CLINICAL INVESTIGATION

MODELING NORMAL TISSUE COMPLICATION PROBABILITY FROM REPETITIVE COMPUTED TOMOGRAPHY SCANS DURING FRACTIONATED HIGH-DOSE-RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY OF THE UTERINE CERVIX

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Purpose: To calculate the normal tissue complication probability (NTCP) of late radiation effects on the rectum and bladder from repetitive CT scans during fractionated high-dose-rate brachytherapy (HDRB) and external beam radiotherapy (EBRT) of the uterine cervix and compare the NTCP with the clinical frequency of late effects.

Methods and Materials: Fourteen patients with cancer of the uterine cervix (Stage IIb–IVa) underwent 3–6 (mean, 4.9) CT scans in treatment position during their course of HDRB using a ring applicator with an Iridium stepping source. The rectal and bladder walls were delineated on the treatment-planning system, such that a constant wall volume independent of organ filling was achieved. Dose–volume histograms (DVH) of the rectal and bladder walls were acquired. A method of summing multiple DVHs accounting for variable dose per fraction were applied to the DVHs of HDRB and EBRT together with the Lyman–Kutcher NTCP model fitted to clinical dose–volume tolerance data from recent studies.

Results: The Dmean of the DVH from EBRT was close to the Dmax for both the rectum and bladder, confirming that the DVH from EBRT corresponded with homogeneous whole-organ irradiation. The NTCP of the rectum was 19.7% (13.5%, 25.9%) (mean and 95% confidence interval), whereas the clinical frequency of late rectal sequelae (Grade 3–4, RTOG/EORTC) was 13% based on material from 200 patients. For the bladder the NTCP was 61.9% (46.8%, 76.9%) as compared to the clinical frequency of Grade 3–4 late effects of 14%. If only 1 CT scan from HDRB was assumed available, the relative uncertainty (standard deviation or SD) of the NTCP value for an arbitrary patient was 20–30%, whereas 4 CT scans provided an uncertainty of 12–13%.

Conclusion: The NTCP for the rectum was almost consistent with the clinical frequency of late effects, whereas the NTCP for bladder was too high. To obtain reliable (SD of 12–13%) NTCP values, 3–4 CT scans are needed during 5–7 fractions of HDRB treatments.

Normal tissue complication probability, Dose–volume histogram, Carcinoma of the uterine cervix, High-dose rate brachytherapy, External beam radiotherapy.

INTRODUCTION

Combined high-dose-rate brachytherapy (HDRB) and external beam radiotherapy (EBRT) of carcinoma of the uterine cervix, Stage II–IV, is the standard treatment in many hospitals (1). EBRT is usually given with large fields resulting in a homogeneous dose to the pelvis, whereas the heterogeneous dose distribution of HDRB gives rise to large individual variations in the dose to the tumor and organs at risk (OR), due to differences in anatomy (1). The rectum and the bladder are at highest risk for late sequelae after this treatment (1–3). Reliable estimates of the normal tissue complication probability (NTCP) would facilitate improved radiotherapy without greatly increasing the risk of unacceptably high complication rates. So far, risk assessment has been based on point doses (1, 3), such as the ICRU bladder and rectum reference point doses (4), whereas a study has indicated that using the complete dose distribution of the OR would provide more accurate risk estimates (5). Calculations of NTCP using dose–volume histograms (DVH) as input have been performed in EBRT studies in the last decade (6). The DVH is derived from the three-dimensional (3D) dose distribution available from treatment-planning systems (TPS) based on multiple CT images. Applying NTCP models to DVHs obtained from a combined HDRB and EBRT treatment, however, requires further investigation: (1) Is a single pretreatment CT scan sufficient to

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provide reliable DVHs, reflecting the entire fractionation regime, or should several CT scans during a course of fractionation be performed? This issue applies to EBRT as well, but may be of particular concern in HDRB, where the dose distribution in the pelvis is highly heterogeneous and variation in organ size and position may influence on the DVH considerably (1), (2) Even if multiple-dose distributions are obtained during a course of fractionated treatment, how should the data to acquire a scalar NTCP be combined? (3) NTCP models have so far solely been applied to EBRT DVHs because of their accessibility from the TPS, which is standard equipment in a modern radiotherapy department. As DVHs from HDRB dose distributions become available, it is an open question whether the models need modifications before incorporating such extremely heterogeneous dose distributions.

