 1 as outlined in the LKB-EQD2 model.

Additionally, it replaces step 2 with:

$$t = \frac{D_{Eff} \cdot e^{\delta \cdot DMF} - TD_{50}}{m \cdot TD_{50}} \quad (11)$$

Where:
δ = Either: Presence of absence of dose modifying factor (e.g. diabetes: yes = 1, no = 0). Or for continuous dose modifying factors, the associated number (e.g. age in years).
DMF = Associated constant that defines magnitude of effect of the dose modifying factor in modulating the effective dose (fitted model parameter)

The LKB-EQD2-DMF model therefore fits: *n, m, TD50,* α/β, *DMF*

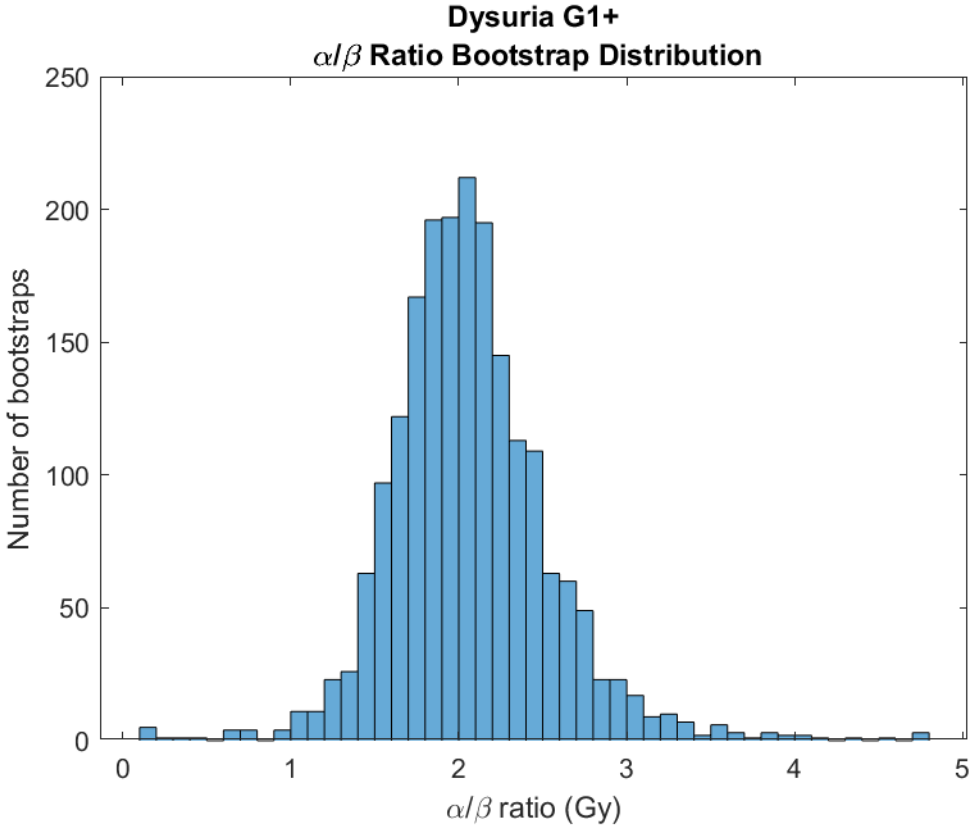
Supplementary Table B. LKBNoEQD2 Model Fits

Fits of the LKB-NoEQD2 model, reported for (going down table) 74 Gy patients only; 57/60 Gy patients; all patients.
Abbreviations: EQD2 = Equivalent Dose in 2 Gy fractions; Gx+ = Grade X or more; LKB-NoEQD2 = Lyman Kutcher Burman model without EQD2 correction; TD50 = Toxic dose 50%.

