Prostate IMRT: Two-dimensional model of rectal NTCP employing the variability of rectal motion and rectum wall thickness

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ABSTRACT

Background: In order to improve the evaluation of possible rectal toxicity based on the rectal normal tissue complication probability (NTCP), we consider the fractional dependence of the NTCP on the wall thickness (tW) and rectal displacement (R₀). Materials and Methods: The two-dimensional NTCP model (NTCP₂D) was developed using radiotherapy plans of ten randomly selected patients with prostate cancer. The clinical rectal structures were substituted with rectal walls of cylindrical shape. To simulate full, partially-full and empty state of the rectum, three tW were generated under the conditions of same length of the rectum and same volume of the rectal wall. A threshold iso-line, NTCP₂₀, was used to split the NTCP₂D field into areas: a lower risk area and a higher risk area for rectal toxicity. Two factors are introduced to help with the estimation of NTCP: a volume factor k₁ which is the ratio between the volumes of the rectal wall and the intersection of the rectal wall with the planning target volume; and a probability factor k₂, which is the ratio between the area of low risk to the entire area of the NTCP₂D. Results: A correlation > 0.9 between factors k₁ and k₂ was found. Conclusion: The NTCP₂D field and the ratios k₁ and k₂ can be used as a patient-specific parameters to evaluate the probability of rectal toxicity.

Keywords: Prostate IMRT, rectal motion, variability of the rectal wall thickness, 2D field of possible rectal NTCPs.

INTRODUCTION

Intensity modulated radiation therapy (IMRT) can be used to achieve a conformal dose distribution in the planning target volume (PTV) while sparing the organs at risk (OAR). Thus, it has become a treatment technique for many types of cancer, including prostate cancer. One of the critical organs for prostate radiotherapy is the rectum. Late rectal bleeding Grade II or higher has been correlated with the volume of the intersection of the rectal wall (R₀ = PTV ∩ rectal wall) with the PTV, the mean dose and the rectal NTCP (Huang et al 2002, Tucker et al 2004 and Livi et al 2007) [¹–³]. In our study, a rectal NTCP = 10% (discussed by Livi et al 2007) will be used as a threshold NTCP₂₀.

For many years, a single static value of NTCP was used as an estimator for rectal complication probability (Lyman 1985) [⁴]. The NTCP value was calculated by the treatment planning system (TPS) based on the calculated dose distribution and on the rectal structure contours drawn on the planning dataset. The fractional dose distribution and the values of the rectal motion (R₀) and wall thickness (tW) are not explicitly considered in the static NTCP calculation. In the semi-dynamic NTCP model, the optimized rectal dose distribution is convolved with a probability.
density function \(pdf_M\) that describes the \(R_M\) over the course of treatment with mean values \(\mu_{\text{AP}}, \mu_{\text{LR}}\) and \(\mu_{\text{SI}}\) and standard deviations \(\sigma_{\text{AP}}, \sigma_{\text{LR}}\) and \(\sigma_{\text{SI}}\) for the anterior–posterior, left–right and superior–inferior (AP, LR and SI) directions, respectively \((5-10)\). This model does not consider the fractional uncertainties of \(t_W\). As a result, the estimated and delivered dose distribution and the value of the rectal NTCP could differ due to immobilization of the patient, positional uncertainties of the rectum and the fractional variability of the rectal wall thickness. In terms of the rectal wall, the most important region is the \(R_{\text{Wint}}\) because this is where the wall lies within the PTV. The risk of over-dosing of the rectal wall will be higher when the treatment uncertainties result in a larger \(R_{\text{Wint}}\) with the PTV (e.g., an empty rectum displaced to anterior direction). Finally, the dynamic model of the rectal NTCP calculation can be based on dose-volume-histogram (DVH) obtained from daily cone beam computed tomography (CBCT) datasets. However, several general complications, e.g., additional dose to the patient, calibration of the Hounsfield Unit to the electron density, and linear accuracy of CBCT derived 3D images, have been reported as limiting factors to this approach \((11-12)\).

