

Geometrical prediction model for late rectal bleeding in radiotherapy of prostate cancer

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Abstract

Introduction: Effective prostate radiotherapy requires integrating radiobiological parameters like the α/β ratio with planning factors such as dose gradients, margins, and adaptive strategies. Predicting late rectal bleeding (LRB) remains challenging but essential for optimizing safety. This study presents a preliminary model to predict LRB using only patient imaging data, offering a practical tool to assess toxicity risk daily and support personalized treatment decisions.

Material and methods: We retrospectively analyzed a cohort of 116 prostate cancer patients treated with radiotherapy, divided into standard (2.0 Gy/fraction) and m-Hypo (2.5 Gy/fraction) groups. The toxicity endpoint was late rectal bleeding (LRB); its incidence was characterized and the rectal α/β ratio estimated and used in subsequent analyses. To assess relationships between toxicity and patient/treatment/planning factors, six metrics were defined: one geometric parameter, P_0 , representing the rectum-PTV intersection volume, and five DVH parameters. We combined these findings in a sector analysis using linear and logistic models between selected parameters.

Results: Late rectal bleeding (LRB) occurred in 11% of the standard group and 26% of the hypofractionated group. The estimated α/β for the LRB endpoint was 1.5 Gy (95% CI: 0–12 Gy). Dose-volume metrics P_2 and P_4 were significantly associated with binary toxicity in logistic regression. Sector analysis using P_0 as the independent variable identified regions with high toxicity rates (>40%), predominantly within the hypofractionated cohort, as well as regions with negligible toxicity.

Conclusions: A linear relationship between the P_0 parameter and toxicity predictors (P_3 , P_4) suggests that volumetric parameters can be integrated into patient-specific risk assessments and treatment planning. Our findings indicate that regions with $P_0 < 10$ cc (L1, H1) may tolerate variations in fractionation and dose, while regions with higher P_0 (L2, H2) require cautious strategies such as dose reduction, margin optimization, and advanced imaging to minimize toxicity. This framework provides a foundation for personalized radiotherapy optimization, pending further validation.

Introduction

Recent advancements in prostate cancer radiotherapy have been significantly influenced by a better understanding of radiobiology¹, which has explained the tumor and normal tissue responses to different fractionation schedules. These insights, combined with economic considerations², have supported the shift towards hypofractionated regimens. The adoption of sophisticated technologies such as IMRT, IGRT, and VMAT has further facilitated this transition by enabling precise delivery of higher doses per fraction while protecting surrounding healthy tissue. Moderates hypofractionation (typically 2.5–3.5 Gy per fraction) capitalizes on the low α/β ratio characteristic of prostate cancer, suggesting a radiobiological

advantage over conventional schemes^{3,4}. This strategy aims to maximize tumor control and minimize toxicity, aligning with radiobiological models that predict increased therapeutic efficacy with fewer, larger fractions. Consequently, the ongoing research continues to refine the balance between efficacy and safety in this evolving treatment paradigm.

In this study, we concentrated on late rectal bleeding, which is among the most extensively investigated toxicity endpoints in prostate radiotherapy research⁵. As a general guideline, as illustrated by Michalski et al.⁶, the volume of rectal tissue receiving the highest doses – closely correlated with the therapeutic dose for prostate cancer – has the most significant influence on the incidence of rectal bleeding toxicity. This provides a fundamental rationale for careful consideration of modifications

in both dose and fractionation schemes during prostate radiotherapy. Alterations in dose delivery can significantly influence the volume of rectal tissue exposed to high radiation doses, thereby affecting the risk of toxicity.

There are three main fields that need to be taken into consideration when one wants to confront the problem: radio-biological – alpha beta ratio of toxicity endpoint, planning and treatment techniques – dose gradients and PTV margins and daily/fraction dose knowledge and related adaptive possibilities.

In this study we proposed a rudiment for prediction model of late rectal bleeding (LRB) using only patient image data and what's more also a way to use and interpret on daily clinical basis its prediction for possible check in advance toxicity level for selected treatment scheme and group of patients.

Materials and methods

Patients

In this is a retrospective study, all data utilized were derived from completed treatments, and no modifications to the actual plans or parameters were possible. Additionally, all patient data were anonymized prior to analysis to ensure confidentiality.

A cohort of 116 prostate cancer patients who underwent prostate radiotherapy was analyzed. All patients have N0 lymph node status and were directed to radiotherapy treatment with radical intention.

