

Normal tissue complication probability models for prospectively scored late rectal and urinary morbidity after proton therapy of prostate cancer

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ABSTRACT

Background and purpose: Photons and protons have fundamentally different properties, i.e. protons have a reduced dose bath but a higher relative biological effectiveness. Photon-based normal tissue complication probability (NTCP) models may therefore not immediately be applicable to proton therapy (PT). The aim was to derive parameters of the Lyman-Kutcher-Burman (LKB) NTCP model using prospectively recorded late morbidity data from PT, focusing on rectal morbidity and prostate cancer.

Materials and methods: Prospectively collected data were available for 1151 prostate cancer patients treated with passive scattering PT and prescribed target doses of 78–82 Gy (RBE = 1.1) in 2 Gy fractions. Morbidity data (CTCAE v3.0) consisted of two alternative late grade 2 rectal bleeding endpoints: Medical Grade2A (GR2A) and procedural Grade2B (GR2B), as well as late grade 3 + urinary morbidity. GR2A + 2B were observed in 156/1047 patients (15%), GR2B in 45/1047 patients (4%), and urinary grade 3 + in 51/1151 patients (4%). LKB NTCP model parameters (D50, m , and n) were derived by maximum likelihood estimation.

Results: For the rectum/rectal wall the volume parameter n was low (0.07–0.14) for both GR2A + 2B and GR2B, as was the m parameter (range: 0.16–0.20). For the bladder/bladder wall both parameters were high (n -range: 0.20–0.36; m -range: 0.32–0.36). D50 parameters were higher for GR2B of the rectum/rectal wall (95.9–98.0 Gy) and bladder/bladder wall (118.1–119.9 Gy), but lower for GR2A2B (71.7–73.6 Gy).

Conclusion: PT specific LKB NTCP model parameters were derived from a population of more than 1000 patients. The D50 parameter differed for all structures and endpoints and deviated from typical photon-based LKB model values.

1. Introduction

Normal tissue complication probability (NTCP) models are used to estimate the risk of morbidity following radiotherapy (RT) when e.g. comparing treatment plans of photon-based RT and proton therapy (PT) [1,2]. For prostate cancer patients, the rectum and bladder are the major organs at risk (OARs) as they are located close to the target volumes. Rectal bleeding is one of the most common side effects caused by exposure of rectal mucosa to radiation therapy and it has been extensively investigated [3–9], while fewer studies have been conducted for bladder effects resulting in fewer models for urinary morbidity [3,9–11]. Follow-up data after PT is sparse, so most available NTCP models are based on photon-based therapy outcomes.

Photons and protons have fundamentally different physical and

biological properties. The primary difference is that PT exposes a significantly reduced volume of non-targeted tissue to low- to intermediate radiation doses compared with photon-based therapy [12]. Protons also have a higher relative biological effectiveness (RBE) [13], which could influence the biological dose and outcome if not properly accounted for [14]. Despite these differences, photon-based NTCP models are often used for NTCP calculations on proton treatment plans. A poor fit between data from a proton cohort and several photon-based NTCP models has already been demonstrated [15], indicating that photon-based NTCP models may not be applicable to proton treatment data. As PT becomes widely more available, proton-based NTCP models might become required for optimal morbidity prediction in proton cohorts and comparisons between modalities for potential patient selection [1,2]. In a recent study, logistic regression was used to develop

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NTCP models in which more complex drivers of morbidity were taken into account [16]. However, the Lyman-Kutcher-Burman (LKB) model is still one of the most common NTCP models, having been applied in many studies due to its simplicity and well understood parameters. In particular the n parameter, which are often exploited for RT plan optimisation by constraining the generalised equivalent uniform dose (gEUD). Additionally, in terms of comparison with photon-based models, most models are historically LKB-based [4–8,17].

Therefore, the aim of the study was to derive PT specific NTCP parameters for the commonly known LKB NTCP model for the rectum, rectal wall, bladder, and bladder wall based on outcome data following PT of prostate cancer.