To introduce a patient-specific two-dimensional field of possible NTCP values (NTCP\(_2D\)), the contours of the rectal wall on CT datasets of prostate cancer patients were used. The clinical rectal structures were substituted with rectal walls of cylindrical shape. To simulate the full, partially-full and empty (F, PF and E) states of the rectum, three wall thicknesses of 2, 5 and 10 mm were generated under the conditions of same length of the rectum and same volume of the rectal wall. For a given prescribed dose \(D_{\text{pr}}\), the shape of the NTCP\(_2D\) field depends on the AP, LR and SI directions of the rectal motion and is a function of the \(t_W\) and \(R_M\) \((13)\). The NTCP\(_2D\) was split by a threshold NTCP iso-line into two sub-fields of low risk and high risk NTCP values, \(S_{\text{LR}}\) and \(S_{\text{HR}}\), correspondingly \((14)\). The fields \(S_{\text{LR}}\) and \(S_{\text{HR}}\) are defined by the values of \(R_M\) and \(t_W\) for which the NTCP values are smaller and bigger than the chosen NTCP\(_{\text{TR}}\), respectively. The aims of this work are: (1) to determine the factors \(k_1 = R_W / R_{\text{Wint}}\) (where \(R_W\) is the volume of the rectal wall) and \(k_2 = (S_{\text{LR}} / S_{\text{2D}}) \times 100\%\), where \(S_{\text{2D}}\) is the size of the NTCP\(_2D\) field; and (2) to show the correlation between \(k_1\) and \(k_2\).

**MATERIALS AND METHODS**

Our model is shown schematically in figure 1. For clarity, the method for determination of the NTCP\(_2D\) field is presented with respect to rectal motion in the AP direction (i.e., assuming zero displacement of the rectum in the LR and SI directions) and the given range of \(t_W\).

The profile of the NTCP\(_2D\) is defined by the lines \(y_2 - y_{10}\) and \(x_1 - x_2\); see figure 1. The lines \(y_2\), \(y_{10}\) and \(x_5\) and \(y_{10}\) represent the bordering lines for constant \(t_W\) (F, PF and E rectum, respectively)

**Figure 1.** The profile of the NTCP\(_2D\) is defined by the lines \(y_2, y_{10}, x_1, x_2, y_5\), and \(y_{10}\). The NTCP\(_{\text{TR}}\) iso-line divides the NTCP\(_2D\) area into two sub-areas, \(S_{\text{LR}}\) with NTCP > NTCP\(_{\text{TR}}\) and \(S_{\text{HR}}\) with NTCP < NTCP\(_{\text{TR}}\) located above and under the iso-line, respectively.
and rectal displacement from the initial rectal position in the range of \(-a\) to \(+a\). The lines \(x_1\) and \(x_2\) represent the vertical bordering lines of the 2D field for a constant position of the rectum at \(-a\) and \(+a\), respectively and for a variable \(t_w\). The NTCP\(_{TR}\) iso-line at NTCP = 10\% (horizontal dashed line), divides the NTCP\(_{2D}\) area into two sub-areas, \(S_{HR}\) with NTCP > 10\% and \(S_{LR}\) with NTCP < 10\% located above and under the iso-line, respectively\(^{(14)}\).

**Patients and treatment planning**

The determination of the NTCP\(_{2D}\) field is based on the CT scans of ten randomly selected patients with T1–T3 staged prostate cancers. Using a slice thickness of 2 mm, each patient was scanned in the supine position. The guideline of the Radiation Therapy Oncology Group, RTOG P–0126, was used to contour the patients’ OARs and PTVs and to setup the DVH objectives for escalated-dose prostate IMRT planning\(^{(15)}\). The OARs were contoured based on the original CT dataset in the TPS. The outer and inner rectal surfaces were contoured from the anal verge to the sigmoid colon. Two sets of PTVs with uniform margins of 10 mm were used: PTV\(_1\) which includes both seminal vesicles and the prostate, and PTV\(_2\) which includes the prostate only. For 10 mm margin, the contoured volumes in the TPS are shown as follows: PTV\(_2\) (from 96.8 to 221.3 cm\(^3\) and 151.1 ± 25.6 cm\(^3\) (mean ± SD), PTV\(_1\) (from 143.8 to 318.1 cm\(^3\) and 231.9 ± 38.1 cm\(^3\)), solid rectum (82.7 to 263.1 and 115.9 ± 49.3 cm\(^3\)), rectal wall (from 29.2 to 62.2 cm\(^3\) and 39.6 ±12.4 cm\(^3\)) and rectal wall intersection (from 4.3 to 11.3 cm\(^3\) and 8.5 ±2.1 cm\(^3\)). The rectum can be approximated as having a cylindrical symmetry\(^{(16)}\). The rectal NTCP values of the cylindrical rectums were calculated for different combinations of rectal motion in the range of ± 10 mm in the AP, LR and SI directions; for \(t_w\) = 2 to 10 mm and for a \(D_{pr}\) of 78 and 82 Gy. The plans were optimized using seven coplanar fields with gantry angles of 40, 80, 110, 250, 280, 310 and 350° using Pinnacle\(^3\) TPS V 7.4 (Philips Medical System–Cleveland, Inc). Examples of contoured organs with an empty and a full rectum are shown in figures 2(a) and 2(b), respectively. As reported by the manufacturer, the planning system uses Kutcher’s model for NTCP calculation and the tissue response database published by Emanmi et al.\(^{(17,18)}\). The tissue parameters to calculate the NTCPs were: dose at 50 \% probability, slope factor, \(n\), and volume factor, \(m\), of 80 Gy, 0.15 and 0.12, respectively.