Patients eligible for this study need to have at least 2 years of follow-up and complete planning and treatment data.

All patients were scanned on standard CT scanner with 3 mm slice thickness. To ensure reproducibility, a standardized patient preparation protocol was implemented. Patients were instructed to drink 500 mL of water approximately 30 minutes prior to each CT scan and treatment session to achieve adequate bladder filling. If a full rectum – evidenced by air bubbles or solid content – was observed on imaging (CT or CBCT), the patient was either rescanned, or the treatment session was postponed and rescheduled after a few hours to allow for rectal emptying.

All patients had three fiducial markers implanted prior to CT scanning to facilitate accurate visualization and localization of the prostate gland during treatment delivery.

Contouring

The organs at risk (OAR) and the clinical target volume (CTV) of the prostate were contoured in accordance with the CT-only ESTRO/ACROP guidelines, as described by Salembier et al.⁷, by an experienced physician.

The clinical target volume (CTV) includes the prostate gland with the seminal vesicles, or at least 1 cm of base, depending on the patient's risk status. The planning target volume (PTV) was generated by adding a 1 cm isotropic margin in all directions, except for the rectal side, where a reduced margin (0.7 cm) was applied to spare the rectum.

Treatment planning

The cohort can be divided into two according to fractionation standard group with 2 Gy per fraction up to 76 Gy and mHypo group (moderately hypofractionated) with 2.5Gy per fraction up to 70Gy.

All treatment plans were generated using Volumetric Modulated Arc Therapy (VMAT) with the Eclipse 16.1 (Varian) Treatment Planning System. The treatment plans utilized 2-3 arcs with 6 MV photons, delivered in either flattening filter free (FFF) or filtered mode, with a 20-degree avoidance sector on the rectal side to minimize dose to the rectum.

Dose constraints conformed to the local standardized clinical protocol for prostate radiotherapy: for the planning target volume (PTV), $V_{95\%PD} > 98\%$ and D_{mean} within $100 \pm 1.5\%$ of the prescribed dose; for the rectum, constraints were $V_{70Gy} < 25\%$ and $V_{50Gy} < 50\%$. In the moderate hypofractionation (mHypo) group, additional rectal constraints included $V_{63.3Gy} \leq 25\%$ and $V_{45.5Gy} \leq 50\%$. For the bladder, the maximum dose (D_{max}) was ≤ 80 Gy, with constraints of $V_{70Gy} < 35\%$ and $V_{50Gy} < 55\%$. In the mHypo group, bladder constraints were $V_{63.3Gy} \leq 35\%$ and $V_{45.5Gy} \leq 55\%$.

Toxicity scoring

Our toxicity endpoint was recognized as a situation where, during first 2 years after radiotherapy^{8,9} patient at least once but was subject of endoscopic plasma coagulation therapy¹⁰ (APC). This corresponds to Grade $\geq 2-3$ toxicity in RTOG/EORTC morbidity scale adopted by Peeters et al.¹¹ or grade 3 (G3) in scale adopted by Cicchetti et al.⁶. We have started from analysis of toxicity rates in both groups separately.

Parameters selection

To found and study relation between toxicity and patient/treatment/planning data we introduced 6 parameters. Geometrical parameter P_0 that represents volume of intersection of rectum and PTV volume (Figure 1), parameters P_1 , P_2 , P_3 associated with differential DVH (Figure 2), P_4 [cm³] related to volume of rectum at dose 70 Gy ($V_{D=70Gy}$) and P_5 [Gy] related to

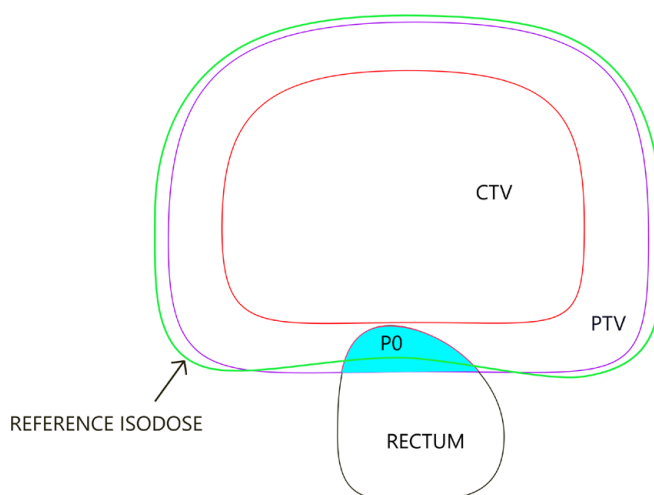


Figure 1. Schema graph for parameter P_0 [cm³] = $V_{PTV} \cap V_{rectum}$.

