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 (t_W) and rectal displacement (R_M). ***Materials and Methods***: The two-dimensional NTCP model ($NTCP_{2D}$) 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 t_W were generated under the conditions of same length of the rectum and same volume of the rectal wall. A threshold iso-line, $NTCP_{TR}$, was used to split the $NTCP_{2D}$ 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 k_1 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 k_2, which is the ratio between the area of low risk to the entire area of the $NTCP_{2D}$. ***Results:*** A correlation > 0.9 between factors k_1 and k_2 was found. ***Conclusion***: The $NTCP_{2D}$ field and the ratios k_1 and k_2 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 (R_{Wint} = 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 $NTCP_{TR}$.

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 (R_M) and wall thickness (t_W) 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 μ_{AP}, μ_{LR} and μ_{SI} and standard deviations σ_{AP}, σ_{LR} and σ_{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_{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_{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_{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_{LR} and S_{HR}, correspondingly [14]. The fields S_{LR} and S_{HR} are defined by the values of R_M and t_W for which the NTCP values are smaller and bigger than the chosen $NTCP_{TR}$, respectively. The aims of this work are: (1) to determine the factors $k_1 = R_W / R_{W\,int}$ (where R_W is the volume of the rectal wall) and $k_2 = (S_{LR} / S_{2D})\ x\ 100\%$, (where S_{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_5 and y_{10} represent the bordering lines for constant t_W (F, PF and E rectum, respectively)

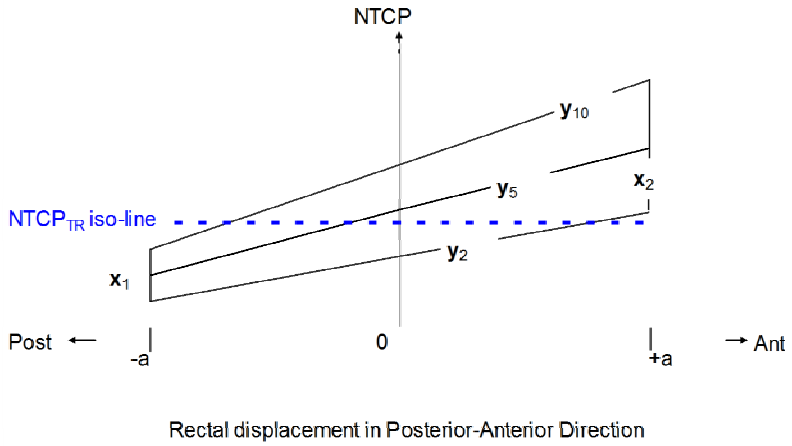

Figure 1. The profile of the $NTCP_{2D}$ is defined by the lines y_2, y_{10}, x_1 and x_2. The $NTCP_{TR}$ iso-line divides the $NTCP_{2D}$ area into two sub–areas, S_{HR} with NTCP > $NTCP_{TR}$ and S_{LR} with NTCP < $NTCP_{TR}$ located above and under the iso-line, respectively.

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 guide-line 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 Pinnacle³ 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.