2. Materials and methods

2.1. Patient cohort

Prospectively collected treatment and morbidity data from 1151 prostate cancer patients treated with passive scattering PT [18,19] between 2006 and 2010 were used in this study (IRB201700516). Originally 1214 patients were treated during this period, but due to missing or erroneous data, 63 of the patients were removed from this study. Of the remaining 1151 patients, 499 patients (43%) had low-risk disease, 520 patients (45%) had intermediate risk while 132 patients (11%) had high-risk disease. Out of the 1151 patients, 104 received anti-coagulants before PT; these cases were excluded from the analysis of the rectum and rectal wall (referred to as the rectum group going forward) as a previous univariate analysis showed anti-coagulant use to be significantly associated with GR2 + rectal bleeding [18]. In total, the resulting subgroup for rectal complication analysis (rectum group) included 1047 patients while the full cohort of 1151 patients were used for the bladder and bladder wall analysis (bladder group).

2.2. Treatment planning

Patient prescription doses ranged from 78 to 82 Gy (RBE) (RBE = 1.1) in fractions of 2 Gy (RBE) [18]. For low-risk patients, the clinical target volume (CTV) included the prostate only, while the prostate and the proximal 2 cm of the seminal vesicles were included in intermediate- and high-risk patients. Pelvic lymph nodes were not irradiated. The planning target volume (PTV) was defined from the CTV with expansion margins of 8 mm and 6 mm in the superior- inferior and axial planes, respectively. These margins were reduced to 6 mm and 4 mm for patients treated after May 2008. Rectal balloons were used for most patients for prostate stabilisation, and image-guidance utilizing orthogonal KV images registered on fiducial markers was used for all patients. Patients were treated with lateral or lateral-oblique beam angle configurations, typically one field each day (range: 260°/100°–285°/75°; median: 275°/85°).

2.3. Endpoints

For rectal morbidity, patients were followed up weekly during treatment and at 6-month intervals afterward. The minimum follow-up was 2 years, and the median actual follow-up for all patients was 3.5 years. Prospectively scored late rectal bleeding of grade ≥ 2 was used as gastrointestinal (GI) morbidity endpoint for the rectum analysis (Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0)) with a total of 156 events (15%). Furthermore, the Grade 2 events were subdivided into two classes: Grade 2A (GR2A) (111 events (11%)) classified as medical (e.g. prescribed suppositories), and Grade 2B (GR2B) (45 events (4%)) classified as procedural (minor cauterisation and topical formalin application). Late rectal morbidity was defined as occurring after 90 days after treatment completion (occurrence time: 16 months; range: 5–46 months).

For bladder morbidity, patients were followed up at 6-month

intervals after treatment. Prospectively scored grade 3 + urinary morbidity was used as genitourinary (GU) endpoint for the bladder analysis (CTCAE v3.0) (GR3CTC) with a total of 51 events (4%). This included complications such as urinary frequency, urgency, transurethral resection of the prostate, and haematuria; more details are described in previous publications [19]. Bladder morbidity occurring ≥ 6 months after treatment were scored as late (occurrence time: 66 months; range: 6–106 months). The median follow-up time for bladder morbidity outcomes was 5.3 years (range: 0.3–8.3 years).

2.4. Normal tissue complication probability modelling

To estimate the best-fit set of parameters $D50$, m , and n of the LKB NTCP model, maximum likelihood estimation (MLE) was employed for the known binary outcomes y_i and the dosimetric data (Suppl. Appendix 1). This was done by maximising the natural log likelihood (LLH) function so that the observed data were most probable, i.e.:

$$LLH(D50, m, n) = \sum_{y_i=0} \ln(\text{NTCP}(D50, m, n)) + \sum_{y_i=1} \ln(1 - \text{NTCP}(D50, m, n)), \quad (1)$$

where the sum was over all patients with different outcomes $y_i = 1$ (with morbidity) or $y_i = 0$ (without morbidity).

The calculation of the MLE was done using a “brute force” method, where a large search grid parameter space was created and used to calculate the NTCPs for every possible combination of parameters for each single patient. In this study, a $2000 \times 100 \times 100$ search grid was used with $D50$ going from 1 to 200 Gy in steps of 0.1 Gy, m going from 0.01 to 1 in steps of 0.01, and n going from 0.01 to 1 in steps of 0.01 as well. This was performed on the rectum and rectal wall for Grade 2A + 2B and Grade 2B rectal bleeding, and the bladder and bladder wall for Grade 3 + GU morbidity. The discriminating ability of each set of parameters was internally validated by area under the curve (AUC) calculations, while calibration plots and the Hosmer-Lemeshow test were used as goodness-of-fit test.

