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Evaluation of a New Method for Calculation of Cumulative Doses in the Rectum Wall using Repeat CT Scans

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The rectum wall is an important organ at risk during irradiation of the prostate, the bladder and other organs in the pelvis. It is therefore of great interest to be able reliably to predict normal tissue complication probabilities (NTCPs) for this organ. Because the rectum wall is a hollow organ capable of large deformations between fractions, dose estimates from a single CT are unreliable, and thereby also NTCP estimates. In this study two methods for calculations of cumulative dose distributions from repetitive CT scans are compared. The first is a method presented in this article that uses tracking of volume elements for a direct summation of the doses delivered in the treatment fractions. The other, presented earlier (1), is based on information from dose-volume histograms. The comparisons were made in terms of equivalent uniform doses (EUDs) and NTCPs. The methods were also compared with mean values of EUD and NTCP values from individual CT scans. The study showed that with the relatively symmetric beam arrangements normally used for treatment of prostate and bladder cancer, it is not necessary to use the more laborious method of element tracking. However, an introduction of artificial lateral rectum movements revealed that element tracking is necessary in less symmetric situations.

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The rectum is an important organ at risk (OR) in pelvic radiotherapy of, for example, prostate and bladder cancer. Late rectal effects may cause a severe degradation of the quality of life, and it is therefore important to be able to reliably predict the risk for complications in this organ. However, the rectum is a hollow organ that displays large temporal variations in shape, volume and position. The dose distribution in the rectum wall will therefore be different from fraction to fraction during a course of radiotherapy (2, 3). Estimates of the total dose distributions to the rectum wall from only one planning CT scan will in general be uncertain, and calculated complication probabilities will have a corresponding uncertainty. Furthermore, if these dose distributions are combined with observed complication frequencies with the aim of deriving NTCP model parameters, this may introduce uncertainty in these parameters.

In a clinical setting, treatment planning is usually based on only one CT examination performed prior to treatment, and to improve on this situation models of rectal motion have been constructed. In Mageras et al. (4), organ motion is simulated according to observed organ motions in a group of reference patients. Using a dose-based endpoint as a means for ranking treatment plans, two dose-volume histograms (DVHs) are presented that represent extreme cases. Fontenla et al. introduced a statistical model that is non-parametric and that does not rely on any assumptions about the organ's shape or biomechanical properties (5, 6). Hoogeman et al. (7) developed a Monte Carlo method for the rectum that relies on probability distributions for only three parameters that are believed to be enough to describe the organ's motion. The distributions were deduced from CT scans in reference patients.

The three models mentioned above can be used to obtain information about the variations in shape and thereby inter-fraction variations in dose distributions and DVHs. They are statistical models that can be used to predict the uncertainty in doses. However, for direct calculation of the cumulative rectal dose distribution from repetitive CT scans, they are not applicable.

In the present study, cumulative doses in the rectum wall are calculated with two different methods. The first is a method presented in this article that uses a simple mathematical model of rectum motion that enables calcula-

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tions of cumulative doses by summing of fraction doses in small volume elements (the element tracking method). The latter is a method published by Dale et al. (1) that uses information from DVHs only (the histogram method). To investigate the necessity of using the more complicated element tracking method, equivalent uniform doses (EUDs) and normal tissue complication probabilities (NTCPs) were calculated for a number of treatment plans for bladder and prostate irradiation using cumulative dose distributions from both these methods. Finally, EUD and NTCP values were also calculated from individual CT scans, and the average values for each treatment plan were included in the comparisons.

MATERIAL AND METHODS

Treatment plans

The patient material included 15 male patients with muscle invading transitional cell urinary bladder cancer, referred for radical conformal radiotherapy at our institution in the period January 2000 to October 2001. They were originally included in a study aiming to decide on target volume margins for conformal bladder irradiation from weekly repeat CT scanning and electronic portal images (2). The bladder patients were treated with a four-field conformal technique that consisted of open anterior and posterior beams and lateral wedge beams. 64 Gy was delivered with 6–15 MV photons.

For further evaluation of the method presented here, the patients were regarded also as prostate cancer patients, and four-field conformal box treatments were set up with 15 MV photon beams. 50 Gy was delivered to the prostate and seminal vesicles, and then a boost of 20 Gy to the prostate. Because of problems with delineation of the prostate, plans were created for only 13 of the 15 patients.

