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CLINICAL INVESTIGATION **Prostate**

GRADING-SYSTEM-DEPENDENT VOLUME EFFECTS FOR LATE RADIATION-INDUCED RECTAL TOXICITY AFTER CURATIVE RADIOTHERAPY FOR PROSTATE CANCER

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Purpose: To assess the association between the dose distributions in the rectum and late Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer (RTOG/EORTC), Late Effects of Normal Tissue SOMA, and Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 graded rectal toxicity among patients with prostate cancer treated with RT.

Methods and Materials: Included in the study were 124 patients who received three-dimensional conformal RT for prostate cancer to a total dose of 70 Gy in 2-Gy fractions. All patients completed questionnaires regarding rectum complaints before RT and during long-term follow-up. Late rectum Grade 2 or worse toxicity, according to RTOG/EORTC, LENT SOMA, and CTCAE v3.0 criteria, was analyzed in relation to rectal dose and volume parameters.

Results: Dose-volume thresholds (V40 $\geq$65%, V50 $\geq$55%, V65 $\geq$45%, V70 $\geq$20%, and a rectum volume $\leq$140 cm^3), significantly discriminated patients with late Grade 0–1 and Grade 2 or worse rectal toxicity, particularly using the LENT SOMA and CTCAE v3.0 systems. The rectum volume receiving $\geq$70 Gy (V70) was most predictive for late Grade 2 or worse rectal toxicity with each of the grading systems. The associations were strongest, however, with use of the LENT SOMA system.

Conclusions: Volume effects for late radiation-induced rectal toxicity are present, but their clinical significance depends on the grading system used. This should be taken into account in the interpretation of studies reporting on radiation-induced rectal toxicity. © 2008 Elsevier Inc.

Prostate cancer, Radiotherapy, Dose-volume effects, Rectal toxicity, Toxicity grading systems.

INTRODUCTION

Patients treated with radiation therapy (RT) for prostate cancer are likely to sustain mild to moderate radiation-induced side effects. Some of these side effects may persist or occur months to years after completion of therapy. Currently, an increasing number of patients will be treated with a higher than conventional total radiation dose on the basis of results of a number of prospective randomized studies clearly indicating that dose escalation up to approximately 80 Gy results in a significant improvement of freedom from treatment failure (1, 2). There has been concern that escalation of the total treatment dose might also increase the probability and severity of adverse side effects. This has motivated a number of investigators to study the relation between dose distributions in rectum and bladder and radiation-induced toxicity (3, 4). Some authors have reported that higher dose levels administered to these normal structures resulted in higher incidences of late radiation-induced toxicity, such as rectal bleeding, cramping, urinary problems, and pain (5, 6). For the rectum in particular, dose-volume effect relationships have been studied to unravel the underlying mechanisms of the observed side effects (7, 8).

A number of toxicity grading systems have been developed to classify the severity of treatment-related toxicity, including the grading system of the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer (RTOG/EORTC) (9); the Late Effects of Normal Tissue working group SOMA scales, representing subjective (S), objective (O), medical management (M), and analytic evaluation of injury (A) (LENT SOMA) (10); and more recently, the National Cancer Institute

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Common Terminology Criteria for Adverse Events (CTCAE version 3.0) (11, 12). In general, the grading of treatment-related toxicity depends on the severity of side effects. Grade 1 effects are generally minimal and asymptomatic. Grade 2 effects are generally considered moderate and usually symptomatic, sometimes requiring interventions. Grade 3 effects are considered severe and undesirable with usually multiple and disruptive symptoms, while Grade 4 effects are potentially life-threatening and may result in permanent loss of function.

Unfortunately, symptoms are translated into various grades of toxicity when different grading systems are used. For example, according to the LENT SOMA grading system, a Grade 2 score for rectal toxicity is defined as a stool frequency of five or more stools per day, whereas according to the CTCAE v3.0 system, Grade 2 is defined as an increase of stool frequency with at least four stools reference to baseline. In the studies that focused on radiation-induced rectal toxicity, various grading systems have been used (13). In some cases, special adaptations or combinations of grading systems were used to correlate specific dose-volume parameters to the risk of developing Grade 2 or worse complications (14). In this way, a range of threshold values has been proposed to help evaluate or compare treatment plans for prostate cancer or to define dose constraints for inverse planning (15, 16). The fact that different toxicity grading systems have been used complicates the ability to make general statements regarding these dose-volume toxicity relationships.