![Figure 2](image-url). A typical transverse view of the organ distribution. The PTV\(_2\) has a margin of 10 mm. In the figure, \(R_w\) denotes the volume of the rectal wall, \(R_{int}\) the volume of the intersection of a solid rectum with PTV\(_2\), \(R_{int}\) the volume of the intersection of the rectal wall with PTV\(_2\), and the volume of the solid rectum, \(R\). a) An empty rectum and b) a full rectum.

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**References**

1. Emanmi, et al. (17,18)
**Cylindrical rectum model**

In our model, for the cylindrical rectum we used the following assumptions:

1) The volume of the rectal wall is obtained by subtracting the volume enclosed by the inner rectal surface from the volume enclosed by the outer rectal surface;

2) The volume and the length of the artificial rectal wall are equal to the volume and the length of the clinical rectal wall (19);

3) The rectal wall volume is assumed to be constant throughout the fractional irradiation (20, 21);

4) The rectum moves in tandem with the prostate and

5) The fractional rectal motion and change of the rectal wall thickness do not cause under-dosing of the target (e.g., the prostate is always inside the PTV2).

Considering a constant length \( L \) of the rectum and an average \( t_w \), the volume of the cylindrical rectal wall \( V_{Rw} \) with inner radius \( r_2 \) and outer radius \( r_1 = (r_2 + t_w) \) can be expressed using the following equation:

\[
V_{Rw} = \pi \times L \times ((r_1)^2 - (r_2)^2) = \pi \times L \times ((r_2 + t_w)^2 - (r_2)^2)
\]

(1)

The inner radius \( r_2 \) can be determined for a given \( V_{Rw} \) and a chosen \( t_w \) using the following equation:

\[
r_2 = \frac{V_{Rw}}{2 \times \pi \times L \times t_w} - 0.5 \times t_w
\]

(2)

The initial clinical rectal contours were replaced in the TPS with the artificial cylindrical rectal contours. To mimic the F, PF and E rectum states, each rectal cylinder was modeled with wall thicknesses of 2, 5, and 10 mm under the conditions that the volume and length of the rectal wall remain constant. Every cylinder was divided using the TPS into segments. The length of each segment is equal to the CT slice thickness of 2 mm. The segments were moved to coincide with the contact line between the prostate and the wall of the clinical rectum. The NTCP was calculated for every combination between the \( t_w \) and the displacement of the cylindrical rectum from the initial position.

For one of the patients (see figure 2(a)), the resulting DVHs for \( t_w = 10 \) mm cylindrical rectal wall and anterior (A), posterior (P), superior (S), Inferior (I) and SI motion of 10 mm from the initial position of the rectum are plotted in figure 3. The rectal wall DVHs were calculated for an escalated prescription of 82 Gy.

**Geometric Volume Factor: Rectal wall – to – Rectal wall intersection**

The method includes a functional expression \( NTCP = f(R_{Wint}) \) describing the NTCP calculated for every patient and defined over the interval of the minimum to the maximum calculated \( R_{Wint} \). Although the discrete values show an increasing tendency as the argument increases, the NTCP for a new patient determined directly from figure 4(a) will likely be wrong. For example, for \( R_{Wint} = 5 \) and 15 cm\(^2\), the NTCP value is in the range of 10 to 20% and 22 to 35%, respectively.