Co-registration of CT scans and rectum delineations

Six to eight weekly CT scans were acquired for each patient in addition to the planning CT scan. The distance between the slices was 5 mm. These were registered with the planning scan using bony structures as described by Muren et al. (2). In each of these CT scans, the rectum was outlined with the first slice below the recto-sigmoid flexure as the superior/cranial limit and the first slice above the anal verge as the inferior/caudal limit. All the rectum delineations were transferred to the planning CT scan using the appropriate transformation parameters.

To further investigate the behaviour of the different methods, the rectum delineations were translated a random distance between -5 and $+5$ cm in the lateral direction (different distances for all scans), and all calculations described below were repeated.

The dose matrices, the CT data and the volume of interest (VOI) data were exported from the Helax TMS treatment planning system (v. 6.0.2; Nucleotron, Uppsala, Sweden), in the form of DICOM files, to a standard PC. All the subsequent file handling and calculations were performed with software written in IDL (Interactive Data Language).

For each individual CT slice, the elements in the dose matrix that corresponded to the rectum wall as indicated in the different rectum contours had to be identified. The inner contours of the rectum walls were generated from the outer contour delineations. This was done twice using two different assumptions about the thickness of the wall: (1) Constant thickness and (2) constant cross-sectional area. When the second assumption was used, the length of the circumference was found, and the thickness was calculated as the area divided by this length. The cross-sectional area was set equal to the mean delineated rectum wall area determined by Meijer et al. (8), 3.6 cm^2. It was shown that the choice of assumption about the wall thickness had only a very small impact on the results, and only results with constant cross-sectional area are reported. For both assumptions the wall thickness was assumed to have a constant thickness on a given slice.

The sets of elements in the dose matrix that belonged to the rectum wall were identified through a two-step procedure. First, the elements that were inside the outer border were found. Second, the subset of these elements whose distance to the outer border was lower than the chosen thickness was found.

To increase the number of dose elements inside the rectum wall, the dose matrix was rebinned using cubic splines (9), i.e. the side length of the elements in the matrix was reduced. It was found that it was sufficient to reduce the side length to 1 mm.

The element tracking method

Rectal motion assumptions. In order to divide the rectum wall into elements that could be identified in different CT series, two assumptions about rectal motion were made:

1) All parts of the rectum wall remain in the same cranial-caudal position at all times.
2) There are no rotational movements around the axis of the rectum.

The posterior–anterior and lateral movements were unconstrained, and the rectum wall could be stretched to give a varying volume of the interior.

Geometrical division of the rectum. Following the ideas of Meijer et al., the rectum wall was given a representation with two parameters (8). The first of these, z, was the position along an axis parallel with the scanning direction. The second parameter was the angle, θ around an axis going through the centre of mass (CM) of the rectum wall in a plane perpendicular to the z axis. The purpose of using the angular parameter was to avoid the problem of irregular curvature on the circumference of the rectum.

The parameter space was divided into a set of rectangular elements, $\lfloor z_i \rightarrow z_i + \Delta z,\ \theta_j \rightarrow \theta_j + \Delta\theta \rfloor$. For simplicity, the values of the z_i's were set equal to the positions of the CT slices in the scanning direction. The resulting geometrical volumes are illustrated in Fig. 1.

Calculations of doses in sub-elements of the rectum wall. The CM of the rectum wall was calculated for each CT slice, and the angles, θ, around these points were found for each voxel. The circumference was divided into 24 angular bins, and the elements of the dose matrix that had been identified as belonging to the rectum wall were assigned to the appropriate bins. For each of these bins the mean dose was calculated. In the following, let the mean dose for rectum delineation r, CT slice number s, and angular bin number a, be denoted by $D_{r,s,a}$.

Calculations of cumulative doses. The total physical dose for angular bin number a on slice no. s is given by $D_{s,a} = \Sigma_r D_{r,s,a}$. However, for the purpose of NTCP calculations, the effects of a tissue receiving fraction doses different from the reference fraction dose (2.0 Gy) were included according to the linear quadratic model:

$$D'_{s,a} = \sum_r \frac{\dfrac{\alpha}{\beta} + d}{\dfrac{\alpha}{\beta} + 2.0\ Gy} D_{r,s,a}. \qquad [1]$$

In these calculations, α/β was set equal to 3.9 Gy (10).