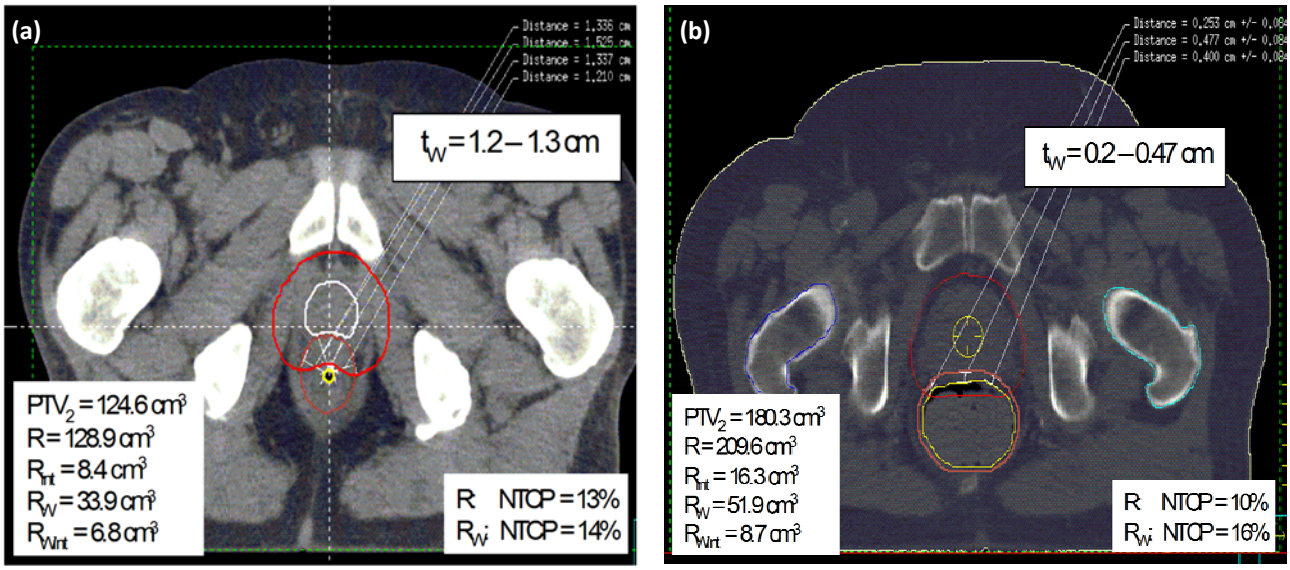

Figure 2. A typical transverse view of the organ distribution. The PTV_2 has a margin of 10 mm. In the figure, R_W denotes the volume of the rectal wall, R_{int} the volume of the intersection of a solid rectum with PTV_2, R_{Wint} the volume of the intersection of the rectal wall with PTV_2, and the volume of the solid rectum, R. a) An empty rectum and b) a full rectum.

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 PTV_2).

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:

$$V_{Rw} = \pi \times L \times ((r_1)^2 - (r_2)^2) = \pi \times L \times ((r_2 + t_W)^2 - (r_2)^2) \quad (1)$$

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

$$r_2 = (V_{Rw} / (2 \times \pi \times L \times t_W)) - 0.5 \times t_W \quad (2)$$

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^3, 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)).

$$k_1 = R_W / R_{W\,int} \quad (3)$$

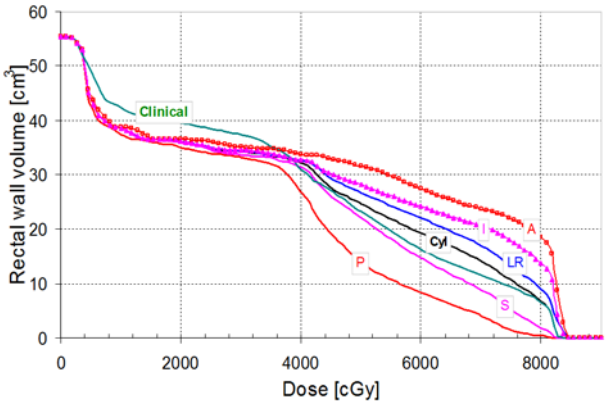

Figure 3. DVHs of the cylindrical rectal wall with an average t_W = 10 mm shifted by 10 mm from the initial rectal position in the directions: A and P, (in red), L and R (in blue), and S and I (in pink). The initial clinical rectal wall in the empty state is in green. The DVH of the cylindrical rectal wall and zero motion in all directions is modeled in black.