Model	**Pts**	***n* (95% CI)**	***m* (95% CI)**	***TD50* (95% CI) [Gy]**	**632 Likelihood**
LKB-NoEQD2 (74Gy Patients)					
Dysuria G1+	683	0.01 (0.01-0.44)	0.29 (0.08-0.82)	100.8 (79.1-999.9)	-263.1
Dysuria G2+	683	0.01 (0.01-9.98)	0.43 (0.07-0.60)	188.7 (82.1-1000)	-150.1
Haematuria G1+	664	0.07 (0.01-2.15)	0.30 (0.10-0.69)	105.7 (78.7-999.6)	-197.1
Haematuria G2+	664	0.05 (0.01-10.00)	0.45 (0.08-0.52)	214.3 (81.4-1000)	-101
Incontinence G1+	628	0.01 (0.01-1.12)	0.16 (0.07-1.21)	81.8 (76.1-994.3)	-332.1
Incontinence G2+	626	0.01 (0.01-10.00)	0.08 (0.04-0.60)	81.0 (76.1-267.9)	-150.5
Reduced Flow / Stricture G1+	547	0.11 (0.01-10.00)	0.50 (0.10-1.40)	82.5 (69.9-419.2)	-313.2
Reduced Flow / Stricture G2+	547	0.09 (0.01-10.00)	0.25 (0.06-0.74)	85.9 (74.8-233.2)	-197.1
Urine Frequency G1+	191	0.01 (0.01-1.38)	3.25 (0.07-10.00)	37.6 (10.0-71.0)	-130.7
Urine Frequency G2+	190	0.01 (0.01-9.99)	1.17 (0.07-1.35)	197.1 (75.1-1000)	-104.8
LKB-NoEQD2 (57Gy/60Gy Patients)					
Dysuria G1+	1428	0.02 (0.01-0.12)	0.18 (0.12-0.42)	69.6 (63.9-93.6)	-531.1
Dysuria G2+	1428	0.03 (0.01-1.17)	0.27 (0.14-0.61)	93.5 (71.0-961.2)	-325.5
Haematuria G1+	1389	0.06 (0.01-0.93)	0.31 (0.16-0.72)	84.0 (68.2-268.4)	-477.1
Haematuria G2+	1386	0.03 (0.01-0.59)	0.20 (0.11-0.54)	79.7 (68.1-227.4)	-302.4
Incontinence G1+	1299	0.01 (0.01-10.00)	0.86 (0.25-1.37)	116.9 (68.8-999.9)	-719.4
Incontinence G2+	1297	0.02 (0.01-1.09)	0.30 (0.14-0.65)	96.1 (70.8-999.9)	-342.9
Reduced Flow / Stricture G1+	1196	0.16 (0.03-0.38)	0.73 (0.33-1.46)	81.7 (61.8-973.5)	-682.9
Reduced Flow / Stricture G2+	1196	0.14 (0.01-10.00)	0.76 (0.27-0.85)	234.5 (79.4-1000)	-458.3
Urine Frequency G1+	463	1.61 (0.03-10.00)	4.33 (0.28-10.00)	12.7 (7.4-50.2)	-314.4
Urine Frequency G2+	457	0.02 (0.01-0.44)	0.21 (0.11-1.01)	66.6 (59.7-250.4)	-229.3
LKB-NoEQD2 (All Patients)					
Dysuria G1+	2111	0.16 (0.01-0.84)	0.66 (0.49-0.83)	185.7 (113.7-1000)	-797.7
Dysuria G2+	2111	0.20 (0.01-10.00)	0.60 (0.44-0.63)	588.4 (179.4-1000)	-475.4
Haematuria G1+	2053	0.83 (0.23-9.95)	0.70 (0.60-0.76)	280.2 (138.2-1000)	-675.4
Haematuria G2+	2050	1.21 (0.04-10.00)	0.58 (0.52-0.59)	972.6 (212.7-1000)	-406
Incontinence G1+	1927	0.43 (0.01-10.00)	1.30 (0.97-1.36)	999.7 (170.0-1000)	-1051.5
Incontinence G2+	1923	0.78 (0.01-10.00)	0.64 (0.47-0.67)	392.4 (143.3-1000)	-494.7
Reduced Flow / Stricture G1+	1743	0.33 (0.13-10.00)	1.05 (0.75-1.48)	118.5 (80.7-897.4)	-995.8
Reduced Flow / Stricture G2+	1743	9.99 (0.07-10.00)	0.79 (0.60-0.85)	274.4 (126.6-1000)	-655.4
Urine Frequency G1+	654	0.76 (0.01-10.00)	9.98 (1.07-10.00)	12.0 (7.5-44.2)	-446.6
Urine Frequency G2+	647	0.03 (0.01-1.07)	0.68 (0.42-1.18)	122.7 (80.8-999.9)	-334.4