METHODS AND MATERIALS

Radiotherapy and repetitive CT scans

Fourteen patients with cancer of the uterine cervix (stage Ib–Ia) underwent 3–6 (mean 4.9) CT scans (3–5 mm slice thickness, axial image matrix resolution 0.8–0.9 mm per pixel) in treatment position during their course of HDRB. Treatment was given with a MicroS-electron (Nucletron BV) using a ring applicator of plastic/carbon fiber with an iridium stepping source. The HDRB doses prescribed were 5 × 4.2 Gy or 7 × 4.2 Gy to point A during 6–7 weeks (Table 1). Dose planning was performed on the Plato Planning System (Nucletron BV). During the same period the patients received EBRT to the pelvis according to tumor size. Patients with tumors of 40–80 mm were given Type A treatment (Table 1), those with tumors larger than 80 mm, Type B treatment, and those with para-aortic lymph node involvement received the Type C. EBRT was planned with TMS (Helax) based on CT scan (5-mm slice thickness) before treatment. EBRT was given as a 4-field box technique with 2 large AP fields and 2 smaller lateral fields. For the Type A and B treatment the two lateral fields were blocked or MLC shaped to conform to the target volume A with 10-mm margin (Table 1). The AP fields were blocked or MLC shaped and limited by anatomical structures:

- Upper border: Between L₄ and L₅
- Lateral borders: 20-mm lateral to linea terminalis where superior aperture has its largest dimensions
- Lower borders: 10-mm below obturator foramen.

All fields were weighted to achieve the prescribed doses to the target volumes, usually 42–44% for the AP fields and 5–7% for the lateral fields. For the Type C treatment, the 4 fields were weighted equally. EBRT was given with linear accelerators using 15-MV photons. HDRB and EBRT given on the same day were separated by at least 6 h. The patients were instructed to empty the bladder before CT examinations and treatments. An informed consent was obtained from the patient before inclusion in the study.

Eleven of 14 patients included in this study were treated according to the Nordic Cervical Cancer (NOCECA) protocol (7). Preliminary results indicate an actuarial 3-years (200 patients, observation time > 24 months, median 53 months) morbidity rate of 13% and 14% [RTOG/EORTC Grade 3–4 (8)] for rectum and bladder, respectively (7). 25% of the patients experienced Grade 3–4 complications. At our hospital, the patients included in the NOCECA protocol were prescribed 6 or 8 fractions of intracavitary treatment. To lower the complication frequency at our institution, the number of fractions was reduced to 5 or 7 in September 1996. For the NTCP calculations we therefore decided to set the number of fractions to 6 or 8 to be able to compare the NTCP estimates with the observed clinical complication frequency.

Delineation of the organs at risk

The external and internal contours of the rectum and bladder were carefully delineated by one of the authors (E.D.). The DVH of a wall volume was acquired by subtracting geometrically the DVH of the filling (without wall tissue) from the DVH of the whole organ (including filling and wall tissue). The delineation procedure for the rectum was partly adopted from Lebesgue et al. (9, 10): The cranial border of the rectum was defined as the position where the rectum turned horizontally into the sigmoid colon, using the caudal border of the sacroiliac joint as a landmark. The caudal border of the rectum was defined as 20–25 mm cranial to the caudal border of the anal sphincter muscles. A convenient landmark in this region is the caudal border of os coccygis as the rectum is attached with connective tissue to this bone.
The resulting caudocranial length of the rectal tube was 100.3 mm ± 7.1 mm (mean ± SD). The delineation of the bladder was most often straightforward but were complicated in a few cases by invasive malignant tissue. The internal contours of the rectum and bladder were sometimes difficult to delineate due to similar CT numbers of the wall tissue and filling. As both organs are hollow and elastic, i.e., the wall becomes thinner as filling increases, the following assumptions were made: (1) The volume of the wall tissue is constant for one patient (independent of filling). (2) The volume of the wall tissue in one CT slice is approximately equal to the wall volumes in adjacent CT slices. Therefore, in CT slices with unclear visualization of the wall tissue, the internal contours were delineated to achieve a wall volume (readily available from the treatment-planning system) approximately equal to the wall volumes from adjacent CT slices, or corresponding CT slices from other CT scans of the same patient. For 12 of 14 patients the resulting total wall volumes were nearly constant regardless of filling. (This was not achieved for 2 patients due to technical difficulties with a computer tape recorder.) The wall volumes were normalized with each patient’s mean wall volume. The constancy of the wall volumes was reflected by the significantly lower standard deviation (SD); 17.0% and 16.1% for the rectal and bladder wall volumes, respectively, as compared to 25.9% and 38.4% for the whole-organ volumes \( (p < 0.001) \).