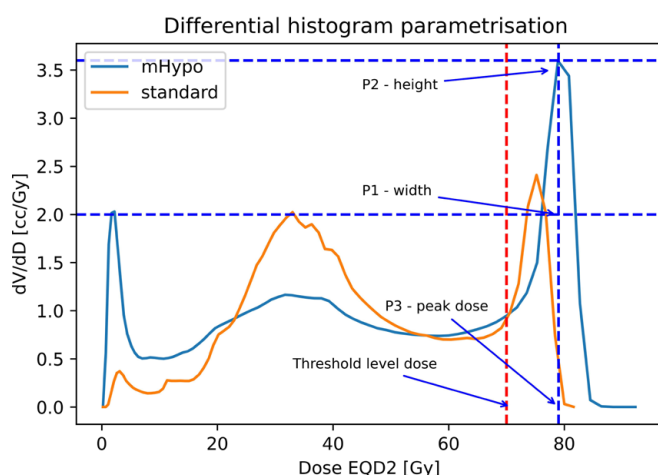


Figure 2. Differential dose volume histogram parameters.

dose at volume 25.5 cc of rectum ($D_{25.5cc}$). The level where the parameter P_1 – width is taken was selected through iterative process and is the lowest that can be used for all patients. All doses are taken as EQD₂ with $\alpha/\beta=1.5$ Gy

α/β estimation

Estimation was conducted using iso-effect analysis method for different fractionation schemes¹². Details of analysis can be found on **figure 3**. Parameter P_5 was chosen as the best dose base toxicity predictor for mHypo group in logistic regression analysis. We assumed one toxicity level for whole standard group represented as mean P_5 value due to lack of any DVH based relation.

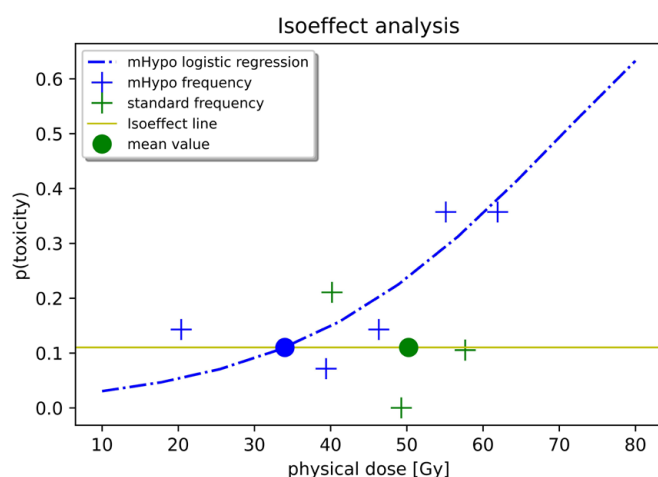


Figure 3. Isoeffect analysis for alpha/beta estimation.

Parameters analysis

Based on the estimated α/β ratio, a combined analysis of both groups was performed. Apart from binary logistic regression against toxicity output for merged groups we have analyzed difference between means of selected parameters either between bleeders/non – bleeders or mHypo/standard groups.

Prediction model

Due to the lack of a direct relationship between patient geometrical features, represented by the P_0 parameter and toxicity

outcomes (**Figure 6a, Table 1**), we explored a linear regression model with P_0 as the independent variable and DVH parameters as dependent variables.

Table 1 Results summary. Statistically significant results are underlined.

Type and details of test	Logistic regression	Linear regression	Mean difference (t-test) between toxicity groups:	
	Binary toxicity output	Independent parameter: P_0	bleeders vs. non – bleeders (22 vs. 94 pts.)	mHypo vs. standard (61 vs. 55 pts.)
Parameter	Test related p – value			
P_0	0.296	NA	0.231	0.011
P_1	0.436	0.461	0.354	0.995
P_2	<u>0.010</u>	<u><<0.01</u>	0.035	<u><<0.01</u>
P_3	0.307	0.760	0.251	<u><<0.01</u>
P_4	<u>0.008</u>	<u><<0.01</u>	0.018	<u><<0.01</u>
P_5	0.052	<u><<0.01</u>	0.071	0.558

It can be interpreted that the relationship between P_0 and the selected DVH parameters reflects the potential for rectal sparing relative to patient geometry, planning, and imaging strategy. The regression line can be used to represent the average planning quality, enabling the division of the parameter space into two sectors: a low (L) sector, indicating a suboptimal situation, and a high (H) sector, representing an optimal planning scenario.

