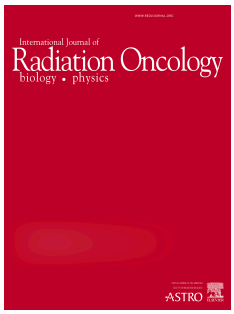

Estimates of Alpha/Beta (α/β) Ratios for Individual Late Rectal Toxicity Endpoints: An Analysis of the CHHiP trial

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Title

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Keywords: Prostate Cancer, Radiotherapy, Toxicity, Radiobiology, Alpha/beta ratio

Conflicts of Interest
DB reports grants from Cancer Research UK, during the conduct of the study.
DD reports personal fees from The Institute of Cancer Research, during the conduct of the study; In addition, DD has a patent EP1933709B1 issued.
AT reports grants, personal fees and other from Elekta, grants from Accuray, grants from Varian, other from Janssen, other from Astellas, other from Bayer, other from Ferring , other from Genesis healthcare, outside the submitted work; .
EH reports grants from Cancer Research UK, during the conduct of the study; grants from Accuray Inc., grants from Varian Medical Systems Inc., grants and non-financial support from Astra Zeneca, grants and non-financial support from Janssen-Cilag, grants and non-financial support from Bayer, grants from Roche Products Ltd, grants and non-financial support from Merck Sharp & Dohm, grants from Prostate Cancer UK, grants and non-financial support from Aventis Pharma Limited (Sanofi), outside the submitted work.
SB, KF, AW, ON, AG, IS, NvA, SG have nothing to disclose.

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Trial Management Group: David Dearnaley (Chair), Angela Baker, Margaret Bidmead, Ananya Choudhury, Clare Cruickshank, John Graham, Clare Griffin, Emma Hall, Shama Hassan, Hayley James, Vincent Khoo, Helen Mayles, Philip Mayles, Olivia Naismith, Julia Pugh, Paul Ridley, Christopher Scrase, Christopher South, John Staffurth, Isabel Syndikus, Jean Tremlett.

Data Sharing Statement

Deidentified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request. The Institute of Cancer Research (ICR) Clinical Trials and Statistics Unit (CTSU) supports wider dissemination of information from the research it conducts and increased cooperation between investigators. Trial data is obtained, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures, with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and Intellectual Property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale, as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee, as required. Restrictions relating to patients' confidentiality and consent will be limited by aggregating and anonymising identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed in line with Cancer Research UK data sharing guidelines.

Title

Estimates of Alpha/Beta (α/β) Ratios for Individual Late Rectal Toxicity Endpoints:

An Analysis of the XXXXXXX trial

Short Running Title

Rectal Fraction Size Sensitivity (α/β ratios)

Abstract

Purpose

Changes in fraction size of external beam radiotherapy (EBRT) exert non-linear impacts on subsequent toxicity. Commonly described by the linear-quadratic model, fraction size sensitivity of normal tissues is expressed by the α/β ratio. Here we study individual α/β ratios for different late rectal side effects after prostate EBRT.

Methods and Materials

The XXXXXXX trial (XX-REGISTRATION-NUMBER-XX) randomised men with non-metastatic prostate cancer 1:1:1 to 74Gy/37 fractions (Fr), 60Gy/20Fr or 57Gy/19Fr. Patients included had full dosimetric data and zero baseline toxicity. Toxicity scales were amalgamated to 6 bowel endpoints: bleeding, diarrhoea, pain, proctitis, sphincter control and stricture. Lyman-Kutcher-Burman models +/- equivalent dose in 2 Gy/fraction correction were log-likelihood fitted by endpoint, estimating α/β ratios. α/β ratio estimate sensitivity was assessed by sequential inclusion of dose modifying factors (DMFs): age, diabetes, hypertension, inflammatory bowel or diverticular disease (IBD/diverticular), and haemorrhoids. 95% confidence intervals (95% CIs) were bootstrapped. Likelihood ratio testing of 632 estimator log-likelihoods compared models.

Results

Late rectal α/β ratio estimates (without DMF) ranged from: bleeding G1+ α/β = 1.6 Gy (95% CI 0.9–2.5 Gy), up to sphincter control G1+ α/β = 3.1 Gy (1.4–9.1 Gy). Bowel pain modelled poorly (α/β 3.6 Gy, 95% CI 0.0 – 840 Gy). Inclusion of

IBD/diverticular disease as a DMF significantly improved fits for stool frequency G2+ (p=0.00041) & proctitis G1+ (p=0.00046). However, the α/β ratios were similar in these no-DMF vs DMF models for both stool frequency G2+ (α/β 2.7 Gy vs 2.5 Gy) and proctitis G1+ (α/β 2.7 Gy vs 2.6 Gy). Frequency-weighted averaging of endpoint α/β ratios produced: G1+ α/β ratio=2.4 Gy; G2+ α/β ratio=2.3 Gy.

Conclusions

We estimated α/β ratios for several common late rectal radiotherapy side effects. When comparing dose-fractionation schedules we suggest using late rectal α/β ratio ≤ 3 Gy.

Introduction

Moderately hypofractionated external beam radiotherapy (EBRT) for the curative treatment of non-metastatic prostate cancer (PCa) has gained broad acceptance following reports of efficacy and safety from the XXXXXXX [1], PROFIT [2] and RTOG 0415 [3] hypofractionation studies. Each trial randomised between moderately hypofractionated and conventional dose-escalated EBRT regimens and all showed non-inferiority of the hypofractionated regimens for 5-year biochemical/clinical progression free survival. A fourth study, HYPRO, unfortunately failed to establish superiority of a dose-escalated, hypofractionated schedule, which demonstrated increased toxicity [4].

Rectal toxicity endpoints are important late side effects of prostate EBRT. Models have been produced for many common individual rectal endpoints such as bleeding, proctitis, stool frequency and faecal incontinence [5–11]. These models incorporate dose-volume histogram (DVH) derived values as dosimetric predictors. In the hypofractionation era, researchers have adjusted the rectal dose bins using the linear-quadratic model [12], describing normal tissue fraction sensitivity by means of the α/β ratio. Commonly, a late rectal $\alpha/\beta = 3$ Gy is assumed [13,14], to produce equivalent dose in 2 Gy fractions (EQD2) and enable comparison with standard 2 Gy fraction treatments [12]. Similarly, EQD2 correction has been used when summating brachytherapy and EBRT doses, with $\alpha/\beta = 3 – 5.4$ Gy [15–17].

These EQD2-corrected comparisons of regimens are dependent on an accurate estimate of the α/β ratio. Researchers have previously provided human estimates for

the α/β ratio of overall late rectal toxicity in the range 2.7 – 7.2 Gy [18–21]. However, individual rectal toxicity endpoints (bleeding, urgency etc.) are driven by different upstream pathophysiological processes [22] and may thus have distinct sensitivity to fraction size, as manifest by the α/β ratio. Although individual endpoint estimates have been produced for the central nervous system [23], to our knowledge, such estimates have not previously been made for pelvic normal tissues.

Using data from a phase III trial of hypofractionated radiotherapy, this study aims to estimate α/β ratios for individual rectal toxicity endpoints: bleeding, stool frequency, proctitis, sphincter control and stricture/ulcer. It also aims to test if such α/β ratio estimates are influenced by inclusion of other predictive clinical factors: age, diabetes, hypertension, inflammatory bowel or diverticular disease (IBD/diverticular), and haemorrhoids.

Methods and Materials

The XXXXXXX *Trial*

The XXXXXXX trial (XX-REGISTRATION-NUMBER-XX) has previously been described in detail [1,24,25]. Briefly, 3216 men were recruited, all with histologically confirmed T1b –T3aN0M0 prostate adenocarcinoma, prostate specific antigen (PSA) ≤40 ng/mL and risk of lymph node involvement <30%. Open-label randomisation was performed 1:1:1 between conventional (74 Gy in 37 fractions (Fr) over 7.4 weeks), higher dose hypofractionated (60 Gy in 20 Fr over 4 weeks) or lower dose hypofractionated (57 Gy in 19 Fr over 3.8 weeks) EBRT. The primary endpoint of

biochemical or clinical failure was met, with non-inferiority of the 60 Gy in 20 fraction regimen confirmed [1]. Ethics approval has been described previously [1]. XX-CLINICAL-TRIAL-UNIT-XX coordinated the study and managed the data used in this analysis.

Patient Cohort and DICOM Files

XXXXXXX trial patients who had received all fractions of one of the protocol radiotherapy regimens were eligible for inclusion in this sub-study. Those without centrally available Digital Imaging and Communications in Medicine (DICOM) data of CT, structures and dose cube were excluded. Non-DICOM treatment plan file types were converted to DICOM.

Rectal Contouring and Dose-Volume-Histogram Generation

The XXXXXXX trial protocol recommended, ideally, an empty rectum. Contouring for the rectum, as a solid structure, was "*from the anus (usually at the level of the ischial tuberosities or 1cm below the lower margin of the PTV whichever is more inferior) to the recto-sigmoid junction"* [1]. Quality assurance (i.e. adherence to the XXXXXXX protocol specifications of rectal contour) was undertaken for the contoured rectums on all DICOM datasets obtained, by one of five trained observers. In particular, attention was paid to the inferior and superior extent of contour. Once the rectal contour was checked, and re-contoured where necessary, the rectal DVH was recalculated for use in this study.

Endpoints

The XXXXXXX trial collected bowel toxicity information in the form of both clinician reported outcomes (CROs) [1] and patient reported outcomes (PROs) [25]. Clinician reported outcomes were chosen, since PRO measures changed during the course of the trial. These were Radiation Therapy Oncology Group (RTOG) late rectal toxicity [26], the Royal Marsden Hospital (RMH) scale [27] and Late Effects Normal Tissue – Subjective, Objective & Management (LENT-SOM) [28]. Only RMH and LENT-SOM were collected at registration (baseline) and pre-radiotherapy (pre-RT). All scales were collected for late rectal toxicity at 6-, 12-, 18-, 24-, 36-, 48- & 60-months follow-up after the start of radiotherapy.

The scales were merged into new amalgamated endpoints representing underlying separate symptomatic issues, using methodology previously described [29]. Grading was simplified to: grade 0 for no toxicity; grade 1 for toxicity not needing intervention; grade 2 for any toxicity requiring intervention. The scores were dichotomised to consider: grade 0 vs grade 1 and grade 2 or above (G1+ comparison); grade 0 and grade 1 vs grade 2 or above (G2+ comparison). For bowel pain, sphincter control and stricture/ulcer, grade 2 or above events were rare (<5%), so only a G1+ comparison was performed. No attempt was made to amalgamate endpoints to generate G3+ models, both due to the rarity of G3+ events and the difficulty of unifying such events between scales.

For each endpoint, patients were excluded if any relevant toxicity was reported at baseline or pre-RT assessments; or if both assessments were missing. This was to

avoid those with pre-existent symptoms registering as having treatment-induced toxicity events during follow-up. Patients were further excluded for an endpoint if they were missing the relevant follow-up data at more than 3 of the 7 (>50%) late toxicity assessments. Toxicity events were scored for any relevant toxicity of sufficient grade at any time point (i.e. worst toxicity). A full description of the endpoint generation process is provided in **Appendix A**.

Generalised Lyman-Kutcher-Burman (LKB) Model

A generalised LKB model has been previously described for rectal α/β ratio estimation [20]. Dose modifying factors (DMFs) were incorporated as modulators of each individual patient's effective dose parameter (D_{Eff}), per prior work by Tucker *et al* [30]. The model is expressed as a definite integral:

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

Where *NTCP* is the normal tissue complication probability. Furthermore:

$$t = \frac{D_{Eff} \cdot e^{\delta \cdot DMF} - TD_{50}}{m \cdot TD_{50}} \#(2)$$

Here, TD_{50} represents the tolerance dose for 50% toxicity, at the median (steepest) part of the NTCP dose response curve. *m* is a parameter inversely controlling the steepness at TD_{50}. *DMF* is the dose modifying factor corresponding to either: ones and zeros for binary risk factors, or a positive integer for age. δ is the dose modifying

coefficient, used to adjust TD_{50} in the presence of the risk factor specified by *DMF*. For binary DMFs, the co-efficient is for presence of risk factor, for numerical DMFs (age only) it is evaluated on a per unit basis. Note that a DMF covariate of zero will result in no change to the effective dose (D_{Eff}), which is defined by:

$$D_{Eff} = \left(\sum_{i=1}^{z} (EQD2_i)^{\frac{1}{n}} \cdot v_i \right)^n \#(3)$$

Where *n* represents the relative seriality of a tissue endpoint dose response: values towards 0 being more serial and towards 1 being more parallel [31]. *z* is the number of dose bins, iterated by dose bin *i*. v_i is the relative volume of an organ present in the dose bin *i*. $EQD2_i$, is the EQD2 for dose bin *i*, which is given by:

$$EQD2_i = D_i \cdot \left(\frac{d_i + \alpha/\beta}{2\ Gy + \alpha/\beta} \right) \#(4)$$

Where D_i is the total dose in Gy, to a given DVH dose bin *i*. d_i is the dose in Gy per fraction, to a given dose bin (i.e. D_i divided by number of fractions). α/β (Gy) is the theoretical single fraction dose giving equal contribution for linear (α) and quadratic (β) components of the linear-quadratic formula [12].

This model is termed LKB-EQD2, or LKB-EQD2-DMF with the inclusion of a DMF in **Equation 2.** The LKB-NoEQD2 model without EQD2 correction uses **Equations 1 & 2** (without DMF inclusion), but substitutes physical dose bin dose for $EQD2_i$ in **Equation 3**. This LKB-NoEQD2 model was fitted separately for 2 Gy per fraction

patients (74 Gy in 37 Fr) and 3 Gy per fraction patients (60 Gy in 20 Fr and 57 Gy in 19 Fr).

Initial Grid Search

For each model, initial fitting was done using the grid search method, as previously described [7]. Each unknown parameter was searched on a grid with dimensionality equal to number of fit parameters (**Appendix Table 1A**). LKB-EQD2 models with fixed α/β were also produced, using the same parameter grid as those with fitted α/β, but fixing the α/β to either 3 Gy or 4.8 Gy, as per prior literature estimates [19,20].

Model performance was assessed in two ways. First the naïve performance was assessed by calculating a log likelihood sum. Better model performance will produce a less negative log likelihood sum. It was calculated as:

$$Likelihood = f(toxicity) = \begin{cases} NTCP & toxicity = 1 \\ 1 - NTCP & toxicity = 0 \end{cases} \#(5)$$

$$Performance = Summed\ Log\ Likelihood = \sum_{j=1}^{c} \ln Likelihood_j \#(6)$$

Where: *c* = number of patients (with *j* as iterator through such patients).

The model parameter values generating the ten least negative performance metrics were recorded at the end of the grid search. The best (least negative) of these was noted as the naïve model performance, for later use in **Equation 8**.

The second action at each grid step was to assess performance of 2000 bootstraps, drawn with replacement, with unique bootstraps for each endpoint. The bootstrap performance was also assessed by **Equation 6**. At the end of the grid search, the parameters giving the ten least negative performance metrics for each bootstrap were recorded. The parameters resulting in best bootstrap performance were noted, so that these could be used later, for out-of-the-bag prediction, in **Equation 7** [32].

Second Stage Search

To account for the known sensitivity of fitting algorithms to initial starting parameters and hence to improve model performance [33], a secondary optimisation search for parameter values was undertaken. For this, the values of *n*, *m*, *TD50*, *α/β* and *DMFs* producing the ten best performance metrics (by **Equation 6**) were used as the initial parameters in a constrained Nelder-Mead simplex algorithm search [34], to see if further improvement in performance could be found. I.e. for each endpoint; 1 naïve model and 2000 bootstraps with 10 searches = 20010 algorithm searches. This algorithm was run with constraints: *n* = 0.01-10; *m* = 0.01-10; *TD50* = 0.01-1000 Gy. Where freely fitted, α/β was searched in space 0.001 to 1000 Gy; The dose modifying factor covariate was searched in space -10 to 10, which when raised to the natural base *e*, searches a dose multiplier range of 4.54×10^{-4} – 22026. This wide bounding of all fit parameters was chosen to prevent bootstrap distributions being inappropriately constrained, which would bias the coverage of the non-parametric 95% confidence interval. For the naïve likelihood and each bootstrap, the final best model parameters were those resulting in best performance (by **Equation 6**) from

any of the grid search positions or any of the subsequent ten Nelder-Mead simplex algorithm searches.

Estimating Test Performance and Model Comparison

A model comprising more free parameters is always likely to improve naïve likelihood performance, but this can be due to overfitting [35]. To address this difficulty, the 632 bootstrap estimator was used as an unbiased estimator of test performance [36]. It balances out the over-optimistic naïve likelihood (fitted on the population) against the negatively biased out-of-the-bag bootstrap estimate. We preferred 632 over the 632+ bootstrap estimator, due to faster calculation and the low risk of near-perfect prediction with a relatively simple model [32]. The first step calculated the out-of-the-bag (OOB) performance for the model:

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

Where *c* is the total number of patients (iterated by *j*), and *z* is the number of bootstraps not containing patient *j* (iterated by *boot*). The predicted likelihood is derived by inserting the predicted NTCP into **equation 5**.