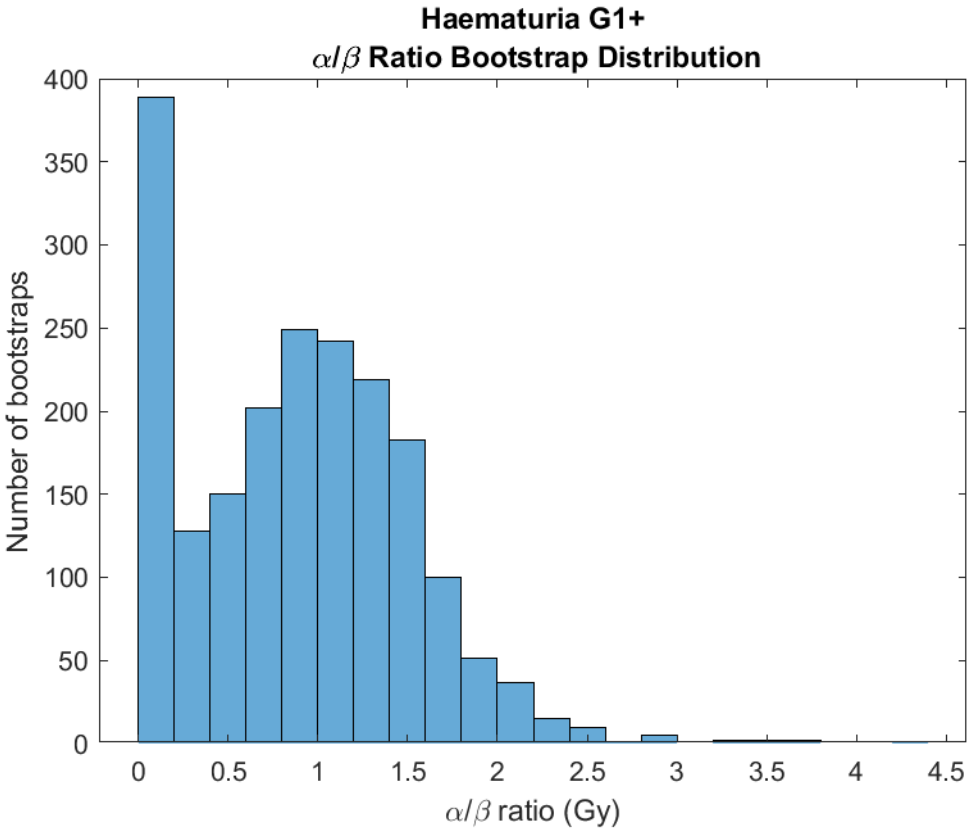
Supplementary Figure A. LKB-EQD2 Dysuria G1+ α/β Ratio Bootstrap Distribution

The bootstrap distribution of the α/β ratio parameter fitted for the LKB-EQD2 Dysuria G1+ model. A total of 7/2000 bootstrap values were >5 Gy and omitted from this plot.