Based on the literature search¹³, we chose a cutoff value of $P_0 = 10$ cc to distinguish between high-risk and low-risk regions.

Finally, four distinct sectors – L1, L2, H1, and H2 – can be identified (**Figure 4**), and the corresponding toxicity rates, sample sizes and group affiliation within each region have been analyzed.

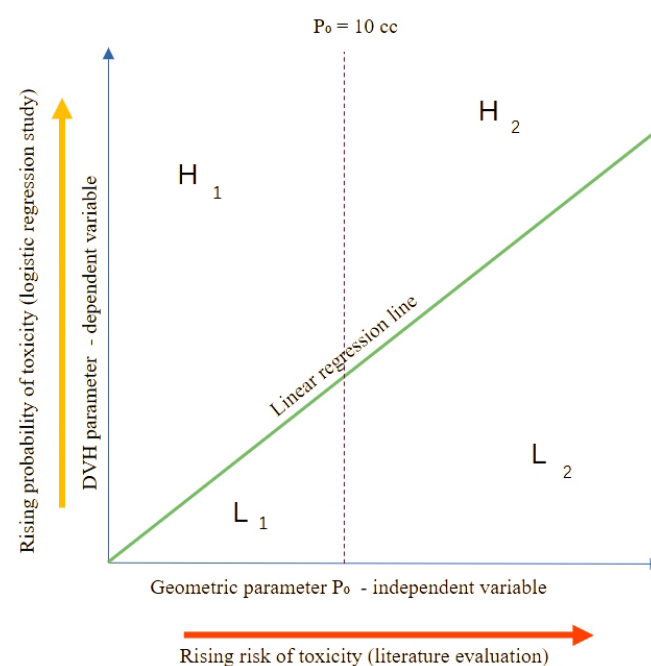


Figure 4. Linear model description and region characteristics.

Statistics and Plots

All plots and calculations were done using Python v.3.12. For mean comparison (t-test), linear regression and logistic regression we used package pingouin v.0.5.5. Plots were done using matplotlib and seaborn packages v.3.9.2 and v. 0.13.2 respectively. We have assumed statistical significance level to be 0.01 for all parameters except α/β where confidence level was set to 95%.

Results

The incidence of reported toxicity was 26 % (16 out of 61 patients) and 11% (6 out of 55) in mHypo and standard and group respectively.

The estimated was $\alpha/\beta = 1.5$ Gy with CI = (0,12).

All further analysis is taken for entire cohort of patients with physical doses converted to EQD₂ dose.

We found statistically significant differences in the mean values of the P₂ and P₄ parameters between the bleeders and non – bleeders groups, as well as significant differences in P₂, P₃, and P₄ parameters between the mHypo and standard groups.

Logistic regression analysis vs. binary toxicity outcome were statistically significant for the P₂ and P₄ parameters.

Detailed results are presented in **table 1** and **figures 5,6**.

We found that there is statistically significant linear dependence between P₀ as an independent value and parameters P₂, P₄ and P₅ (table 1). We have chosen parameters P₂ and P₄ to further investigation due to their significance in toxicity prediction. Graphical representation of the results for both parameters can be found in pictures 5a, b. In addition to regression line for whole cohort we also introduce regression lines for mHypo and standard group separately. The difference between these lines reflects statistically meaningful difference in means of selected parameters for both groups (**Table 1**). On