The 632 estimator was then calculated [32]:

$$632\ Estimator = 0.368 \cdot Naive\ Performance + 0.632 \cdot OOB\ Performance \#(8)$$

Models were compared by means of the likelihood ratio test of the 632 estimators. Firstly, comparing whether the LKB-EQD2 model with free fitted α/β ratio had significantly better 632 estimator than the model with the α/β ratio fixed at two reported literature values: α/β = 3 Gy [19] or 4.8 Gy [20]. Secondly, examining for significant improvement from LKB-EQD2 to LKB-EQD2-DMF, sequentially tested with each of the DMFs. Tests were only planned where log likelihood improvement occurred; with approximately 50 tests anticipated, a penalised p-value of 0.001 was used for interpretation of significance [37]. Parameter estimates were obtained at the 50^{th} centile of the bootstrap distribution. 95% bootstrap confidence intervals (CIs) for the optimum model parameter values were obtained as the 2.5^{th} and 97.5^{th} centiles of the corresponding parameter values producing the best summed log likelihood performance metric for each bootstrap.

Graphical Outputs of Calibration

Model calibration was fitted as a logistic regression of predicted NTCP values for each patient as single predictor against observed binary outcomes (toxicity/no toxicity). The fitted model was then displayed graphically against ideal (perfect) prediction; termed the calibration curve. Furthermore, binned calibration plots were examined, with patients grouped into deciles of predicted risk: average bin NTCP plotted against observed bin toxicity proportion.

Software

Processing of trial data into the endpoints used for this study was by Stata (version 15, Statacorp, TX, USA). VODCA (v5.4.1, Medical Software Solutions GmbH, Switzerland) was used to convert non-DICOM data to DICOM and for the checking of rectal contours. MATLAB (v2018b, Mathworks, MA, USA) was used to import DVH data from DICOM files and for all modelling using custom scripts. Nelder-Mead simplex algorithm searches were by a modified bounded version of *fminsearch* (fminsearchbnd, v 1.4.0.0) [38]. Tables were formatted in Excel 2019 & Word 2019 (Microsoft, CA, USA). All plots were produced in MATLAB.

Results

A total of 2215 patients from the XXXXXXX trial had appropriate data for this analysis. **Figure 1** is a CONSORT-style flow diagram accounting for all patients that were originally randomised into the XXXXXXX study and their reasons for non-inclusion in this analysis. Key relevant baseline and treatment characteristics for the included patients are shown in **Table 1**, which are similar to those in the XXXXXXX trial as a whole. This indicates that patients in this study are representative of the whole trial cohort. The cumulative rectal DVH curves for all patients, separated by fractionation arm, are shown in **Appendix B**. in A summary of the number of patients meeting requirements (≥50% follow-up form completion) for each endpoint modelled are shown in **Table 2**, with the proportion of patients expressing toxicity ranging from 3.6% for stricture/ulcer G1+ (79/2206) to 38.1% for stool frequency G1+ (771/2025). The influence of excluding patients with baseline toxicity on categorical DMF proportions is examined in **Table 2A**. For some endpoints, patients with DMF present were overrepresented in those excluded for baseline toxicity vs those

included in study: IBD/Diverticular disease and both rectal bleeding G1+ & G2+; Pelvic surgery and stricture/ulcer G1+; Haemorrhoids and rectal bleeding G1+ & G2+, frequency G1+ & G2+, pain G1+, proctitis G1+ & G2+.

Table 3 (upper 2 sections) shows parameter estimates of *n*, *m* and *TD50* for fits of the LKB-NoEQD2 model to two groups: 74 Gy only; 57 Gy and 60 Gy combined. Each endpoint is presented separately. **Table 3** then shows LKB-EQD2 model fits for all patients combined, across the same endpoints, including estimates for the α/β ratio. We note that the α/β ratio estimates for most endpoints were below 3 Gy, with the upper bound of the 95% confidence interval for rectal bleeding G1+ being less than 3 Gy. The 95% confidence interval for Pain G1+ was extremely wide (α/β 0.0 to 840 Gy), suggesting a poor fit for this endpoint; i.e limited dose dependency. **Table 3** also shows fits for the LKB-EQD2 model, with α/β ratio fixed at 3 Gy and 4.8 Gy. The p-values for likelihood ratio test comparison between the LKB-EQD2 model (unfixed α/β) and the two fixed α/β models are shown. In many cases, the less flexible model (LKB-EQD2 with fixed α/β ratio) had a better fit (by 632 estimator), implying overfitting, making likelihood ratio testing inappropriate. The LKB-EQD2 model with free α/β ratio was significantly better than the model with fixed α/β 4.8 Gy for rectal bleeding G1+ (p = **0.00032**). Other comparisons, where the LKB-EQD2 model with fitted α/β ratio was better, did not meet the adjusted significance threshold.

The effect on model parameters of sequential inclusion of each DMF is reported in **Table 4**. For each endpoint, the LKB-EQD2 model results without inclusion of DMF are reproduced in the first row for ease of comparison. Where the goodness of fit (as assessed by 632 estimator) was improved with inclusion of DMF, p-values for likelihood ratio testing of the LKB-EQD2-DMF model against the LKB-EQD2 model

are presented. Only two LKB-EQD2-DMF models improved on LKB-EQD2, by adjusted significance: IBD/Diverticular disease for both stool frequency G2+ (DMF=1.37, 95% CI 1.13 – 1.82, p=0.00041) and proctitis G1+ (DMF=1.27, 95% CI 1.10 – 1.58, p=0.00046). In both of these cases, α/β ratio estimates of the LKB-EQD2 vs LKB-EQD2-DMF fits did not differ by a clinically relevant margin: stool frequency G2+ (2.7 Gy vs 2.5 Gy), proctitis G1+ (2.7 Gy vs 2.6 Gy). Although inclusion of other DMFs did not meet adjusted significance for model fit improvement, it can be seen in **Table 4** that any differences between LKB-EQD2-DMF model and LKB-EQD2 model α/β ratio estimates are not clinically meaningful.

The calibration curve and binned calibration plot for Rectal Bleeding G1+ LKB-EQD2 model is shown in **Figure 2**. Note that this is a well calibrated example. Calibration curves and binned calibration plots are presented for the LKB-EQD2 model fitted to each endpoint in **Appendix C (Appendix Figures 1A-16A)**. The best calibrated models are those with the higher event rates (rectal bleeding G1+, stool frequency G1+, proctitis G1+). For those with lowest event rates (pain G1+, stricture/ulcer G1+), the calibration bin separation is less pronounced. Similar plots for the LKB-EQD2-DMF model, where it provided a statistically significant improvement in fit (IBD/Diverticular disease for stool frequency G2+ & proctitis G1+) are presented in **Appendix D (Appendix Figures 17A-20A)**. It can be seen that DMF inclusions causes higher decile risk bins to achieve better separation from other bins, compared to the equivalent LKB-EQD2 models without DMF (**Appendix Figures 6A and 10A**) .

One overall late rectal α/β ratio for use in the comparison of expected late rectal side effects between differing dose-fractionation schedules is desirable. The frequency weighted average for modelled late rectal G1+ events (excluding pain re poor fit) was α/β = 2.4 Gy and the equivalent for G2+ events was α/β = 2.3 Gy. Unfortunately, no transformation was found to normalise the highly positively skewed bootstrapped α/β ratio 95% confidence intervals, meaning pooling standard errors for a unified 95% confidence interval is not appropriate [39]. We would advise caution in the application of any single figure, since as demonstrated, the true fraction size sensitivity may differ between endpoints. The calculation of these estimates is shown in **Appendix Table 3A.**

Discussion

In this study we have used data from a large phase III trial of moderately hypofractionated radiotherapy for non-metastatic PCa. Through fitting an EQD2-corrected LKB model, estimates of the relative fraction size sensitivity (expressed as α/β ratio) for various clinician reported late rectal endpoints have been made. We have shown that these estimates do not vary markedly with inclusion of several possible dose modifying factors. To our knowledge, these are the first such individual rectal endpoint α/β ratio estimates in the literature.

Our α/β ratio estimates are generally lower than previous published articles with estimates of late rectal α/β ratio in humans. Brenner estimated late rectal RTOG G2+ α/β ratio = 5.4 Gy (95% CI 3.9 – 6.9 Gy) using the proportions of patients experiencing toxicity from eight dose-fractionation schedules in USA/Japan PCa

EBRT studies [18]. Dose heterogeneity was limited, with 2254/2306 patients receiving 1.8-2 Gy per fraction. Marzi and colleagues used 162 patients from the Roma hypofractionation trial to model RTOG G2+ late rectal toxicity, estimating α/β = 2.3 Gy (95% CI 1.1 – 5.6 Gy) using a similar LKB-EQD2 correction method to this study [19]. However, fixed LKB parameters (*n* = 0.12 *m* = 0.15) were used during modelling, which artificially reduces confidence intervals and may influence the α/β ratio estimate obtained. Tucker and colleagues used 509 patients from RTOG 94-06, estimating late rectal RTOG G2+ α/β 4.8 Gy, although with wide confidence intervals (**68%** CI 0.6 – 46 Gy) [20]. This wide estimate likely results from limited dose per fraction heterogeneity (1.8 Gy and 2 Gy), plus only 77 patients experiencing toxicity. In abstract form, Zhu *et al*. reported data from 213 patients receiving conventional or moderately hypofractionated radiotherapy [21]. Using an EQD2-corrected LKB model, they estimated G2+ LENT-SOM rectal α/β = 7.2 Gy (95% CI 5.2 – 9.1), higher than other estimates.

Regarding the components of the traditional LKB model (*n*, *m*, *TD50*), it is reassuring that the LKB-NoEQD2 estimates for conventionally fractionated patients are similar to those previously reported for individual rectal endpoints [7,40–42]. Estimates from these cohorts for bleeding, stool frequency and proctitis are compared to our data in **Appendix Table 4A**. The landmark QUANTEC study meta-analysed LKB parameters from four of these studies, examining either G2+ rectal bleeding or G2+ late toxicity [43]. Comparing our G2+ rectal bleeding LKB-NoEQD2 values for 74 Gy patients versus these QUANTEC meta-analysis values, we see fairly similar findings: n = 0.13 (0.01-0.42) vs 0.09 (0.04–0.14) ; m = 0.21 (0.06-0.43) vs 0.13 (0.10–0.17); and TD50 = 74.0 (67.2-96.6) vs 76.9 (73.7–80.1) Gy. Separately, we note that our

models for pain produced very wide confidence intervals (e.g. LKB-EQD2 α/β ratio estimate 3.6 Gy, 95% CI 0.01 – 840), suggestive of poor model fit for this endpoint. This is perhaps expected, given the relative subjectivity of pain.

Strengths of this study are drawn from the nature of the inputted data. The XXXXXXX trial is the largest study of hypofractionated radiotherapy for PCa, with two thirds of patients' data used for this analysis. We have included only patients reporting zero baseline toxicity, in order to reduce possible pre-existent toxicity noise. Furthermore, we have undertaken data quality assurance by checking every rectal contour for protocol adherence and recalculating DVHs. This large, clean sample, combined with multiple dose-fractionation regimens, has permitted α/β ratio estimation with tight confidence intervals and good calibration for more frequently occurring endpoints. This is without the need to fix any of the parameters when modelling as has been done previously [19]. This study has also been aided by modern computing power facilitating usage of computationally intensive bootstrapping techniques. These have permitted nested model comparison using bootstrap-dependent estimates of test performance (632 estimate), reducing the potential influence of overfitting.

Limitations must also be considered, starting with the modelling approach itself. The LKB model is a traditional parametric method for the fitting of radiotherapy data and more recent machine learning and artificial intelligence type modelling methodologies have been applied [44]. It does however, provide a model which permits fitting of data, with and without EQD2 correction, to estimate endpoint α/β ratios. Future toxicity modelling work with newer methodologies may benefit from

these α/β ratio estimates, when using the linear-quadratic model to rescale DVH data predictors from disparate dose-fractionation regimens.

For the DMF coefficient estimates, it must be remembered that these have been estimated on cohorts where those with baseline toxicity were excluded. While this means that the risk attributable to radiotherapy is hopefully more closely approximated, the absolute risk may be higher for those with a DMF where disproportionately more patients were excluded for baseline toxicity (e.g. haemorrhoids and rectal bleeding G1+; refer to **Table 2A**)."

A further limitation is that motion has been demonstrated inter-fractionally for the rectum [45] during prostate radiotherapy, so the use of CT planned doses in this study is a limitation. We acknowledge that the endpoints modelled here are unlikely to recur in future trials, due to the amalgamation of multiple scales. This was a pragmatic choice based on the toxicity scales available, so there would be benefit to confirmatory studies with modern clinician reported scales (e.g. Common Terminology Criteria for Adverse Events) or patient reported scales (e.g. EPIC [46]). Finally, despite the use of out-of-the-bag techniques, this is data from a single study and future validation on another hypofractionated prostate radiotherapy dataset would be desirable.

It is worth examining the α/β ratio assumptions (**Appendix Table 5A**) and subsequent toxicity outcomes (**Appendix Table 6A**) of the published phase III hypofractionation trials. XXXTHIS-STUDYXXXX assumed a late rectal α/β ratio = 3 Gy, isoeffective design, with the 60 Gy and 57 Gy arms reflecting uncertainty in the

prostate α/β ratio (assumed α/β 2.5 Gy and 1.5 Gy respectively). Both 60 Gy and 57 Gy arms showed non-significantly reduced cumulative rectal grade 2+ toxicity by 5 years (11.9% & 11.3% vs 13.7% control arm), with the 60 Gy arm shown to be non-inferior for disease control [1]. PROFIT assumed late rectal α/β ratio = 3 – 5 Gy with isoeffective design (prostate α/β ratio 1 – 3 Gy), achieving non-inferior disease control with reduced late grade 2+ rectal toxicity in the test arm (8.9% vs 13.9%) [2]. RTOG 0415 assumed both tumour and late rectal α/β = 3 Gy, with the trial design escalating EQD2 to both [3]. The trial achieved non-inferior disease control with hypofractionation. Given the rectal dose escalation, the increased G2+ rectal toxicity in the hypofractionated arm (22.4% vs 14.0%) is not surprising. The HYPRO trial adopted an isotoxic design, assuming the highest α/β ratio for late rectal toxicity (α/β = 4-6 Gy). Unfortunately, this study demonstrated increased late G2+ rectal toxicity (21.9% vs 17.7%), without superior disease control. It is worth noting that HYPRO is the only phase III moderately hypofractionated study where the relative test vs control late rectal toxicity was worse than trial design anticipated, most likely due to the higher assumed rectal α/β ratio and therefore dose delivered to the test arm.

Both large phase III randomised trials of prostate ultra-hypofractionation: PACE-B [47] and HYPO-RT-PC [48] have assumed a late rectal α/β = 3 Gy. The HYPO-RT-PC trial showed isoeffective cumulative grade 2 or worse late RTOG rectal toxicity for both arms: 42.7 Gy in 7 fractions (9.5%) and 78 Gy in 39 fractions (9.7%) [48]. The QUANTEC study paper on rectal toxicity also recommended dose adjustment by an α/β ratio of 3 Gy [43], an opinion our data supports. Corrected for multiple testing, our LKB-EQD2 models with freely fitted α/β ratios did not significantly outperform the same model with fixed α/β = 3 Gy. We do note that the upper bound of 95%

confidence interval for rectal bleeding G1+ was below 3 Gy and that the results were close to corrected significance. This is perhaps worth noting, given that the randomised ProtecT trial showed bloody stools to be the most common radiotherapy patient reported adverse event compared to radical prostatectomy, although the long term impact on bowel habits and bother was very small [49].

Future studies might utilise individual patient data level analysis (accounting for baseline toxicity and dose distributions) of late toxicity from HYPO-RT-PC and, once released, PACE-B [47], to more definitively confirm applicability of the LQ model to late toxicity in ultra-hypofractionation, an area of some debate [50]. It is possible that improving radiotherapy delivery techniques may lower rectal doses below the level where fraction size sensitivity meaningfully influences toxicity.

Conclusions

We believe this study is the first to provide α/β ratio estimates for individual late rectal toxicity endpoints seen following hypofractionated external beam radiotherapy for prostate cancer. Although symptom endpoints may occur concurrently, for G1+ rectal bleeding, one of the most objective endpoints, the α/β ratio 95% confidence interval upper bound was lower than 3 Gy. For G1+ endpoints, the frequency-weighted pooled estimate was late rectal α/β ratio = 2.4 Gy. However, adjusting for multiple testing, no significant improvement from an LKB-EQD2 model with α/β = 3 Gy was demonstrated. Future individual patient data level analysis on ultra hypofractionated trials is desirable, but at present we suggest a late rectal α/β ratio of no more than 3 Gy be used when comparing dose-fractionation regimens.

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Figure Captions

Figure 1. Patient Flow Diagram

Showing any reasons for exclusion of all patients originally randomised into the XXXXXXX trial. Abbreviations: DICOM = Digital Imaging and Communications in Medicine; ID = IDentity; OAR = Organ At Risk;

Figure 2. Calibration Plots for Rectal Bleeding G1+ LKB-EQD2 Model

Panel A shows the fit of the model calibration (blue line) compared against optimal calibration (orange line), demonstrating a good overall fit. The lower histogram shows the predicted NTCP for patients, separated by toxicity (red, above line) or no toxicity (blue, below line). Panel B has patients grouped into deciles by predicted NTCP, showing this against observed toxicity within each decile. Bin ordering is generally appropriate.

Supplementary Appendix

Contents

Appendix A. Individual Late Rectal Endpoint Generation

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

- Bowel obstruction
- Diarrhoea
- Proctitis
- Rectal-anal stricture
- Rectal ulcer

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.

