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CLINICAL INVESTIGATION **Prostate**

MATHEMATICAL MODEL FOR EVALUATING INCIDENCE OF ACUTE RECTAL TOXICITY DURING CONVENTIONAL OR HYPOFRACTIONATED RADIOTHERAPY COURSES FOR PROSTATE CANCER

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Purpose: To describe the radiation-induced acute rectal toxicity (ART) using a modified Lyman-Kutcher-Burman normal tissue complication probability model and parameters set, taking into account the overall treatment time.
Methods and Materials: A total of 160 patients underwent three-dimensional conformal radiotherapy to the prostate and seminal vesicles and were randomized to receive 80 Gy in 40 fractions within 8 weeks (Group A) or 62 Gy in 20 fractions within 5 weeks, 4 d/wk (Group B). An additional 52 patients (Group C) underwent intensity-modulated radiotherapy with a hypofractionation schedule consisting of 56 Gy, delivered in 16 fractions (4/wk) of 3.5 Gy. Patients were followed for ART weekly during treatment. The overall treatment time, rectal dose–volume histograms, and ART status, defined as Radiation Therapy Oncology Group Grade 2 or greater gastrointestinal toxicity, were used to determine the modified Lyman-Kutcher-Burman model parameters. The m and n values were obtained from the cohort, and the tolerance doses for 50% complication probability for uniform irradiation [$TD_{50}(1)_k$] were obtained for each fractionation schedule indicated with k.
Results: Of 212 patients treated with localized prostate radiotherapy, 65 developed Grade for ≥1 week during treatment. The m and n value was 0.17 and 0.08, respectively. The $TD_{50}(1)_k$ parameter was 79, 62.5, and 53 Gy, respectively for Group A, B, and C.
Conclusion: The optimized modified Lyman-Kutcher-Burman normal tissue complication probability model allowed us to describe the ART data from conventional and hypofractionated regimens, using the dose–volume histograms and overall treatment time. This model could prove useful in designing hypofractionation schedules to reduce the incidence of ART. © **2009 Elsevier Inc.**

Prostate cancer, Radiation-induced rectal acute toxicity, Normal tissue complication probability, Hypofractionation.

INTRODUCTION

Acute rectal toxicity (ART) might be a dose-limiting complication of external beam radiotherapy (RT) for prostate cancer and a predictor of late toxicity (1–4), even though it is reported ever more frequently (4–7) and can be severe enough to interrupt the planned treatment course (8). Some investigators have found a close correlation between early rectal toxicity and a number of dosimetric parameters, together with several other clinical patient-related factors (5, 9–11). However, previous studies have investigated ART with conventional fractionation schemes (at 2 Gy/fraction and 5 fractions/wk), a common, but not necessarily optimal, schedule for all tumor types.

A number of models estimating the volume dependence of normal tissue toxicity have been used to compare rival plans (12–14). The Lyman normal tissue complications probability (NTCP) model assumes a sigmoid relationship between a dose uniformly delivered to a given organ and the possibility of complications (12). However, the irradiated normal tissue volumes generally receive nonhomogeneous dose distributions; therefore, to calculate the NTCP, the dose–volume histograms (DVHs) must be converted by an algorithm into an effective volume, receiving a maximal uniform dose (12, 15, 16) to permit the use of the estimated tolerance dose for the uniform RT to the volume. The Lyman model can be implemented using the Lyman-Kutcher-Burman (LKB) DVH reduction scheme (15).

Because the tolerance doses apply for uniform partial and full-volume RT delivered in a conventional fractionation scheme, new tools are needed to optimize and evaluate the

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plans for hypofractionated schedules (HFSs). Thus, when the dose per fraction/dose rate is increased, the total dose must be adjusted to avoid an increase in late complications using the linear-quadratic model, which describes the shape of cell survival curves as a function of the radiation dose. Then, the overall treatment time (OTT) must also be adjusted to keep the acute mucosal reaction within a tolerable limit using a model including the appropriate values of some biologic parameters, as shown by Fowler (17). The acute mucosal reaction could be dose limiting when the OTT is too short.

The aim of this study was to quantitatively describe ART according to the DVHs and the OTT to optimize a modified LKB NTCP model. To establish the model parameters, the method of maximal likelihood, which determines the optimal values of the parameters by maximizing the likelihood of the given observations, was used.

METHODS AND MATERIALS

Patient population

The data analyzed in this study came from patients with clinically localized prostate cancer, and included 160 patients who had undergone 9 months of androgen deprivation combined with three-dimensional conformal RT (3D-CRT) to the prostate and seminal vesicles for high-risk prostate tumors. The patients were enrolled between January 2003 and September 2007 in a Phase II randomized trial comparing conventional fractionation (80 Gy in 40 fractions within 8 weeks, Group A) and hypofractionation (62 Gy in 20 fractions within 5 weeks, 4 fractions weekly, Group B).