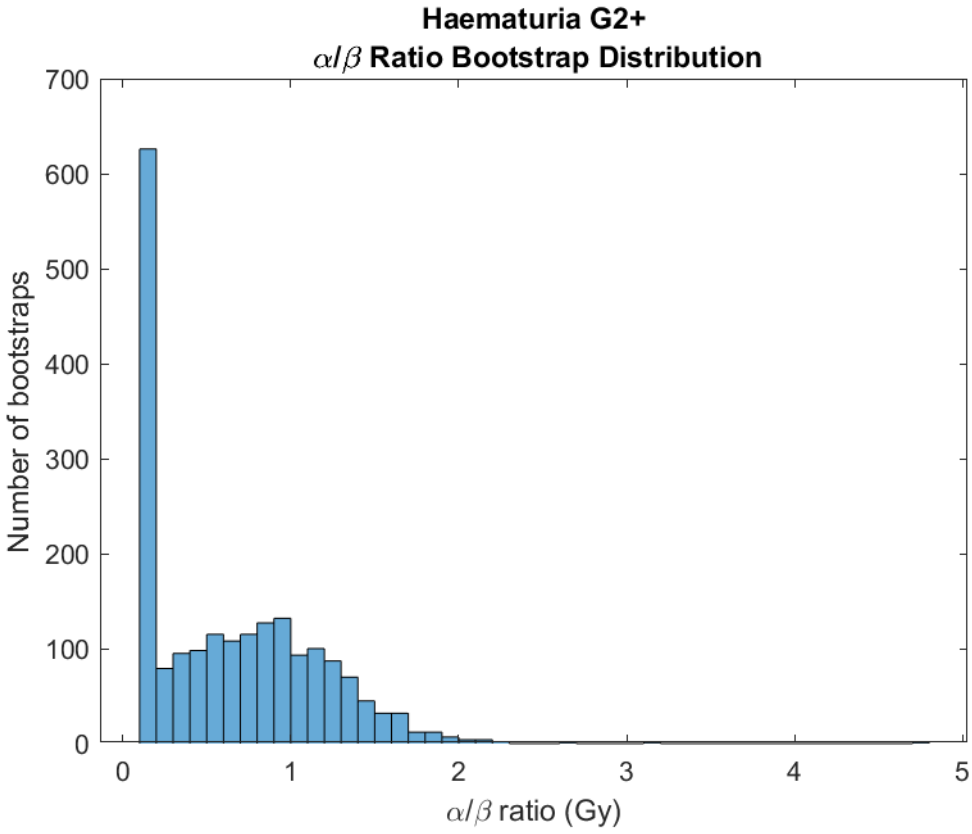
Supplementary Figure B. LKB-EQD2 Haematuria G1+ α/β Ratio Bootstrap Distribution

The bootstrap distribution of α/β Ratio parameter fitted for the LKB-EQD2 Haematuria G1+ model. It can be seen that the distribution is capped above zero by constraints in the modelling fitting range. This is to prevent negative α/β ratios from being fitted (since they imply either the α or β parameter is negative, suggesting more radiation resulting in less cell death). A total of 12 values were >5 Gy and omitted from this plot.