To estimate the reproducibility of the delineation procedure, 3 patients (6, 6, and 5 CT scans) were chosen at random 3 months after the first planning. The structures were redelineated by the same author, and the resulting relative (compared to the wall volumes of the first delineation) differences between the wall volumes were calculated. The delineation reproducibility was measured by the SDs of these relative differences and were 16.5% and 14.1% for the rectal and bladder wall volumes, respectively. The total SDs of the wall volumes (previous paragraph) did not differ significantly from the delineation SDs, which indicated that the variation in wall volumes between CT scans were explained by the uncertainty in delineation (rectum; \( p = 0.94 \), bladder; \( p = 0.57 \)). The reproducibilities of delineation of the whole organs including filling were 9.9% and 7.9%. We also looked at the reproducibility of the doses of the DVH (HDRB) and found SDs (calculated from the relative differences between the first and second delineation) of approximately 7% (rectal wall) and 10% (bladder wall) in the high-dose region.

**DVHs and estimating NTCPs**

In this work DVHs from several HDRB treatments were available. In Fig. 1 a typical DVH of the rectal wall is shown, demonstrating the heterogeneous dose distribution resulting from HDRB. DVHs from the EBRT planning were also calculated. To estimate the effect of the total treatment on 1 patient, the multiple cumulative DVHs available were summed according to:

\[
D_{\text{tot}}(v) = \sum_{j=1}^{N} \lambda(d_j(v)) \cdot n_j \cdot d_j(v)
\]

\( d_j(v) \) is the minimum dose per fraction given to the volume fraction \( v \), \( n_j \) is the fraction number of treatment \( j \), \( N \) is the total number of different treatments, \( D_{\text{tot}} \) is the total dose for the whole treatment given with 2 Gy per fraction and

![Fig. 1. Cumulative dose–volume histograms (DVHs) of 1 of the patients after 1 fraction of high-dose-rate brachytherapy (HDRB), after total HDRB treatment consisting of 8 × 4.2 Gy, after external beam radiotherapy (EBRT) treatment of 25 × 2 Gy alone and the total treatment (HDRB and EBRT) for a) rectum and b) bladder. The dose axis values have been corrected with the linear–quadratic formula so that each dose is assumed given in 2 Gy fractions. Dose–volume tolerance levels from the Appendix are shown (filled circles).](image-url)
is the correction factor according to the linear–quadratic (L–Q) formalism, transforming a total dose \( n \cdot d \) given in fractions of \( d \) to \( \alpha \cdot n \cdot d \) given in fractions of 2.0 Gy (11). Data on the \( \alpha/\beta \) value for the rectum and bladder in the literature are sparse. In the study of Deore et al., \( \alpha/\beta \) was estimated to be 3.9 Gy ± 0.7 Gy for the human rectum with bowel stricture/perforation as endpoints (12). A study on mice of Stewart et al. indicated \( \alpha/\beta = 6 \) Gy ± 1 Gy for the bladder with increased urination frequency/reduced capacity as endpoints (13). The \( \alpha/\beta \) was, therefore, set to 3.9 Gy (rectum) and 6 Gy (bladder), but the calculations revealed negligible differences (±1%) in the NTCP values for \( \alpha/\beta \) ratios within the above-mentioned uncertainties, consistent with other studies (14).

