Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 1, pp. 41–49, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.12.003

CLINICAL INVESTIGATION **Prostate**

RELATIONSHIPS BETWEEN RECTAL WALL DOSE–VOLUME CONSTRAINTS AND RADIOBIOLOGIC INDICES OF TOXICITY FOR PATIENTS WITH PROSTATE CANCER

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Purpose: The purpose of this article was to investigate how exceeding specified rectal wall dose–volume constraints impacts on the risk of late rectal bleeding by using radiobiologic calculations.

Methods and Materials: Dose–volume histograms (DVH) of the rectal wall of 250 patients with prostate cancer were analyzed. All patients were treated by three-dimensional conformal radiation therapy, receiving mean target doses of 80 Gy. To study the main features of the patient population, the average and the standard deviation of the distribution of DVHs were generated. The mean dose <D>, generalized equivalent uniform dose formulation (gEUD), modified equivalent uniform dose formulation $(mEUD)_0$, and normal tissue complication probability (NTCP) distributions were also produced. The DVHs set was then binned into eight classes on the basis of the exceeding or the fulfilling of three dose–volume constraints: $V_{40} = 60\%$, $V_{50} = 50\%$, and $V_{70} = 25\%$. Comparisons were made between them by <D>, gEUD, $mEUD_0$, and NTCP.

Results: The radiobiologic calculations suggest that late rectal toxicity is mostly influenced by V_{70}. The gEUD and $mEUD_0$ are risk factors of toxicity always concordant with NTCP, inside each DVH class. The mean dose, although a reliable index, may be misleading in critical situations.

Conclusions: Both in three-dimensional conformal radiation therapy and particularly in intensity-modulated radiation therapy, it should be known what the relative importance of each specified dose–volume constraint is for each organ at risk. This requires a greater awareness of radiobiologic properties of tissues and radiobiologic indices may help to gradually become aware of this issue. © 2007 Elsevier Inc.

Late rectal bleeding, Dose–volume constraints, Normal tissue complication probability, Equivalent uniform dose, Prostate cancer.

INTRODUCTION

The visualization of cumulative dose–volume histograms (DVH) of the structures of interest has become a very common instrument to evaluate a treatment plan and is extensively used to compare different treatment techniques. High conformality of three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) plans allow the sparing, total or partial, of normal tissues surrounding the tumor, especially at the highest doses. Consequently, the DVHs of the sensitive structures typically show inhomogeneous dose distributions, from which it is not straightforward to predict the complication risk. For this reason, several clinical studies have been published that retrospectively analyzed partial organ irradiation data for many clinical sites (1).

For patients with prostate cancer, a variety of dose–volume constraints have been proposed, differently correlated with an increase of late rectal bleeding, to keep the risk of developing Grade 2 or worse toxicity reasonably low (2–8).

Unfortunately, many situations being possible in which one constraint is fulfilled and another violated, it is not always clear how to quantify the risk of developing a late toxicity. If, for example, the DVH evaluation is based on three dose–volume constraints, up to eight different combinations are possible, in which none, some, or all the dose limitations are satisfied.

This issue can have an important role in the IMRT treatment planning that is the result of an iterative search for the best solution to fulfill specified dose and dose–volume constraints to the planning target volume (PTV) and critical structures. In fact, when the organs at risk (OARs) sur-

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Conflict of interest: none.

Received Aug 7, 2006, and in revised form Dec 4, 2006. Accepted for publication Dec 4, 2006.

rounding the target have a high radiosensitivity or they and the PTV overlap, the desired dose distribution cannot be achievable and a compromise has to be reached. To fine tune the convergence to the best compromise, different weighting factors to the whole structures (PTV or OARs) and to a single dose or dose–volume constraint can be generally specified. For these reasons, it should be well known what the importance of each dose limitation is for each structure, PTV or OAR, and how exceeding a particular constraint impacts on the tumor control probability or on the toxicity risk, respectively.

Radiobiologic indices, such as tumor control probability, normal tissue complication probability (NTCP), or equivalent uniform dose (EUD), may provide a valid support to investigate this issue and they can help to evaluate, *a posteriori*, the quality of a treatment plan or to compare different plans, in critical situations.

