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CLINICAL INVESTIGATION **Prostate**

SECONDARY MALIGNANCIES FROM PROSTATE CANCER RADIATION TREATMENT: A RISK ANALYSIS OF THE INFLUENCE OF TARGET MARGINS AND FRACTIONATION PATTERNS

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Purpose: This study explores the implications for cancer induction of treatment details such as fractionation, planning target volume (PTV) definition, and interpatient variations, which are relevant for the radiation treatment of prostate carcinomas.

Methods and Materials: Treatment planning data from 100 patients have been analyzed with a risk model based on the United Nations Scientific Committee on the Effects of Atomic Radiation competition model. The risk model can account for dose heterogeneity and fractionation effects characteristic for modern radiotherapy. Biologically relevant parameters from clinical and experimental data have been used with the model.

Results: The results suggested that changes in prescribed dose could lead to a modification of the risks for individual organs surrounding the clinical target volume (CTV) but that the total risk appears to be less affected by changes in the target dose. Larger differences are observed for modifications of the margins between the CTV and the PTV because these have direct impact onto the dose level and dose heterogeneity in the healthy tissues surrounding the CTV. Interpatient anatomic variations also have to be taken into consideration for studies of the risk for cancer induction from radiotherapy.

Conclusions: The results have shown the complex interplay between the risk for secondary malignancies, the details of the treatment delivery, and the patient heterogeneity that may influence comparisons between the long-term effects of various treatment techniques. Nevertheless, absolute risk levels seem very small and comparable to mortality risks from surgical interventions, thus supporting the robustness of radiation therapy as a successful treatment modality for prostate carcinomas.

Prostate cancer, Carcinogenesis, Radiation treatment, DVH, Fractionation.

INTRODUCTION

Ionizing radiation is an important modality for the treatment of malignancies. However, the carcinogenic potential of radiation is a concern for the long-term survivors. Studies investigating the occurrence of secondary cancers in radiotherapy patients indicate that radiation-induced cancers represent a small but significant late complication (1). This is considered the price of success for modern radiation treatment, resulting in improved survival and better quality-of-life for many patients. Nevertheless, quantification of the risks for radiation-induced cancers is important because it apparently depends on treatment technique (2–4).

The greatest interest in radiation-induced cancers has been for pediatric patients that have a long life span (5–6), but increased early detection and improved survival have highlighted the issue for adult cancer patients. Several studies showed that prostate radiotherapy patients have an increased risk for secondary cancers compared with surgery patients. The most significant contributors to the increased risk appear to be carcinomas of the bladder, rectum and lung, and sarcomas within the treatment field (7–9). Thus, estimations of the risk for radiation-induced cancers could be introduced into the clinical decision-making process, together with risks for deterministic effects. However, quantification of risks for individual patients is difficult because reliable epidemiological data are scarce.

Many patient cohorts come from time periods with limitations in procedures for recording and reporting radiation doses, which unavoidably introduce inaccuracies in establishing dose–response relationships. Studies of survivors of accidental irradiations showed that for irradiations with low and uniform doses, there is a linear dependence of the effect (10). However, such a relationship may no longer be relevant

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for therapeutic irradiations employing different dose rates and higher doses heterogeneously distributed in tissues. Thus, it has been proposed that a competition model should be used in these conditions (11) because the process of cancer induction is the result of the interplay between induction of DNA mutations and cell killing (12). Such a model predicts a maximum effectiveness for cancer induction at moderately high radiation doses. This is supported by clinical studies showing a maximum occurrence of secondary tumors in regions close to the irradiated targets that have received doses less than approximately 6 Gy (13). Another important aspect of therapeutic irradiations is the dose heterogeneity and proposals have been made for its inclusion into calculations (4, 14). Similarly, dose fractionation is also believed to modulate the induction of mutations and hence the cancer risk (15–17). A model proposed to account for these effects (4) had been employed in recent years for several risk analyses in clinical patient groups (18–21).

Differences among radiotherapy techniques have been studied theoretically (2, 3, 22), but other aspects still require investigation. Thus, in the particular case of prostate carcinomas, clinical findings indicate that a therapeutic gain could be achieved through the use of hypofractionation rather than conventionally fractionated external beam radiotherapy (23, 24). The aim this study was to investigate the potential implications for cancer induction of the change of dose, fractionation, and size of the margins between the clinical target volume (CTV) and the planning target volume (PTV).