The volume factor \( k_1 \) is introduced in equation 3 to show the impact of the volume of the rectal wall and the \( R_{Wint} \) on the possible rectal toxicity for a given \( D_{pr} \). The \( k_1 \) was used to rescale the calculated NTCPs to a system of patient-specific continuous linear dependences of NTCP proportional to \( R_{Wint} \) and \( k_1 \) (figure 4(b)).

\[
k_1 = \frac{R_{W}}{R_{Wint}}
\]

(3)
where, $R_W$ is the volume of the rectal wall calculated in the TPS, and $R_{\text{Wint}}$ is equal to the intersection of $\text{PTV}_2$ and the wall of the cylindrical rectum with $t_W = 5\, \text{mm}$ and zero motion in the AP, LR and SI directions. A new function, $(k_1 \times \text{NTCP}) = f(R_{\text{Wint}})$, was employed in the study.

**Probability of Rectal Toxicity**

The 2D field was divided into two areas with a $\text{NTCP}_{\text{TR}}$ iso-line: low risk NTCP values $< \text{NTCP}_{\text{TR}}$ and high risk NTCP values $> \text{NTCP}_{\text{TR}}$. We can assess the probability of avoiding rectal toxicity by examining the ratio of the area of the field of lower-risk NTCP values, $S_{LR}$, to the area of the field of all possible NTCPs, $S_{2D}$:

$$k_2 = \left( \frac{S_{LR}}{S_{2D}} \right) \times 100\% \quad (4)$$

The next equation gives an example of how to calculate $S_{LR}$, $S_{2D}$ and $k_2$ using figure 5 for a patient with $k_1 = 7.38$.

Where, $y_2 = 85.267e^{0.561x}$ and $y_{10} = 117.91e^{0.707x}$, plotted in figure 6, are the functions bordering the 2D field for motion in the AP direction, for full and empty rectum, respectively.

$$k_2 = \frac{S_{LR}}{S_{2D}} \times 100\% = \frac{\int_{-1}^{1} (y_{10} - y_2) \, dx + \int_{-0.65}^{-0.25} (\text{NTCP}_{\text{TR}} k_1 - y_2) \, dx}{\int_{-1}^{1} (y_{10} - y_2) \, dx} \times 100\% \quad (5)$$

**RESULTS**

Figure 3 shows the DVHs for one of the patients. The DVHs are for $D_{\text{pr}} = 82\, \text{Gy}$, $t_W = 10\, \text{mm}$ and a displacement of $R_W = \pm 10\, \text{mm}$ in the AP, LR and SI directions. The DVHs for the Left and Right displacement were found to be almost identical. For zero displacement, the DVHs for the clinical and the cylindrical rectums are similar. Both contours correspond to the initial rectal position and have the same contact line with the prostate. The cylindrical rectum has $t_W$ equal to the average wall thickness of the clinical rectum.

The initially calculated discrete NTCP values for a $D_{\text{pr}} = 82\, \text{Gy}$, $R_M = \pm 10\, \text{mm}$ in the AP, LR and SI directions and for $t_W = 2$ to $10\, \text{mm}$ for the entire group of CT scans are plotted in figure 4(a). The fitted linear curves, plotted in figure 4(b), have correlation coefficients of $R^2 = 0.92 - 0.97$. Two patients have almost the same $R_{\text{Wint}}$ and identical NTCP. Therefore, red points are shown in figure 4(a) with one bigger point. In figure 4(b), only six curves are plotted because
for four patients the curves coincided to those belonging to others.

The NTCP_{2D} fields for two of our patients (with minimum and maximum $k_1 = 2.17$ and $k_1 = 7.38$), are plotted in figures 5(a) to 5(c). The $y_2$ and $y_{10}$ functions for the given AP, LR and SI directions were found to have exponential, quadratic and linear equations, respectively. Craig et al. (2005) (5) reported a similar conclusion. The interpolation series fitting the $y$ functions have an $R^2$ value in the range from $R^2 = (0.96$ to 0.99); $(0.85$ to 0.95); and $(0.97$ to 0.98) for functions $y_2$ and $y_{10}$ in the AP, LR and SI directions, respectively.