2.5. Confidence intervals for best-fit parameters

Confidence intervals (CIs) for the best-fit parameters were determined by profile likelihood and non-parametric bootstrapping. Profile likelihood involves finding the maximum log-likelihood and then varying each parameter until the log-likelihood is decreased by an amount equal to half the critical value (i.e. 1.92) of the $\chi^2(1)$ distribution at the desired significance level (95% in this case). Non-parametric bootstrapping is more computationally intensive but will often provide more reliable CIs. This was done by randomly resampling the population (with replacement) and estimating $D50$, m , and n again. By resampling multiple times (1000), this yielded a distribution of parameter values, for which the CIs were found by finding the value of each parameter distribution at the percentile cut-off point required for the requested CI (95% chosen).

3. Results

Best-fit LKB parameters as well as their CIs and related validation statistics were found for all structures and endpoints (Table 1). The internal validation, i.e. HL statistics (range: 0.19–0.92) showed no reason to reject the models, while the calibration plots showed good agreement between calculated and observed morbidities (Fig. 1). The AUC values were in general relatively low (range: 0.58–0.63).

For the rectum and rectal wall, the n parameter ranged from 0.07 to 0.14 and m ranged from 0.16 to 0.20 (Table 1), while for the bladder and bladder wall, these two parameters were somewhat higher (n range: 0.20–0.36; m range: 0.32–0.36).

For the $D50$ parameter, there was a large difference between the two

Table 1
Lyman-Kutcher-Burman (LKB) parameters and model performance metrics based on maximum likelihood estimation (MLE).

Structure	Morbidity grade	D50 [Gy] [Profile CI] [Bootstrap CI]	m [Profile CI] [Bootstrap CI]	n [Profile CI] [Bootstrap CI]	p	Calibration slope and intercept	AUC [95% CI]
Rectum	GR2A + 2B	73.6 [72.3, 74.9][66.6, 80.9]	0.16 [0.15, 0.17] [0.11, 0.25]	0.10 [0.1, 0.1] [0.05, 0.19]	0.92	0.99 0.0	0.63 [0.52, 0.65]
	GR2B	98.0 [94.3, 102.3] [54.8, 211.8]	0.20 [0.19, 0.21] [0.09, 0.54]	0.07 [0.06, 0.08] [0.01, 2.0]	0.19	-0.83 0.77	0.58 [0.50, 0.60]
Rectal wall	GR2A + 2B	71.6 [70.4, 72.9][63.8, 80.6]	0.16 [0.15, 0.17] [0.11, 0.24]	0.14 [0.14, 0.15] [0.07, 0.25]	0.98	-0.05 0.97	0.63 [0.52, 0.65]
	GR2B	95.9 [92.2, 100.0] [50.0, 147.3]	0.20 [0.19, 0.21] [0.09, 0.51]	0.10 [0.08, 0.12] [0.01, 2.0]	0.25	-0.80 0.78	0.60 [0.50, 0.61]
Bladder	GR3CTC	119.9 [110.3, 131.7] [89.0, 264.8]	0.32 [0.30, 0.34] [0.11, 0.51]	0.20 [0.15, 0.26] [0.03, 2.0]	0.86	-0.18 0.97	0.60 [0.50, 0.61]
Bladder wall	GR3CTC	118.1 [106.8, 132.9] [85.8, 251.6]	0.35 [0.33, 0.37] [0.12, 0.51]	0.36 [0.28, 0.46] [0.05, 2.0]	0.56	-0.42 0.89	0.59 [0.50, 0.61]

