Int. J. Radiation Oncology Biol. Phys., Vol. 67, No. 4, pp. 1066–1073, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.10.014

CLINICAL INVESTIGATION **Prostate**

INCIDENCE OF LATE RECTAL BLEEDING IN HIGH-DOSE CONFORMAL RADIOTHERAPY OF PROSTATE CANCER USING EQUIVALENT UNIFORM DOSE–BASED AND DOSE–VOLUME–BASED NORMAL TISSUE COMPLICATION PROBABILITY MODELS

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Purpose: Accurate modeling of rectal complications based on dose–volume histogram (DVH) data are necessary to allow safe dose escalation in radiotherapy of prostate cancer. We applied different equivalent uniform dose (EUD)–based and dose–volume–based normal tissue complication probability (NTCP) models to rectal wall DVHs and follow-up data for 319 prostate cancer patients to identify the dosimetric factors most predictive for Grade ≥ 2 rectal bleeding.

Methods and Materials: Data for 319 patients treated at the William Beaumont Hospital with three-dimensional conformal radiotherapy (3D-CRT) under an adaptive radiotherapy protocol were used for this study. The following models were considered: (*1*) Lyman model and (*2*) logit-formula with DVH reduced to generalized EUD, (*3*) serial reconstruction unit (RU) model, (*4*) Poisson-EUD model, and (*5*) mean dose– and (*6*) cutoff dose–logistic regression model. The parameters and their confidence intervals were determined using maximum likelihood estimation.

Results: Of the patients, 51 (16.0%) showed Grade 2 or higher bleeding. As assessed qualitatively and quantitatively, the Lyman- and Logit-EUD, serial RU, and Poisson-EUD model fitted the data very well. Rectal wall mean dose did not correlate to Grade 2 or higher bleeding. For the cutoff dose model, the volume receiving > 73.7 Gy showed most significant correlation to bleeding. However, this model fitted the data more poorly than the EUD-based models.

Conclusions: Our study clearly confirms a volume effect for late rectal bleeding. This can be described very well by the EUD-like models, of which the serial RU- and Poisson-EUD model can describe the data with only two parameters. Dose–volume–based cutoff-dose models performed worse. © 2007 Elsevier Inc.

Prostate cancer, Rectal toxicity, Normal tissue complication probability, Volume effects, Dose–volume histograms, Equivalent uniform dose.

INTRODUCTION

The essential dose-limiting organs in prostate radiotherapy are the bladder and rectum. One of the most relevant side effects that can significantly compromise a patient's quality of life is chronic rectal bleeding.

Conventional external beam radiotherapy (RT) treatment typically does not allow prostate doses beyond 65 to 70 Gy without an unacceptably high risk of rectal toxicity, although higher tumor doses are favorable for improved tumor control. The possibility of dose escalation beyond 70 Gy to the prostate is based on the volume–effect of rectum, *i.e.,* the observation of increased tolerance to high doses if the high dose region is confined to a small volume. Technically, this becomes feasible because of conformal techniques such as three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT), especially when aided by image-guided adaptive approaches.

Safe dose escalation necessitates accurate quantitative modeling of the volume effect based on the detailed dose–volume information provided by modern treatment planning systems. Numerous studies have established evidence of a significant correlation between parameters derived from rectal dose–volume histograms (DVHs) and toxicity (see

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Presented in part at the 48th Annual American Society for Therapeutic Radiology and Oncology Meeting (ASTRO), Philadelphia, PA, Nov. 5–9, 2006.

Supported in part by Deutsche Krebshilfe e.V. Grant No. 106280 and National Institutes of Health Grant No. RO1 CA091020.

Conflict of interest: none.

Received Sept 6, 2006, and in revised form Oct 2, 2006. Accepted for publication Oct 9, 2006.

Table 1. Toxicity score for chronic rectal bleeding based on Common Terminology Criteria for Adverse Events (v. 3.0)

Grade	Description
1	Mild hemorrhage/bleeding; intervention (other than iron supplements) not indicated
2	Symptomatic and medical intervention or minor cauterization indicated
3	Transfusion, interventional radiology, endoscopic or operative intervention indicated
4	Life-threatening consequences; perforation/dysfunction requiring urgent intervention