Note that in the figures 5(a) to 5(c) the threshold iso-lines have been scaled by $k_1$ to 2.17 and 7.38, respectively. The dependence of the NTCP_{2D} field on the $D_{pr}$ for one of the patients is plotted in figure 6. A correlation between $k_1$ and $k_2$ of 0.937 and 0.986 for $D_{pr} = 82$ Gy and 78 Gy, respectively, is shown in figure 7. The values of

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**Figure 5.** NTCP_{2D} fields for rectal motion of ±10 mm and the functions $y_2$ (empty circle) and $y_{10}$ (full circle) showing $t_w$ = 2 and 10 mm, respectively. The NTCP_{2D} for $k_1$ of 2.17 (dashed) and 7.38 (dotted) is rescaled to NTCP_{2D} = 21.7 and 73.8%, respectively. a) Anterior-Posterior, b) Left-Right and c) Superior-Inferior directions.

**Figure 6.** 2D fields for the Anterior-Posterior direction, $R_{m} = -10$ to $+10$ mm and $t_w$ = 2 to 10 mm; $k_1 = 7.38$, Prescribed dose of 78 Gy (squares and dotted lines) and 82 Gy (circles and full lines); NTCP_{2D} iso-line is at 10% (dashed line). The factor $k_2$ = 5% and 36.5% for 82 and 78 Gy, respectively.

**Figure 7.** Correlation between $k_1$ and $k_2$ for a prescribed dose of 78 and 82 Gy for the AP direction, with $R_{m} = -10$ to $+10$ mm and $t_w$ = 2 to 10 mm. An average volume factor of $k_1$ = 5.15, as well as an average probability factor of $k_2$ = 12.9 and 23.9% for 82 and 78 Gy, respectively, was calculated.
The probability factor \( k_2 \) used to evaluate possible rectal toxicity Grade II or higher for three prostate patients with different \( k_1 \). The factor \( k_2 \) is a function of the motion in the AP, LR and SI directions, \( D_{pr} \), and the ranges of \( R_M \) and \( t_W \).

The table shows the dependence of \( k_2 \) on the prescribed dose (78 and 82 Gy); for two ranges of the motion of the rectum in the AP, LR and SI directions (±10 mm and ±5 mm) and wall thickness from 2 to 5 mm and from 2 to 10 mm; for min, mid and max values of factor \( k_1 \) of 2.17, 4.94 and 7.38, respectively.

### DISCUSSION

The immobilization uncertainty, internal organ motion, body shape, weight changes and geometric uncertainties of the rectal wall may cause a disagreement between the optimized and delivered dose distribution and consequently between the calculated and delivered DVH control points, mean dose and NTCP of the rectum. In this work we presented an investigation of two-dimensional model of rectal NTCP. The model was based on the simulation of the rectal motion and wall thickness variability of ten randomly selected prostate cancer patients. In the simulation the clinical rectal structures were substituted by cylindrical contours. The non-clinical structures were generated under the condition of same length and volume of the new rectal wall as they were measured in the TPS for the clinical rectums. The contours were displaced in the range of ± 10 mm in the AP, LR and SI directions to simulate the motion of the rectum. Similar rectal deviation from the initial position was reported [5-10]. However, in these works the variability of the thickness of rectal wall was not taken into account. In our model, for every rectal position, cylindrical rectal contours of 2, 5 and 10 mm wall thicknesses simulating the F, P and E states of the rectum, respectively, were generated.

A good agreement between the DVHs calculated for the clinical (in green) and cylindrical (in black) rectum for one of our patients is shown in figure 4. The calculations were done for zero motion of the cylindrical rectum of an average \( t_W \). These values of rectal NTCP were calculated in TPS based on Kutcher’s model and Emami’s tissue parameters [17,18]. It may be possible to assume that the tissue parameters and the level of the NTCP iso-line may have an effect on the scale of the NTCP field and the value of the probability parameter \( k_2 \). For one of the patients, a rectal NTCP of 13.1%, 20.3% and 11% was calculated applying the tissue parameters of our TPS (0.12, 0.15 and 80); Rancati et al. 2004 (0.23, 0.19 and 81.9) and Michalski et al. 2010 (0.09, 0.13 and 76.9), respectively [22-23]. The \( y \) lines bordering the profile of the NTCP were found to be exponential, quadratic and linear functions for the AP, LR and SI directions, respectively. Similar equations were reported by Craig et al. (2005) [5].