Bleeding G1+

- Toxicity scored if:
    - Any ≥6 month f/u RMH Rectal bleeding (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Objective bleeding (G1+) **OR**
    - Any ≥6 month f/u LENT-SOM Management bleeding (G1+)
- Exclude unless:
    - Baseline RMH Rectal bleeding = G0 **AND**
    - Baseline LENT-SOM Objective bleeding = G0 **AND**
    - Baseline LENT-SOM Management bleeding = G0
- Exclude if missing >50% follow-up scores for any of:
    - RMH Rectal bleeding **OR**
    - LENT-SOM Objective bleeding **OR**
    - LENT-SOM Management bleeding

Bleeding G2+

- Toxicity scored if:
  - Any ≥6 month f/u RMH Rectal bleeding (G2+) **OR**
  - Any ≥6 month f/u LENT-SOM Objective bleeding (G2+) **OR**
  - Any ≥6 month f/u LENT-SOM Management bleeding (G1+)
- Exclude unless:
  - Baseline RMH Rectal bleeding = G0 **AND**
  - Baseline LENT-SOM Objective bleeding = G0 **AND**
  - Baseline LENT-SOM Management bleeding = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - RMH Rectal bleeding **OR**
  - LENT-SOM Objective bleeding **OR**
  - LENT-SOM Management bleeding

Frequency G1+

- Toxicity scored if:
  - Any ≥6 month f/u RTOG Diarrhoea (G1+) **OR**
  - Any ≥6 month f/u RMH Bowel frequency (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Subjective stool frequency (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Management tenesmus/stool freq. (G1+)
- Exclude unless:
  - Baseline RMH Bowel frequency = G0 **AND**
  - Baseline LENT-SOM Subjective stool frequency = G0 **AND**
  - Baseline LENT-SOM Management tenesmus/stool freq. = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - RTOG Diarrhoea **OR**
  - RMH Bowel frequency **OR**
  - LENT-SOM Subjective stool frequency **OR**
  - LENT-SOM Management tenesmus/stool freq.

Frequency G2+

- Toxicity scored if:
  - Any ≥6 month f/u RTOG Diarrhoea (G2+) **OR**
  - Any ≥6 month f/u RMH Bowel frequency (G2+) **OR**
  - Any ≥6 month f/u LENT-SOM Subjective stool frequency (G2+) **OR**
  - Any ≥6 month f/u LENT-SOM Management tenesmus/stool freq. (G1+)
- Exclude unless:
  - Baseline RMH Bowel frequency = G0 **AND**
  - Baseline LENT-SOM Subjective stool frequency = G0 **AND**
  - Baseline LENT-SOM Management tenesmus/stool freq. = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - RTOG Diarrhoea **OR**
  - RMH Bowel frequency **OR**
  - LENT-SOM Subjective stool frequency **OR**
  - LENT-SOM Management tenesmus/stool freq.

Pain G1+

- Toxicity scored if:
  - Any ≥6 month f/u LENT-SOM Subjective pain (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Management pain (G1+)
- Exclude unless:
  - Baseline LENT-SOM Subjective pain = G0 **AND**
  - Baseline LENT-SOM Management pain = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - LENT-SOM Subjective pain **OR**
  - LENT-SOM Management pain

Proctitis G1+

Note: It was decided to include LENTSOM Management tenesmus / stool frequency in the stool frequency category. It could therefore not be included here to avoid double representation of that endpoint

- Toxicity scored if:
  - Any ≥6 month f/u RTOG Proctitis (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Subjective tenesmus (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Subjective mucosal loss (G1+)
- Exclude unless:
  - Baseline LENT-SOM Subjective tenesmus = G0 **AND**
  - Baseline LENT-SOM Subjective mucosal loss = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - RTOG Proctitis **OR**
  - LENT-SOM Subjective tenesmus **OR**
  - LENT-SOM Subjective mucosal loss

Proctitis G2+

Note: It was decided to include LENTSOM Management tenesmus / stool frequency in the stool frequency category. It could therefore not be included here to avoid double representation of that endpoint

- Toxicity scored if:
  - Any ≥6 month f/u RTOG Proctitis (G2+) **OR**
  - Any ≥6 month f/u LENT-SOM Subjective tenesmus (G2+) **OR**
  - Any ≥6 month f/u LENT-SOM Subjective mucosal loss (G2+)
- Exclude unless:
  - Baseline LENT-SOM Subjective tenesmus = G0 **AND**
  - Baseline LENT-SOM Subjective mucosal loss = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - RTOG Proctitis **OR**
  - LENT-SOM Subjective tenesmus **OR**
  - LENT-SOM Subjective mucosal loss

Sphincter Control G1+

- Toxicity scored if:
  - Any ≥6 month f/u LENT-SOM Subjective sphincter control (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Management sphincter control (G1+)
- Exclude unless:
  - Baseline LENT-SOM Subjective sphincter control = G0 **AND**
  - Baseline LENT-SOM Management sphincter control = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - LENT-SOM Subjective sphincter control **OR**
  - LENT-SOM Management sphincter control

Stricture/Ulcer G1+

- Toxicity scored if:
  - Any ≥6 month f/u RTOG bowel obstruction (G1+) **OR**
  - Any ≥6 month f/u RTOG rectal-anal stricture (G1+) **OR**
  - Any ≥6 month f/u RTOG rectal ulcer (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Objective ulceration (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Objective stricture (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Management ulceration (G1+) **OR**
  - Any ≥6 month f/u LENT-SOM Management stricture (G1+)
- Exclude unless:
  - Baseline LENT-SOM Objective ulceration = G0 **AND**
  - Baseline LENT-SOM Objective stricture = G0 **AND**
  - Baseline LENT-SOM Management ulceration = G0 **AND**
  - Baseline LENT-SOM Management stricture = G0
- Exclude if missing >50% (4/7) follow-up scores for any of:
  - RTOG bowel obstruction **OR**
  - RTOG rectal-anal stricture **OR**
  - RTOG rectal ulcer **OR**
  - LENT-SOM Objective ulceration **OR**
  - LENT-SOM Objective stricture **OR**
  - LENT-SOM Management ulceration **OR**
  - LENT-SOM Management stricture

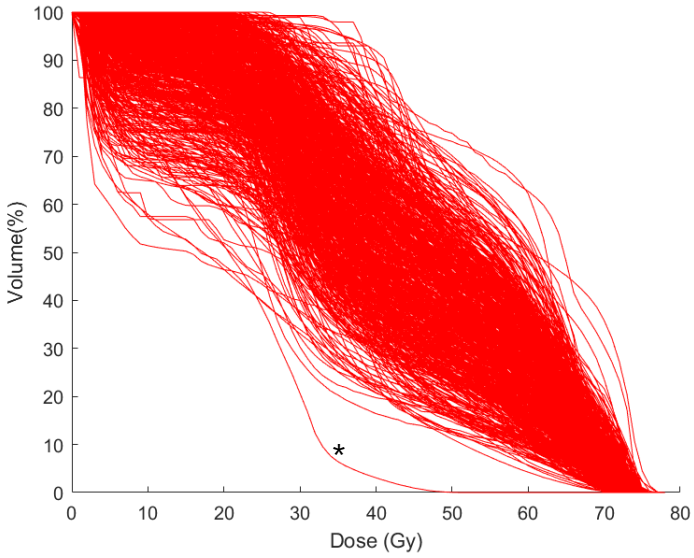
Table 1A. Constraints for Initial Grid Search in Fitted Models

Endpoint Name	Patients	Model Type	DMF	n LB	n UB	n step	m LB	m UB	m step	TD50 LB	TD50 UB	TD50 step	α/β LB	α/β UB	α/β step	DMF LB	DMF UB	DMF step
Rectal Bleeding G1+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Rectal Bleeding G1+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Rectal Bleeding G1+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Rectal Bleeding G1+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Rectal Bleeding G1+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Rectal Bleeding G1+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Rectal Bleeding G1+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Rectal Bleeding G1+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Rectal Bleeding G1+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04
Rectal Bleeding G2+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Rectal Bleeding G2+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Rectal Bleeding G2+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Rectal Bleeding G2+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Rectal Bleeding G2+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Rectal Bleeding G2+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Rectal Bleeding G2+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Rectal Bleeding G2+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Rectal Bleeding G2+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04
Pain G1+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Pain G1+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Pain G1+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Pain G1+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Pain G1+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Pain G1+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Pain G1+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Pain G1+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Pain G1+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04

Table 1A continued…																		
Endpoint Name	**Patients**	**Model Type**	**DMF**	**n LB**	**n UB**	**n step**	**m LB**	**m UB**	**m step**	**TD50 LB**	**TD50 UB**	**TD50 step**	**α/β LB**	**α/β UB**	**α/β step**	**DMF LB**	**DMF UB**	**DMF step**
Proctitis G1+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Proctitis G1+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Proctitis G1+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Proctitis G1+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Proctitis G1+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Proctitis G1+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Proctitis G1+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Proctitis G1+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Proctitis G1+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04
Proctitis G2+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Proctitis G2+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Proctitis G2+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Proctitis G2+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Proctitis G2+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Proctitis G2+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Proctitis G2+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Proctitis G2+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Proctitis G2+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04
Sphincter Control G1+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Sphincter Control G1+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Sphincter Control G1+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Sphincter Control G1+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Sphincter Control G1+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Sphincter Control G1+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Sphincter Control G1+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Sphincter Control G1+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Sphincter Control G1+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04

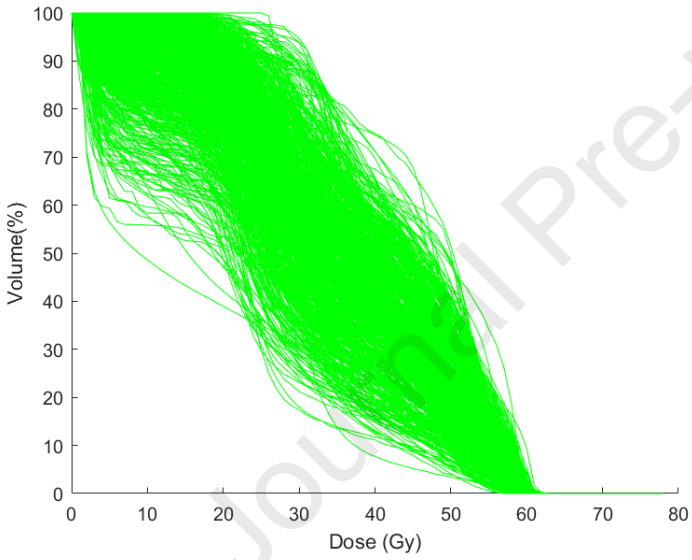
Table 1A continued…																		
Endpoint Name	Patients	Model Type	DMF	n LB	n UB	n step	m LB	m UB	m step	TD50 LB	TD50 UB	TD50 step	α/β LB	α/β UB	α/β step	DMF LB	DMF UB	DMF step
Stool Frequency G1+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Stool Frequency G1+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Stool Frequency G1+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Stool Frequency G1+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Stool Frequency G1+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Stool Frequency G1+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Stool Frequency G1+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Stool Frequency G1+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Stool Frequency G1+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04
Stool Frequency G2+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Stool Frequency G2+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Stool Frequency G2+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Stool Frequency G2+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Stool Frequency G2+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Stool Frequency G2+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Stool Frequency G2+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Stool Frequency G2+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Stool Frequency G2+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04
Stricture/Ulcer G1+	57 & 60	No EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Stricture/Ulcer G1+	74	No EQD2	nil	0.05	0.95	0.05	0.05	3	0.05	30	90	3	N/A	N/A	N/A	N/A	N/A	N/A
Stricture/Ulcer G1+	All	EQD2	nil	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	N/A	N/A	N/A
Stricture/Ulcer G1+	All	EQD2	Age	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	6.2	0.4	-0.018	0.009	0.003
Stricture/Ulcer G1+	All	EQD2	Diabetes	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	4.2	0.4	-0.28	0.12	0.04
Stricture/Ulcer G1+	All	EQD2	Hypertension	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.15	0.15	0.03
Stricture/Ulcer G1+	All	EQD2	IBD/Diverticular	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	4.2	0.4	-0.12	0.45	0.03
Stricture/Ulcer G1+	All	EQD2	Pelvic Surgery	0.05	0.95	0.05	0.05	0.85	0.05	30	90	3	0.2	5	0.4	-0.12	0.33	0.03
Stricture/Ulcer G1+	All	EQD2	Haemorrhoids	0.05	0.95	0.05	0.05	0.95	0.05	30	90	3	0.2	5	0.4	-0.24	0.36	0.04

Appendix B. Rectal Cumulative DVHs by Dose-Fractionation Arm

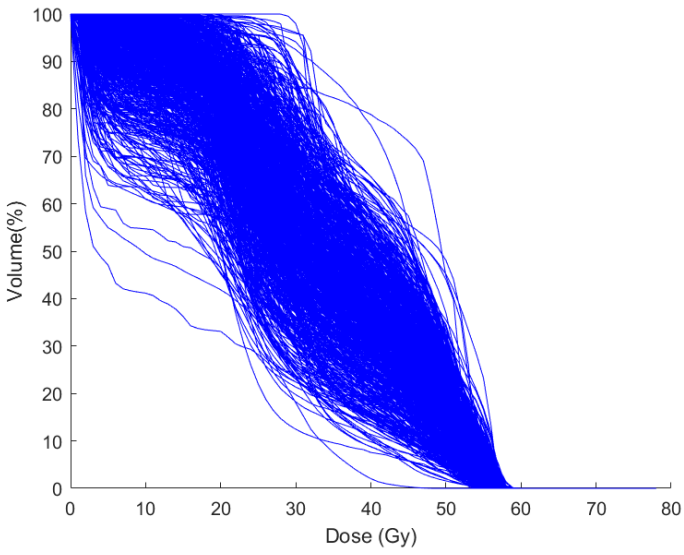


74 Gy in 37 Fraction Patients
n=711

*Single very low DVH due to good patient anatomy and excellent Tomotherapy plan.



60 Gy in 20 Fraction Patients
n=752



57 Gy in 19 Fraction Patients
n=752

Table 2A. Proportions Expressing Categorical Dose-Modifying Factors Compared Between Patients Included, and Excluded Due to Baseline Toxicity

Categorical Dose Modifying Factor	Endpoint	Included (n)	DMF presence amongst included (%)	Excluded for baseline toxicity (n)	DMF presence amongst excluded (%)	Chi-square p-val
Diabetes	Bleeding G1+	2008	10.4%	206	8.7%	0.4643
	Bleeding G2+	2006	10.4%	206	8.7%	0.4617
	Frequency G1+	2025	10.4%	176	10.8%	0.8594
	Frequency G2+	2021	10.3%	176	10.8%	0.8498
	Pain G1+	2185	10.3%	28	3.6%	0.2406
	Proctitis G1+	2147	10.4%	70	7.1%	0.3793
	Proctitis G2+	2146	10.4%	70	7.1%	0.3787
	Sphincter Control G1+	2199	10.2%	14	21.4%	0.1695
	Stricture/Ulcer G1+	2206	10.2%	2	0.0%	0.6328
Hypertension	Bleeding G1+	2008	39.2%	206	41.3%	0.5723
	Bleeding G2+	2006	39.2%	206	41.3%	0.5702
	Frequency G1+	2025	39.5%	176	39.8%	0.9447
	Frequency G2+	2021	39.4%	176	39.8%	0.9301
	Pain G1+	2185	39.6%	28	28.6%	0.2341
	Proctitis G1+	2147	39.2%	70	45.7%	0.2737
	Proctitis G2+	2146	39.2%	70	45.7%	0.2751
	Sphincter Control G1+	2199	39.4%	14	50.0%	0.4177
	Stricture/Ulcer G1+	2206	39.4%	2	50.0%	0.7600
IBD or Diverticular Disease	Bleeding G1+	2008	3.3%	206	8.7%	**0.0001**
	Bleeding G2+	2006	3.3%	206	8.7%	**0.0001**
	Frequency G1+	2025	3.5%	176	6.3%	0.0652
	Frequency G2+	2021	3.5%	176	6.3%	0.0662
	Pain G1+	2185	3.8%	28	7.1%	0.3602
	Proctitis G1+	2147	3.7%	70	7.1%	0.1429
	Proctitis G2+	2146	3.7%	70	7.1%	0.1432
	Sphincter Control G1+	2199	3.8%	14	7.1%	0.5190
	Stricture/Ulcer G1+	2206	3.9%	2	0.0%	0.7771
Pelvic Surgery	Bleeding G1+	2008	7.3%	206	9.7%	0.2058
	Bleeding G2+	2006	7.3%	206	9.7%	0.2073
	Frequency G1+	2025	7.2%	176	10.2%	0.1362
	Frequency G2+	2021	7.2%	176	10.2%	0.1383
	Pain G1+	2185	7.3%	28	10.7%	0.4948
	Proctitis G1+	2147	7.2%	70	12.9%	0.0761
	Proctitis G2+	2146	7.2%	70	12.9%	0.0764
	Sphincter Control G1+	2199	7.4%	14	7.1%	0.9745
	Stricture/Ulcer G1+	2206	7.3%	2	50.0%	**0.0211**
Haemorrhoids	Bleeding G1+	2008	4.2%	206	35.0%	**0.0000**
	Bleeding G2+	2006	4.2%	206	35.0%	**0.0000**
	Frequency G1+	2025	6.6%	176	10.8%	**0.0339**
	Frequency G2+	2021	6.5%	176	10.8%	**0.0320**
	Pain G1+	2185	6.7%	28	25.0%	**0.0001**
	Proctitis G1+	2147	6.8%	70	12.9%	**0.0481**
	Proctitis G2+	2146	6.8%	70	12.9%	**0.0483**
	Sphincter Control G1+	2199	6.9%	14	7.1%	0.9730
	Stricture/Ulcer G1+	2206	6.9%	2	0.0%	0.6995