As not all of the DVHs from HDRB were available, these were estimated by averaging the accessible DVHs according to:

\[
d(v) = \frac{1}{M} \sum_{j=1}^{M} \lambda(d_j(v)) \cdot d_j(v)
\]

where \( M \) is the number of available DVHs from HDRB. The calculations were performed for \( v = 0–100\% \) in steps of 5%. The assumption of Eq. 1 is that the same volume fraction, \( v \), is irradiated with the dose \( d(v) \) (or higher) at each treatment \( j \). \( D_{\text{tot}}(v) \) is an upper boundary of the true total dose given to a small \( v \). The NTCP was calculated according to the Lyman–Kutcher (LK) model, which summarized in 2 steps comprises: (1) The total DVH (Eq. 1) is entered into the DVH reduction algorithm of Kutcher et al. (15), reducing an arbitrary DVH to one corresponding with irradiating the volume fraction, \( v_{\text{eff}} \), with the dose, \( D_{\text{max}} \). (2) \( D_{\text{max}} \) and \( v_{\text{eff}} \) are entered into the Lyman NTCP formula (6) and an NTCP is obtained. Traditionally, the rather crude model parameters of Burman et al. (16) have been applied when calculating NTCP values with the LK model. Recent progress in the work with acquiring dose volume tolerance levels for rectum (17, 18) and bladder (19) have made it necessary to estimate new parameter values (Appendix).

**Statistics**

DVHs were exported to a UNIX workstation for analysis. Calculations were performed with routines written in Interactive Data Language 5.0 (Research Systems Inc., Boulder, CO). Confidence intervals (95%) for \( \mu \) were calculated from the \( t \) distribution. Comparisons of standard deviations (SD) were performed with the F-test.

### RESULTS

In Fig. 1 DVHs for HDRB, the total HDRB resulting from the summation of 8 HDRB DVHs, the EBRT and the total treatment (Eq. 1) are shown. Descriptive statistics \( D_{\text{mean}} \) and \( D_{\text{max}} \) of the DVHs were calculated and compared for the rectum and bladder (Table 2). The finding that \( D_{\text{mean}} \) and \( D_{\text{max}} \) for the EBRT both were close to the central axis dose (100%) indicated that the DVHs for the EBRT represented homogeneous whole-organ irradiation. The \( D_{\text{mean}} \) of the bladder after EBRT was significantly higher than for the rectum (\( p = 0.009 \), two-sided paired \( t \) test). This combined with a slightly higher \( D_{\text{mean}} \) of the bladder after HDRB (\( p = 0.34 \)) gave a significantly higher \( D_{\text{mean}} \) for the total treatment (HDRB + EBRT) for bladder (\( p < 0.001 \)).

The calculated mean NTCP for rectum was somewhat higher than the clinical frequency of Grade 3–4 late effects (\( p = 0.04 \)), while the mean NTCP for bladder was markedly higher (\( p < 0.001 \)) than the observed clinical incidence of Grade 3–4 late effects (Table 3). The impact of parameter uncertainties was also investigated (Table 4 and Appendix), and could explain that the NTCP of the rectum was too high compared with the clinical incidence. The NTCP of the bladder could not be explained by the parameter uncertainties. Variation of the \( m \) parameter, determining the slope of the NTCP curve, had insignificant influence on the NTCP. However, the uncertainties of the volume parameter, \( n \), and the whole-organ tolerance dose \( TD_{50}(1) \), changed the NTCP significantly as can be observed from the 95% C.I. (Tables 3 and 4).

The importance of acquiring several CT scans during a

| Table 2. Statistics (mean ± 95% CI) from HDRB, EBRT, and total (HDRB + EBRT) DVHs; all DVHs were LQ corrected (Eq. 2); \( D_{\text{max}} \) is the maximum dose to the high-dose 5% volume |
|-------------------------------------------------|-------------|-------------|
| Rectum                                         | Bladder     |
| Dose/prescribed dose ± 95% CI (%)              | Dose/prescribed dose ± 95% CI (%)              |
| \( D_{\text{mean}} \) (HDRB)                    | 20.7 (17.7, 23.8) | 23.3 (19.6, 27.0) |
| \( D_{\text{max}} \) (HDRB)                    | 63.2 (53.4, 72.9) | 69.7 (57.9, 81.6) |
| \( D_{\text{mean}} \) (EBRT)                   | 88.4 (84.4, 92.3) | 94.7 (92.7, 96.7) |
| \( D_{\text{max}} \) (EBRT)                    | 102.7 (101.5, 103.8) | 102.0 (101.3, 102.7) |
| \( D_{\text{mean}} \) (tot)                    | 56.8 (53.3, 60.2) | 63.3 (60.3, 66.3) |
| \( D_{\text{max}} \) (tot)                     | 84.3 (80.0, 88.6) | 87.9 (82.6, 93.2) |