As the orientation of the rectum wall varies with regard to the CT scanning direction, the elements in $D'_{s,a}$ actually represent a varying volume. Therefore, for the purpose of calculating EUD and NTCP values, individual weights were assigned to these elements. With an angle, α_s, relative to the CT scanning direction, the volumes are larger with a factor equal to $\cos^{-1}\alpha_s$, and the elements of $D'_{s,a}$ were assigned an appropriate weight $w_s = \cos^{-1}\alpha_s$. The angles were estimated from the calculated CMs of the individual CT slices.

As the number of available CT scans was lower than the total number of fractions in a treatment regime for prostate and bladder patients, $D'_{s,a}$ was multiplied with a factor equal to the ratio between the total number of fractions (32 for bladder and 35 for prostate patients) and the number of available CT scans for each specific patient.

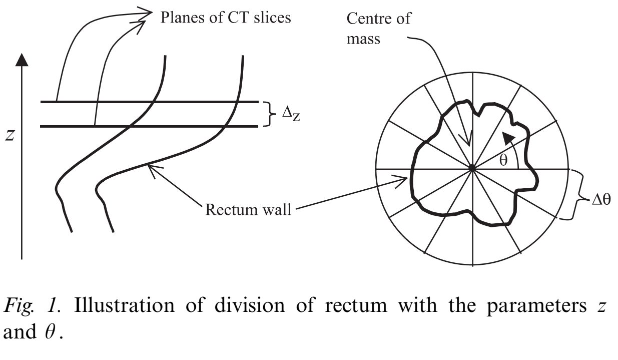

Fig. 1. Illustration of division of rectum with the parameters z and θ.

The histogram method

Cumulative doses were also found using a method proposed by Dale et al. (1). Because of the left–right symmetry in the body and the beam configurations, they assumed that it is the same volume of the rectum that receives the high dose in all fractions (and the same volume that receives the low dose). Therefore, the spatial information is no longer needed, and the necessary information is contained in the dose–volume histograms for each fraction.

The rectum wall is divided into k elements of equal volume. The location of these elements in the rectal wall is not known and an element may consist of several non-adjacent volumes, but it is decided that element k represents the part of the wall that receives the highest dose, element $k-1$ receives the second highest dose, and so forth. For a specific CT scan, doses are assigned to these elements such that a fraction $\frac{i-1}{k}$ of the total volume of the rectal wall received a dose equal to or greater than the dose assigned to element i. An attractive feature of this method is that these doses can be read out from the dose–volume histograms. The total dose to element i was found by summing over all the CT scans. The authors of this article altered this approach slightly by setting the dose to element i equal to the dose that was received by a fraction $\frac{i-0,5}{k}$ of the total volume as this would serve as an estimate of the mean value for element i.

The dose–volume histograms used were generated from the elements of the dose matrix exported from the treatment planning system that were identified as part of the rectal wall, as described earlier in the text. In the same way as with the tracking method, corrections were included for varying rectum wall orientations and for deviations from the reference dose of 2 Gy.

Calculations of EUD and NTCP values

EUD and NTCP values were calculated using the cumulative dose distributions obtained with the tracking method, the cumulative dose distributions obtained with the histogram method of Dale et al., and dose distributions from single CT scans. EUD values were calculated using the formula of Mohan et al. (11):

$$D_{eff} = \left[\frac{\sum_i D_i^{1/n} V_i}{\sum_i V_i} \right]^n \qquad [2]$$

The parameter n was set equal to 0.12 according to Burman et al. (12).

NTCP values were calculated with both the relative seriality (RS) model (13) and the Lyman–Kutcher–Burman (LKB) model (14, 15). The RS model is defined by

$$NTCP = \left(1 - \prod_i [1 - P(D_i)^s]^{v_i}\right)^s \quad [3]$$

where

$$P(D_i) = 2^{-\exp\left(e\gamma\left(1 - \frac{D_i}{D_{50}}\right)\right)}. \quad [4]$$

v_i is the volume fraction of volume element i, while D_i is the corresponding dose. For the organ dependent parameters the values $s = 2{,}0$, $\gamma = 2{,}2$ and $D_{50} = 80$ Gy were used (16, 17).