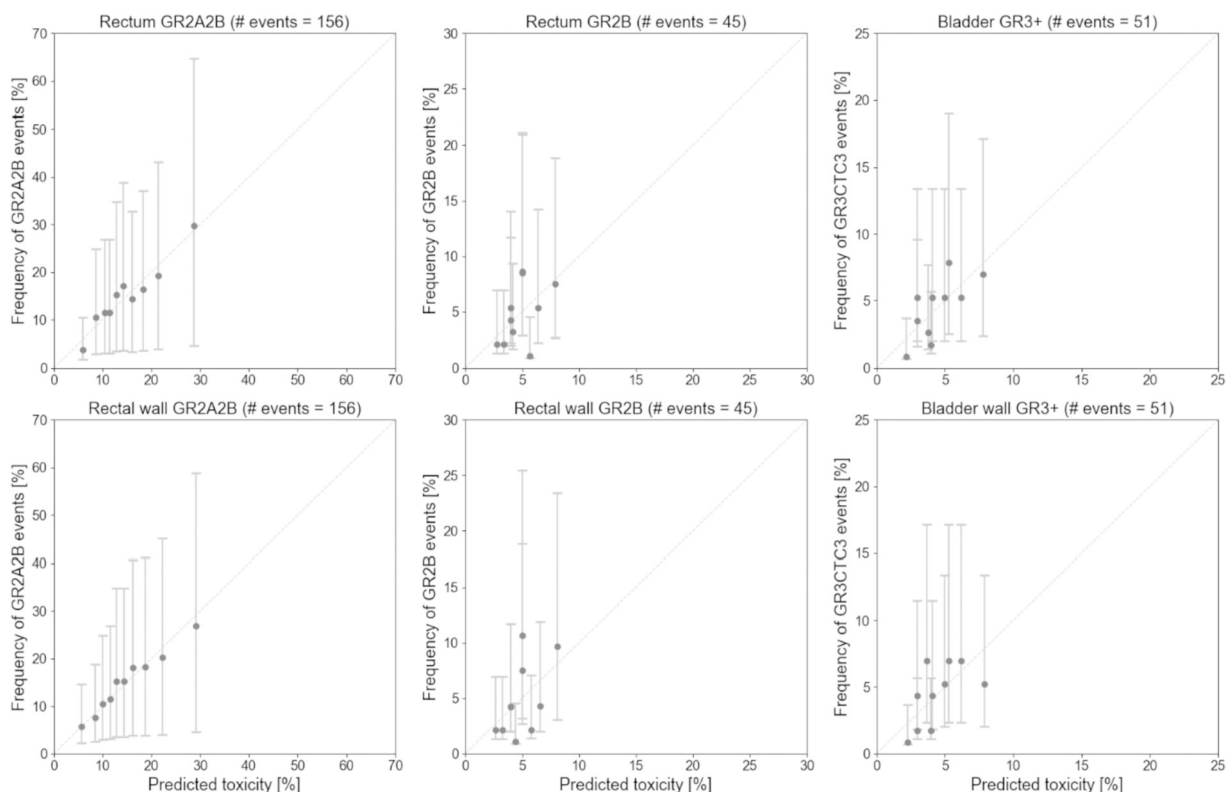


Fig. 1. Calibration plots for all structures and endpoints. Patients were divided into ten equally large groups, with the frequency of each observed endpoint plotted against the mean predicted morbidity. The binomial uncertainty equal to two standard deviations is displayed in the error bars.

GI morbidity endpoints. The D50 of rectum and rectal wall ranged from 71.6 to 73.6 Gy for the GR2A + 2B endpoint and from 95.9 to 98.0 Gy for GR2B. For the bladder and bladder wall, high values were observed for the D50 parameter (range: 118.1–119.9 Gy). In general, the CIs for all the parameters were narrow when using profile likelihood (Fig. 2) and much broader when using the bootstrap method, in particular the D50 parameter for endpoints with the fewest events (i.e. GR2B for GI morbidity and GR3CTC for GU morbidity).

There was a non-significant difference between the average cumulative DVHs of patients who had events vs. no events (Fig. 3).

4. Discussion

In this study, we derived PT specific LKB NTCP parameters for the rectum and bladder based on prospectively scored morbidity data from 1151 prostate patients treated with passive scattering proton therapy.