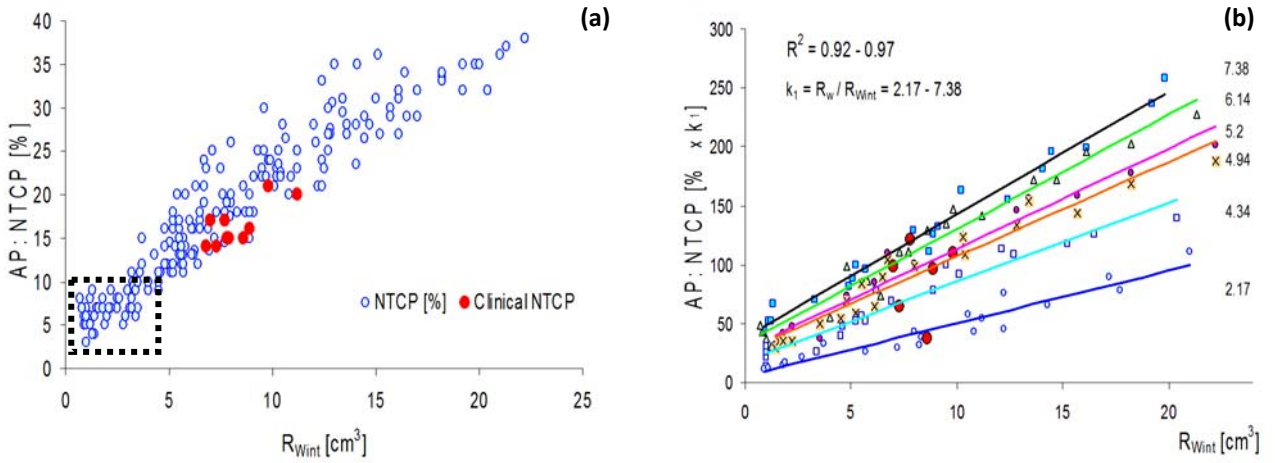

Figure 4. The light blue circles denote the values for the cylindrical rectums. The values of the clinical rectums are plotted with red circles. Dependence of the NTCP on R_{Wint} for the A and P directions, D_{pr} = 82 Gy and PTV margin 10 mm: a) Distribution of the discrete NTCP values before the rescaling with k_1. b) Distribution of the fitting curves after rescaling with k_1. A small rectangle of dotted lines shows the range of R_{Wint} for which the resulting number-NTCP are below $NTCP_{TR}$.

where, R_W is the volume of the rectal wall calculated in the TPS, and R_{Wint} is equal to the intersection of PTV_2 and the wall of the cylindrical rectum with t_W = 5 mm and zero motion in the AP, LR and SI directions. A new function, (k_1 × NTCP) = $f(R_{Wint})$, was employed in the study.

Probability of Rectal Toxicity

The 2D field was divided into two areas with a $NTCP_{TR}$ iso-line: low risk NTCP values < $NTCP_{TR}$ and high risk NTCP values > $NTCP_{TR}$. We can asses 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}:

$$k_2 = (S_{LR} / S_{2D}) \times 100\% \qquad (4)$$

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.

RESULTS

Figure 3 shows the DVHs for one of the patients. The DVHs are for D_{pr} = 82 Gy, t_W = 10 mm and a displacement of R_M = ± 10 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_{pr} = 82 Gy, R_M = ± 10 mm in the AP, LR and SI directions and for t_W = 2 to 10 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_{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

$$k_2 = \frac{S_{LR}}{S_{HR}} \times 100\% = \frac{\int_{-1}^{-0.65}(y_{10} - y_2)dx + \int_{-0.65}^{-0.25}(NTCP_{TR}\,k_1 - y_2)dx}{\int_{-1}^{+1}(y_{10} - y_2)dx} \times 100\% \qquad (5)$$