Another group of 52 patients (Group C), accrued by our institute between April 2004 and December 2006 in a multicenter Phase II study, testing a HFS of 56 Gy in 16 fractions within 4 weeks, was also included.

Both HFSs were calculated to be equivalent to 80 Gy in 2-Gy fractions as the standard normalized total dose at 2 Gy/fraction (NTD_2), using an α/β of 1.5 Gy for the prostate, as suggested by Fowler *et al*. (18).

Treatment technique and dose planning

In Groups A and B, all 160 patients were immobilized in a supine position using a custom-made cast for computed tomography (CT) simulation and treatment; the other 52 patients (Group C) were immobilized in a prone position. The patients were requested to spontaneously void the rectum without an enema before simulation and each RT fraction. Only in the case of protracted constipation was the daily administration of a light laxative suggested. The bladder was to be voided 1 h before simulation and before each treatment. The planning CT scan of pelvis was obtained at 5-mm intervals from the top of L5 to 3 cm below the ischial tuberosities.

For the 160 patients (Groups A and B), the clinical target volume (CTV) was considered the prostate plus the entire seminal vesicles; for Group C, the CTV was the prostate plus the entire seminal vesicles, except for those with Stage T1-T2 lesions with a risk of seminal vesicle involvement of $\leq$15% for whom the CTV was the prostate only. In all patients, the planning target volume (PTV) was considered the CTV plus a uniform expansion of 0.8 cm in all directions. The femoral heads, bladder, and rectum, defined from the level of the anus to the sigmoid flexure, were outlined on the planning CT scan as organs at risk. The dose was delivered with a linear accelerator (CLINAC 2100/CD, Varian Associates, Palo Alto, CA) using 15-MV X-rays. The CT data sets were transferred to the Eclipse, version 6.5 (Varian Associates), treatment planning system. Portal film verification was mandatory before starting treatment and at least every week for the anteroposterior and lateral setup fields and daily for intensity-modulated RT (IMRT).

Statistical analysis

The PTV, CTV, rectal DVHs, and OTT were considered and recorded for each patient.

The observed ART was used, as ''truth'' (*i.e.,* the reference standard for nonparametric clustered receiver operating characteristic [ROC] analysis to evaluate the predictive utility of a modified NTCP model) (19). By comparing the observed and calculated ART, the true positive ratio and false positive ratio were plotted in the form of a ROC curve (20). When a perfect correlation of the predicted vs. observed failure from biopsy specimens was found, the area under the curve was 1. Random assignment of the outcome led to an ROC area under the curve of 0.5.

Multivariate analysis (MVA) of the prognostic factors was performed using the Cox proportional hazard model, including, when possible, the covariates as continuous variables. Differences between groups were calculated using a two-tailed *t* test. The data analysis was performed with Statistical Package for Social Sciences, version 10 (SPSS, Chicago, IL).

Endpoint ART

A complication (yes vs. no) was defined as ART of Grade 2 or greater. The value of ART was registered for each patient, weekly during treatment and at 1 and 2 months after treatment, using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring system (21), summarized as follows: Grade 1 toxicity, minimal side effects not requiring medication; Grade 2 toxicity, symptoms requiring medication; Grade 3, requiring minor surgical intervention (transurethral resection, laser coagulation, or blood transfusion); and Grade 4, hospitalization and major intervention.

Maximal likelihood estimation

For NTCP calculations, we used the LKB DVH reduction method and the standard normalized total dose. In particular, the rectal DVH was used to compute the effective volume ($v_{eff,in}$) and the maximal dose expressed as $NTD_{2,\max,i}$ for each patient (see Appendix A), and consequently the parameter s_i and the corresponding normal tissue complication probability $NTCP(s_i)$ using Eqs. B.2 and B.1, respectively (see Appendix B).

A probit model was assumed for the probability of Grade 2 or greater ART of patient *i*:

$$p_i = p(m, n, TD_{50}(1); s_i) = NTCP(s_i) \tag{1}$$

The NTCP model parameters—the tolerance dose to the whole organ leading to 50% of complication probability, $TD_{50}(1)_K$ for each fraction schedule, the slope of the NTCP curve (m), and n—were adjusted to maximize the probability of predicting complications for those patients who did or did not experience Grade 2 or greater ART (R_i = 1 or 0, respectively). For binomially distributed data such as the NTCP data, the log-likelihood (22)(1) for the entire data set was given by

$$L(m, n, TD_{50}(1)) = \sum_{i=1}^{N} [1n(p_i)^{Ri} + 1n(1 - p_i)^{1-Ri}] \tag{2}$$

and it was maximized for all feasible values of m, n, and $TD_{50}(1)_k$ for each group, using a homemade optimization package written in Visual Basic.