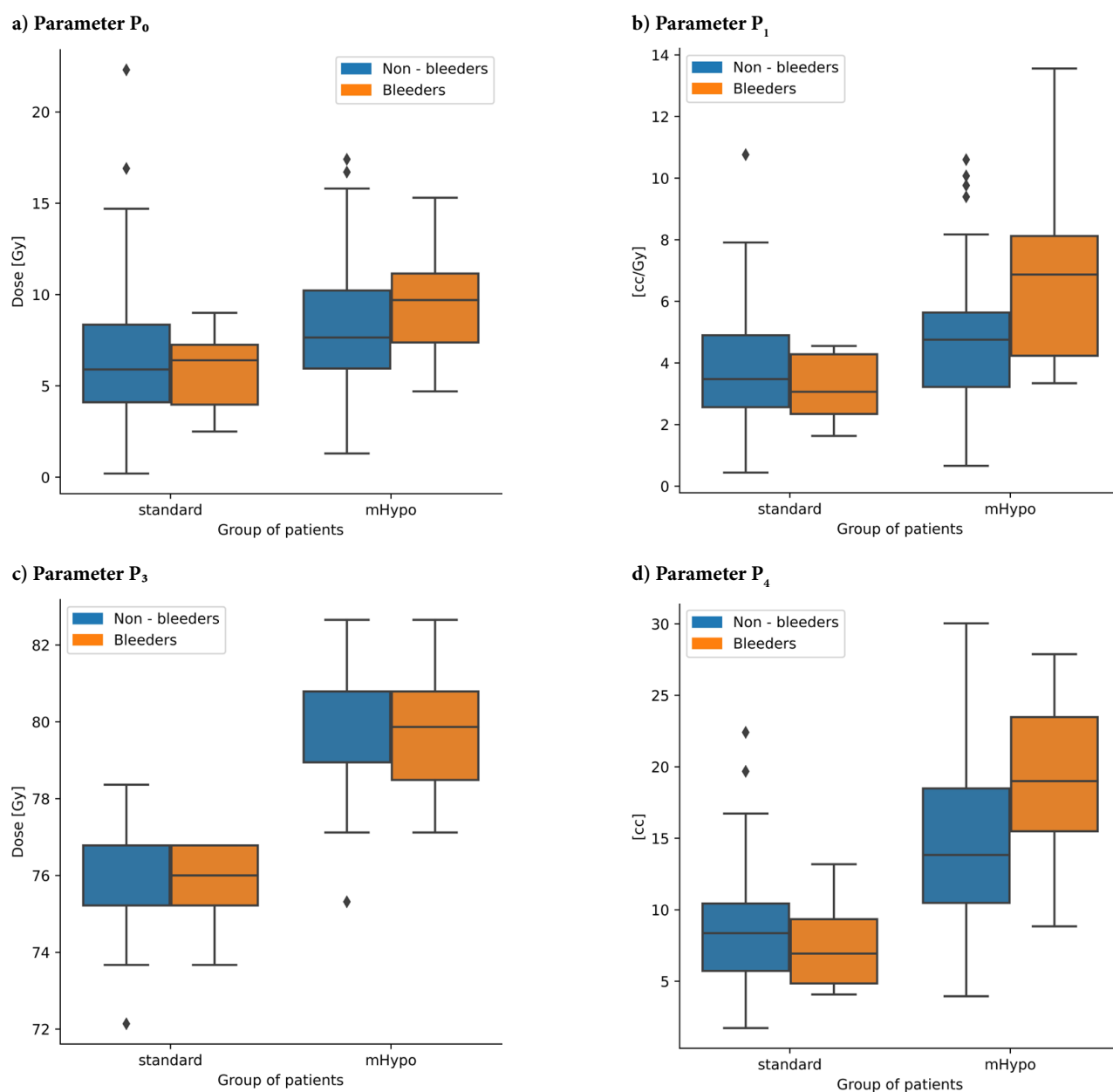


Figure 5. Differences of the means for different subgroups and selected parameters.