| Table 3. Calculated mean NTCP for 14 cervix cancer patients compared with the clinical incidence of Grade 3–4 late effects for approximately 200 patients (7); the parameters of the Lyman–Kutcher model were \( n = 0.06 \), \( m = 0.15 \) and \( TD_{50}(1) = 80 \) Gy for rectum and \( n = 0.13 \), \( m = 0.11 \) and \( TD_{50}(1) = 62 \) Gy for bladder (Appendix) |
|-----------------|-------------|-------------|
| Rectum          | Bladder     |
| NTCP (%) (95% CI) | 19.7 (13.5, 25.9) | 61.9 (46.8, 76.9) |
| Clinical incidence (%) | 13 | 14 |
course of fractionated HDRB treatment for improving the precision in calculated NTCP is indicated in Fig. 2. If only the first CT scan was used as the basis for the calculations, the SD of the relative deviations from the “true” NTCPs (calculated from 6 CT scans of 6 patients) was 20% (12%, 49%) (mean and 95% CI) and 30% (19%, 73%) for the rectum and bladder, respectively. As the number of CT scans were increased, the deviation decreased. Four CT scans provided a precision of 13% (8%, 33%) and 12% (7%, 29%).

The LK model was fitted to tolerance data from 3 recent studies (18–20). In the clinical routine, the cumulative DVH curve may quickly be compared with dose–volume tolerance data (filled circles in Fig. 1). An NTCP model should give the same results as a simple check-up. The patients were ranked into 4 categories according to the number of dose-volume thresholds exceeded and the categories were correlated with NTCP (Fig. 3). For bladder DVHs, 0 tolerance levels exceeded corresponded to an NTCP of 0–40%, 1 tolerance level, 40–60%, and 2–3 tolerance levels, 60–100%. For the rectum DVHs, only the tolerance level (D = 76 Gy, v = 5%) were exceeded (9 of 14 patients) and the NTCP was 15–40% for this group.

**DISCUSSION**

This study is the first to combine the highly heterogeneous dose–volume distributions from HDRB with that of EBRT, to obtain a single NTCP value for ORs of each patient. The method is easy to use and might be of value to more than a limited group of specialists. As CT scans from 3–6 of 5–7 brachy treatments were acquired, errors in the dose–volume distribution due to organ movement and filling were practically eliminated. The limited 3D information of the EBRT, i.e., only one pretreatment CT scan available, was potentially a problem. However, the organ dose distributions were nearly homogeneous, resulting in mean doses close to the central-axis dose. Hence, our method of summing cumulative DVHs of the EBRT with the HDRB DVH is justified.

How to combine multiple highly heterogeneous dose–volume distributions from HDRB is an open question. The ideal method is probably to match the organ 3D structures by labourous techniques as suggested by some groups (20, 21). The aim of tracing a point of an organ from one treatment to the next may be compromised by the precision of organ delineation on the treatment planning system (TPS) and of the warping method in question. As long as such tools are not available on the TPS, the method will turn out to be extremely labor-demanding to establish for most groups in the field. The method presented here is considerably more simple. The cumulative DVHs were added to-

<table>
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<th>Parameter value</th>
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<td>23.3</td>
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<tr>
<td>TD_{so}(1) = 86 Gy</td>
<td>10.8</td>
<td>TD_{so}(1) = 67 Gy</td>
<td>39.4</td>
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Fig. 2. The standard deviation (SD) of the relative deviations of normal tissue complication probabilities (NTCPs) (95% CI) from the “true” NTCPs (based on 6 CT scans) as a function of the number of CT scans used as a basis for the calculations for bladder. The curve is very similar for rectum (data not shown). Six patients underwent 6 CT scans.