Appendix C. Calibration Plots for LKB-EQD2 Model

Figure 1A. Rectal Bleeding G2+ Calibration Curve: LKB-EQD2 Model

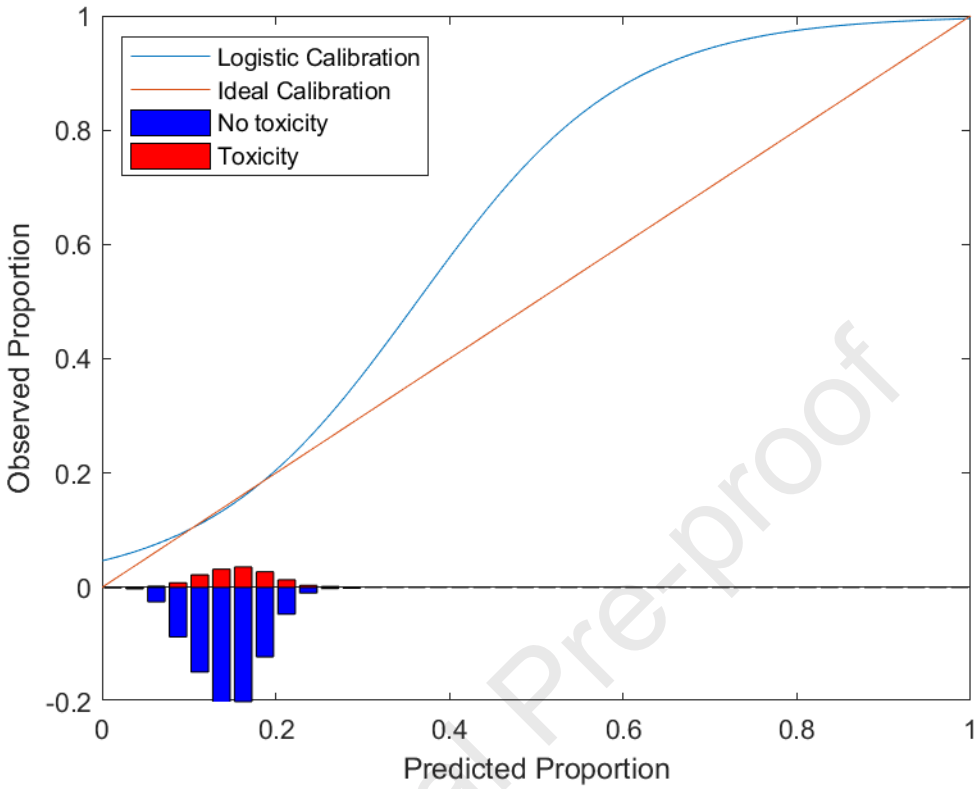


Figure 2A. Rectal Bleeding G2+ Binned Calibration Plot: LKB-EQD2 Model

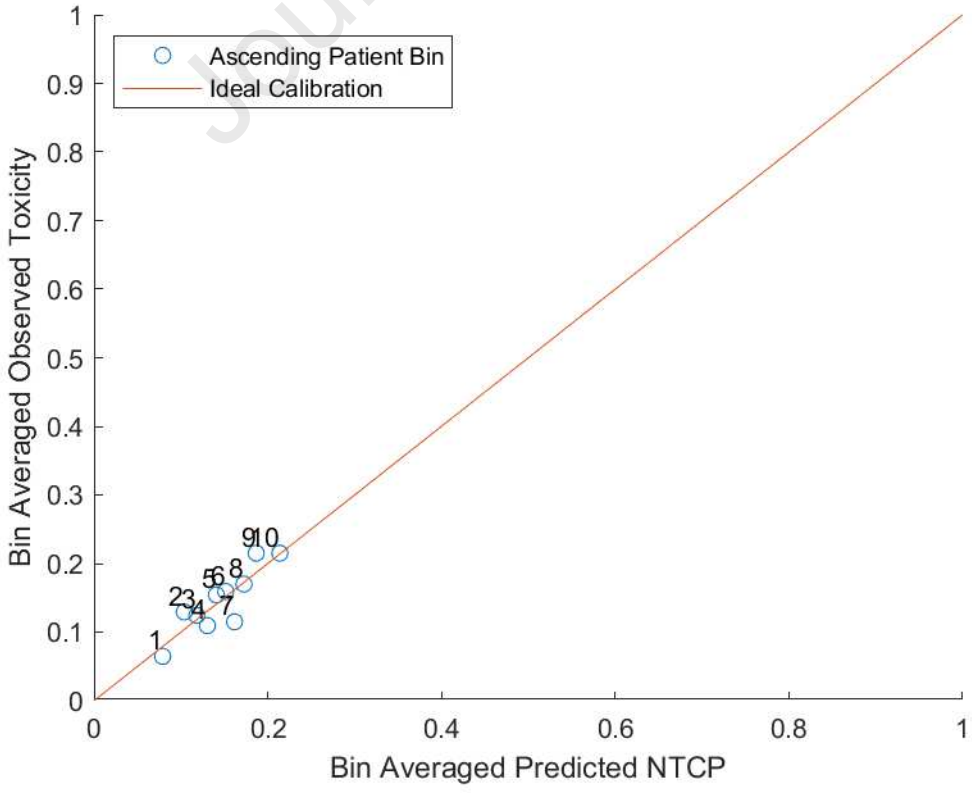


Figure 3A. Stool Frequency G1+ Calibration Curve: LKB-EQD2 Model

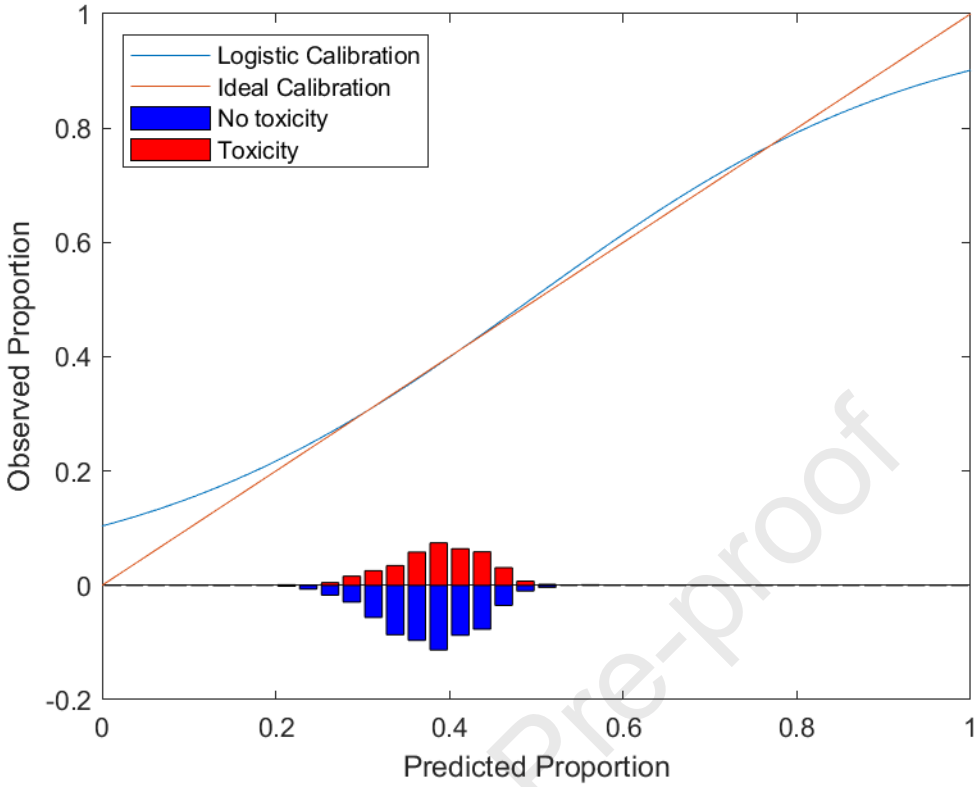


Figure 4A. Stool Frequency G1+ Binned Calibration Plot: LKB-EQD2 Model

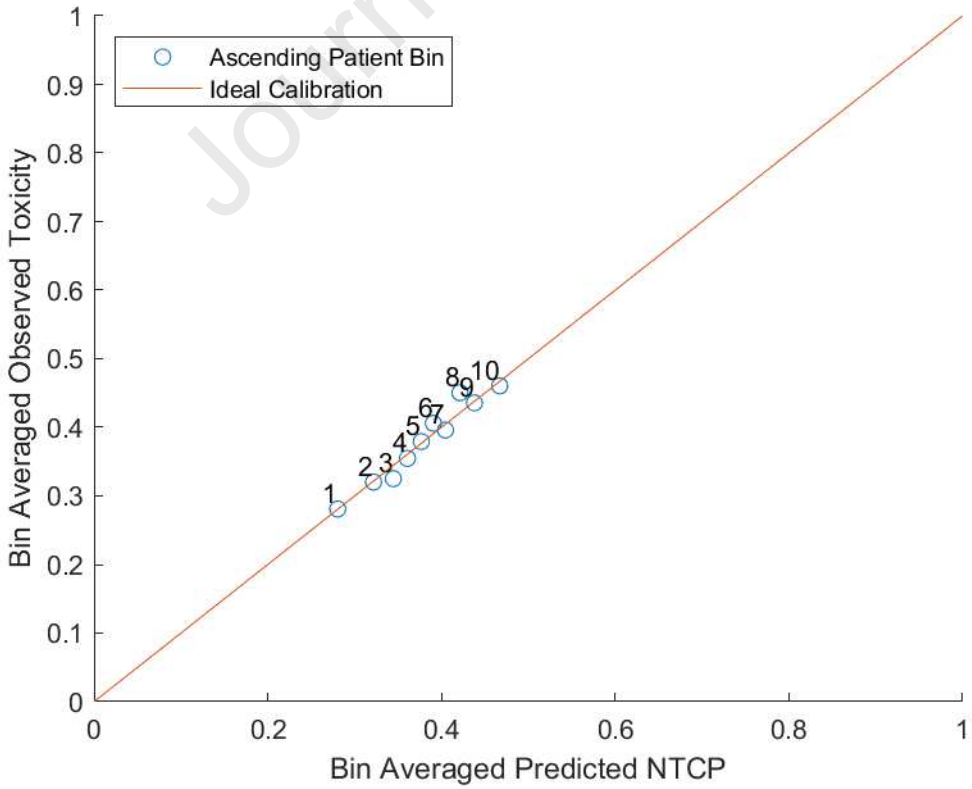


Figure 5A. Stool Frequency G2+ Calibration Curve: LKB-EQD2 Model

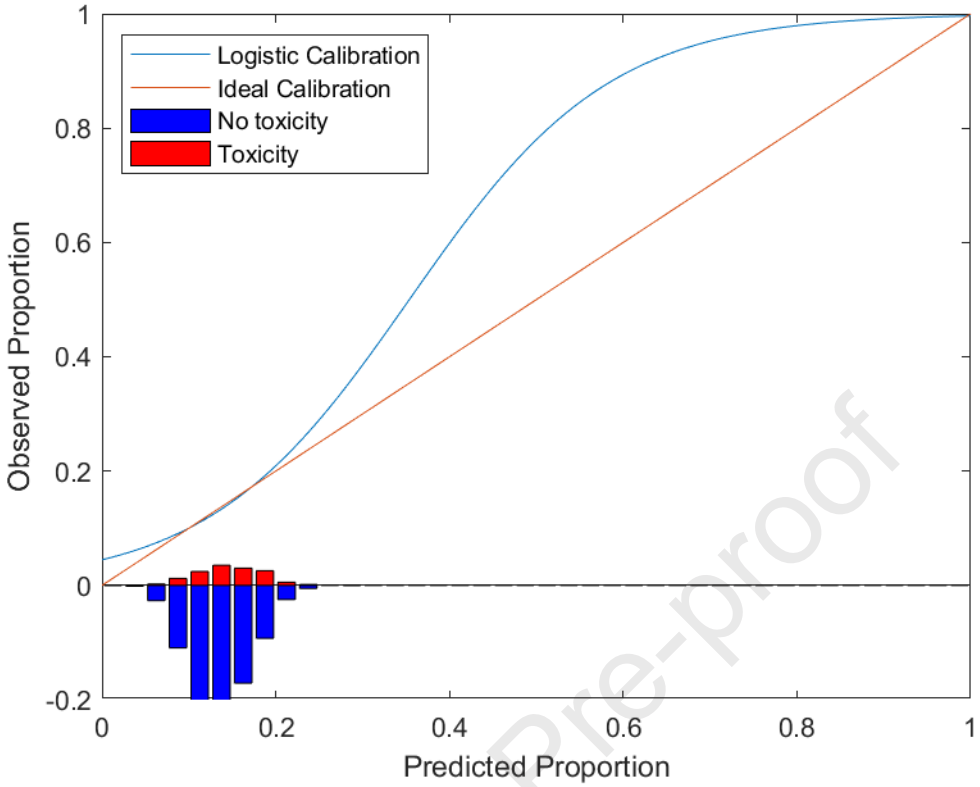


Figure 6A. Stool Frequency G2+ Binned Calibration Plot: LKB-EQD2 Model

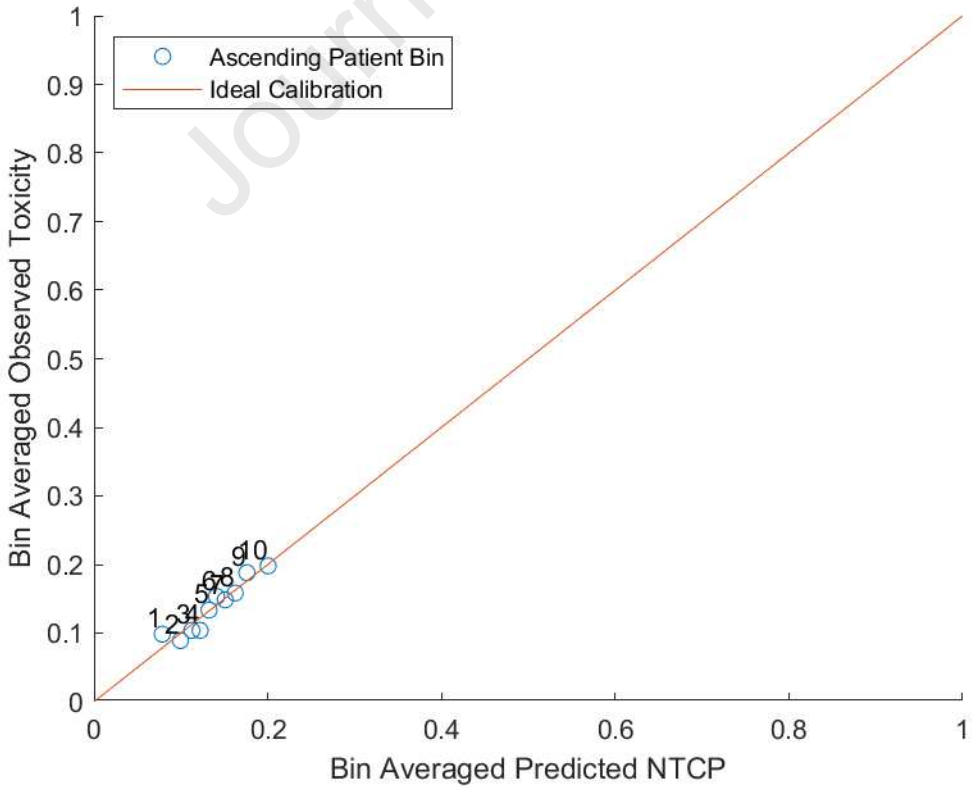


Figure 7A. Pain G1+ Calibration Curve: LKB-EQD2 Model

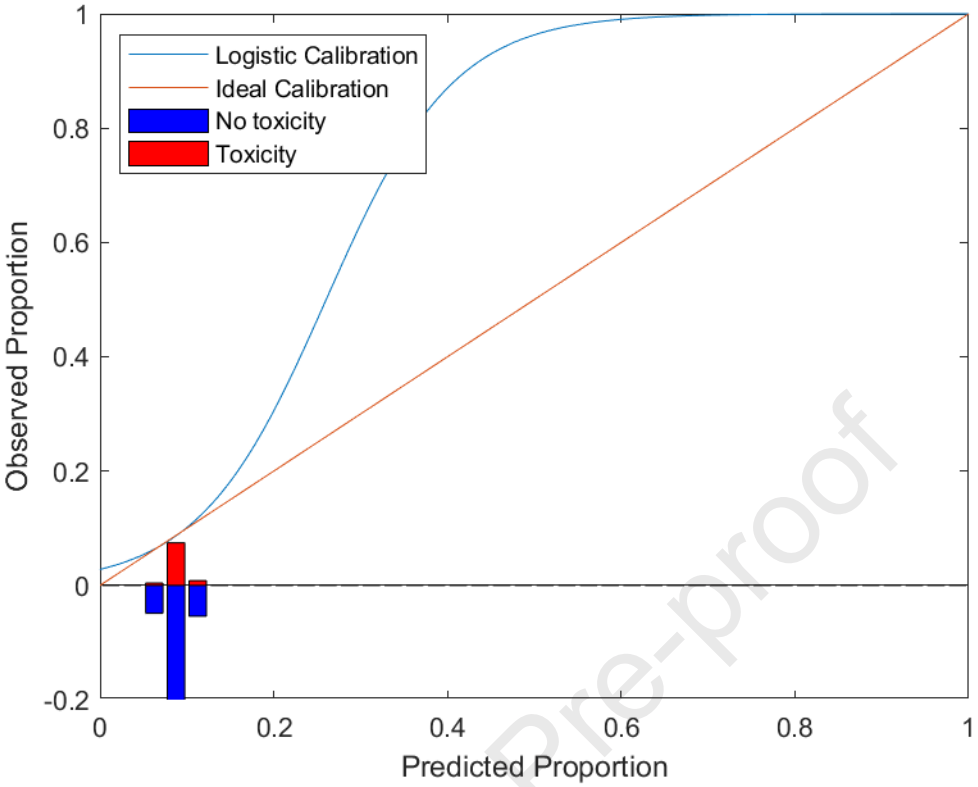


Figure 8A. Pain G1+ Binned Calibration Plot: LKB-EQD2 Model

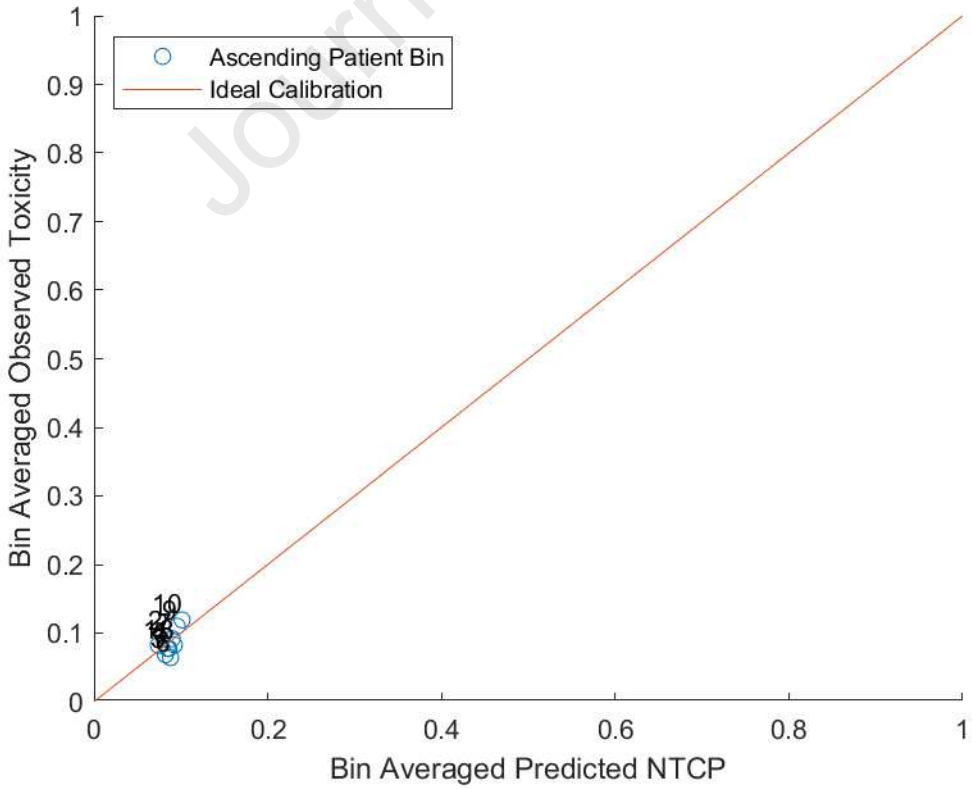


Figure 9A. Proctitis G1+ Calibration Curve: LKB-EQD2 Model

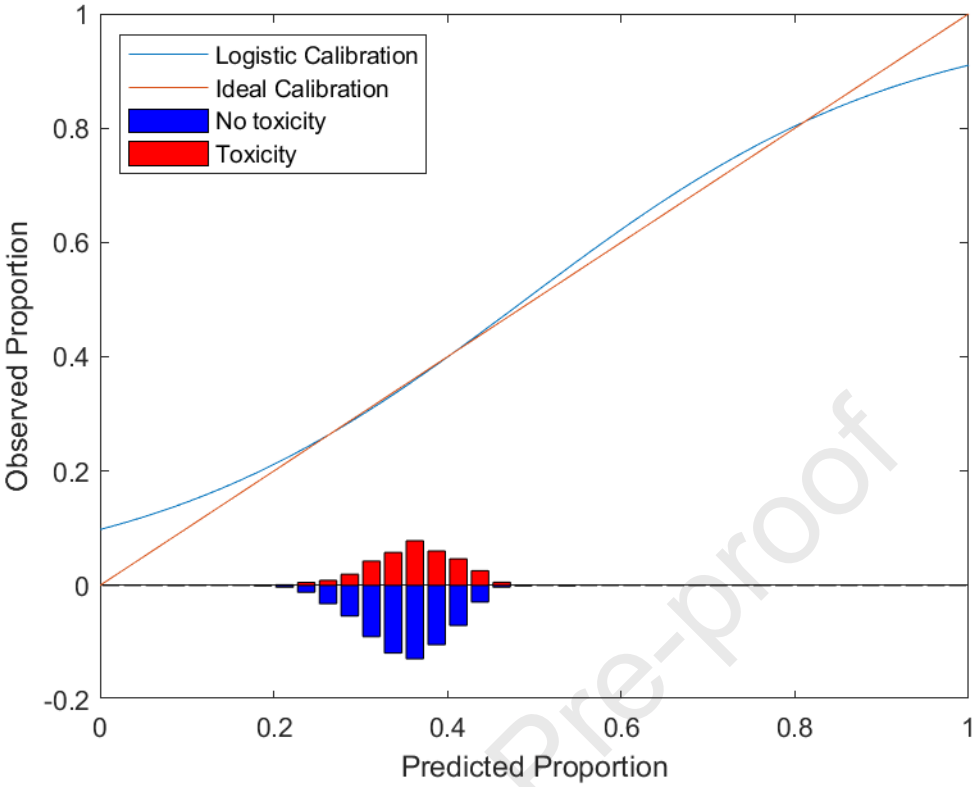


Figure 10A. Proctitis G1+ Binned Calibration Plot: LKB-EQD2 Model

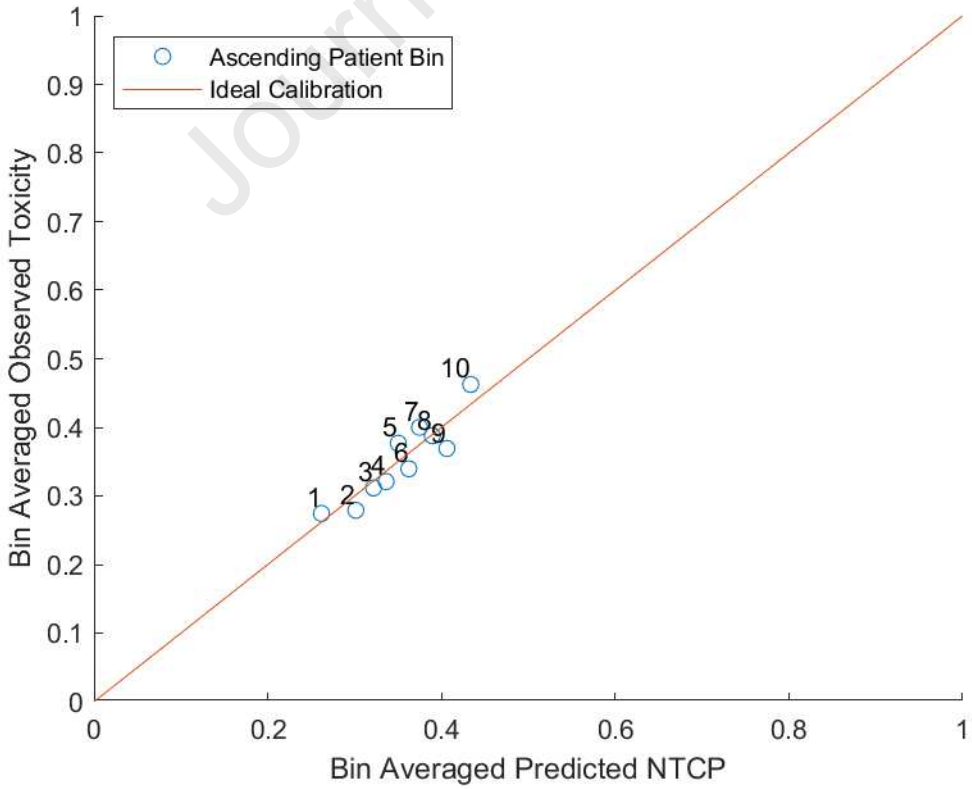