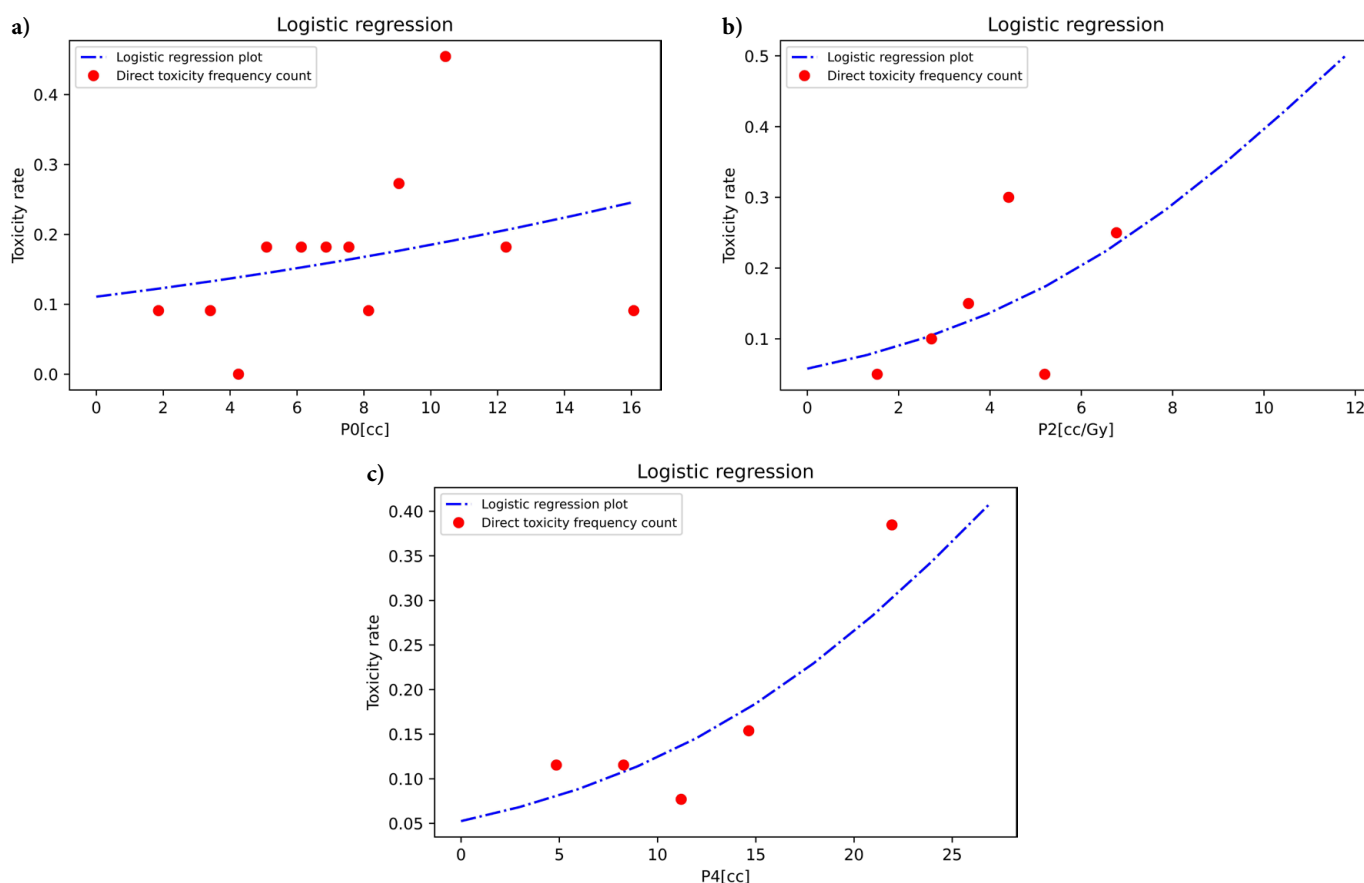


Figure 6. Logistic regression plots for selected parameters.

Table 2 Number of patients and percentage outputs divided into sectors.

Parameter ↓	Regions (Figure 4)					
	$H_1 \cup H_2$	$L_1 \cup L_2$	H_1	L_1	H_2	L_2
P_2	P = 25.0 % Pts :64	P = 8.8 % Pts: 68	P = 16.7% Pts 48	P = 12.7% Pts 55	P = 43.7 % Pts:16	P = 0% Pts:13
P_4	P = 21.5% Pts = 65	P = 11.9 % Pts = 67	P:14.9 % Pts: 47	P = 14.2 % Pts: 56	P = 41.1 % Pts: 17	P=0% Pts:12

graph we have also distinguish bleeding cases between both groups (yellow and red dots).

Selected results for sector analysis can be found in **table 2**. Sector H_2 can be recognized as most toxic which correlate toxicity rates above 40 %. All cases of toxicity in this region come from mHypo group for both studied parameters. In contrast sector L_2 has toxicity rate of 0% and consists of almost only patients from standard group.

In the L_1 and H_1 sectors there is no clear difference in toxicity rate outcome but in P_4 parameter we can see significant difference in mean levels (regression lines) between mHypo and standard group cases.

Discussion

To begin with, we investigated and described the direct relation between high dose volumes in rectum (P_3 and P_4 parameter) and grade 2 late rectal bleeding toxicity level. This is confirmation of well establish knowledge^{6,9,14}. One can state that

Grade 2 LRB in all cited studies including our relates closely to prescribed PTV dose.