In general, the *n* and *m* best-fit parameters were within the range of photon-based LKB parameters for the rectum [3,4,6–8,20,21] and bladder [3,10,11]. However, for the D50 parameter the values were much higher, in particular for the GR2B morbidity. The higher D50 value for GR2B than that for GR2A + 2B might be due to the endpoint being more severe by GR2B itself than when both GR2A and GR2B are

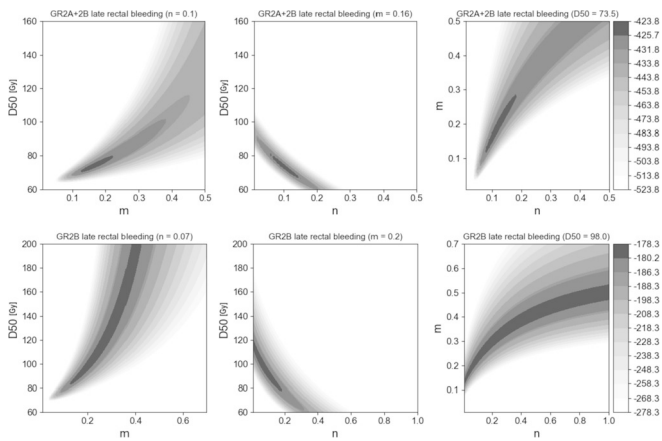


Fig. 2. Maximum likelihood estimation (MLE) values plotted as a function of LKB parameters D50, m , and n with fixed values fitted to GR2A + 2B (first row) and GR2B (second row) late rectal bleeding. The fixed values are the best-fit parameters from the MLE indicated in the title of each plot. The variation of each parameter is in general low for all plots.

combined. In addition, the influence of a single event may have more impact on the variation in parameter estimates due to the low number of events for GR2B (4%). This argument is strengthened by the broader bootstrap confidence intervals for the endpoint. Furthermore, an analysis based on the full patient cohort where anti-coagulant patients were included did not show any large difference in terms of parameter values or AUC values (Suppl. Table 1).

Our best-fit rectum parameters were compared to six published photon-based rectum parameter sets [3–8] (Suppl. Fig. 2). For whole organ irradiation with a EUD of 60 Gy (a common value in our cohort for

all parameter sets), the NTCP ranged from 1 to 20% between all parameter sets (both photon parameters and our proton parameters) depending on parameter set, and 0–10% for 1/3 uniform organ irradiation for the same EUD. The difference between the proton parameter sets were 12% (GR2A + 2B) vs. 3% (GR2B) for whole organ irradiation, and 11% (GR2A + 2B) vs. 2% (GR2B) for 1/3 uniform organ irradiation. This shows the importance of having the right model, model parameters, and endpoint, since the difference in NTCP between two models potentially could be almost 20%. Other bladder models were not investigated in this study due to the endpoint of the proton cohort being a mix of many different symptoms, making it hard to compare with other available models. Overall, few previous studies have derived proton specific LKB parameters, and to our knowledge none exist for the rectum or bladder [22–24]. To accurately compare treatment plans between photon-based RT and PT (e.g. for patient selection) or to evaluate PT plans on their own, proton specific NTCP models are needed.

Patients from this cohort were treated with passive scattering PT. This modality is more robust towards intra-fractional motion in regards to target coverage, however, the dose distributions are usually not as conformal as those that can be achieved with pencil beam scanning. In addition, the linear energy transfer (LET) difference between the two techniques may also contribute to a difference in relative biological effectiveness (RBE) [25]. However, others have shown that the LET distributions between passive and active modulation are almost identical when used in cultured cell lines [26], whereas one retrospective analysis of the Proton Collaborative Group data showed a higher complication rate for active scanning compared with passive scattering [27]. Nevertheless, one should still consider the potential difference in effect between the modalities, as this could influence the applicability of the models when used on cohorts treated with a different technique. Additionally, the uncertainty of RBE and even variable RBE is not present for photon-based models. The RBE depends on factors such as