The LKB model is given by the following equations

$$NTCP = 1/\sqrt{2\pi} \int_{-\infty}^{t} \exp(-t'^2/2)dt' \quad [5]$$

$$t = \frac{D - D_{50}(v)}{m \cdot D_{50}(v)} \quad [6]$$

$$D_{50}(v) = D_{50}(1) \cdot v^{-n} \quad [7]$$

$$v = \frac{V}{V_{ref}} \quad [8]$$

Model parameters were assigned the values $n = 0.12$, $m = 0.15$, and $D_{50} = 80$ Gy (12, 17). v is the relative volume found by the algorithm of Kutcher & Burman (15):

$$V_{eff} = \sum_i V_i (D_i/D_{\max})^{1/n}. \quad [9]$$

In all the formulas above, V_i was substituted by the weight assigned to the elements of the dose matrix. V_{ref} in eq. 8 was set equal to the sum of the weights.

RESULTS

Figure 2 compares EUD and NTCP values for cumulative doses calculated with the tracking method, the histogram method of Dale et al., and finally the mean of the EUD and NTCP values for individual CT scans. Small but systematic differences between the different methods were observed: The values obtained with the histogram method and by averaging over CT scans were consistently larger than those of the tracking method (Table 1). For the EUD values the differences ranged from 0.6% to 1.1%, while they ranged from 3.9% to 11.0% for the NTCP values.

Figure 2 also shows the standard deviations for the individual CT scans. These were considerably larger than the differences between cumulative doses calculated with the different methods, from 3.6% to 4.8% for the EUD values and from 16.3% to 29.7% for the NTCP values (Table 1).

Figure 3 shows DVHs for the patient with the largest variation between EUD values for individual CT scans. Curves are shown for the two different cumulative dose distributions and for dose distributions for individual CT scans. The difference between the DVHs for the cumulative dose distributions, derived with the two different methods, was small, while the differences between individual scans were substantial.

The introduction of random translations of the rectum delineations led to a large increase in the differences between the results of the different methods (Fig. 4 and Table 2). The tracking method still gave the lowest results, and the relative differences grew to over 100% for the prostate plans. For the bladder plans the increase was up to 27%. The standard deviations between individual CT scans also became considerably larger.

In accordance with Muren et al. (18), Fig. 2 demonstrates that the RS model gives higher NTCP estimates than the LKB model for the dose levels in these calculations. Interestingly, the relative differences between results for individual patients were not the same for the two NTCP models. In fact, if the patients were ordered after ascending NTCP values, the orderings may be different for the RS and the LKB model. For example, patient 2 of the prostate patients had a lower value than patients 5 and 6 with the RS model while both patients 5 and 6 had lower values than patient 2 with the LKB model. The orderings for EUD values were of course the same as for the LKB model, as the LKB NTCP value may be calculated as a function of the EUD value.

DISCUSSION

The main finding of this investigation is that there were only small differences between the EUD and NTCP values obtained with the tracking method and the histogram method of Dale et al., and these were also quite similar to the EUDs and NTCPs derived by averaging over individual CT scans. This finding relies on the assumption that there are no cranial–caudal movements. Such movements could have an effect on the cumulative doses calculated with the tracking method.

Hoogeman et al. developed a Monte Carlo method with the purpose of giving realistic movements of the rectum (7). In the underlying model, it was assumed that the anus was in a fixed position. It was also assumed that the movements of the upper part were limited by fixing a virtual extension of 1 cm length. The projected cross-sectional areas and the corresponding centre positions were allowed to vary according to measured probability density functions. The movements in the lateral positions were found to be very small, and were not included in the simulations. Overall, this is a model that very much resembles the model of this work.

In the above-mentioned study, it was revealed that there were variable extensions on the upper anterior side of the rectum, and that the model underestimated these. If these extensions take place perpendicularly to the axis of the rectum, this means that because the axis of the rectum may have a rather large angle with respect to the scanning direction (up to 45°), parts of the rectum undergo non-