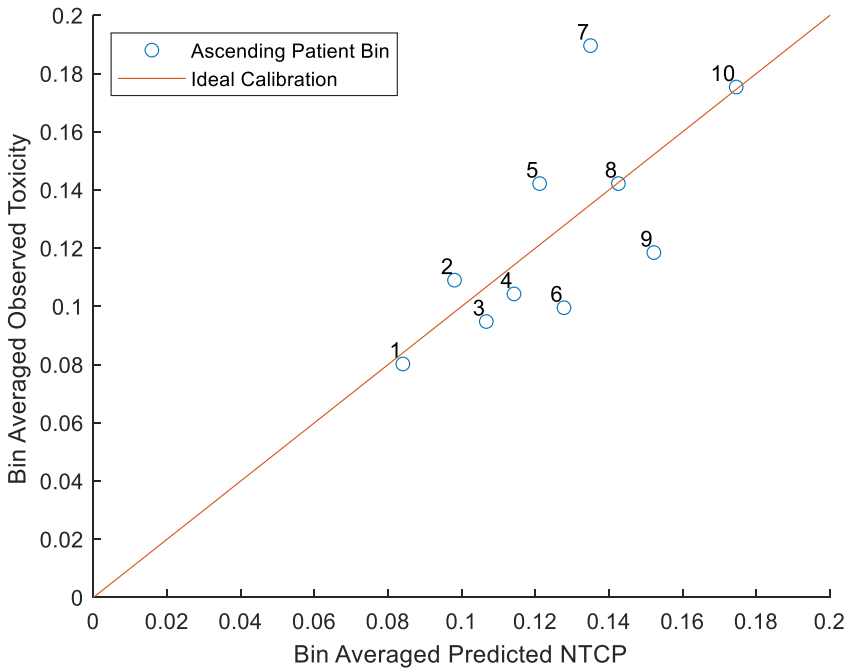


Supplementary Figure C. LKB-EQD2 Haematuria G2+ α/β Ratio Bootstrap Distribution

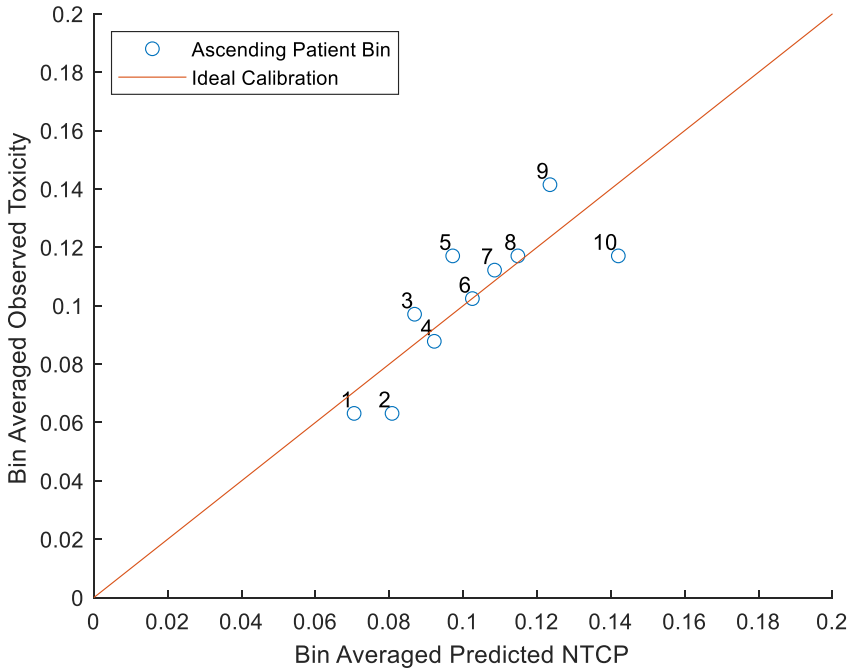
The bootstrap distribution of α/β Ratio parameter fitted for the LKB-EQD2 Haematuria G2+ model. It can be seen that the distribution is capped above zero by constraints in the modelling fitting range. This is to prevent negative α/β ratios from being fitted (since they imply either the α or β parameter is negative, suggesting more radiation resulting in less cell death). A total of 2 values were >5 Gy and omitted from this plot.



Supplementary Figure D. LKB-EQD2 Dysuria G1+ Calibration Plot



Supplementary Figure E. LKB-EQD2 Haematuria G1+ Calibration Plot



Decile binned calibration plots for LKB-EQD2 Dysuria G1+ (Figure A) and Haematuria G1+ (Figure B) models. Bins are by decile of predicted NTCP, plotted on the x-axis versus observed toxicity on the y-axis. Perfect prediction is shown as the orange identity line.