Figure 11A. Proctitis G2+ Calibration Curve: LKB-EQD2 Model

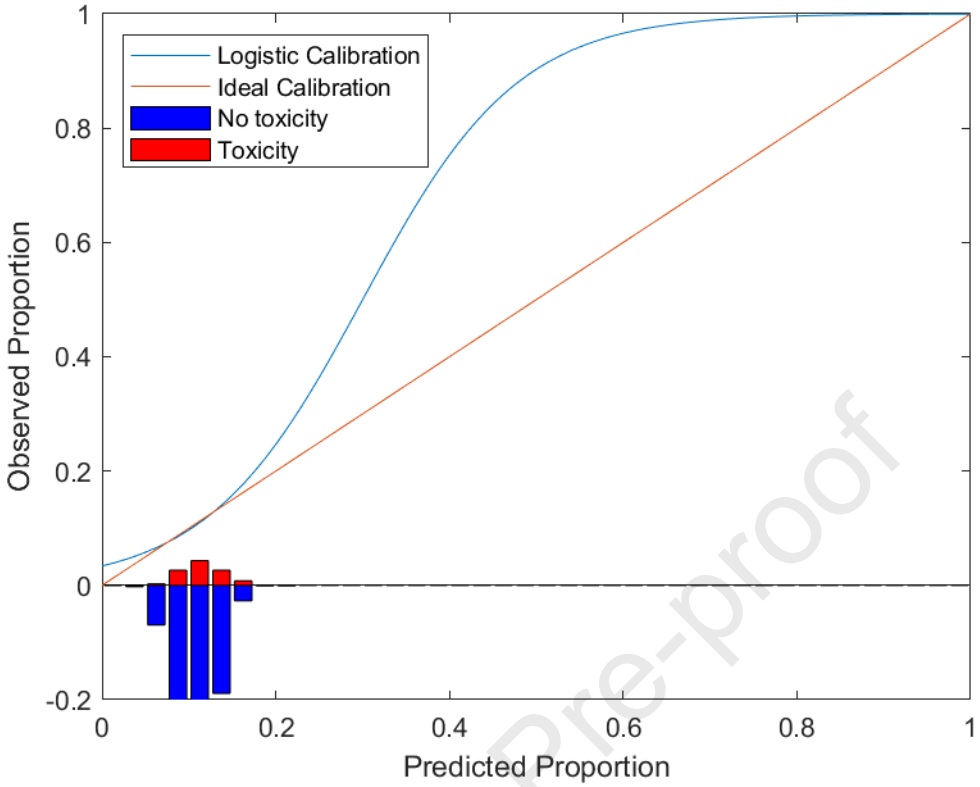


Figure 12A. Proctitis G2+ Binned Calibration Plot: LKB-EQD2 Model

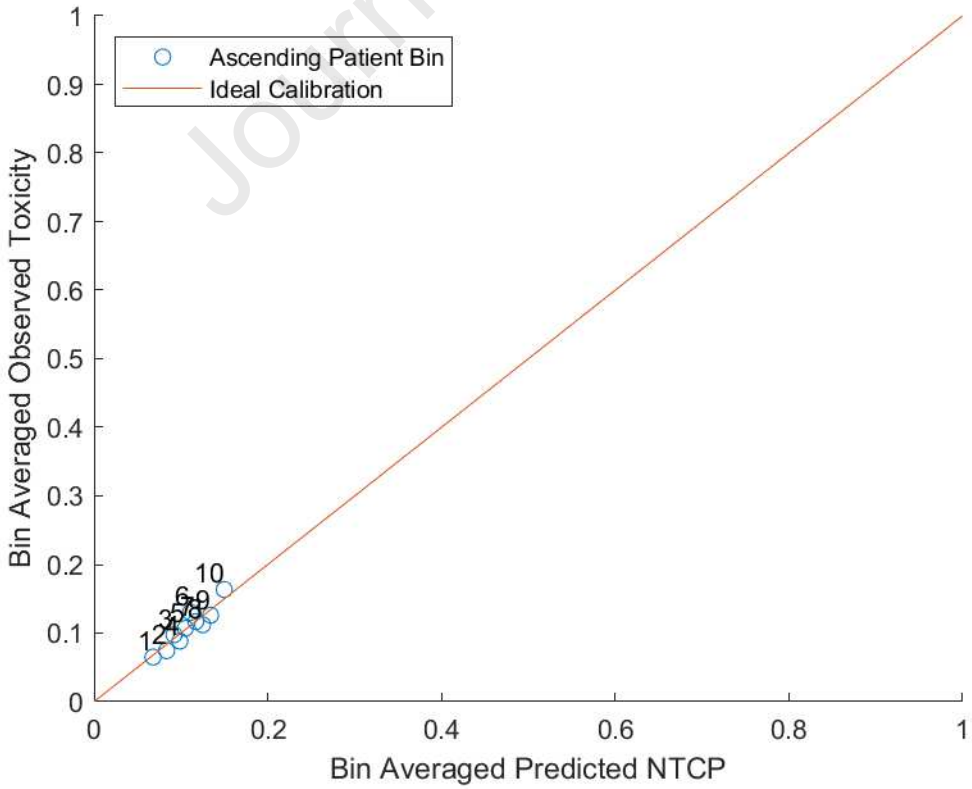


Figure 13A. Sphincter Control G1+ Calibration Curve: LKB-EQD2 Model

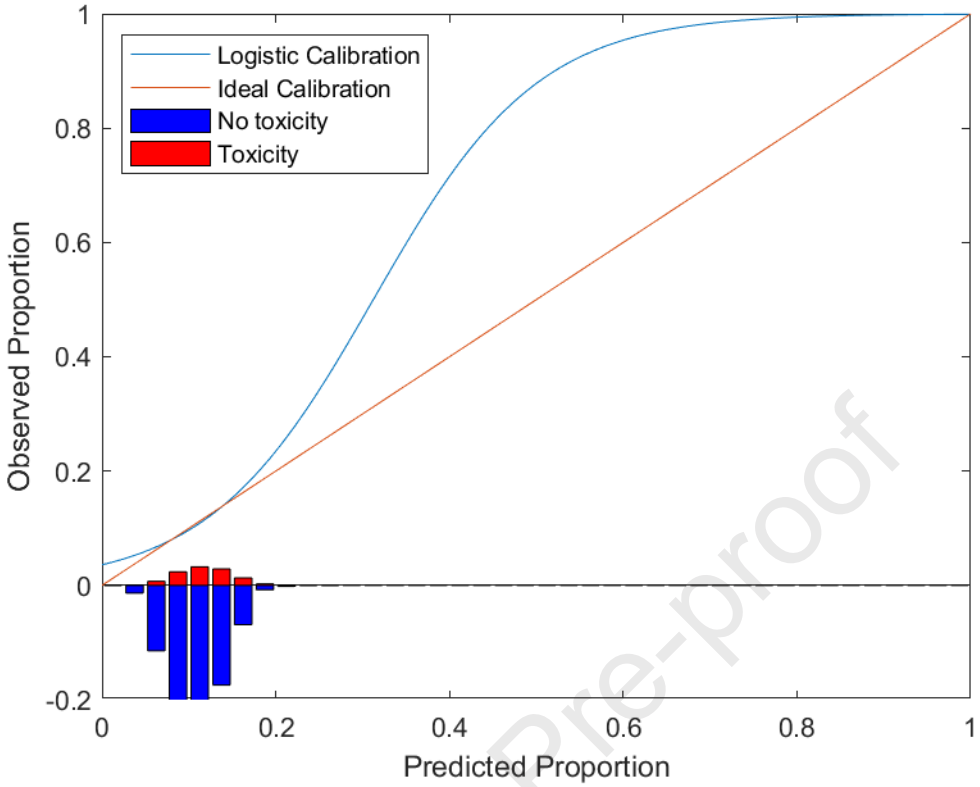


Figure 14A. Sphincter Control G1+ Binned Calibration Plot: LKB-EQD2 Model

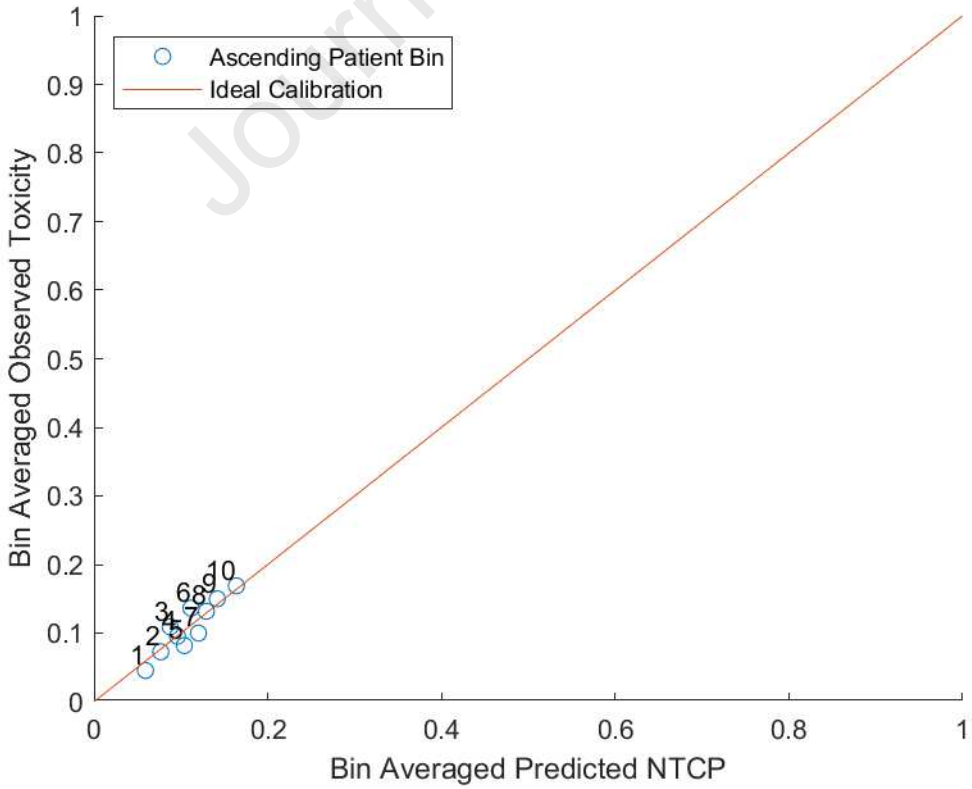


Figure 15A. Stricture/Ulcer G1+ Calibration Curve: LKB-EQD2 Model

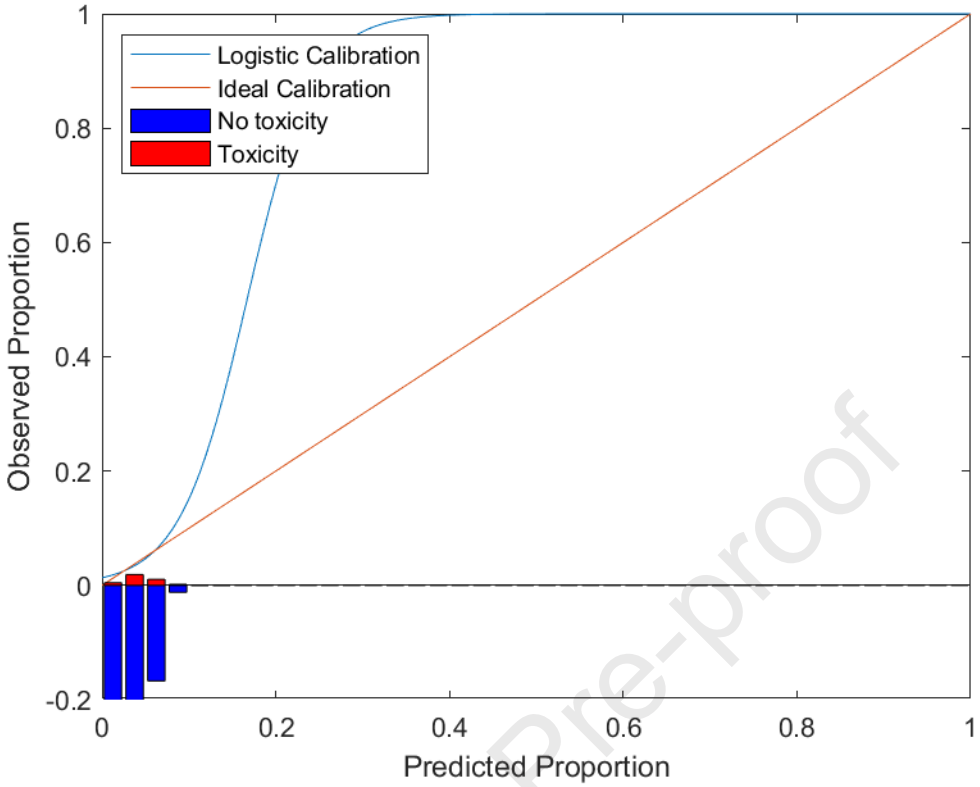
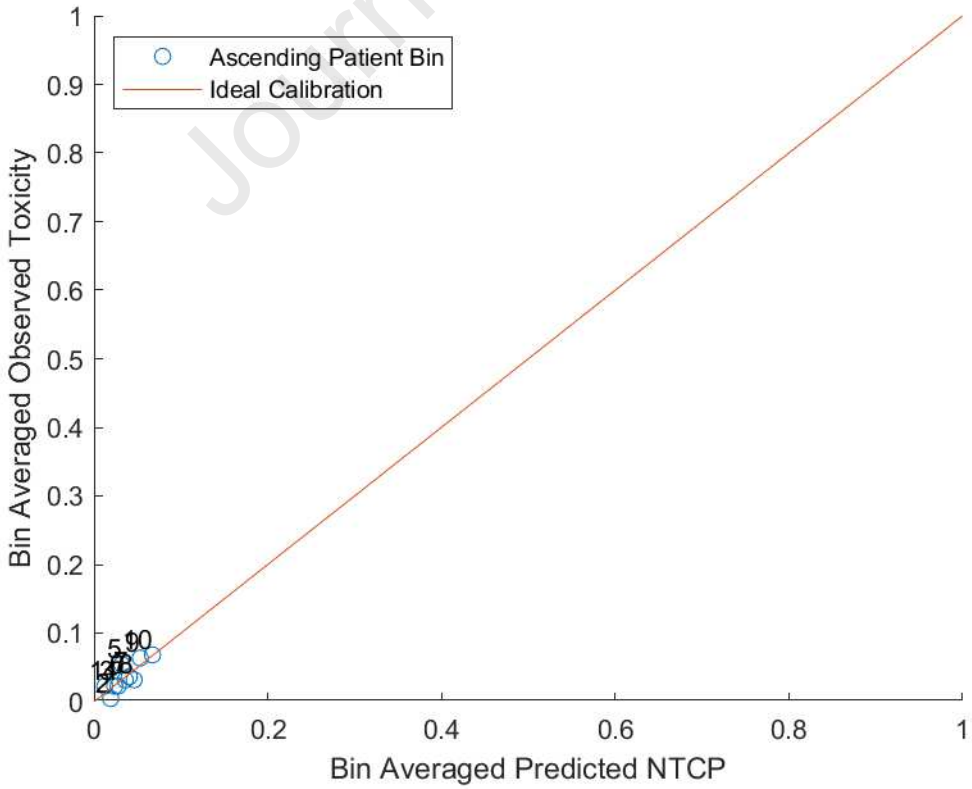


Figure 16A. Stricture/Ulcer G1+ Binned Calibration Plot: LKB-EQD2 Model



Appendix D. Calibration Plots for LKB-EQD2-DMF Models Significantly Improving on LKB-EQD2 Model

Figure 17A. Stool Frequency G2+ Calibration Curve: LKB-EQD2-DMF Model (DMF = IBD/Diverticular)

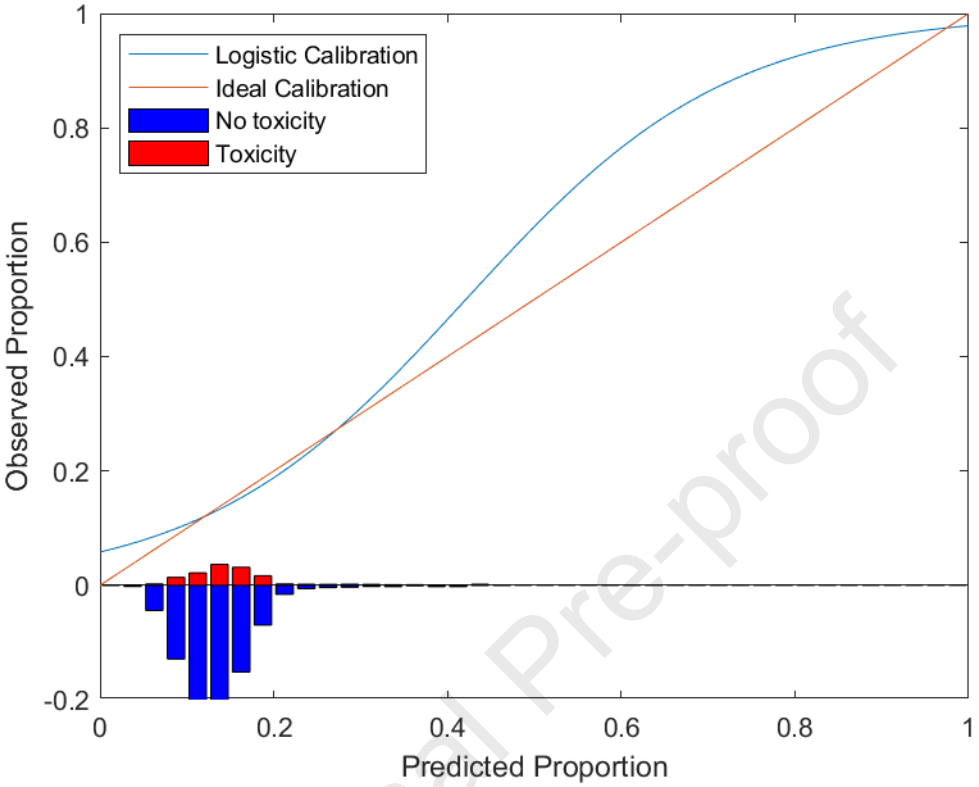


Figure 18A. Stool Frequency G2+ Binned Calibration Plot: LKB-EQD2-DMF Model (DMF = IBD/Diverticular)

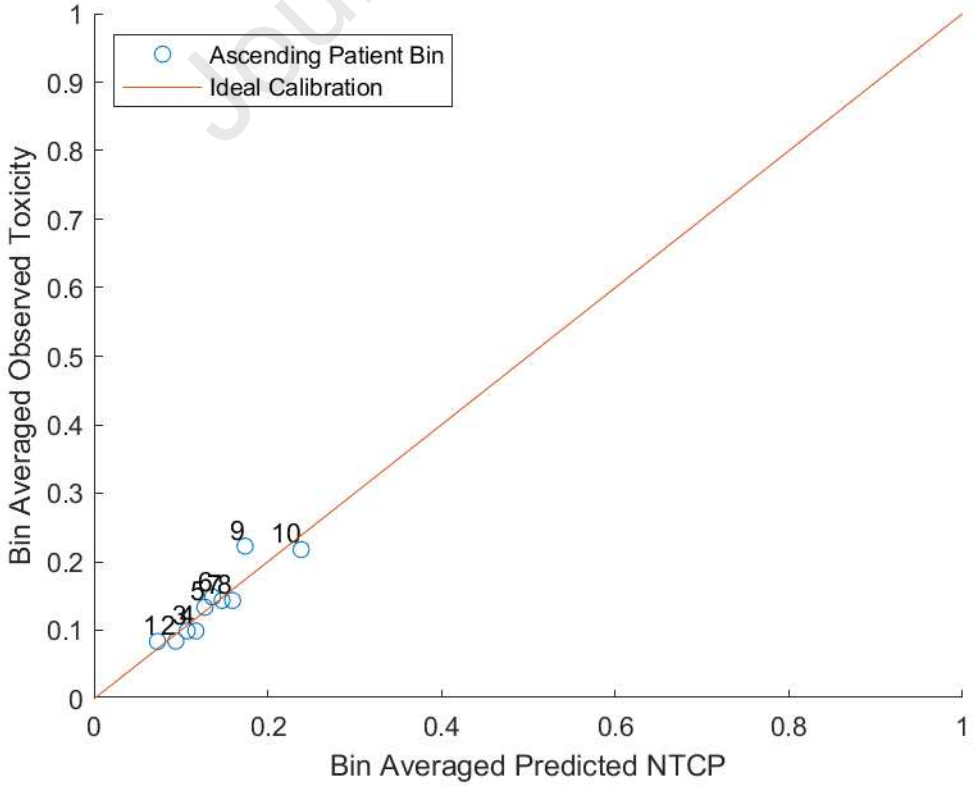


Figure 19A. Proctitis G1+ Calibration Curve: LKB-EQD2-DMF Model (DMF = IBD/Diverticular)

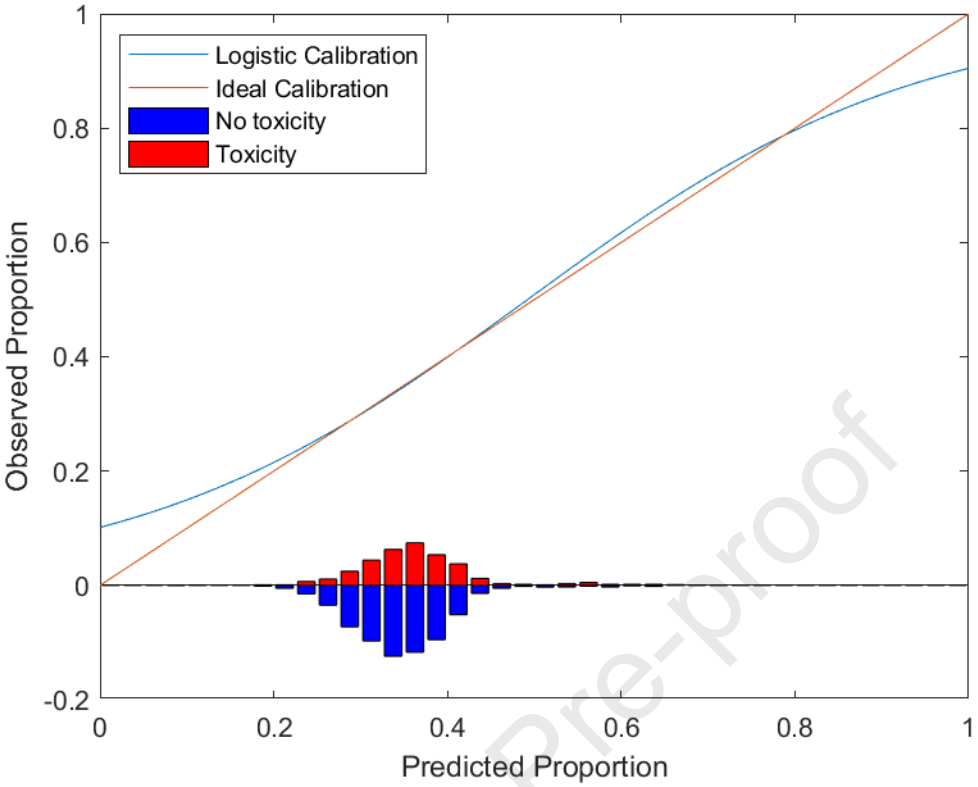