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

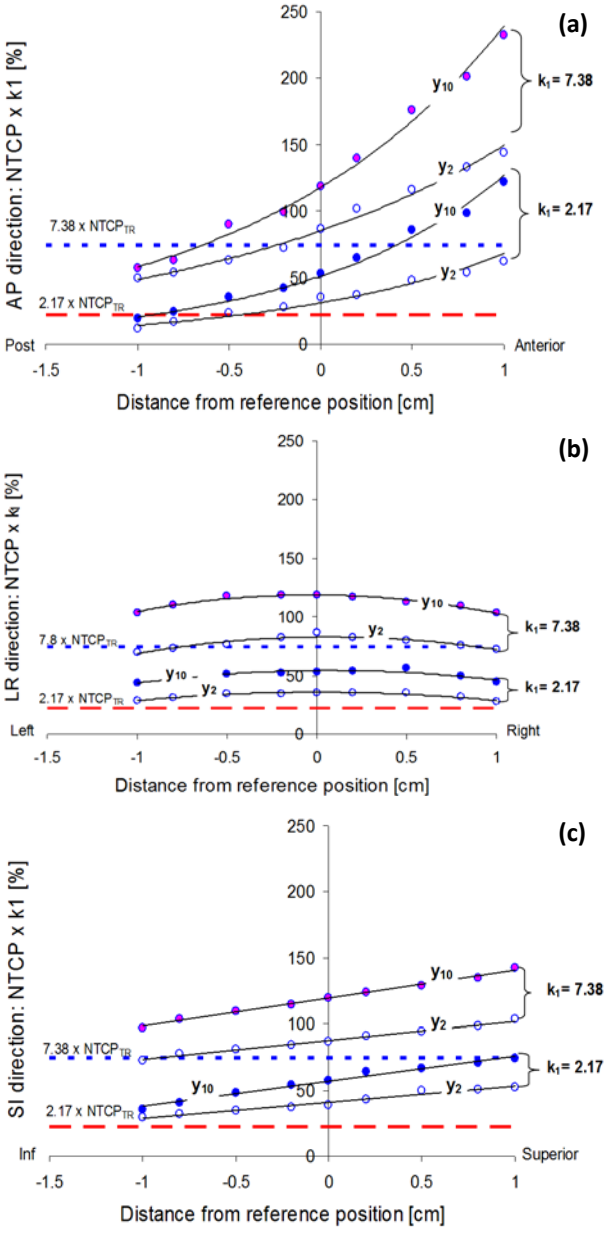

Figure 5. $NTCP_{2D}$ fields for rectal motion of ± 10 mm and the functions y_2 (empty circle) and y_{10} (full circle) showing t_W = of 2 and 10 mm, respectively. The $NTCP_{TR}$ for k_1 of 2.17 (dashed) and 7.38 (dotted) is rescaled to $NTCP_{TR}$ = 21.7 and 73.8%, respectively. a) Anterior-Posterior,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

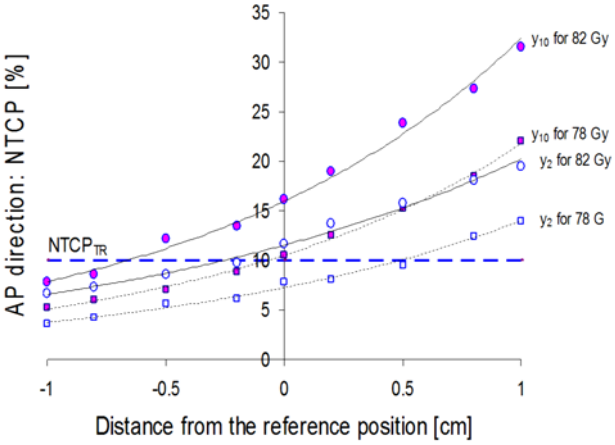

Figure 6. 2D fields for the Anterior-Posterior direction, R_M = –10 to +10 mm and t_W = 2 to 10 mm; k_1 = 7.38, Prescribed dose of 78 Gy (squares and dotted lines) and 82 Gy (circles and full lines); $NTCP_{TR}$ iso-line is at 10% (dashed line). The factor k_2 = 5 % and 36.5 % for 82 and 78 Gy, respectively.