In IMRT, a future approach could be the direct optimization of radiobiologic indices to find the best beam intensity modulation. A few articles have described how a biophysical optimization could allow a therapeutic benefit compared with a physical optimization (9–11), giving the possibility to explore a wider range of dose distributions because there are many (infinite) DVHs that lead to the same dose response of tissues.

In the present study, a large number of rectal wall DVHs of patients with prostate cancer, treated by 3D-CRT, will be examined. The impact of different dose distributions on the risk of rectal bleeding will be analyzed by performing radiobiologic calculations. Three dose–volume constraints, both at intermediate and high doses, have been established to subdivide the entire population of DVHs into eight different classes, and comparisons will be made between them to investigate the importance of each dose limitation.

METHODS AND MATERIALS

Patient population

The analyzed patient population comprising 250 patients, was treated by external photon beam 3D-CRT for localized prostate cancer, between 2002 and 2005. The prescription dose was, for each patient, 80 Gy, 2 Gy per fraction.

All patients were scanned by computed tomography in the supine position, with an immobilization device for their feet. A standardized six-field technique, with two lateral and four oblique fields, was used. Weekly orthogonal portal images were performed to verify a correct patient positioning. Two different treatment planning systems, Cadplan (Release 6.3.5, Varian Medical Systems Inc., Palo Alto, CA) and Eclipse (Release 6.5, Varian Medical Systems Inc., Palo Alto, CA), were used for dose calculations. The rectum has been defined as rectal wall between the inner and the outer rectum contour. The inferior limit has been considered the anal verge, and the superior limit the sigmoid flexure. Only manual outlines were produced, without any automatic contour generation. The clinical target volume was expanded in three dimensions with 1-cm margin to obtain the PTV, except at the prostate-rectum interface, where a 0.6-cm margin was adopted to decrease the rectum involvement. The dose was calculated so that at least 90% of the PTV (D_{90}) was to receive the prescribed dose of 80 Gy. The maximum dose heterogeneity allowable in the PTV was 17% (from 90% to 107%). Each treatment plan was optimized to ensure, whenever achievable, that no more than 60% of rectal wall received more than 40 Gy ($V_{40} \leq 60\%$) and that no more than 30% of rectal wall received more than 70 Gy ($V_{70} \leq 30\%$). This was done by varying beam weighting or wedges and, if necessary, gantry angles.

DVH

Treatment plans of 250 patients were restored from institutional archives, and rectal wall contours were examined by either of two physicians (G.A., B.S.) and modified when they were found not to fulfill the above definition of rectum (in these cases, the dose distribution was recalculated, leaving field sizes and monitor units unchanged). Then the differential rectal wall DVHs were exported and stored. Cumulative DVHs were obtained from differential DVHs by integration, then linearly interpolated at 1-Gy intervals and normalized to 100% to produce the average DVH and its standard deviation.

Radiobiologic models

To better identify the patient population of this study, radiobiologic calculations were performed on the entire data set. The Lyman-Burman Kutcher (LBK) model (12) was used to calculate the NTCP of late rectal bleeding. For uniform irradiation of a fraction v of the organ at dose D, NTCP can be calculated by

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{t^2}{2}\right) dt \tag{1}$$

where t is defined as

$$t = \frac{D - TD_{50}(v)}{m \cdot TD_{50}(v)} \tag{2}$$

and

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n}. \tag{3}$$

As known, the parameters n, m, and TD_{50} (1) determine the volume dependence of NTCP, the slope of NTCP vs. dose and the tolerance dose to the whole organ, leading to a 50% complication probability, respectively. The values estimated by Emani (13) were involved in the calculation: $n = 0.12$, $m = 0.15$, and $TD_{50} = 80$ Gy. Note that only standard fractionations of 1.8–2 Gy per day, 5 days per week, was considered to estimate TD_{50} (1).

The effective volume method (14) was chosen as histogram reduction scheme for nonuniform organ irradiations:

$$v_{eff} = \sum_{1}^{N} v_i \cdot \left(\frac{D_i}{D_{\max}}\right)^{1/n} \tag{4}$$

where D_i is the dose delivered to the volume fraction v_i and N is the number of points of the differential DVH. By Eq. 4, an inhomogeneous dose distribution is converted to an equivalent uniform irradiation of a fraction v_{eff} of the organ at the maximum dose D_{max}.