Fig. 3. NTCP as a function of the number of dose–volume tolerance levels (Appendix) exceeded for bladder.
A small volume fraction was set to 5%. There is consensus that a volume smaller than 1.5–2.0 cm³ is clinically negligible (4) which is 3–4% of the wall volume, both for the rectum (48.4 cm³ (38.8 cm³, 58.0 cm³), and bladder 60.1 cm³ (50.1 cm³, 70.0 cm³) (mean and 95% C.I.). In addition, as the dose decreased monotonously with increasing distance from the HDRB applicator, the method should provide reasonable estimates of the total DVH, at least for the moderate doses (Fig. 4). For the small, high-dose part of the organ, it is crucial that the isodose intersects approximately the same part of the organ for each fraction. If this is not so, different parts of the organ would receive the highest doses for each fraction and the present method would provide a too large estimate of the highest doses to the OR. To counteract the problem of an extreme high-dose tail building up as a substantial number of DVHs were added, the dose distribution over the ORs varied as well. However, the dose decreased monotonously with increasing distance from the HDRB applicator.

Another aspect is the OR’s functional architecture characterized by the LK model’s volume parameter, \( n \) (22). A small \( n \) corresponds to an OR organised serially, reflecting sensitivity of high doses to relatively small volumes, such as the rectum \( n = 0.06 \). A larger \( n \) implies that the OR is organized in parallel, e.g., lung \( n = 0.87 \) requiring that a larger fraction of the organ (large threshold volume) is irradiated before injury is manifest. One would anticipate that a serially organized organ should develop side effects after HDRB to a greater extent than an organ with a parallel architecture, because of the high doses of the DVH. As the volume involved may be clinically negligible, this may result in uncertainties in the estimated NTCP values, especially for serial organs. Moreover, if the maximum doses are delivered to different volumes for each HDRB fraction in an unpredictable way, it will be difficult to detect a correlation between NTCP and radiation side effects.

In this report, calculated NTCP values were compared with clinical complication frequencies. The NTCP of the rectum was slightly larger than the actual clinical frequency of Grade 3–4 sequelae. However, the NTCP represented Grade 2–4 sequelae, which may explain the discrepancy. The bladder NTCP was too high, as compared to Grade 3–4 sequelae. The discrepancy between the NTCP of the rectum and the clinical frequency could be explained by the stated uncertainties in the tolerance data, whereas the discrepancy of the bladder values could not. Several studies have indicated that the position of the bladder varies substantially, giving rise to large variations in the bladder DVH during a fractionation regime (9, 23). Our total bladder DVHs may therefore represent an overestimation of the high-dose part of the bladder volume as the bladder position may vary and a different volume is given the high dose during the fractionation regime.

The LK model was applied to calculate NTCP values for a combined HDRB and EBRT treatment. Ideally, an NTCP model should be independent of treatment technique, but it should be kept in mind that most dose–volume-response data are derived from EBRT studies. A DVH reduction algorithm traditionally applied to EBRT DVHs may especially need a modification when used in HDRB calculations.

It has been known for some time that an NTCP based on only 1 pretreatment CT scan may be unreliable in the case of EBRT of carcinoma of the prostate (9). Several CT scans are needed, especially for a reliable NTCP value for the bladder. These findings seem to be valid for a combined treatment of HDRB and EBRT as well, as only one HDRB CT scan provided an NTCP value with a relative uncertainty of 20–30% as compared to the NTCP based on 6 CT scans. Four CT scans were necessary to obtain a precision of 12–13%. Based on the results in this study, the patients will in the future undergo 3–4 CT scans at our institution, when reliable NTCP estimates are required.

Both the estimated mean and maximum doses to the ORs were close to the central axis dose for the EBRT treatment. This ensured that the dose distribution over the ORs were homogeneous and fluctuations in organ filling and position would lead to negligible alterations in the DVHs during the fractionation regime. Therefore one pretreatment CT scan should be sufficient to provide a reasonable estimate of the total DVH of the EBRT treatment.