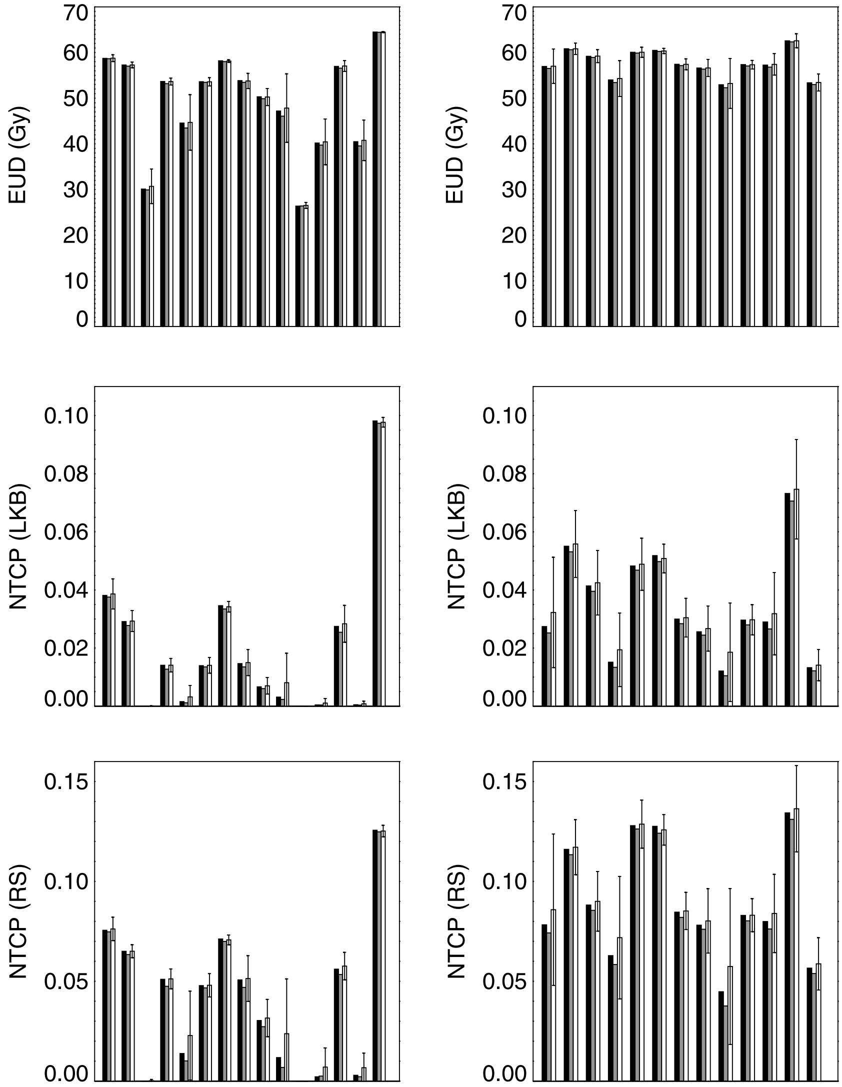

Fig. 2. Comparison of EUDs and NTCPs of the rectal wall for different cumulative dose calculation methods. Left panel gives results for bladder treatment plans while right panel gives results for prostate treatment plans. In each diagram, columns in solid black represent results for the histogram method, the hatched columns are for the tracking method, and the white columns show the mean of the values for individual CT scans (error bars show standard deviations). The two upper rows give EUD calculations while the middle and lower rows give NTCP calculated with the relative seriality model and the LKB model, respectively.

negligible movements in the cranial–caudal direction. The first assumption of the tracking method might therefore be violated, and the accuracy in the calculated cumulative dose is limited. However, in the same study it was found that the variations in the DVHs from the Monte Carlo method were only slightly smaller than the variations between the DVHs of the repeat CT scans. In conclusion, this must imply that the underestimation of the movements of the upper anterior parts of the rectum is not of great importance for the shape of the DVHs.

The increase in the differences between the methods when random translations of the rectum delineations were introduced indicates that there is an overestimation in the results of the histogram method of Dale et al. and the method of averaging over CT scans. Because the translations are in the left–right direction with no organ deformation, the changes in the results for the tracking method must be correct. As there is an *increase* in the *difference* between the results, this indicates that the models that do not use element tracking did not give results with a sufficient decrease. This is also supported by the fact that the increase was larger for the prostate plans than for the bladder plans. The typical high dose volume is much wider for the bladder plans than for the prostate plans, and therefore the chance of a rectum delineation coming outside this volume is smaller. These observations indicate that the tracking

Table 1

The first column gives the relative difference between the mean values for the histogram method and the tracking model. The second gives the relative difference between the mean values of the averages over each patient's CT scans and the mean value for the tracking method. The last column gives the mean standard deviations for the individual scans normalized to the patient mean value

	Histogram method vs. tracking method (%)	Average over CT scans vs. tracking method (%)	CT scan standard deviation (%)
Prostate cancer			
EUD	0.6	0.7	3.6
NTCP (RS)	3.9	7.6	20.3
NTCP (LKB)	5.4	11.0	29.7
Bladder cancer			
EUD	0.8	1.1	4.8
NTCP (RS)	4.8	10.6	18.9
NTCP (LKB)	4.0	7.3	16.3

method presented in this paper should be used with treatment plans that are less symmetric or with narrower beams, which may be the case for IMRT plans.