Let us discuss and compare the severity and incidence levels of late rectal bleeding (LRB) toxicity observed in the study. We focused on the results from moderate hypo-fractionated trials involving Grade 2 late rectal bleeding (LRB), as assessed by the RTOG grading scale. Akimoto et al.⁸ reported that, among patients receiving 69 Gy in 3 Gy fractions administered three days per week, 25% experienced toxicity. All cases of toxicity occurred within a 2-year follow-up period. In the study from Jongen et al.¹⁵ with data from HYPRO trial (78 Gy in 39 fractions of 2 Gy (CF) or 64.6 Gy in 19 fractions of 3.4 Gy (HF)) cumulative incidences of grade 2 LRB at 5 years were 10.7% for CF vs 18.2% for HF ($p=0.007$). Kim et al.¹⁶ with 70 Gy or 67.2 Gy in 28 fractions have 16.9 % grade 2 LRB and in CHHIP trial Brand et al.¹⁷ reveals 16.2% in hypo-fractionated arm 60Gy in 20 fractions vs. 14.5 % in standard arm 74 Gy in 37 fractions.

To explain and visualize toxicity level associations, we develop the idea of P_0 parameter that came from analysis of studies describing geometrical features of rectal dose. Similar

parameters to those used in our study were investigated by Munbodh et al.¹⁸. As in our research, they found no statistically significant correlation between the parameter P_0 and the occurrence of rectal bleeding. They also examined differential histogram parameters analogous to P_1 and P_2 but did not observe significant associations. Their conclusion was that patients who developed bleeding tended to have a larger volume exposed to doses between 65 and 70 Gy. In the study by Lee et al.¹⁹, the investigation focused on a dose-distance metric that considers both the dose and its spatial distribution across the rectal surface. Their findings indicate that the incidence of grade ≥ 2 rectal bleeding is influenced by localized damage to the rectal surface, specifically related to the presence of “hot spots.”

According to the planning goals, the part of volume P_0 must receive at least 95% of the prescribed dose (Figure 1). Consequently, this volume contributes to the highest dose regions within the rectum and rectal wall. P_0 can contain both rectal wall tissue and prostate (cancer) tissue. For proper understanding how different fractionations affect therapeutic ratio and future toxicity one needs to know relation of α/β values between TCP of prostate and toxicity. In our study we have found that for grade 2 LRB $\alpha/\beta = 1.5\text{Gy}$. Our findings are supported by detailed studies of G2 LRB for moderate hypo-fractionated trials. Brand et al.¹⁶ where $\alpha/\beta = 1.7\text{Gy}$ for grade 2 LRB in CHHIP trial cohort with LKB modelling. Jongen et al.¹⁵ found that $\alpha/\beta = 2\text{Gy}$ were more suitable for modelling grade 2 LRB for patients from HYPRO trial cohort. For the sake of clarity, we need to emphasize that explicit value of α/β deeply depends on clear toxicity endpoint selection and when different toxicities (i.e. diarrhea or stool frequency) are considered the value can differ. Value $\alpha/\beta = 3\text{Gy}$ can be used as proper averaged version Michalski et al.⁶ and Brenner et al.¹⁹. For prostate cancer TCP in hypo-fractionated trials α/β value is well established as low as 1-1.7Gy^{21,22}. Nevertheless, again we need to clearly state what is desired output (TCP, overall survival, 5 years free bFS etc.) and take into special consideration dose per fraction size Cui et al.²³. In summary, both endpoints – involving prostate tissue and late rectal bleeding (LRB) – appear to have similar α/β values.

Let us now discuss what are the factors that can influence P_0 value? We will focus on three sources that in my opinion have the biggest impact. First, its value depends on planning patient CT what means daily rectum filling and prostate position. On this step we can affect its value with prior patient preparations: rectal spacer, laxatives, diet or eventually repeated CT. The second factor is the CTV-PTV margin size and third is daily precision of patient positioning (IGRT or/and adaptive procedures) and preparation.