The Burman NTCP model parameters (16) based on the Emami tolerance data (24) appeared in 1991. These data represent quite serious complications (Grade 4), and there seems to be consensus that tolerance data should be based on less serious, yet unacceptable, endpoints (17–19). A recent study of Boersma et al. (17) estimated a crude 10% risk of Grade 2–4 rectal bleeding (SOMA-LENT) if at least 1 of 3 dose–volume thresholds was exceeded (Appendix). The 10% risk at \( D = 76 \) Gy, \( \nu = 5\% \) is confirmed by Kutcher et al.’s study (18). They estimated that 75 Gy to 30% of the anterior rectum would give approximately 10%
Grade 2 rectal complications. Taking into account that only the anterior rectal wall and half the length of the rectal tube was delineated [30%/2 × 2 = 7.5%] as compared to the Boersma et al. delineation procedure, the risk estimates are consistent.

The tolerance data of Marks et al. represent Grade 3–4 bladder complications (19). These are less serious endpoints than those used by Emami et al. (24). Moreover, the Marks et al. data describe the dose–volume-response curve for a low risk (5–10%) with 3 sets of dose–volume values where the Emami et al. data have only 2. It is important to emphasize the lower part of the NTCP curve so that at least this range is estimated with confidence. In this report, the NTCP values calculated from model parameters derived from the Marks et al. data, were too large as compared with the clinical complication frequency. The explanation may be that the bladder tolerance dose and/or volume effect is larger than indicated by Marks et al.

In conclusion, a method of calculating NTCP from multiple CT scans from high dose rate brachytherapy and external beam radiotherapy was presented. The Lyman–Kutcher model provided a reasonable NTCP for the rectum, whereas the NTCP for the bladder was too high compared to the clinical complication frequency. Three to 4 CT scans during 5–7 fractions of brachytherapy are needed to obtain reliable NTCP values. Regrettably, the dose–volume-response data on rectum and bladder in the literature are sparse. To validate and improve the model, further studies are needed.

REFERENCES

The volume parameter $n$, was estimated by first observing the model prediction (6):

$$D_1 v_1^n = D_2 v_2^n = \text{const.} = C \quad \text{(A1)}$$

for a given complication probability level and endpoint; i.e., there is a power law relationship between the volume fraction $v_1$ given the dose $D_1$ and the volume fraction $v_2$ receiving $D_2$. This should apply to the data of Table A1. $n$ was estimated by minimising:

$$
\sum_{i=1}^{N} (D_i v_i^n - C)^2
$$

\text{(A2)}

where $N$ is the number of tolerance dose-volume levels available. Here, $N = 3$, both for rectum and bladder. $C$ is given as:

$$
C = \frac{1}{N} \sum_{i=1}^{N} D_i v_i^n
$$

\text{(A3)}

Due to the sparse tolerance data, $m$ was set to the same value as in the original work of Burman et al. (16). However, our calculations revealed that the exact value of this parameter was not critical and this is also indicated by the narrow range of $m$ values (0.10 – 0.27) for the 28 organs of Burman et al. The whole organ tolerance dose $TD_{50}(1)$ was calculated from

$$
TD_{50}(1) = \frac{C}{1 + m \cdot t_{cp}}
$$

\text{(A4)}

derived from the Lyman–Kutcher model, where $t_{cp}$ is standard normal cp percentile corresponding with the relevant complication probability levels 10% (rectum) and 7.5% (bladder) (Table A1). The estimated parameter values are shown in Table A2 with uncertainties according to uncertainties in the tolerance dose–volume data (Table A1). The uncertainty in the $n$ parameter was obtained by noting that $n$ is a function of $D_i$ and $v_i$ (Eq. A2). The uncertainties in $D_i$ and $v_i$, $\Delta D_i$ and $\Delta v_i$, shown in Table 4, were obtained from the literature (19) or set at a rough estimate if unavailable. These uncertainties were used with the error propagation formula (25):

$$
\Delta n = \sqrt{\Delta n_D^2 + \Delta n_{v_1}^2 + \Delta n_{v_2}^2 + \Delta n_{n_1}^2 + \Delta n_{n_2}^2} \quad \text{(A5)}
$$

where $\Delta n_D$ is the uncertainty in $n$ due to the uncertainty in $D_i$.

**APPENDIX**

Fig. A1. NTCP values calculated from new parameters (Table A2) and dose-volume tolerance data from the literature (17–19). (Please note that the NTCP values in this plot are based on other materials (17–19), and have no relevance to the patient material presented in this study.) NTCP values calculated from the conventional Burman parameters (16) and the clinical complication frequencies (triangles) of the materials are shown (17–19). The error bars represent ±2.5% uncertainties (19).