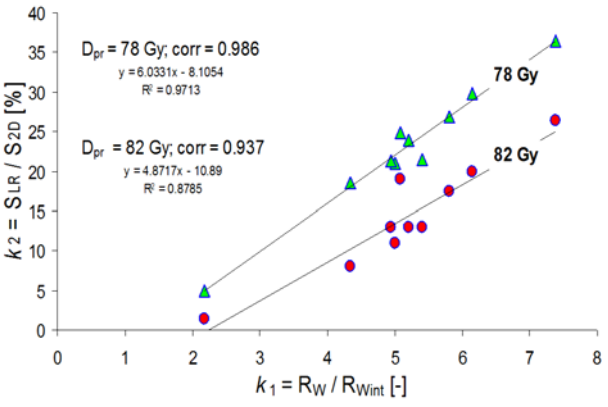

Figure 7. Correlation between k_1 and k_2 for a prescribed dose of 78 and 82 Gy for the AP direction, with R_M = –10 to +10 mm and t_W = 2 to 10 mm. An average volume factor of k_1 = 5.15, as well as an average probability factor of k_2 = 12.9 and 23.9% for 82 and 78 Gy, respectively, was calculated.

Table 1. 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.

$k_2 = f(k_1, D_{pr}, R_M \text{ and } t_W)_{AP, LR \text{ and } SL} = S_{LR} / S_{2D} \times 100[\%]$										
		k_1 = **2.17**			k_1 = **4.94**			k_1 = **7.38**		
R_M and t_W range	Dose	AP	LR	SI	AP	LR	SI	AP	LR	SI
R_M = ± 10 mm	82 Gy	0.025	n/a*	n/a	2.3	n/a	n/a	4.62	n/a	n/a
t_W=2¸10mm	78 Gy	20.2	n/a	n/a	21.3	18.5	14.7	29.5	83	60.7
R_M = ± 5 mm	82 Gy	1.4	n/a	n/a	3.9	n/a	n/a	5.02	5.66	n/a
t_W=2¸5mm	78 Gy	26.04	1.48	6.1	29.3	33.2	43.2	36.5	100	100
**n/a means that the number of R_M and t_W combinations in the 2D field resulted in NTCP < $NTCP_{TR}$ decreases. The size of $S_{LR} \rightarrow 0$ i.e., $k_2 \rightarrow 0$ %.*										

k_2 for different D_{pr}, R_M (in the AP, LR and SI directions), t_W and k_1 are presented in table 1. 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, PF 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 $NTCP_{TR}$ iso-line may have an effect on the scale of the $NTCP_{2D}$ 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 $NTCP_{2D}$ 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_{HR} are based on a $NTCP_{TR}$ iso-line at 10%. If other motional displacements, thickness of rectal wall, prescribed dose and $NTCP_{TR}$ are used, other values for the probability factor k_2 can be calculated. The investigation of dependences of the size and profile of the $NTCP_{2D}$, S_{LR} and S_{HR} on the R_M, t_W, D_{PR} and $NTCP_{TR}$ is in progress.

In comparison to the k_2 value calculated by the tissue parameters of our TPS and $NTCP_{TR}$ = 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_{Wint}. 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_{Wint} 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_{Wint} 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_M and t_W combinations for which NTCP < $NTCP_{TR}$, then $S_{LR} \rightarrow 4$, i.e., $k_2 \rightarrow 0$ and $S_{HR} \rightarrow S_{2D}$ (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 derivates 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 $NTCP_{TR}$ iso-line. The $NTCP_{2D}$ field is a function of the rectal motion, variability of the rectal wall thickness, prescribed dose, $NTCP_{TR}$ 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.

