

Investigation of EUD- and Dose-Volume Based NTCP Models for Rectal Bleeding, augmented by Principal Component Analysis of DVH Patterns



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Introduction

We compare different approaches to model the normal tissue complication probability (NTCP) for late rectal bleeding. Therefore we applied several NTCP models to rectal wall dose-volume histograms (DVHs) and follow-up data of 319 prostate cancer patients in order to identify the dosimetric factors predictive for a higher risk of bleeding. Principal component analysis (PCA) was used to investigate the variability of DVH patterns in the patient population and its relationship to toxicity.

Materials/Methods

Data of 319 prostate cancer patients treated between 1999-2002 at the William Beaumont Hospital were used for this study. The patients were part of a Phase II dose-escalation study and were treated using a 4-field box treatment technique with image-guided off-line correction under an adaptive radiotherapy (ART) protocol. The dose to the PTV was limited by dose-volume constraints of rectal wall and bladder based on the geometry of the planning CT. For rectal wall these were: $D_{30\%}=75.6\text{Gy}$ and $D_{5\%}=82\text{Gy}$. The possible dose levels (minimal prostate dose) were chosen under the requirement to meet the constraints and were as follows: 70.2Gy, 72Gy, 73.8Gy, 75.6Gy, 77.4Gy and 79.2Gy. The rectal toxicity variable considered in this study is chronic rectal bleeding, which was graded according to CTCAE v3.0. The median follow-up time in the patient population was 2.8 years (range 0.1-6.4), with a 68% median centered quartile-range of 0.9-4.4 years.

NTCP-models: An NTCP model assigns a complication probability for an organ at risk to a dose-distribution. The models for late rectal bleeding regarded here are of the following general form: First, a *summary measure* μ (mean dose, equivalent uniform dose (EUD) or similar) is calculated from the dose distribution. Then, a (sigmoid-type) function $NTCP(\mu)$ which assigns complication probabilities to the values of the summary measure is defined. Tab. 1 gives an overview of the five models considered in this study. The parameters of the models were determined based on DVH data and follow-up information using maximum likelihood estimation, where the endpoint of modeling was chronic rectal bleeding of grade ≥ 2 . In addition, PCA was used to analyse DVH shape variability in the population (Dawson et al. 2005, Söhn et al. 2005), and correlation of the first principal components with toxicity was investigated with uni- and multivariate logistic regression.

summary measure	NTCP function
Lyman-EUD model	
power-law EUD $\mu := EUD_{PL} = \left(\sum_i V_i D_i^a \right)^{1/a}$ (sum calculated over all bins (V_i, D_i) of differential DVH)	$NTCP_{probit}(\mu) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\mu} \exp(-x^2/2) dx$
Logit-EUD model	
power-law EUD	$NTCP_{logit}(\mu) = 1 / \left(1 + \left(\frac{D_{50}}{\mu} \right)^m \right)$
serial reconstruction unit model (Alber, Belka 2006)	
$\mu := EUD_{SRU} = \frac{1}{\sigma} \log \left(\sum_i V_i \exp(\sigma D_i) \right)$	$NTCP_{SRU}(\mu) = 1 - \exp(-\exp(\sigma(\mu - D_0)))$
mean dose logistic regression model	
$\mu := D_{mean}$	$NTCP_{logistic}(\mu) = 1 / (1 + \exp(-\beta_0 - \beta_1 \mu))$
cutoff dose logistic regression model	
μ : rectal wall volume V_{Dc} with dose equal or above a (cutoff) dose level D_c	$NTCP_{logistic}(\mu)$

Tab. 1: Summary measures and NTCP-function definitions of the NTCP-models under consideration

Results

Of the 319 patients, 45/5/1 (14.1/1.6/0.3%) showed bleeding of grade 2/3/4. Fig. 1 shows an overview of the 319 rectal wall DVHs, color-coded with the observed toxicity. This dataset has been used to fit the NTCP models in Tab. 1. The resulting parameter estimates (and 95% CIs) are given in Tab. 2. The 3-parametric Lyman- and Logit-EUD model and the 2-parametric serial RU model fitted the data similarly well (fig. 2a-c). Mean dose did not correlate to bleeding of grade ≥ 2 . For the cutoff-dose model, the volumes V_{Dc} receiving more than $D_c=73.7\text{Gy}$ resp. 79.6Gy showed highest significance (maxima in fig. 2d). However, the fit of this model (fig. 2e) was worse than for the first three EUD-based models. To mention, formally all volumes V_{Dc} in the dose range $D_c \sim 50\text{--}80\text{Gy}$ showed significant correlation ($p < 0.05$) with toxicity, see fig. 2d. The latter finding can be attributed to the four-field box treatment technique used, which induces correlations of the DVH dose bins. Quantitatively, these correlations were analysed with PCA: Fig. 1b shows the first three eigenvectors (EVs), where the first two describe (anti-)correlated variability of the DVH dataset in the low- and high dose region, and EV3 represents correlations of the maximal dose and intermediate doses as resulting from the four-field box technique.