The calculations of the \( S_{LR} \) and \( S_{IR} \) are based on a NTCP iso-line at 10%. If other motional displacements, thickness of rectal wall, prescribed dose and NTCP are used, other values for the probability factor \( k_2 \) can be calculated. The investigation of dependences of the size and profile of the NTCP2D, \( S_{LR} \) and \( S_{IR} \) on the \( R_M \), \( t_W \), \( D_{pr} \) and NTCP is in progress.

In comparison to the \( k_2 \) value calculated by the tissue parameters of our TPS and NTCP = 10%, by using the parameters reported by Rancati and Michalski, we observed a reduction and an increase of the probability factor, \( k_2 \),
respectively. According to this, it is possible to assume that every tissue parameters may need a specific NTCP_{TR} iso-line to calculate the probability of avoiding high rectal toxicity. It should be noted that the selection of a widely applicable NTCP_{TR} would be arbitrary. In practice the selection would be based on the level of risk that the prescribing doctor is willing to accept in the case of any specific patient. For example, the threshold should be set lower if the patient has a certain health history of the rectum and/or if the age of the patient is considered

(Hamstra et al. 2013) (24). The methodology presented in this work is applicable irrespective of the NTCP_{TR} selected. We can conclude that using different tissue parameters and value for the NTCP_{TR}, a rescaling of the NTCP_{2D} and the probability factor, k_2, can be expected.

In our study, k_2 was calculated under the assumption of homogeneous probability for every R_M and t_W combination. Further improvements to the 2D model could be achieved by including an inhomogeneous probability density function of the thickness of the rectal wall. This may significantly change the value of k_2 if one of the F, PF and E states of the rectum is dominating as a thickness of the wall during the treatment. It is possible to assume that k_2 for a single patient can be different when it is calculated under the homogenous and inhomogeneous probability of the R_M and t_W combinations. In the future, an improvement of the dose delivery technique could achieve a steeper dose gradient between the PTV and the rectal wall. As a result, new tissue parameters and/or a new NTCP_{TR} can be generated.

The main contributions of this work are as follows: 1) Introducing a simple method, applicable to every TPS, to map the profile of the NTCP_{2D} fields as a function of the R_M, t_W, D_{pr} and NTCP_{TR} iso-line; and 2) Determining that the correlation between the volume and the probability factors, k_1 and k_2, allows the estimation of the probability for rectal toxicity (see figure 7). For a given volume of the rectal wall, the factor k_1 depends on the R_{Win}. Proportionally, it depends on the t_W and the PTV margin. Therefore, patients with a smaller volume of the rectal wall and bigger prostate may have lower k_1 and an increased probability for higher-risk NTCPs (i.e., lower k_2). Additionally, if the position of the prostate has to be compensated by a fractional immobilization of the patient in the anterior direction, the patient may develop higher rectal toxicity than the predicted.

Initially, in this study we used a group of 25 randomly selected prostate cancer patients. Many of them had very close values of their R_W, R_{Win} and, respectively, the same ratio k_1. Thus, only ten of them, covering the whole range of the factor k_1 (from 2.17 to 7.38), were included in the study. As shown in figures 4 and 7, the k_1 ratio is an effective parameter for a pre-treatment estimation of the rectal toxicity. A higher value of k_1 predicts a higher probability of avoiding the rectal toxicity.

The impact of the prescribed dose on the probability of avoiding high rectal toxicity is shown in table 1. An escalated prescribed dose of 82 Gy reduces the probability of avoiding rectal toxicity in the range from 1.4% to 5.02%. Using D_{pr} = 78 Gy allows an increase of the probability of avoiding rectal toxicity of up to 26 –36.5 % for the AP direction, R_M = ± 5 mm and t_W is between 2 and 5 mm. Similar changes were found for the LR and SI directions as well. As described in table 1, under the conditions of NTCP_{TR} = 10%, and using Kutcher’s model (17) for NTCP calculation and Emami’s tissue (18) response database, the calculations of factor k_2 show that if the range of the total error is reduced from ± 10 mm to ± 5 mm the probability of avoiding rectal toxicity Grade II will be higher. For example, for the AP direction, dose of 78 Gy, R_M = ± 5 mm and t_W = 2 , 5 mm the probability of avoiding toxicity increases for k_1 = 2.17 from 20.2% to 26.04%; for k_1 = 4.94 from 21.3% to 29.3%; and k_1 = 7.38 from 29.5% to 36.5%, respectively.