For the purpose of relating damage to the rectum wall with a known location to the corresponding dose, it is more difficult to discuss the tracking method. To validate the model on the sub-element level, it will be necessary to do physical measurements with for example TLDs, or one could check the tracking by introducing markers in the tissue that are easily detectable in CT scans.

Another source of inaccuracy is of course that of the dose distribution calculated by the treatment planning system. It is calculated once with only the planning CT as input, and the true dose distribution will change as the patient geometry changes throughout the course of treatment, and as a result of set-up errors. However, if a CT examination is done once for each fraction, re-planning could be done using updated CT data.

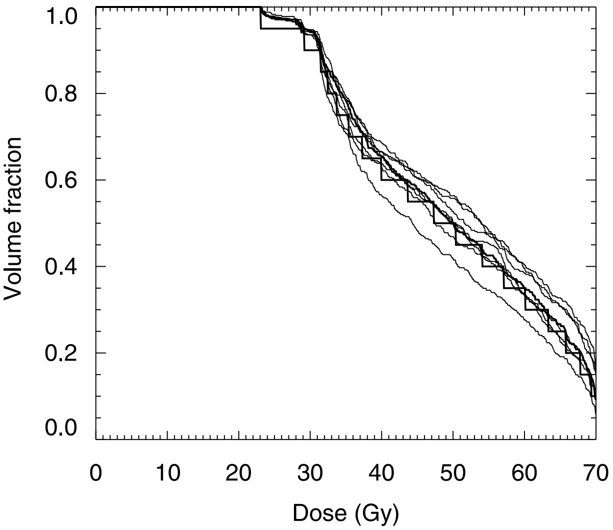

Fig. 3. DVHs for cumulative dose distributions calculated with the tracking method (smooth thick line), the histogram method (staircase thick line), and DVHs calculated from individual CT scans, for the patient with the largest variation between CT scans.

This study has also clearly demonstrated the different behaviour of the two NTCP models. Overall, the RS model gives estimates that are larger by a factor of two than the estimates from the LKB model, demonstrating the limited validity of absolute NTCP estimates. What is more surprising is that the sensitivity of the models to the shape of the DVHs must also be very different. This conclusion can be drawn as the ordering of the patients with regard to NTCP values are different with the two models. This means that the choice of NTCP model may be of importance for evaluations of different treatment configurations by means of relative NTCP values. At any rate, when a choice of NTCP model is done, there is no doubt that cumulative doses give much more reliable results than estimates based on individual CT scans. The variations between scans are much larger than the uncertainties resulting from the choice of method.

An alternative to the method presented here is the biomechanical model published by Yan et al. (19). Their approach is to mark fiducial points on the boundary of the organ as primary information about boundary conditions for the solution of the differential equations that contain the characteristics of the tissues. Together with assumptions about elasticity and compressibility, these data allow for calculations of the positions of individual elements also at arbitrary moments of time. The strength of this method is that it allows for any kind of movements and deformations of the organ in question. However, for the rectum, this means that one has to be able to track the positions of the fiducial markers with good accuracy. In addition, this model is much more computationally intensive.

The DVH of the rectum with filling has traditionally been used instead of the dose histogram for the rectum wall. Only recently have investigators started to undertake the extra work of delineating the rectum wall so that dose histograms of the rectum wall can be found (20–22). The scope of this work was calculations of the cumulative rectum *wall* doses, and the relations between these different dose histograms are not discussed here. This topic has, however, been investigated by Fiorino et al. (23), and a Monte Carlo study is under way in our department that will give further insight on these matters.