The relation between P_0 and P_2 , P_4 parameters reflects rectal sparing possibility within the same prescription levels and

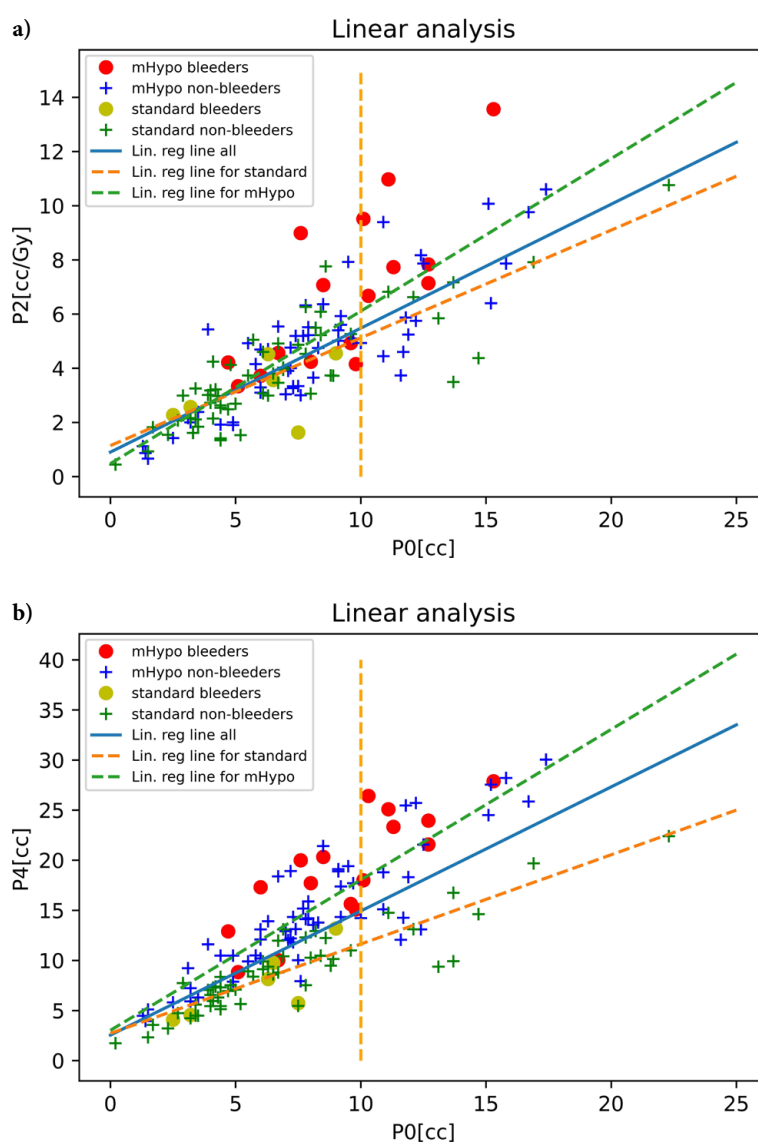


Figure 7. Linear analysis summary for selected parameters.

similar patient related geometry. In figure 7 we can notice that even in such restricted situation (all plans were created using the same technique in the same department and with the same criteria) can provide some variety. We can speculate that there are some planning-related issues (e.g. physicist skills, technique used) that can affect this relation.

Our study acknowledges limitations that merit further investigation. Notably, analysis of figure 5 and table 1 shows no significant correlation between dose peaks and toxicity, except at doses above certain thresholds. This highlights the importance of detailed spatial characterization of high dose “hot spots,” especially relevant for SBRT in prostate cancer. Future work should employ advanced methods – such as those proposed by Dréan et al.²⁴ – to subdivide the P_0 volume into smaller regions, enabling precise assessment of spatial dose distributions. Additionally, exploring intra-fractional variations of P_0 through daily imaging modalities like CBCT or MR could provide insights into the potential role of adaptive radiotherapy. These avenues are critical for refining personalized treatment approaches and optimizing clinical outcomes.

Conclusion

The demonstrated linear correlation between the P_0 parameter and key toxicity predictors, such as P_3 and P_4 , provides a robust and practical framework for integrating toxicity risk assessment into personalized treatment planning and clinical decision-making. Utilizing these volumetric metrics enables clinicians to reliably estimate and monitor the probability of rectal toxicity at both the individual and cohort levels. Based on our findings, we hypothesize that regions with $P_0 < 10$ cc (L1, H1) are

sufficiently tolerant to variations in fractionation schemes and total dose, allowing for flexible treatment adjustments without compromising safety or efficacy. Conversely, regions L2 and H2 demand cautious strategies, including dose reduction, targeted plan optimization, margin reduction via advanced image-er-guided radiotherapy (IGRT), and adaptive approaches to better preserve rectal tissue and mitigate toxicity risks. This conceptual framework lays a promising foundation for advancing personalized radiotherapy, warranting further validation and refinement to enable clinical translation and improved patient outcomes.

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