The highest values for k_2 were received for k_1 = 7.8 and D_{pr} = 78 Gy using a range of the motion of ± 5 mm and wall thickness from 2 to 5 mm. Patients with bigger volume of the rectal wall and smaller R_{Win} have bigger k_1 and a better chance of avoiding rectal damage. The lowest k_2 value was received for the patient with k_1 = 2.17, planned for D_{pr} = 82 Gy using a range of the R_M.
of ± 10 mm and $t_w$ from 2 to 10 mm. If for a given $D_{PR}$ in the field of possible rectal NTCP$_{2D}$ existing less number of $R_{k}$ and $t_w$ combinations for which NTCP < NTCP$_{PR}$, then $S_R \rightarrow 4$, i.e., $k_2 \rightarrow 0$ and $S_{IR} \rightarrow S_{2D}$ (see table 1), which results in 100% probability for rectal toxicity to the patient. In this case, a reduction of the PTV margin and/or the $D_{PR}$ must be concerned. The tendency of the dependence $k_2 = f(k_1)$ is shown in figure 7. The overall aim of the study as stated is to use $k_2$ as a probability factor for toxicity evaluation of a given prostate treatment plan. In order to utilize the result presented in figure 7, the value of $k_1$ needs be computed for each plan of a patient and then the corresponding $k_2$ has to be determined.

The method can be considered for other cancer locations and critical organs (bladder, lungs, kidney, head and neck, heart, spinal cord, etc.) However, it must be recognized that the cylindrical model of the rectum and the shape of $y_2$ and $y_{10}$ may not be applicable for all organs. Additionally, our 2D model may be applicable to other DVH derivatives such as the DVH control points, mean dose, and EUD. Finally, the method can be adapted to any TPS as a pre-treatment QA program and used as an objective estimation of the probability for rectal toxicity. An important result from this investigation is the possibility to better explain to the patients how sensitive the rectal toxicity is to their rectal filling and the resulting fractional rectal wall thickness during the treatment.

**CONCLUSIONS**

The substitution of the 3D contours of the clinical rectums with contours of cylindrical shape is a simple technique to map the profile and the position of the NTCP$_{2D}$ fields in the AP, LR and SI directions in comparison to the NTCP$_{PR}$ iso-line. The NTCP$_{2D}$ field is a function of the rectal motion, variability of the rectal wall thickness, prescribed dose, NTCP$_{PR}$ iso-line and the volume ratio $k_1$. The higher is the value of $k_2$, the lower is the probability for rectal damage. In conclusion, the highest probability for rectal toxicity can be ascribed to patients with a smaller volume of the rectal wall and a larger prostate volume who are treated using an escalated prescribed dose > 78 Gy, for a fractional range of the rectal wall thickness from 5 to 10 mm and range of rectal motion from −10 to +10 mm.

**ACKNOWLEDGMENTS**

The study was supported by the Medical Physics Department at the Grand River Regional Cancer Centre. Thanks to Dr. Rob Barnett and Dr. Marcin Wierzbicki for their helpful discussion and advice.

**Conflict of interest:** Declared none.

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Approximation rectal wall thickness and motional displacement

Approximation of the rectal NTCP

The idea how clinically to use the NTCP2D field to determine the dynamic and semi-dynamic rectal NTCP is shown in figures 8(a) and 8(b), respectively. For every prostate patient, both models can be easily generated by the TPS. In this section, the idea of the 2D NTCP field is shown graphically with the NTCPTR iso-line and probability factor $k_2$. First the dynamic model and second the semi-dynamic model are discussed.