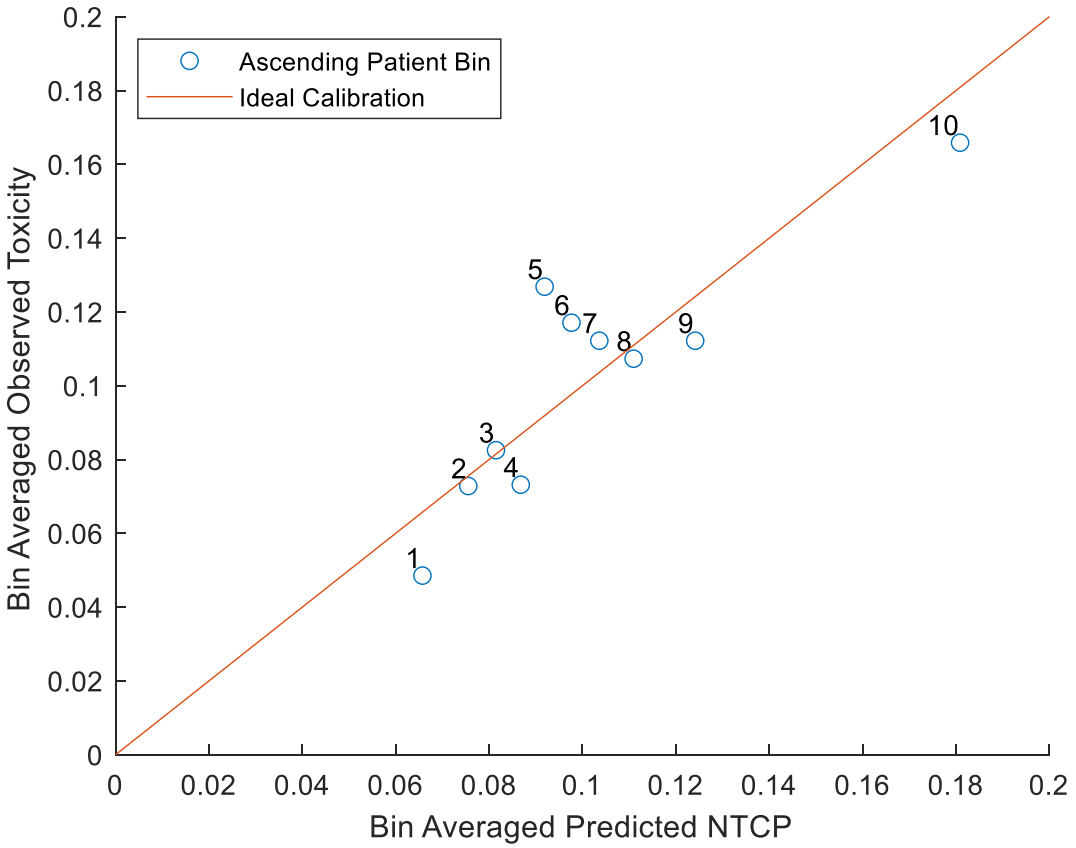
Abbreviations: LKB-EQD2 = Lyman-Kutcher-Burman model with Equivalent Dose in 2Gy/fraction Correction; NTCP = Normal Tissue Complication Probability.

Supplementary Table C. Fits of the LKB-EQD2-DMF Models

Showing fitted model parameters for LKB-EQD2-DMF models fitted to different potential dose-modifying factors. Shown for those endpoints where in main analysis EQD2 correction significantly improved the LKB-LKB-NoEQD2 model: Dysuria G1+, Haematuria G1+, Haematuria G2+. Only Haematuria G1+ LKB-EQD2-DMF model with DMF=*Prior TURP* meets adjusted significance threshold for improvement on the LKB-EQD2 model. It can be seen that fitted α/β ratios are fairly stable with the inclusion of any DMFs; for *Treatment Days* the α/β ratio fittings are lower rather than higher.