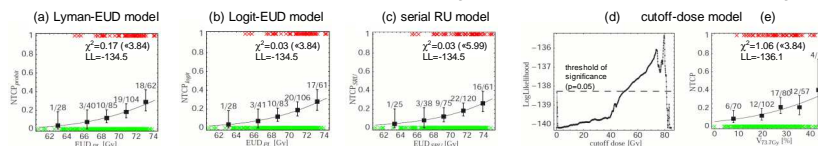


Fig. 2: Predicted probability of chronic rectal bleeding of grade ≥ 2 according to the EUD-based NTCP models (a)-(c), and the dose-volume based cutoff-dose model for $D_c=73.7\text{Gy}$ (e). The red resp. green symbols represent patients with resp. without toxicity. The observed toxicity rates are shown in centers of equally sized bins (except for two bins in the low incidence regime which were combined). Results of chi-squared goodness-of-fit tests and the LogLikelihood (LL) values are given for each model. For the cutoff dose model, (d) shows the values of LogLikelihood in dependence of the cutoff dose D_c .

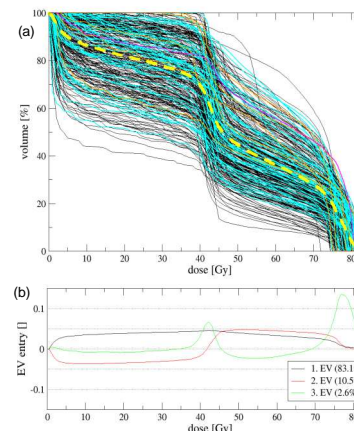


Fig. 1: (a) Rectal wall DVHs of the 319 patients included in this study, together with the population-mean DVH (dashed yellow). DVHs of patients who showed chronic rectal bleeding of grade ≥ 2 are plotted color-coded (cyan-orange-magenta - toxicity grade 2-3-4). (b) First three eigenvectors resulting from principal component analysis of the 319 DVHs. The dataset variability described by the EVs is given in the legend (rel. eigenvalues).

DVHs can be represented as weighted sum of these EVs with the weight factors given by the so-called principal components (PCs). According to uni- and multivariate logistic regression, both PC2 as single variable and combinations of the first two resp. three PCs correlate to toxicity (data not shown), which expresses the importance of the high dose region for increased risk of rectal bleeding.

model	parameter estimates (68% CI)
Lyman-EUD model	$a=11.9 \pm 3.8$, $m=0.11 \pm 0.03$, $D_{50}=78.4 \pm 2.1$
Logit-EUD model	$a=12.1 \pm 3.8$, $k=15.4 \pm 4.5$, $D_{50}=78.1 \pm 2.1$
serialRU model	$\sigma=0.18 \pm 0.05$, $D_0=80.6 \pm 0.9$
mean dose model	-not significant-
cutoff dose model ($D_c=73.7\text{Gy}$)	$\beta_0=-2.9 \pm 0.3$, $\beta_1=0.05 \pm 0.01$

Tab. 2: Estimated parameter values of the NTCP models for chronic rectal bleeding of grade ≥ 2 .

Conclusions

This study clearly confirms a volume effect for late rectal bleeding. The EUD-based Lyman-EUD, Logit-EUD and serial reconstruction unit models fit the observed complication rates very well, with the latter having only two parameters. The dose-volume based cutoff-dose model performed worse. Unlike findings of some other studies, mean dose did not correlate to bleeding of grade ≥ 2 . Generally, when comparing different studies, specific DVH shape differences imposed by the treatment technique, which can be revealed by PCA, should be considered.

Acknowledgements

This work has been supported by in part by Deutsche Krebshilfe e.V. grand No. 106280 and NIH grand No. R01 CA091020.

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