CONCLUSIONS

A method for calculation of cumulative doses in the rectum from repetitive CT scans has been proposed. It is based on simple assumptions about rectum motion that allow for tracking of individual volume elements in repetitive CT scans, and thereby direct summation of doses. With regard to calculations of rectum EUDs and NTCPs, it has been shown that tracking of volume elements of the rectum is not

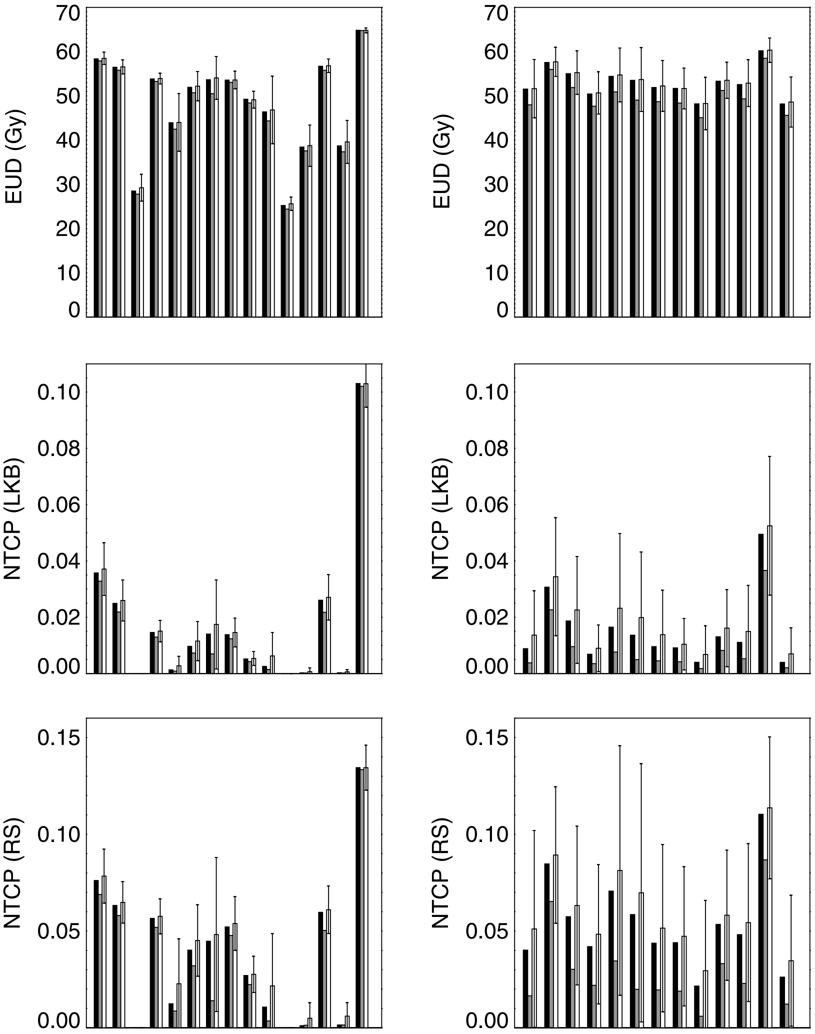

Fig. 4. EUD and NTCP values after random translations of the rectum delineations. Organization of diagrams is the same as in Fig. 2.

Table 2

Results with random translations of the rectum delineations. The first column gives the relative difference between the mean values for the histogram method and the tracking model. The second gives the relative difference between the mean values of the averages over each patient's CT scans and the mean value for the tracking method. The last column gives the mean standard deviations for the individual scans normalized to the patient mean value

	Histogram method vs. tracking method (%)	Average over CT scans vs. tracking method (%)	CT scan standard deviation (%)
Prostate cancer			
EUD	5.9	6.3	9.7
NTCP (RS)	80.6	104.2	70.0
NTCP (LKB)	70.3	112.7	87.1
Bladder cancer			
EUD	2.2	2.8	6.4
NTCP (RS)	17.4	26.9	32.6
NTCP (LKB)	11.8	18.9	30.3

important with beam configurations that are approximately symmetric in the left–right and anterior–posterior directions. With bladder and prostate treatment plans, the histogram method of Dale et al. and averaging over dose-based quantities for individual CT scans give almost similar results. With less symmetric situations, this study documents that tracking of volume elements is necessary, and that the tracking method gives results of better accuracy than other approaches.