LKB-EQD2 (all Pts)	n	m	TD50	α/β ratio	Dose-Modifying Factor	632 Likelihood	Likelihood ratio test p-value
Dysuria G1+ (n=2111)							
LKB-EQD2 (No DMF)	*0.02 (0.01-0.07)*	*0.19 (0.13-0.37)*	*89.9 (82.5-118.4)*	*2.0 (1.2-3.2)*	*N/A*	*-793.7*	*N/A*
Age (years)	0.02 (0.01-0.08)	0.19 (0.13-0.44)	84.0 (65.5-126.8)	2.0 (1.2-3.8)	0.9991 (0.9934-1.0025)	-794.7	Worse fit
Diabetes Y/N	0.02 (0.01-0.07)	0.19 (0.13-0.38)	89.8 (82.3-120.6)	2.0 (1.2-3.2)	0.98 (0.86-1.04)	-794.6	Worse fit
Hypertension Y/N	0.02 (0.01-0.06)	0.19 (0.13-0.37)	90.6 (82.6-121.5)	2.0 (1.2-3.2)	1.01 (0.98-1.07)	-794.3	Worse fit
Pelvic Surgery Y/N	0.02 (0.01-0.07)	0.19 (0.13-0.38)	90.2 (82.5-120.3)	2.0 (1.2-3.2)	1.01 (0.93-1.10)	-794.6	Worse fit
Prior TURP Y/N	0.02 (0.01-0.07)	0.19 (0.13-0.37)	90.2 (82.6-119.7)	2.0 (1.2-3.2)	1.06 (0.99-1.19)	-793.1	0.27
Treatment Days (Days)	0.02 (0.01-0.07)	0.19 (0.13-0.40)	100.8 (57.2-173.1)	1.3 (0.1-302.9)	1.0018 (0.9915-1.0085)	-795.1	Worse fit
Haematuria G1+ (n=2053)							
LKB-EQD2 (No DMF)	*0.07 (0.02-0.40)*	*0.32 (0.19-0.58)*	*110.3 (89.4-184.1)*	*0.9 (0.1-2.2)*	*N/A*	*-673.2*	*N/A*
Age (years)	0.07 (0.02-0.96)	0.33 (0.19-0.69)	102.1 (22.6-235.6)	0.8 (0.1-2.3)	0.9988 (0.9685-1.0072)	-674.2	Worse fit
Diabetes Y/N	0.07 (0.02-0.74)	0.32 (0.19-0.64)	110.1 (89.0-185.5)	0.9 (0.1-2.1)	0.88 (0.01-1.02)	-672.9	0.46
Hypertension Y/N	0.07 (0.02-0.23)	0.33 (0.19-0.57)	115.2 (90.8-226.1)	0.9 (0.1-2.2)	1.07 (0.98-1.34)	-672.8	0.37
Pelvic Surgery Y/N	0.07 (0.02-0.58)	0.32 (0.19-0.61)	109.6 (89.1-185.2)	0.9 (0.1-2.2)	0.97 (0.67-1.16)	-674.2	Worse fit
Prior TURP Y/N	0.08 (0.02-7.45)	0.33 (0.19-0.74)	114.6 (90.0-999.6)	0.9 (0.1-2.6)	1.26 (1.08-19.58)	-668.1	**0.0015**
Treatment Days (Days)	0.06 (0.02-0.78)	0.33 (0.18-0.65)	112.7 (53.4-166.8)	0.8 (0.1-974.7)	0.9993 (0.9721-1.0060)	-673.8	Worse fit
Haematuria G2+ (n=2050)							
LKB-EQD2 (No DMF)	*0.04 (0.01-0.12)*	*0.24 (0.14-0.40)*	*120.1 (93.6-204.5)*	*0.6 (0.1-1.7)*	*N/A*	*-403.1*	*N/A*
Age (years)	0.04 (0.01-0.15)	0.25 (0.15-0.42)	90.6 (52.8-162.2)	0.6 (0.1-1.7)	0.9961 (0.9830-1.0018)	-403.2	Worse fit
Diabetes Y/N	0.04 (0.01-0.12)	0.24 (0.14-0.40)	119.8 (93.5-205.2)	0.6 (0.1-1.7)	0.99 (0.78-1.14)	-404.1	Worse fit
Hypertension Y/N	0.03 (0.01-0.12)	0.25 (0.15-0.42)	129.8 (95.5-277.4)	0.5 (0.1-1.7)	1.09 (1.01-1.49)	-401.5	0.075
Pelvic Surgery Y/N	0.04 (0.01-0.12)	0.24 (0.15-0.40)	120.5 (93.9-209.5)	0.6 (0.1-1.7)	1.02 (0.81-1.21)	-404.2	Worse fit
Prior TURP Y/N	0.04 (0.01-9.99)	0.26 (0.15-0.58)	129.3 (95.0-1000)	0.3 (0.1-1.7)	1.19 (1.04-18.79)	-400.3	0.02
Treatment Days (Days)	0.04 (0.01-0.20)	0.24 (0.15-0.47)	128.4 (80.3-187.9)	0.1 (0.1-6.7)	1.0017 (0.9844-1.0053)	-403.1	Worse fit

Supplementary Figure F. LKB-EQD2-DMF Haematuria G1+ (Prior TURP) Calibration Plot



Decile binned calibration plot for LKB-EQD2-DMF Haematuria G1+ model. Bins are by decile of predicted NTCP, plotted on the x-axis versus observed toxicity on the y-axis. Perfect prediction is shown as the orange identity line.

Abbreviations: LKB-EQD2 = Lyman-Kutcher-Burman model with Equivalent Dose in 2Gy/fraction Correction; NTCP = Normal Tissue Complication Probability.