Figure 20A. Proctitis G1+ Binned Calibration Plot: LKB-EQD2-DMF Model (DMF = IBD/Diverticular)

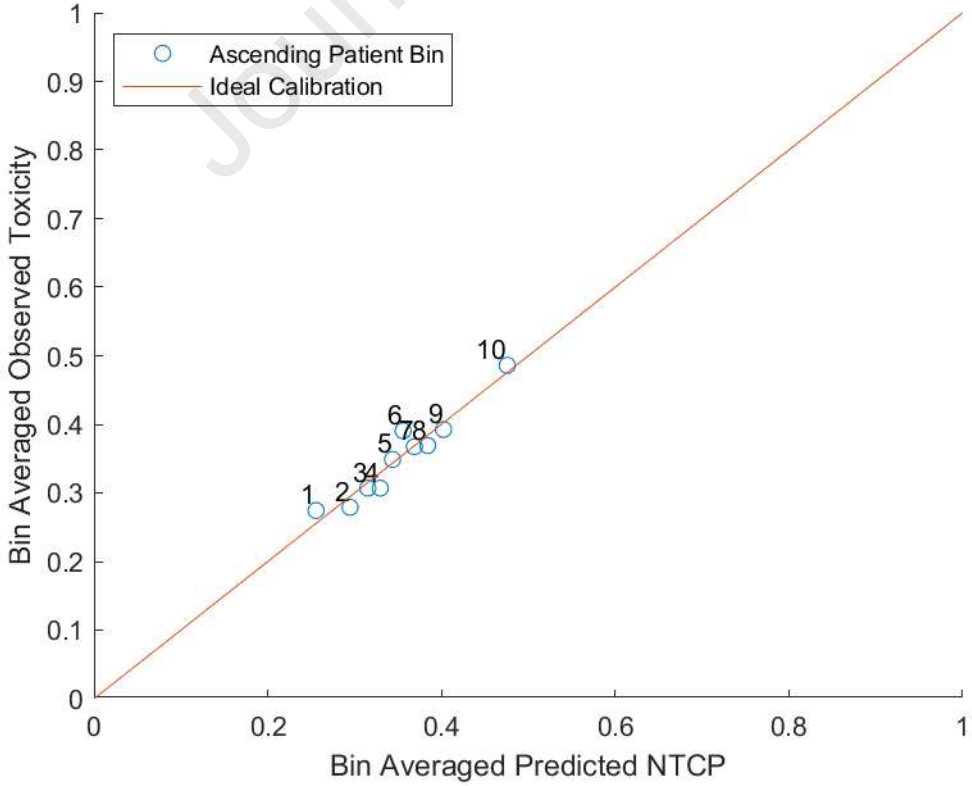


Table 3A. Calculation of Pooled Rectal Late α/β Ratio

Calculation for the pooled averaged late rectal α/β ratio for those more common endpoints fitted best during modelling. Weighting is by the frequency of side effect occurrence seen in patients modelled (per **Table 2**).

Late Rectal Endpoints	Frequency	Weights	α/β Ratio (Gy)
Grade 1+ Endpoints			
Bleeding G1+	0.329	9.139	1.58
Frequency G1+	0.381	10.583	2.26
Pain G1+	0.087	2.417	3.64
Proctitis G1+	0.352	9.778	2.65
Sphincter Control G1+	0.109	3.028	3.09
Stricture/Ulcer G1+	0.036	1	2.49
Grade 1+ weighted average			**2.36**
Grade 2+ Endpoints			
Bleeding G2+	0.146	1.352	1.71
Frequency G2+	0.138	1.278	2.66
Proctitis G2+	0.108	1	2.70
Grade 2 weighted average			**2.32**

Table 4A. LKB-NoEQD2 Parameter Comparison

Parameters n, m, TD50 for LKB model without EQD2 correction fitted on conventionally fractionated 74Gy Patients. Comparing with other studies fitting similar endpoints. Defraene and Peeters incontinence data omitted as modelled only on anal wall OAR.