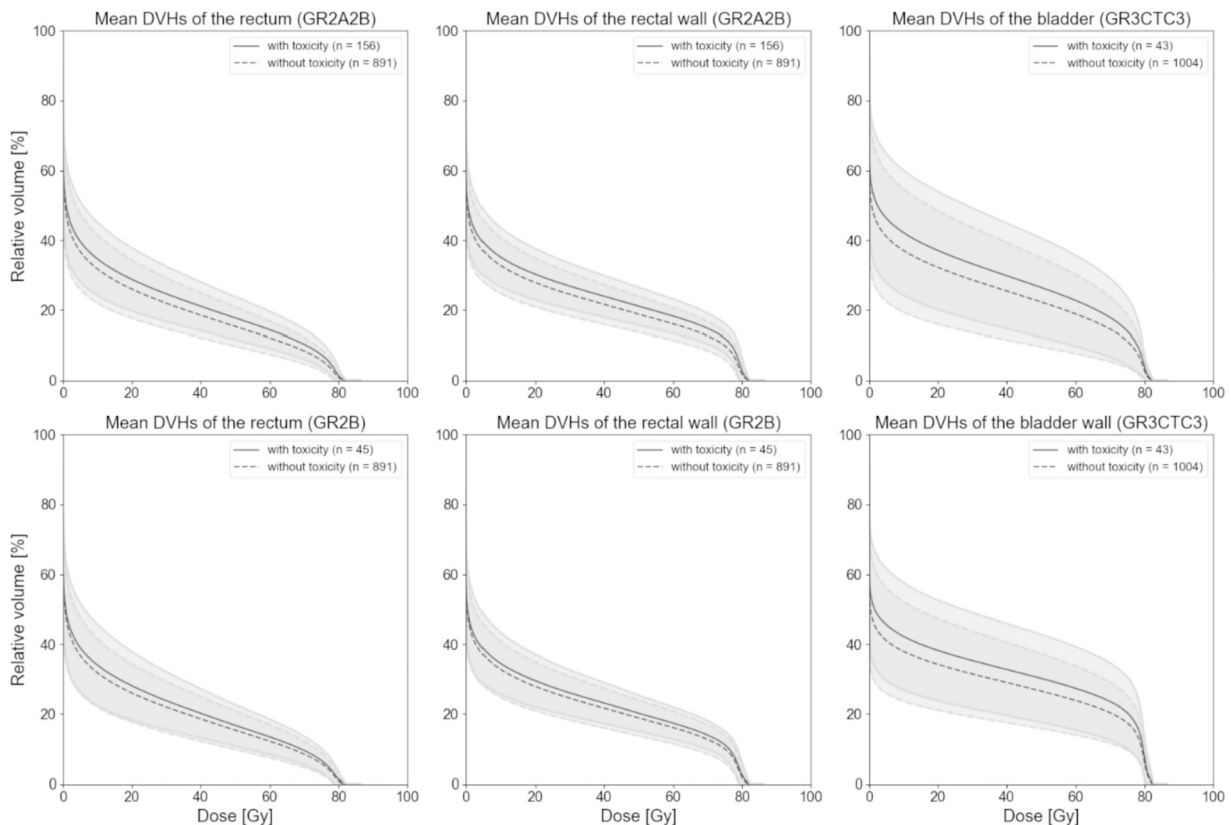


Fig. 3. Mean DVH curves for patients with (solid lines) and without (dashed lines) morbidity for all endpoints and structures indicated in the title of each plot. The two greyed out areas are one standard deviation from the mean DVH curves.

endpoint [28], dose per fraction [29], the α/β ratio of the tissue [30], as well as the LET [13]. A variable RBE might result in a uneven dose distribution [31–34], and if not accounted for may influence the risk prediction for morbidity [14].

This study was based on data from a single-centre cohort. An advantage of this is that every patient was treated with the same treatment strategy and techniques tailored to that institution. However, there is also a risk that a single-centre cohort might lead to a very homogenous cohort. This might produce uncertainties from systematic errors and hence the planned vs. delivered dose will introduce uncertainties to the dose/volume endpoints, which are not counterbalanced by data and variability from other institutions. Therefore, the NTCP models reported herein should be externally validated in other cohorts before use for internal treatment predictions or comparisons with other modalities [35].