Table A1. Tolerance data from the literature for the rectum and bladder; confidence intervals in parentheses were based on crude uncertainties taken from the literature (Ref. 19) or were set at a rough estimate if unavailable

<table>
<thead>
<tr>
<th>Volume fraction</th>
<th>Tolerance dose (Gy)</th>
<th>Risk (%)</th>
<th>Endpoint</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 (0.4, 0.6)</td>
<td>66* (63.5, 68.5)</td>
<td>10 (7.5, 12.5)</td>
<td>Grade 2–4 bleeding</td>
<td>Boersma et al. (17)</td>
</tr>
<tr>
<td>0.3 (0.2, 0.4)</td>
<td>71* (69.5, 73.5)</td>
<td>10 (7.5, 12.5)</td>
<td>Grade 2–4 bleeding</td>
<td>Boersma et al. (17)</td>
</tr>
<tr>
<td>0.05 (0.025, 0.15)</td>
<td>76* (73.5, 78.5)</td>
<td>10 (7.5, 12.5)</td>
<td>Grade 2–4 bleeding</td>
<td>Boersma et al. (17), Kutcher et al. (18)</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 (0.9, 1.0)</td>
<td>52.5 (50, 55)</td>
<td>7.5 (5, 10)</td>
<td>Grade 3–4 complications</td>
<td>Marks et al. (19)</td>
</tr>
<tr>
<td>0.4 (0.3, 0.5)</td>
<td>57.5 (52.5, 62.5)</td>
<td>7.5 (5, 10)</td>
<td>Grade 3–4 complications</td>
<td>Marks et al. (19)</td>
</tr>
<tr>
<td>0.1 (0.025, 0.2)</td>
<td>70 (65, 75)</td>
<td>7.5 (5, 10)</td>
<td>Grade 3–4 complications</td>
<td>Marks et al. (19)</td>
</tr>
</tbody>
</table>

* The tolerance levels for rectum of Boersma et al. (17) have been increased by 1 Gy to account for that these doses were not point estimates for a 10% risk but separated the patients having 0% and 10% risk for rectal complications.
the tolerance dose $D_1$, $\Delta n_{1/v}$ is the uncertainty in $n$ due to the uncertainty in the corresponding tolerance volume $v_1$, and so on. The uncertainty in $m$ was calculated according to Eq. 6 in the paper by Burman et al. (17); $\Delta m = 0.03$. $TD_{50}(1)$ is a function of $n$, $m$, and $t_{cp}$ (Eq. A3 and A4). Thus,

$$\Delta TD_{50}(1) = \sqrt{\Delta TD_{50}(1)^2_n + \Delta TD_{50}(1)^2_m + \Delta TD_{50}(1)^2_{t_{cp}}}$$

(A6)

where $\Delta TD_{50}(1)_n$, $\Delta TD_{50}(1)_m$ and $\Delta TD_{50}(1)_{t_{cp}}$ are the uncertainties in $TD_{50}(1)$ due to uncertainties in $n$ (Eq. A5), $m$ and $t_{cp}$, respectively.

Table A2. Estimated parameter values from the tolerance data of Table A1 with corresponding uncertainties in brackets calculated according to the Appendix: the parameter values of Burman et al. (Ref. 16) are shown for comparison, but please note that these are for more serious complications; the parameter $m$ was set to the same value as in the work of Burman et al.

<table>
<thead>
<tr>
<th></th>
<th>$n$</th>
<th>$m$</th>
<th>$TD_{50}(1)$ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>Burman et al.</td>
<td>0.12</td>
<td>0.15 (0.12, 0.18)</td>
</tr>
<tr>
<td></td>
<td>Estimated</td>
<td>0.06 (0.03, 0.11)</td>
<td>80 (72, 86)</td>
</tr>
<tr>
<td>Bladder</td>
<td>Burman et al.</td>
<td>0.5</td>
<td>0.11 (0.08, 0.14)</td>
</tr>
<tr>
<td></td>
<td>Estimated</td>
<td>0.13 (0.06, 0.19)</td>
<td>62 (57, 67)</td>
</tr>
</tbody>
</table>