METHODS AND MATERIALS

Treatment planning data

Risk assessments were carried out on dose–volume histograms (DVH) obtained from 100 patients included in a multi-institutional randomized Phase III study of intermediate-risk localized prostate cancer comparing a hypofractionation schedule for prostate cancer radiotherapy of 7 × 6.1 Gy with a conventionally fractionated schedule of 39 × 2.0 Gy. This article presents only the analysis of the predictions for secondary malignancies based retrospectively on the patient DVHs. It will not present any clinical outcome data from the ongoing trial.

A treatment-planning CT was acquired for each patient in supine position. The CTV was defined as the prostate gland without the seminal vesicles. For approximately half of the patients, the planning target volume (PTV1) was created by adding a margin to the CTV of 4 mm in the posterior direction toward the rectum and 6 mm in the other directions. For the remaining patients, wider margins around the CTV were used to form a PTV2 (10 mm in the posterior and cranial direction and 15 mm in the other directions).

Three-dimensional conformal RT treatment planning was performed for all patients. Further details on the treatment technique for each patient were decided at their respective clinics. The prescribed dose was specified to the International Commission on Radiation Units and Measurements (ICRU) reference point (25, 26).

Calculations were performed for the rectum and the urinary bladder, which are considered the most significant contributors to the increased risk. The rectal volume was defined by the outer contour of the rectum including the rectal wall. The volume of the urinary bladder was defined by the outer contour of the bladder including the muscle wall.

Table 1. Details of the patient data used for this study.

	Narrow margins group	Wide margins group
n	49	51
Treated with 10 MV	3	4
Treated with 18 MV	22	23
Treated with 20 MV	24	24
Age	67.2±5.2 (55–75)	65.9±5.2 (54–75)
CTV (cm^3)	57.2±22.9 (28–152)	55.7±18.6 (24–113)
PTV1 (cm^3)	113.6±35.5 (68–253)	–
PTV2 (cm^3)	–	225.3±51.4 (130–377)
Rectum volume (cm^3)	83.0±40.0 (28–204)	81.4±51.2 (30–331)
Bladder volume (cm^3)	130.9±60.4 (39–338)	136.7±63.2 (43–302)
D_{mean} rectum (%)*	37.1±6.0 (26–58)	55.6±6.3 (43–66)
D_{mean} bladder (%)*	42.5±15.4 (13–75)	56.7±18.0 (24–89)

Abbreviations: CTV = clinical target volume; PTV = planning target volume.

Average values are given with uncertainty defined as one standard deviation. The values in between brackets are the minimum and the maximum values in the patient group.

* Relative to the ICRU reference point dose.

For the purpose of the estimations in this study, it was assumed that the two groups of patients could receive both fractionation schedules. It was therefore possible to investigate the effects on the risk predictions of four combinations of prescribed doses and CTV-to-PTV margins.

The characteristics of the patients are summarized in Table 1.

Risk model

DVHs from the treatment-planning software were used for risk calculations using a model designed to take into account dose heterogeneity and fractionation effects (4). The model has been built on the single-dose competition model proposed by UNSCEAR (11). Thus, for a uniform irradiation with a total dose D, delivered in n fractions, the effect in terms of risk is given by Eq. 1.

$$Effect = \left(\alpha_1 D + \frac{\beta_1 D^2}{n}\right) \times \exp\left[-\left(\alpha_2 D + \frac{\beta_2 D^2}{n}\right)\right], \quad (1)$$

where α_1 and β_1 are parameters describing the induction of carcinogenic mutations in irradiated cells and α_2 and β_2 are parameters describing the cellular survival in irradiated tissues. As detailed elsewhere (4), α_1 is the linear risk coefficient for low-dose irradiation.

For heterogeneous irradiations the total effect is given by the weighted average of the partial effects throughout the volume (4). Thus, for a finite DVH, the total effect is described by Eq 2.

$$Total\ effect = \frac{\sum_i v_i \times Effect(D_i)}{\sum_i v_i}, \quad (2)$$

where v_i is the volume of tissue receiving dose D_i given in n individual fractions and *Effect* (D_i) is the dose response relationship in Eq. 1.