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REFERENCES

1. Huang E, Pollack A, Levy L, Starkschall G, Dong L, Rosen I and Kuban D (2002) Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. *Int J Radiation Oncology Biol Phys, **54**: 1314–21*.
2. Tucker S, Cheung R, Dong L, et. al. (2004) Dose–Volume Response Analyses of Late Rectal Bleeding After Radiotherapy for Prostate Cancer. *Int J Radiation Oncology Biol Phys, **59**: 353–65*.
3. Livi L, Detti B, Meattini M, Sánchez L, Biti G (2007) Organ-Confined Prostate Cancer: Treatment With High Doses Of Radiotherapy (Intensity Modulated Radiation Therapy). *Actas Urol Esp*, ***31**: 611–6*.
4. Lyman L, 1985 Complication probability as assessed from dose volume histograms, *Radiat Res Suppl, **104**: 13–19*.
5. Craig T, Wong E, Bauman G, Battista J, and Van Dyk J (2005) Impact of geometric uncertainties on evaluation of treatment techniques for prostate cancer. *Int J Radiation Oncology Biol Phys*, ***62**: No. 2, 426–36*.
6. Lattanzi J, McNeely S, Hanlon A, Das I, Schultheiss T and Hanks E (1998) CT localization for correcting portal errors in the treatment of prostate cancer. *Int J Radiation Oncology Biol Phys*, ***41**: 1079–86*.
7. Pouliot J, Aubin M, Langen K, Liu Y, Pickett B, Shinnohara K and Roach M (2003) (Non)- migration of radiopaque markers used for on-line localization of the prostate with an electronic portal imaging device. *Int J Radiation Oncology Biol Phys, **56**: 862–6*.
8. Van Herk, Bruce A, Kroes A, et al. (1995) Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. *Int J Radiation Oncology Biol Phys*, ***33**: 1311–20*.
9. Britton K, Takai Y, Mittsuya M, Nemoto K, Ogawa Y and

Yamada S (2005) Evaluation of inter- and intrafraction organ motion during IMRT for localized prostate cancer measured by a newly developed on-board image-guided system. *Radiation Medicine*, ***23****: 14–24*.
10. Moseley D, White E, Wiltshire K, et. al. (2007) Comparison of localization performance with implanted fiducial markers and cone-beam computed tomography for on-line image-guided radiotherapy of the prostate. *Int J Radiation Oncology Biol Phys*, ***67****: 942–53*.
11. Sawyer L, Whittle S, Matthews, Starritt H and Jupp T (2009) Estimation of organ and effective doses resulting from cone beam CT imaging for radiotherapy treatment planning. *British Journal of Radiology*, ***82****: 577–84*.
12. Pauwelsa R, Beinsbergera J, Collaertb B, Theodorakouc C, Rogerse J, Walkerc A, Cockmartinf L, Jacobsa R, Bogaertsg R, Hornerd K (2012) Effective dose range for dental cone beam computed tomography scanners. *Eur J Radiol*, ***81****: 267–71*.
13. Grigorov G, Chow J and Barnett R (2007) A novel algorithm for calculation of dynamic rectal NTCP. *Radiother Oncol*, ***84****/2: S30, The annual CARO-COMP meeting, Toronto*.
14. Grigorov G, Chow J and Foster K (2012) Prostate IMRT QA: Prediction of the range of rectal NTCP using a 2D field approach based on variations of the rectal wall motion and thickness. *Med Phys*, ***39****: 3837*.
15. Michalski J, Purdy J, Bruner D and Amin M (1993) *ICRU Report* **50** Prescribing, Recording, and Reporting Photon Beam Therapy (Bethesda, MD: International Commission on Radiation Units and Measurements).
16. Fontenla E, Pelizzari C, Roeske J and Chen G (2001) Numerical analysis of a model of organ motion using serial imaging measurements from prostate radiotherapy. *Phys Med Biol*, ***46****: 2337–58*.
17. Kutcher G, Burman C (1989) Calculation of complication probability factors for non-uniform normal tissue irradiation: The effective volume method. Int. J. Radiat. *Oncol Biol Phys*, ***16****: 1623–130*.
18. Emanmi B, Lyman J and Brown A (1991) Tolerance of normal tissue to therapeutic irradiation. *Int J Radiation Oncology Biol Phys*, ***21****: 109–22*.
19. Booth J and Zavgorodni S (2001) Modeling the dosimetric consequences of organ motion at CT imaging on radiotherapy treatment planning. *Phys Med Biol*, ***46****: 1369–77*.
20. Meijer M. Brink M. Hoogeman, Meiders J and Lebesque J (1999) Dose-wall histograms and normalized dose-surface histograms for the rectum: a new method to analyze the dose distribution over the rectum in conformal radiotherapy. *Int J Radiation Oncology Biol Phys, **45**: No. 4, 1073–80*.
21. J. Leong 1987 Implementation of random positioning error in computerised radiation treatment planning systems as a result of fractionation. *Phys Med Biol*. **32,** 327–34.
22. Rancati T, Fiorino C, Gagliardi G et al (2004) Fitting late rectal bleeding data using different NTCP models: results from an Italian multi-centric study (AIROPROS0101). *Radiother Oncol*, ***73****: 21–32*
23. Michalski JM, Gay H, Jackson A, et al. (2010) Radiation dose volume effects in radiation-induced rectal injury. *Int J Radiation Oncology Biol Phys, **76**: 123-9*.
24. Hamstra D, Stenmark M, Ritter T, Litzenberg D, Jackson W, Johnson S, et al (2013) Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. *Int J Radiation Oncology Biol Phys*, ***85****: 1246–53*.