Dosimetric variables such as the EUD (the only dosimetric variable of the LKB model) might not be the only driver of morbidity. The low AUC values seen for all parameter sets are also an indicator of this and are reflected in the higher D50 values for the GR2B endpoint, which may also be caused by imbalanced data due to the fewer events registered and the small spread in EUD. This may explain the instability of the Grade 2B parameters seen in the bootstrapped CI's and in Fig. 2. The small spread in the EUD values potentially make these models (in particular GR2B) unstable in terms of discriminating between patients with and without morbidity. In general, many LKB-based models for rectal bleeding show AUC values around 0.60 [7,21]. This again indicates that EUD may not be a good predictor of rectal bleeding in this study. Several recent NTCP models have used a logistic regression where more and different predictors have been included (in particular clinical predictors) [16,36–43] often resulting in better AUC values.

In this study, we performed an internal model validation. Because of the differences between our D50 parameter and usual photon-based D50 parameters, external validation is even more important in order to assess whether this is a cohort- or proton specific property. It is our plan to conduct the external validation using data from prostate cancer patients treated at the Danish Centre for Particle Therapy when sufficient data is available.

Two different grades of late rectal bleeding and one grade of GU morbidity have been analysed in this study. It is important to note that scoring for rectal bleeding may vary among physician practices; e.g., one physician might choose to leave temporary minor rectal bleeding untreated resulting in a code of Grade 1 while another might choose to treat with suppositories resulting in a code of Grade 2 and a third might choose to apply cautery resulting in a code of Grade 3. In this study, the GR2B endpoint on its own is consistent with what is usually seen in other studies in terms of late rectal bleeding. Hence, the separation of the two grades was needed in order to make comparisons between other studies. It should, however, be noted, that the here defined GR2B may partly overlap with G3 toxicity reported in other studies. This could provide an explanation of the higher D50 obtained in our analysis.

Other endpoints may be more important in regards to patient quality of life (QoL) following RT [44,45]. Therefore, functional effects such as defecation urgency or faecal leakage, based on patient reported outcome measures (PROMs), may be better endpoints for association with patient QoL than physician assessed morbidity [46–48]. As such, spatial information, derived from two-dimensional (2D) dose maps (achievable for a cylindrical structure like the rectum), have been shown to better explain PROM based morbidities [49–53], which could be incorporated into logistic-based response models. For the bladder, the endpoint (GR3CTC) encompassed several different symptom complexes (haematuria, urethral stricture, bladder obstruction, and urinary retention) [19], but the small number of events required analysis based on the collective event rate of all GR3CTC symptoms. In our study, the urinary functionality was relatively stable after a 5 year follow-up. However, it is acknowledged that studies of GU morbidity have shown baseline urinary functionality to be an important risk factor [54], which is a property that

could be further investigated through PROM-based endpoints. PROM-based endpoints in combination with dosimetric predictors other than EUD may very well lead to better models with higher predictive power and ability to better capture the true patient QoL.

In general, the aim of NTCP models is to estimate risk. However, due to technological advancements in RT, certain treatment options may no longer be state-of-the-art or even standard modality when studies on prospective or retrospective patients are published. Therefore, NTCP models should ideally be independent of treatment modality and dependent on dose distribution regardless of RT technique. Hence, with the appropriate training strategies, training cohorts with highly heterogeneous dose patterns, and corrections for fraction schemes and radiobiological effects, generalised NTCP models should be possible.

As previous results have shown [15], for some endpoints (i.e. GR2B) an intercept update may not be sufficient for photon-based models to achieve a useful model. Therefore, we encourage the use of these proton-based LKB parameters for the rectum, rectal wall, bladder, and bladder wall for NTCP calculations specific to proton cohorts, but also validation of this model with other data sets and the updating of this model as practice patterns change, e.g., with the use of rectal spacers. This is a necessary first step towards the use of modelling to determine potential benefits for PT compared with photon-based therapy.

In conclusion, PT specific LKB NTCP model parameters for prospectively recorded late rectal and urinary morbidity in more than 1000 patients were derived. The D50 parameter differed for the rectum, rectal wall, bladder, and bladder wall, and deviated from typical photon-based LKB model values.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phro.2021.10.004>.

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