Endpoint	**Study**	**Pts**	**n**	**95% CI** *(68% CI)*	**m**	**95% CI** *(68% CI)*	**TD50**	**95% CI** *(68% CI)*
Bleeding G1+	This Study	644	0.26	0.01-1.12	0.33	0.09–0.68	61.5	54.5–74.0
	Gulliford *et al* [1]	361	0.14	0.09–0.16	0.26	0.18–0.48	59.2	57.8–61.9
Bleeding G2+	This Study	642	0.13	0.01–0.42	0.21	0.06–0.43	74.0	67.2–96.6
	Gulliford *et al*	361	0.12	0.10–0.16	0.14	0.12–0.16	68.2	64.9–69.3
	Peeters *et al* [2]	468	0.13	*(0.04–0.25)*	0.14	*(0.11–0.19)*	81.0	*(75–90)*
	Defraene *et al* [3] *	512	0.18	*(0.09–0.33)*	0.15	*(0.12–0.20)*	79.0	*(74.0–86.5)*
	Rancati *et al* [4]	547	0.23	*(0.14–0.42)*	0.19	*(0.15–0.25)*	81.9	*(76.8–91.2)*
Frequency G1+	This Study	643	0.17	0.01–0.53	0.30	0.09–0.76	60.8	53.7–72.8
	Gulliford *et al*	344	0.30	0.16–0.6	0.60	0.41–>1	61.5	56.3–68.3
Frequency G2+	This Study	642	0.11	0.03–0.69	0.20	0.09–0.49	73.8	66.2–98.6
	Peeters *et al*	468	0.39	*(0.19–1.11)*	0.24	*(0.18–0.35)*	84.0	*(75–103)*
	Defraene *et al* *	512	1.18	*(0.94–1.53)*	0.34	*(0.27–0.44)*	97.4	*(82.4–137.5)*
Proctitis G1+	This Study	691	0.10	0.01–0.18	0.22	0.08–0.50	64.9	60.8–73.7
	Gulliford *et al*	388	0.14	0.11–0.20	0.28	0.19–0.60	58.2	55.7–60.1
Proctitis G2+	This Study	691	0.05	0.01–0.14	0.14	0.06–0.44	78.0	71.6-111.6
	Gulliford *et al*	388	0.15	0.11–0.20	0.20	0.19–0.24	67.0	64.8–69.3

* Rectal wall instead of solid rectum.

Table 5A. Moderate Hypofractionation Trial Design Assumptions

PACE-B not included as late toxicity not reported, however late rectal α/β ratio was assumed to be 3 Gy in that trial [5]. Trial references are the same as those in **Table 5A**.

Abbreviations: EQD2 = Equivalent Dose in 2 Gy Fractions.

Trial	Prostate Assumptions			Rectum Assumptions			Design
	α/β Ratio	Test EQD2	Control EQD2	α/β Ratio	Test EQD2	Control EQD2	
XXXXX 57Gy	1.5 - 2.5	73.3 – 69.7	74	3	68.4	74	Isoeffective
XXXXX 60Gy	1.5 - 2.5	77.1 – 73.3	74	3	72	74	Isoeffective
PROFIT	1 - 3	80 - 72	78	3 - 5	72 - 68.6	78	Isoeffective
RTOG 0415	3	77	70.8	3	77	70.8	Dose Escalation
HYPRO	1.5	90.4	78	4 - 6	79.7 - 76	78	Isotoxic
HYPO-RT-PC	<3	>78	78	3	77.7	78	Isotoxic

Table 6A. Bowel Toxicity in Phase III Hypofractionation Trials

Trial	Patients	Treatment Arms	Timepoint for Toxicity	Cumulative RTOG Late Bowel Toxicity	
	n	Gy / Fractions / Weeks		G2+	G3+
XXXXX [6]	1065 1074 1077	C 74 Gy / 37 Fr / 7.4 w H 60 Gy / 20 Fr / 4.0 w H 57 Gy / 19 Fr / 3.8 w	5 years median	13.7% 11.9% 11.3%	0% <1% <1%
PROFIT [7]	598 608	C 78 Gy / 39 Fr / 7.8 w H 60 Gy / 20 Fr / 4.0 w	6 years median	13.9% 8.9%	2.9% 1.5%
RTOG 0415 [8]	558 557	C 73.8 Gy / 41 Fr / 8.2 w H 70 Gy / 28 Fr / 5.6 w	5.8 years median	14.0% 22.4%	2.6% 4.1%
HYPRO [9]	410 410	C 78 Gy / 39 Fr / 7.8w H 64.6 Gy / 19 Fr / 6.5w	At 3 years	17.7% 21.9%	2.6% 3.3%
HYPO-RT-PC [10]	602 598	C 78 Gy / 39 Fr / 7.8w H 42.7 Gy / 7 Fr / 2.5w	5 years median	9.7% 9.5%	1.9% 1.5%

Legend

Table 1. Summary of the phase III trials of hypofractionated radiotherapy for localised prostate cancer, with reference to subsequent late bowel toxicity. PACE-B not included, as late toxicity not yet reported.

RTOG = Radiation Therapy Oncology Group

GX+ = Grade X toxicity or worse. Fr = Fractions. w = Weeks over which treatment delivered

Bibliography for Supplementary Appendix

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[5] Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2019;20:1531–43. doi:10.1016/S1470-2045(19)30569-8.

[6] XXXXX

[7] Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. J Clin Oncol 2017;35:1884–90. doi:10.1200/JCO.2016.71.7397.

[8] Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 2016;34:2325–32. doi:10.1200/JCO.2016.67.0448.

[9] Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2016;17:1061–9. doi:10.1016/S1470-2045(16)30070-5.

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randomised, non-inferiority, phase 3 trial. Lancet 2019;394:385–95. doi:10.1016/S0140-6736(19)31131-6.

Tables – Redacted Version

Table 1. Baseline characteristics for patients included in this study

Hypertension included even if medically controlled.
Abbreviations: NCCN = National Comprehensive Cancer Network; ADT = Androgen Deprivation Therapy; PSA =Prostate Specific Antigen; IBD = Inflammatory Bowel Disease.

Characteristic	**This Study**		**Whole XXXXX Trial**	
	No.	**%**	**No.**	**%**
Age	**69 years**	**44-85 (range)**	**69 years**	**44-85 (range)**
Arm				
57Gy/19f	755	34%	1077	33%
60Gy/20f	753	34%	1074	33%
74Gy/37f	707	32%	1065	33%
NCCN Risk Group				
Low risk	308	14%	484	15%
Intermediate risk	1655	75%	2347	73%
High risk	252	11%	385	12%
Gleason score				
≤6	750	34%	1122	35%
7	1399	63%	1995	62%
8	66	3%	99	3%
Clinical T Stage				
T1	851	38%	1170	36%
T2	1196	54%	1766	55%
T3	167	8%	277	9%
Missing	1	<1%	3	<1%
Pre-ADT PSA				
<10 ng/mL	1082	49%	1567	49%
10-20 ng/mL	1006	45%	1415	44%
≥20 ng/mL	127	6%	208	6%
Missing	0	0%	26	<1%
Comorbidities				
Diabetes	227	10%	342	11%
Hypertension	874	40%	1276	40%
IBD or diverticular disease	85	4%	124	4%
Pelvic Surgery	162	7%	252	8%
Symptomatic Haemorrhoids	153	7%	209	6%
Total	**2215**	**100%**	**3216**	**100%**

Table 2. Summary of Patient Numbers in Each Modelling 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.

Rectal 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.	%
Bleeding G1+								
No	479	70.5%	434	63.4%	434	67.4%	**1,347**	**67.1%**
Yes	200	29.5%	251	36.6%	210	32.6%	**661**	**32.9%**
Excluded	73		67		67		207	
Bleeding G2+								
No	590	86.9%	575	83.9%	549	85.5%	**1,714**	**85.4%**
Yes	89	13.1%	110	16.1%	93	14.5%	**292**	**14.6%**
Excluded	73		67		69		209	
Frequency G1+								
No	437	62.8%	428	62.4%	389	60.5%	**1,254**	**61.9%**
Yes	259	37.2%	258	37.6%	254	39.5%	**771**	**38.1%**
Excluded	56		66		68		190	
Frequency G2+								
No	611	87.9%	587	85.8%	545	84.9%	**1,743**	**86.2%**
Yes	84	12.1%	97	14.2%	97	15.1%	**278**	**13.8%**
Excluded	57		68		69		194	
Pain G1+								
No	686	93.1%	671	90.1%	638	90.8%	**1,995**	**91.3%**
Yes	51	6.9%	74	9.9%	65	9.2%	**190**	**8.7%**
Excluded	15		7		8		30	
Proctitis G1+								
No	509	69.3%	449	62.2%	433	62.7%	**1,391**	**64.8%**
Yes	225	30.7%	273	37.8%	258	37.3%	**756**	**35.2%**
Missing	18		30		20		68	
Proctitis G2+								
No	666	90.9%	641	88.8%	607	87.8%	**1,914**	**89.2%**
Yes	67	9.1%	81	11.2%	84	12.2%	**232**	**10.8%**
Excluded	19		30		20		69	
Sphincter Control G1+								
No	680	91.0%	664	88.7%	615	87.5%	**1,959**	**89.1%**
Yes	67	9.0%	85	11.3%	88	12.5%	**240**	**10.9%**
Excluded	5		3		8		16	
Stricture/Ulcer G1+								
No	732	97.5%	719	95.9%	676	95.9%	**2,127**	**96.4%**
Yes	19	2.5%	31	4.1%	29	4.1%	**79**	**3.6%**
Excluded	1		2		6		9	
Total	**752**	**100%**	**752**	**100%**	**711**	**100%**	**2,215**	**100%**

Table 3. Parameters for LKB-NoEQD2 model and LKB-EQD2 model

First two sections show LKB-NoEQD2 model fitted for each endpoint to the conventionally fractionated (74Gy) patients and the hypofractionated (57 & 60 Gy) patients. The next three sections show the LKB-EQD2 model fitted with a varying α/β ratio, then fixed to α/β = 3 Gy and α/β = 4.8 Gy. p-values are from likelihood ratio tests between an endpoint 632 likelihood in the fixed α/β LKB-EQD2 models and same endpoint 632 likelihood in the unfixed LKB-EQD2 model. Note that "Better Fit" implies that the simpler fixed α/β ratio model has better (less negative) 632 estimator than the more complex model (varying α/β ratio), implying the more complex model is overfitted and making likelihood ratio testing inappropriate. Bold p-values are significant at adjusted $p<0.001$.

Abbreviations: LKB-NoEQD2 = Lyman-Kutcher Burman model with No Equivalent Dose in 2Gy correction; 95% CI = 95% confidence interval; LKB-EQD2 = Lyman-Kutcher Burman model with Equivalent Dose in 2Gy correction; Pts = patients; G1+ = grade 1 or above; G2+ = grade 2 or above.

(See table overleaf)

Model	Pts	n (95% CI)	m (95% CI)	TD50 (95% CI) [Gy]	α/β Ratio [Gy]	632 Likelihood	p-value vs LKB-EQD2
LKB-NoEQD2 (74Gy Patients)							
Bleeding G1+	644	0.26 (0.01-1.12)	0.33 (0.09-0.68)	61.5 (54.5-74.0)	N/A	-401.8	N/A
Bleeding G2+	642	0.13 (0.01-0.42)	0.21 (0.06-0.43)	74.0 (67.2-96.6)	N/A	-262.6	N/A
Frequency G1+	643	0.17 (0.01-0.53)	0.30 (0.09-0.76)	60.8 (53.7-72.8)	N/A	-427.7	N/A
Frequency G2+	642	0.11 (0.03-0.69)	0.20 (0.09-0.49)	73.8 (66.2-98.6)	N/A	-269.9	N/A
Pain G1+	703	0.24 (0.01-3.15)	0.33 (0.15-0.61)	92.7 (72.2-271.6)	N/A	-216.5	N/A
Proctitis G1+	691	0.10 (0.01-0.18)	0.22 (0.08-0.50)	64.9 (60.8-73.7)	N/A	-452.2	N/A
Proctitis G2+	691	0.05 (0.01-0.14)	0.14 (0.06-0.44)	78.0 (71.6-111.6)	N/A	-254.3	N/A
Sphincter Control G1+	703	0.19 (0.09-3.30)	0.29 (0.16-0.63)	81.7 (68.5-185.3)	N/A	-263.8	N/A
Stricture/Ulcer G1+	705	0.28 (0.01-5.79)	0.16 (0.05-0.31)	74.4 (66.2-92.8)	N/A	-117.6	N/A
LKB-NoEQD2 (57Gy/60Gy Patients)							
Bleeding G1+	1364	0.13 (0.07-0.20)	0.22 (0.15-0.31)	50.7 (48.2-53.8)	N/A	-845.9	N/A
Bleeding G2+	1364	0.11 (0.01-0.28)	0.22 (0.13-0.40)	61.7 (56.3-74.2)	N/A	-560.6	N/A
Frequency G1+	1382	0.20 (0.12-0.33)	0.47 (0.30-0.89)	50.5 (46.8-59.2)	N/A	-908.2	N/A
Frequency G2+	1379	0.26 (0.02-0.73)	0.33 (0.20-0.53)	64.9 (56.5-94.4)	N/A	-531.9	N/A
Pain G1+	1482	0.02 (0.01-9.99)	0.37 (0.16-0.69)	105.4 (69.5-619.1)	N/A	-429.8	N/A
Proctitis G1+	1456	0.09 (0.01-0.17)	0.34 (0.18-0.70)	56.5 (52.0-67.8)	N/A	-931.3	N/A
Proctitis G2+	1455	0.12 (0.01-4.16)	0.28 (0.15-0.58)	73.8 (61.6-153.8)	N/A	-477.8	N/A
Sphincter Control G1+	1496	0.17 (0.09-0.29)	0.26 (0.17-0.43)	65.8 (58.0-93.9)	N/A	-486.6	N/A
Stricture/Ulcer G1+	1501	0.17 (0.01-0.47)	0.20 (0.09-0.35)	72.3 (60.6-113.6)	N/A	-217.4	N/A
LKB-EQD2 (All Patients)							
Bleeding G1+	2008	0.21 (0.08-0.34)	0.33 (0.20-0.47)	58.8 (54.2-66.0)	1.6 (0.9-2.5)	-1248.1	N/A
Bleeding G2+	2006	0.16 (0.01-0.34)	0.27 (0.14-0.42)	75.8 (68.2-88.6)	1.7 (0.7-3.0)	-822.6	N/A
Frequency G1+	2025	0.27 (0.17-0.44)	0.55 (0.39-0.86)	56.0 (51.4-62.3)	2.3 (0.9-5.3)	-1334.7	N/A
Frequency G2+	2021	0.31 (0.10-0.71)	0.36 (0.23-0.52)	75.7 (66.2-96.8)	2.7 (0.9-8.5)	-801.3	N/A
Pain G1+	2185	0.15 (0.01-9.89)	0.48 (0.21-0.68)	139.7 (88.7-499.1)	3.6 (0.0-839.6)	-647.4	N/A
Proctitis G1+	2147	0.14 (0.02-0.22)	0.42 (0.22-0.68)	63.6 (58.7-75.5)	2.7 (1.5-5.4)	-1384.1	N/A
Proctitis G2+	2146	0.11 (0.01-0.25)	0.30 (0.17-0.51)	87.8 (75.2-137.0)	2.7 (1.3-15.1)	-731.9	N/A
Sphincter Control G1+	2199	0.23 (0.15-0.38)	0.32 (0.24-0.45)	79.3 (69.8-103.3)	3.1 (1.4-9.1)	-749.7	N/A
Stricture/Ulcer G1+	2206	0.31 (0.01-0.74)	0.25 (0.10-0.34)	83.8 (71.5-110.3)	2.5 (0.9-8.2)	-335.1	N/A
LKB-EQD2 (All Patients). Fixed α/β = 3 Gy							
Bleeding G1+	2008	0.23 (0.15-0.35)	0.37 (0.28-0.51)	57.3 (53.5-61.8)	3.0 (3.0-3.0)	-1250.2	0.042
Bleeding G2+	2006	0.19 (0.03-0.36)	0.32 (0.21-0.46)	75.8 (67.8-92.3)	3.0 (3.0-3.0)	-822.9	0.49
Frequency G1+	2025	0.27 (0.17-0.42)	0.56 (0.40-0.86)	55.7 (51.5-62.2)	3.0 (3.0-3.0)	-1334	Better fit
Frequency G2+	2021	0.31 (0.10-0.71)	0.36 (0.25-0.52)	75.8 (66.3-97.4)	3.0 (3.0-3.0)	-800.3	Better fit
Pain G1+	2185	0.17 (0.01-9.98)	0.49 (0.24-0.70)	142.6 (89.4-701.6)	3.0 (3.0-3.0)	-646.6	Better fit
Proctitis G1+	2147	0.14 (0.02-0.22)	0.43 (0.25-0.68)	63.4 (58.6-75.6)	3.0 (3.0-3.0)	-1383.2	Better fit
Proctitis G2+	2146	0.12 (0.01-0.25)	0.30 (0.18-0.51)	88.1 (75.3-136.5)	3.0 (3.0-3.0)	-730.8	Better fit
Sphincter Control G1+	2199	0.24 (0.15-0.38)	0.32 (0.24-0.45)	79.1 (69.9-103.4)	3.0 (3.0-3.0)	-748.7	Better fit
Stricture/Ulcer G1+	2206	0.32 (0.01-0.74)	0.25 (0.13-0.35)	84.4 (71.7-115.0)	3.0 (3.0-3.0)	-334.2	Better fit
LKB-EQD2 (All Patients). Fixed α/β = 4.8 Gy							
Bleeding G1+	2008	0.28 (0.20-0.42)	0.46 (0.36-0.63)	57.0 (53.1-62.5)	4.8 (4.8-4.8)	-1254.6	**0.00032**
Bleeding G2+	2006	0.24 (0.14-0.46)	0.39 (0.30-0.54)	80.0 (69.5-105.9)	4.8 (4.8-4.8)	-824.9	0.032
Frequency G1+	2025	0.29 (0.19-0.45)	0.63 (0.46-0.96)	55.6 (51.2-63.0)	4.8 (4.8-4.8)	-1335.2	0.34
Frequency G2+	2021	0.34 (0.16-0.75)	0.40 (0.30-0.54)	77.5 (67.0-103.5)	4.8 (4.8-4.8)	-800.7	Better fit
Pain G1+	2185	0.21 (0.01-9.97)	0.52 (0.30-0.70)	152.5 (93.6-745.7)	4.8 (4.8-4.8)	-646.4	Better fit
Proctitis G1+	2147	0.16 (0.09-0.24)	0.52 (0.38-0.81)	63.3 (58.2-74.1)	4.8 (4.8-4.8)	-1383.8	Better fit
Proctitis G2+	2146	0.14 (0.02-0.27)	0.36 (0.25-0.54)	93.4 (77.7-148.5)	4.8 (4.8-4.8)	-731	Better fit
Sphincter Control G1+	2199	0.24 (0.16-0.38)	0.34 (0.27-0.47)	81.3 (71.1-106.6)	4.8 (4.8-4.8)	-749	Better fit
Stricture/Ulcer G1+	2206	0.36 (0.15-0.84)	0.28 (0.21-0.37)	87.5 (73.2-127.9)	4.8 (4.8-4.8)	-334.2	Better fit

Table 4. Effects of dose modifying factor inclusion

Model fits for the sequential inclusion of each dose modifying factor, including the 632 estimator for model performance. Each DMF model is compared against the LKB-EQD2 (No DMF) model for the same endpoint by likelihood ratio test. Note that "Worse Fit" implies that the more complicated LKB-EQD2-DMF has a worse 632 estimator fit than the simpler LKB-EQD2 (No DMF) model, implying overfitting and making likelihood ratio testing inappropriate. Bold p-values are significant at adjusted $p<0.001$.