APPENDIX

Approximation of the rectal NTCP

The idea how clinically to use the $NTCP_{2D}$ 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 $NTCP_{TR}$ 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 2Gy/fraction is presented in the 2D field by 38 dots. An NTCP iso-line divides the field into two subfields. The points, 15 (green) and 23 (red) are placed in the S_{LR} and S_{HR} 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 $k_2 = S_{LR}/S_{2D} \times 100\% = S_{LR}/(S_{LR} + S_{HR}) \times 100\%$.

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.

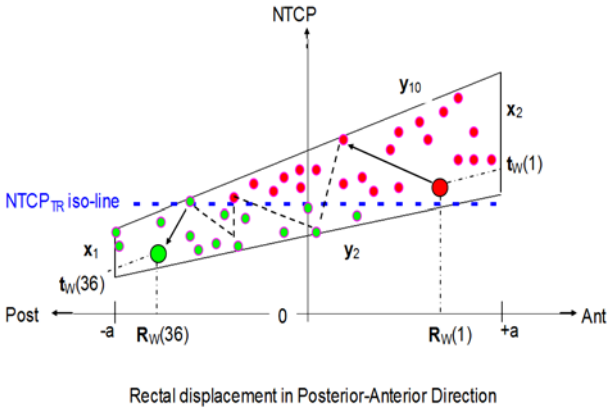

Figure 8 (a). 2D field for determination of the dynamic rectal NTCP. The "zig-zag" curve represents schematically a track of fractional NTCPs as a function of two uncontrolled parameters of the rectum, rectal motion and wall thickness.

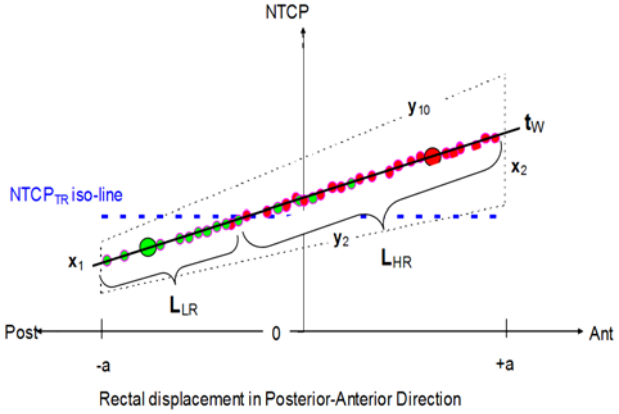

Figure 8 (b). Semi-dynamic distribution of fractional NTCPs as a function of the R_M from –a to +a and for a constant t_W. L_{LR} and L_{HR} are the sub-lines on which the NTCPs < $NTCP_{TR}$ and NTCPs > $NTCP_{TR}$, respectively.