Refs. 1–4 and references therein). However, only a few publications have quantified the risk of rectal complications in terms of normal tissue complication probability (NTCP) models (5–9). Such empiric or semiempiric models parameterize the vast information about inhomogeneous dose distributions and corresponding outcome data from large patient populations into few-parametric models that assign a single probability value to an individual treatment plan. This enables evidence-based ranking of alternative plans in the planning process according to their predicted complication risk. Two important types of NTCP-models can be distinguished. The first are dose–volume–based models, which use a single DVH parameter (*e.g.,* the volume V_D irradiated to a certain dose-level D) for ranking plans according to their complication probability. In contrast, EUD-like models define an equivalent uniform dose, $EUD = f^{-1}(\Sigma_i v_i f(D_i))$, as surrogate parameter calculated using all bins (v_i, D_i) of a DVH, where the form of the (monotonic) function f depends on the model. Besides possible differences in the quality of fit as investigated in this study, it should be mentioned that the choice between dose–volume–based vs. EUD-like models when used for treatment planning, especially IMRT, affects the process of plan optimization (10–12).

In this study, we apply one dose–volume–based and five EUD-like NTCP models for chronic rectal bleeding of Grade $\geq$ 2 to a population of 319 prostate cancer patients treated with a 3D-CRT adaptive radiotherapy (ART) technique to doses between 70.2 and 79.2 Gy at the William Beaumont Hospital. This is, so far, the largest published, single-institution patient population studied for fitting of rectal NTCP-models. Thus, this study not only provides valuable information for identification of the superior modeling approaches but also statistically well-based estimates of the corresponding model parameters.

METHODS AND MATERIALS

Patient data

Data for 319 prostate cancer patients treated between 1999 and 2002 at the William Beaumont Hospital were used for this study. The characteristics of this patient population have been described in previous studies (3, 13). The patients were part of a Phase II dose-escalation study and underwent 3D-CRT with image-guided off-line correction under an ART protocol.

All patients had one pretreatment planning CT scan, daily portal images to determine and correct for setup errors, four additional CT scans during the first week of the treatment used for individual adaptation of the treatment plan, and weekly CT scans in the following to preclude undetected drifts. The (solid) rectum was contoured on the initial CT scan from the anal verge or ischial tuberosities (whichever was higher) to the sacroiliac joints or rectosigmoid junction (whichever was lower). Rectal wall was defined based on the solid rectum contours with 3- to 4-mm wall thickness.

The ART scheme used has been described elsewhere (14, 15). In short, a four-field box technique with 18 MV photons was used both for the initial treatment plan of the first week and the following adapted plan. In the first week, the patients were treated for a dose of 9 Gy to the target, where the planning target volume (PTV), was generated based on the clinical target volume (CTV), of the initial CT (prostate, or prostate + seminal vesicles) with a population-based margin of 1 cm. For the adapted plan, information from daily portal imaging and the five CT scans available after the first week of treatment were used to estimate setup error and individual prostate mobility, which allowed to define a (generally smaller) patient-specific PTV.

The final dose to the PTV was limited by dose–volume constraints of rectal wall and bladder based on the geometry of the initial planning CT image. For rectal wall these were: (*1*) $D_{30\%}$ = 75.6 Gy, and (*2*) $D_{5\%}$ = 82 Gy. The possible dose levels (minimal prostate dose) were chosen under the requirement to meet rectum (and bladder) constraints, and were as follows: 70.2, 72, 73.8, 75.6, 77.4, and 79.2 Gy.

For each patient the dose distributions of the initial and adapted plan were calculated using Pinnacle 6.2b (ADAC Laboratories, Milpitas, CA). An in-house developed software was used to calculate DVHs of the rectal wall. This software used the contours from the initial (planning) CT and calculated the overall dose as sum of initial and adapted (physical) dose distributions. The DVH-dose bin size was 0.1 Gy, with volume defined as relative (percentage) volume irradiated.

The rectal toxicity variable regarded in this analysis is chronic rectal bleeding. The follow-up scheme defined examinations at 3-month intervals during the first 2 years, and every 6 months from the second to the fifth year. As mentioned above, this study is based on the patient population analyzed in Vargas *et al.* (3, 13). However, for the current study, all patient files were re-examined to improve follow-up time. Complications were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 (Table 1). Of the 331 patient datasets, 12 used by Vargas *et al.* could not be used because of technical problems in restoring dose distributions or lost, incomplete, or inconsistent follow-up information. The median clinical follow-up for the remaining 319 patients was 2.8 years (range, 0.1–6.4), with an interquartile range of 1.5 to 4.0 years (25th–75th percentile).

The NTCP models

An NTCP model assigns a complication probability for an organ at risk to a generally inhomogeneous dose distribution. The func-