Dynamic model

In this model, we assume a variability of the rectal wall thickness and motional displacement in one direction only and a zero displacement of the rectum in another two directions. Functions $y_2$ and $y_{10}$ (figure 8(a)) represent the bordering lines for constant $t_W = 2$ and 10 mm (F and E rectum, respectively). The rectal displacement from the initial rectal position is in the range from $-a$ to $+a$. As mentioned previously, in the Methods and Materials section, 2D field of all combinations of the $R_M$ and $t_W$ has equal probability and every point in the field represents the planned static NTCP value of one treatment plan. A simulation of a prostate treatment of 76 Gy by 2 Gy/fraction is presented in the 2D field by 38 doses. An NTCP iso-line divides the field into two subfields. The points, 15 (green) and 23 (red) are placed in the $S_{IR}$ and $S_{IR}$ subfields, respectively. The “zig-zag” NTCP truck-line shows schematically how the fractional rectal NTCP depends on the $R_M$ and $t_W$, from the first ($R_M(1)$, $t_W(1)$, big red dot) to the last fraction ($R_M(36)$, $t_W(36)$, big green dot).
There is a possibility to express the probability to avoid the rectal toxicity as the ratio \(k_2 = \frac{S_{LR}}{S_{2D}} \times 100\% = \frac{S_{LR}}{(S_{LR} + S_{HR})} \times 100\%\).

**Semi-dynamic model**

In this model, the variability of \(t_W\) is not considered. In the TPS only one thickness is used. The \(t_W\) in different hospitals can be different. The model uses the \(R_M\) only. As a result the 2D field of possible rectal NTCP is transferred to a line, the \(t_W\) iso-line, of possible NTCPs (see figure 8(b)). An NTCP iso-line divides the \(t_W\) iso-line into two sub-lines \(L_{LR}\) and \(L_{HR}\). In figure 8 (b), some NTCPs < NTCP_{TR} are on the sub-line \(L_{HR}\) with the NTCP values > NTCP_{TR} (green dots between red dots). In contrast, some NTCPs > NTCP_{TR} are replaced on the sub-line \(L_{LR}\) with NTCP values < NTCP_{TR} (red dots between green dots). In this model, the possible probability to avoid the rectal toxicity is expressed by the ratio between the sub-lines field \(L_{LR}/(L_{LR} + L_{HR}) \times 100\%\).

If both field and line ratios, \(S_{LR}/(S_{LR} + S_{HR})\) and \(L_{LR}/(L_{LR} + L_{HR}) \rightarrow 0\), then probability of rectal damage of 100% is possible. In this situation, there is no \(R_M\) and \(t_W\) combination for which the rectal NTCP < NTCP_{TR}. If both ratios \(\rightarrow 1\), then for all \(R_M\) and \(t_W\) combinations the rectal NTCP < NTCP_{TR} and the rectal toxicity is 100% avoided. A difference between the dynamic and semi-dynamic models for probability estimation is possible. If the rectal wall has a constant \(t_W\) in the TPS, some NTCPs > NTCP_{TR} can be added to the group of NTCPs < NTCP_{TR} and vice versa. Both models can be used in the pre-treatment QA of the prostate IMRT plan optimization. However, it can be assumed that the 2D model has higher resolution and accuracy of the probability estimation to avoid the rectal toxicity than the semi-dynamic model.

The models were set-up under the assumption of homogeneous probability for every \(R_M\) and \(t_W\) combination. To determine the rectal displacement and thickness of rectal wall, both models need a fractional scanning of patients. To escape the additional dose to patients during the fractional scanning, a further improvements to the 2D model could be achieved by using a two dimensional probability density functions, pdf: one for the motion of rectum, pdf_{M}, and another for the variability of rectal wall thickness, pdf_{TW}. The outer product of the two pdf functions (pdf_{M} and pdf_{TW}) results into two dimensional pdf_{M&TW} function.

**Figure 8 (a).** 2D field for determination of the dynamic rectal NTCP. The “zig-zag” curve represents schematically a track of fractional NTCPs as a function of two uncontrolled parameters of the rectum, rectal motion and wall thickness.

**Figure 8 (b).** Semi-dynamic distribution of fractional NTCPs as a function of the \(R_M\) from -a to +a and for a constant \(t_W\). \(L_{LR}\) and \(L_{HR}\) are the sub-lines on which the NTCPs < NTCP_{TR} and NTCPs > NTCP_{TR}, respectively.