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REFERENCES

1. Dale E, Hellebust TP, Skjønsberg A, et al. Modeling normal tissue complication probability from repetitive computed tomography scans during fractionated high-dose-rate brachytherapy and external beam radiotherapy of the uterine cervix. Int J Radiat Oncol Biol Phys 2000; 47: 963–71.
2. Muren LP, Smaaland R, Dahl O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. Radiother Oncol 2003; 69: 291–304.
3. Yan D, Xu B, Lockman D, et al. The influence of interpatient and intrapatient rectum variation on external beam treatment of prostate cancer. Int J Radiat Oncol Biol Phys 2001; 51: 1111–9.
4. Mageras GS, Kutcher GJ, Leibel SA, et al. A method of incorporating organ motion uncertainties into three-dimensional conformal treatment plans. Int J Radiat Oncol Biol Phys 1996; 35: 333–42.
5. Fontenla E, Pelizzari CA, Roeske JC, et al. Using serial imaging data to model variabilities in organ position and shape during radiotherapy. Phys Med Biol 2001; 46: 2317–36.
6. Fontenla E, Pelizzari CA, Roeske JC, et al. Numerical analysis of a model of organ motion using serial imaging measurements from prostate radiotherapy. Phys Med Biol 2001; 46: 2337–58.
7. Hoogeman MS, Van Herk M, Yan D, et al. A model to simulate day-to-day variations in rectum shape. Int J Radiat Oncol Biol Phys 2002; 54: 615–25.
8. Meijer GJ, Van den Brink M, Hoogeman MS, et al. 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 Radiat Oncol Biol Phys 1999; 45: 1073–80.
9. Pratt WK. Image sampling and reconstruction. In: Digital image processing. New York: Wiley; 1991. p. 91–121.
10. Deore SM, Shrivastava SK, Supe SJ, et al. Alpha/beta value and importance of dose per fraction for the late rectal and recto-sigmoid complications. Strahlenther Onkol 1993; 169: 521–6.
11. Mohan R, Mageras GS, Baldwin B, et al. Clinically relevant optimization of 3-D conformal treatments. Med Phys 1992; 19: 933–44.
12. Burman C, Kutcher GJ, Emami B, et al. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991; 21: 123–35.
13. Källman P, Ågren A, Brahme A. Tumor and normal tissue responses to fractionated nonuniform dose delivery. Int J Radiat Biol 1992; 62: 249–62.
14. Lyman JT. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl 1985; 8: S13–9.
15. Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation – the effective volume method. Int J Radiat Oncol Biol Phys 1989; 16: 1623–30.
16. Ågren-Cronqvist A-K. Quantification of the response of heterogeneous tumours and organized normal tissues to fractionated radiotherapy. Department of Medical Radiation Physics. Stockholm: Stockholm University; 1995.
17. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21: 109–22.
18. Muren LP, Jebsen N, Gustafsson A, et al. Can dose–response models predict reliable normal tissue complication probabilities in radical radiotherapy of urinary bladder cancer? The impact of alternative radiation tolerance models and parameters. Int J Radiat Oncol Biol Phys 2001; 50: 627–37.
19. Yan D, Jaffray DA, Wong JW. A model to accumulate fractionated dose in a deforming organ. Int J Radiat Oncol Biol Phys 1999; 44: 665–75.
20. Lebesque JV, Bruce AM, Kroes APG, et al. Variation in volumes, dose–volume histograms, and estimated normal tissue complication probabilities of rectum and bladder during conformal radiotherapy of T3 prostate cancer. Int J Radiat Oncol Biol Phys 1995; 33: 1109–19.
21. Boersma LJ, van den Brink M, Bruce AM, et al. Estimation of the incidence of late bladder and rectum complications after high-dose (70–78 Gy) conformal radiotherapy for prostate cancer, using dose-volume histograms. Int J Radiat Oncol Biol Phys 1998; 41: 83–92.
22. Jackson A, Skwarchuk MW, Zelefsky MJ, et al. Late rectal bleeding after conformal radiotherapy of prostate cancer (II): volume effects and dose–volume histograms. Int J Radiat Oncol Biol Phys 2001; 49: 685–98.
23. Fiorino C, Gianolini S, Nahum AE. A cylindrical model of the rectum: comparing dose-volume, dose-surface and dose-wall histograms in the radiotherapy of prostate cancer. Phys Med Biol 2003; 48: 2603–16.