Abbreviations: DMF = Dose Modifying Factor; LKB-EQD2 (No DMF) = Lyman-Kutcher Burman model with No DMF; 95% CI = 95% confidence interval; LKB-EQD2-DMF = Lyman-Kutcher Burman model with Equivalent Dose in 2Gy correction and DMF inclusion; Pts = patients; G1+ = grade 1 or above; G2+ = grade 2 or above; IBD = Inflammatory Bowel Disease.

(See table overleaf, continued over 2 sides)

Rectal Endpoints & Dose Modifying Factors	Pts	n covariate	m covariate	TD50 covariate (Gy_{EQD2})	α/β ratio (Gy)	Dose modifying factor covariate	632 Likelihood	Likelihood ratio p-value
Bleeding G1+								
LKB-EQD2 (No DMF)	2008	0.21 (0.08-0.34)	0.33 (0.20-0.47)	58.8 (54.2-66.0)	1.6 (0.9-2.5)	N/A	-1248.1	N/A
Age (years)	2008	0.21 (0.08-0.35)	0.33 (0.21-0.47)	51.0 (36.0-68.9)	1.6 (0.9-2.5)	0.9976 (0.9937-1.0016)	-1248.3	Worse Fit
Diabetes Y/N	2008	0.20 (0.08-0.34)	0.32 (0.20-0.47)	58.6 (54.0-66.1)	1.6 (0.9-2.5)	0.96 (0.87-1.03)	-1248.3	Worse Fit
Haemorrhoids Y/N	2008	0.21 (0.09-0.35)	0.33 (0.21-0.47)	58.9 (54.3-66.1)	1.6 (0.9-2.5)	1.07 (0.96-1.20)	-1248.3	Worse Fit
Hypertension Y/N	2008	0.21 (0.09-0.35)	0.33 (0.21-0.47)	58.4 (53.7-65.8)	1.6 (0.9-2.5)	0.98 (0.93-1.03)	-1248.8	Worse Fit
IBD/Diverticular Y/N	2008	0.21 (0.10-0.35)	0.33 (0.21-0.46)	58.9 (54.3-65.0)	1.6 (0.9-2.5)	1.13 (1.01-1.30)	-1246.8	0.11
Pelvic Surgery Y/N	2008	0.20 (0.08-0.34)	0.33 (0.21-0.47)	59.3 (54.5-66.7)	1.6 (0.9-2.5)	1.08 (1.00-1.18)	-1247.3	0.21
Bleeding G2+								
LKB-EQD2 (No DMF)	2006	0.16 (0.01-0.34)	0.27 (0.14-0.42)	75.8 (68.2-88.6)	1.7 (0.7-3.0)	N/A	-822.6	N/A
Age (years)	2006	0.16 (0.01-0.36)	0.27 (0.14-0.44)	81.0 (57.0-124.3)	1.7 (0.7-3.0)	1.0004 (0.9956-1.0055)	-823.5	Worse Fit
Diabetes Y/N	2006	0.16 (0.01-0.35)	0.27 (0.14-0.42)	75.4 (67.7-88.5)	1.7 (0.7-3.0)	0.94 (0.80-1.03)	-822.6	0.91
Haemorrhoids Y/N	2006	0.16 (0.01-0.34)	0.27 (0.14-0.42)	76.1 (68.2-89.6)	1.7 (0.7-3.1)	1.11 (0.99-1.33)	-821.9	0.21
Hypertension Y/N	2006	0.16 (0.01-0.33)	0.27 (0.14-0.42)	74.6 (66.9-87.5)	1.7 (0.7-3.0)	0.96 (0.89-1.01)	-822.2	0.36
IBD/Diverticular Y/N	2006	0.17 (0.01-0.36)	0.28 (0.14-0.42)	75.9 (68.3-90.1)	1.7 (0.7-3.0)	1.17 (1.03-1.44)	-820.2	0.026
Pelvic Surgery Y/N	2006	0.16 (0.01-0.35)	0.27 (0.14-0.42)	76.2 (68.3-89.3)	1.7 (0.7-3.1)	1.04 (0.94-1.16)	-823.2	Worse Fit
Stool Frequency G1+								
LKB-EQD2 (No DMF)	2025	0.27 (0.17-0.44)	0.55 (0.39-0.86)	56.0 (51.4-62.3)	2.3 (0.9-5.3)	N/A	-1334.7	N/A
Age (years)	2025	0.27 (0.17-0.44)	0.54 (0.39-0.81)	38.8 (30.0-57.9)	2.3 (0.9-5.3)	0.9942 (0.9903-1.0003)	-1334	0.25
Diabetes Y/N	2025	0.27 (0.17-0.43)	0.55 (0.39-0.83)	56.6 (51.7-63.3)	2.3 (0.9-5.3)	1.09 (0.97-1.25)	-1334.5	0.52
Haemorrhoids Y/N	2025	0.28 (0.17-0.45)	0.56 (0.40-0.88)	56.8 (51.9-63.3)	2.2 (0.8-5.1)	1.21 (1.06-1.48)	-1331.8	0.016
Hypertension Y/N	2025	0.27 (0.17-0.44)	0.55 (0.39-0.86)	55.6 (50.9-62.4)	2.2 (0.8-5.2)	0.98 (0.89-1.06)	-1335.5	Worse Fit
IBD/Diverticular Y/N	2025	0.27 (0.17-0.44)	0.55 (0.39-0.84)	56.4 (51.4-62.9)	2.3 (0.9-5.5)	1.19 (1.00-1.47)	-1334	0.23
Pelvic Surgery Y/N	2025	0.26 (0.16-0.42)	0.56 (0.40-0.85)	56.8 (51.8-63.7)	2.3 (1.0-5.6)	1.13 (0.99-1.33)	-1334.1	0.28
Stool Frequency G2+								
LKB-EQD2 (No DMF)	2021	0.31 (0.10-0.71)	0.36 (0.23-0.52)	75.7 (66.2-96.8)	2.7 (0.9-8.5)	N/A	-801.3	N/A
Age (years)	2021	0.31 (0.11-0.73)	0.35 (0.24-0.50)	54.4 (30.0-90.0)	2.7 (0.9-8.2)	0.9947 (0.9852-1.0026)	-801.4	Worse Fit
Diabetes Y/N	2021	0.31 (0.10-0.70)	0.36 (0.24-0.51)	75.7 (66.2-93.9)	2.6 (0.9-8.7)	1.02 (0.86-1.17)	-802.2	Worse Fit
Haemorrhoids Y/N	2021	0.31 (0.10-0.71)	0.36 (0.24-0.51)	76.6 (66.6-95.0)	2.7 (1.0-8.9)	1.15 (0.98-1.40)	-800.6	0.22
Hypertension Y/N	2021	0.31 (0.10-0.73)	0.36 (0.23-0.51)	75.2 (65.7-91.8)	2.6 (0.9-8.2)	0.97 (0.86-1.07)	-802.1	Worse Fit
IBD/Diverticular Y/N	2021	0.31 (0.10-0.68)	0.36 (0.23-0.50)	76.2 (66.5-95.3)	2.5 (0.8-7.1)	1.37 (1.13-1.82)	-795.1	**0.00041**
Pelvic Surgery Y/N	2021	0.31 (0.09-0.73)	0.36 (0.24-0.51)	76.7 (66.6-96.3)	2.7 (1.0-9.8)	1.11 (0.95-1.33)	-801.2	0.71
Bowel Pain G1+								
LKB-EQD2 (No DMF)	2185	0.15 (0.01-9.89)	0.48 (0.21-0.68)	139.7 (88.7-499.1)	3.6 (0.0-839.6)	N/A	-647.4	N/A
Age (years)	2185	0.15 (0.01-1.74)	0.50 (0.25-0.74)	87.0 (42.0-179.4)	5.0 (0.2-39.4)	0.9911 (0.4328-1.0064)	-647.9	Worse Fit
Diabetes Y/N	2185	0.16 (0.01-9.79)	0.48 (0.21-0.68)	138.0 (88.0-522.4)	3.7 (0.0-838.7)	0.95 (0.05-1.83)	-648.3	Worse Fit
Haemorrhoids Y/N	2185	0.16 (0.01-9.89)	0.48 (0.21-0.69)	142.5 (88.8-606.3)	3.9 (0.0-921.1)	1.26 (0.85-4.47)	-647.2	0.54
Hypertension Y/N	2185	0.14 (0.01-9.97)	0.46 (0.21-0.68)	137.5 (89.0-591.5)	3.5 (0.0-951.1)	1.04 (0.69-2.07)	-648.2	Worse Fit
IBD/Diverticular Y/N	2185	0.31 (0.01-9.95)	0.52 (0.21-0.70)	151.1 (89.6-867.0)	3.3 (0.0-942.9)	1.79 (1.07-13.76)	-644.2	0.011
Pelvic Surgery Y/N	2185	0.19 (0.01-9.90)	0.49 (0.21-0.69)	142.2 (88.8-647.6)	4.1 (0.0-945.8)	1.06 (0.31-3.28)	-648.2	Worse Fit

Proctitis G1+								
LKB-EQD2 (No DMF)	2147	0.14 (0.02-0.22)	0.42 (0.22-0.68)	63.6 (58.7-75.5)	2.7 (1.5-5.4)	N/A	-1384.1	N/A
Age (years)	2147	0.14 (0.02-0.22)	0.42 (0.22-0.68)	54.2 (36.0-79.8)	2.7 (1.5-5.4)	0.9975 (0.9912-1.0030)	-1384.6	Worse Fit
Diabetes Y/N	2147	0.14 (0.02-0.23)	0.42 (0.21-0.68)	62.8 (57.8-74.2)	2.6 (1.5-5.3)	0.84 (0.65-0.94)	-1379	0.0013
Haemorrhoids Y/N	2147	0.14 (0.02-0.22)	0.43 (0.22-0.69)	64.1 (59.3-75.2)	2.7 (1.6-6.0)	1.12 (1.01-1.32)	-1382.6	0.081
Hypertension Y/N	2147	0.14 (0.02-0.21)	0.42 (0.21-0.68)	62.9 (57.8-74.4)	2.6 (1.5-5.2)	0.97 (0.90-1.02)	-1384.3	Worse Fit
IBD/Diverticular Y/N	2147	0.14 (0.02-0.22)	0.43 (0.22-0.68)	64.0 (59.3-75.1)	2.6 (1.5-5.4)	1.27 (1.10-1.58)	-1378	**0.00046**
Pelvic Surgery Y/N	2147	0.14 (0.02-0.21)	0.43 (0.23-0.70)	65.1 (59.6-76.6)	2.7 (1.6-6.2)	1.15 (1.04-1.38)	-1381	0.012
Proctitis G2+								
LKB-EQD2 (No DMF)	2146	0.11 (0.01-0.25)	0.30 (0.17-0.51)	87.8 (75.2-137.0)	2.7 (1.3-15.1)	N/A	-731.9	N/A
Age (years)	2146	0.12 (0.02-0.26)	0.30 (0.16-0.49)	90.1 (75.0-252.8)	2.7 (1.2-9.0)	1.0021 (0.9966-1.0129)	-732	Worse Fit
Diabetes Y/N	2146	0.11 (0.01-0.26)	0.30 (0.17-0.50)	86.9 (74.7-131.7)	2.7 (1.3-12.6)	0.90 (0.62-1.01)	-731.4	0.31
Haemorrhoids Y/N	2146	0.11 (0.01-0.27)	0.30 (0.17-0.51)	88.1 (75.3-136.6)	2.7 (1.3-14.6)	1.06 (0.92-1.31)	-732.2	Worse Fit
Hypertension Y/N	2146	0.11 (0.01-0.29)	0.30 (0.17-0.49)	86.7 (74.6-125.7)	2.6 (1.2-9.4)	0.96 (0.84-1.03)	-732.2	Worse Fit
IBD/Diverticular Y/N	2146	0.11 (0.01-0.26)	0.30 (0.17-0.51)	88.8 (75.5-138.6)	2.6 (1.2-11.2)	1.22 (1.04-1.69)	-728.9	0.015
Pelvic Surgery Y/N	2146	0.11 (0.01-0.28)	0.30 (0.17-0.51)	89.2 (75.9-142.2)	2.8 (1.3-14.7)	1.11 (0.99-1.42)	-730.9	0.16
Sphincter Control G1+								
LKB-EQD2 (No DMF)	2199	0.23 (0.15-0.38)	0.32 (0.24-0.45)	79.3 (69.8-103.3)	3.1 (1.4-9.1)	N/A	-749.7	N/A
Age (years)	2199	0.24 (0.15-0.38)	0.34 (0.24-0.45)	90.0 (63.0-186.1)	3.0 (1.4-8.5)	1.0024 (0.9968-1.0102)	-750	Worse Fit
Diabetes Y/N	2199	0.24 (0.15-0.39)	0.32 (0.24-0.45)	78.8 (69.4-99.7)	3.1 (1.4-9.4)	0.93 (0.73-1.06)	-750.2	Worse Fit
Haemorrhoids Y/N	2199	0.24 (0.15-0.38)	0.32 (0.24-0.44)	80.3 (70.2-104.1)	3.2 (1.5-10.2)	1.15 (1.00-1.37)	-748.5	0.14
Hypertension Y/N	2199	0.24 (0.15-0.38)	0.32 (0.24-0.42)	79.4 (69.7-95.4)	3.1 (1.4-8.8)	1.01 (0.93-1.10)	-750.5	Worse Fit
IBD/Diverticular Y/N	2199	0.24 (0.15-0.40)	0.33 (0.24-0.45)	80.6 (70.2-104.0)	3.1 (1.4-8.8)	1.29 (1.10-1.64)	-745.3	0.0032
Pelvic Surgery Y/N	2199	0.24 (0.15-0.39)	0.33 (0.24-0.45)	80.5 (70.2-103.6)	3.2 (1.4-10.2)	1.11 (0.96-1.30)	-749.4	0.48
Stricture/Ulcer G1+								
LKB-EQD2 (No DMF)	2206	0.31 (0.01-0.74)	0.25 (0.10-0.34)	83.8 (71.5-110.3)	2.5 (0.9-8.2)	N/A	-335.1	N/A
Age (years)	2206	0.28 (0.01-0.63)	0.25 (0.15-0.31)	136.4 (78.7-343.7)	2.4 (0.9-6.7)	1.0071 (0.9990-1.0184)	-333.9	0.12
Diabetes Y/N	2206	0.31 (0.01-0.74)	0.25 (0.11-0.34)	83.6 (71.4-110.0)	2.5 (0.9-8.1)	0.97 (0.74-1.12)	-336.1	Worse fit
Haemorrhoids Y/N	2206	0.31 (0.01-0.75)	0.25 (0.11-0.34)	83.8 (71.6-109.4)	2.5 (0.9-8.2)	1.04 (0.84-1.23)	-336	Worse fit
Hypertension Y/N	2206	0.31 (0.01-0.74)	0.24 (0.11-0.33)	84.5 (71.9-108.3)	2.5 (0.9-7.5)	1.03 (0.93-1.13)	-335.8	Worse fit
IBD/Diverticular Y/N	2206	0.32 (0.01-0.76)	0.25 (0.12-0.35)	84.1 (71.6-112.7)	2.5 (0.9-8.5)	1.05 (0.73-1.33)	-336.3	Worse fit
Pelvic Surgery Y/N	2206	0.32 (0.01-0.76)	0.25 (0.11-0.35)	85.0 (72.0-113.8)	2.6 (1.0-9.4)	1.08 (0.91-1.30)	-335.5	Worse fit