Therefore, the main purpose of this prospective study was to grade radiation-induced rectal toxicity of patients receiving RT for prostate cancer using the RTOG/EORTC, the LENT SOMA, and the CTCAE v3.0 grading systems simultaneously and to investigate the association between each of these toxicity grading systems and the dose distributions in the rectum. Eventually, we aimed to apply the different grading systems to identify clinically relevant thresholds for dose volume constraints for the rectum to be used in treatment planning for prostate cancer.

METHODS AND MATERIALS

Patients

The study sample included 124 patients who received three-dimensional (3D)-conformal RT for prostate cancer between 1998 and 2003 at the department of Radiation Oncology of the University Medical Center Groningen. All patients had a World Health Organization (WHO) performance status ≤ 2, no previous treatment for prostate cancer, and good command of the Dutch language. All patients provided informed consent before starting therapy, and the ethics committee at the university approved the procedures followed. All patients received a total dose of 70 Gy in 35 fractions over 7 weeks to the prostate and seminal vesicles. The study population was treated according to two protocols. Group 1 consisted of 95 patients (T1–4, N0–1, M0), and Group 2 consisted of 29 patients (T1–2, N0, M0). Patients in Group 2 were instructed to take laxatives, starting on the day before the planning CT scan, to obtain the scan with an empty rectum. Sixty-three patients received Luteinizing Hormone Releasing Hormone Analogue (LHRH-A) for 6 months, 45 patients received LHRH-A for 36 months, and 16 patients received RT alone.

Treatment simulation, planning, and delivery

A planning CT scan of the pelvis was obtained in treatment position (supine), with a slice thickness and index of 5 mm. All patients had a full bladder during the planning CT scan and during treatment to spare bladder wall and small intestines. The CT data for all patients were transferred to the Helax-TMS 3D treatment-planning system, version 6.1B (Nucletron, Veenendaal, The Netherlands).

In Group 1, the clinical target volume (CTV) was defined as the prostate and the seminal vesicles. The distal part of the seminal vesicles was excluded from the CTV in the last 10 fractions. Each CTV was expanded 10 mm in three dimensions to obtain the planning target volume (PTV), using the automatic expansion algorithm of the treatment-planning system. The prescribed dose to the initial PTV was 50 Gy, using 2 Gy per fraction, five times per week, and the prescribed dose to the boost PTV was 70 Gy, using similar fractionation. The dose was specified to the International Commission on Radiation Units and Measurements reference point (17). In Group 2, the target volumes were similar as in Group 1. However, the prescribed dose to the initial PTV was 46 Gy, using 2 Gy per fraction, five times per week, and the prescribed dose to the boost PTV was 70 Gy, given in an additional 12 fractions of 2 Gy.

The outer contour of the rectum was defined to include rectum and anus. The cranial border of the rectum was defined at the location were the rectum turned horizontally into the sigmoid colon but never superior to the caudal border of the sacroiliac joint. The caudal border of the rectum was defined to include the anus but never inferiorly to the most inferior aspect of the ischial tuberosities.

All patients were treated using a 3D-conformal RT three-field technique (one anterior, one wedged right-lateral, and one wedged left-lateral field, weighted approximately 4:3:3), with 15-MV photons. The lower field edge was typically placed at the inferior most aspect of the ischial tuberosities regardless of the inferior border of the PTV. For all other field edges, multileaf collimator (MLC) shielding was adapted in beam's-eye view, in such a way that the 95% isodose closely encompassed the PTV. Setup accuracy was verified during delivery by matching bony anatomy, and setup errors were corrected by using a shrinking-action-level protocol (18). After four fractions, a setup tolerance level of 3.7 mm was applied in all three directions.

Dose-volume data

For each patient, the relative rectum volumes receiving $\geq$10, 20, 30, 40, 50, 55, 60, 65, and 70 Gy (V10–V70) were calculated. In addition, the mean rectum dose and the rectum volume were obtained from the dose-volume histograms.

Toxicity assessment

To determine the severity and incidence of late (>3 months after the completion of RT) rectal toxicity, patients were asked to complete questionnaires concerning symptoms of rectal injury before the start of RT and at each follow-up visit. These questionnaires were composed in such a way that toxicity grading could be derived according to the RTOG/EORTC and LENT SOMA criteria in addition to objective findings as assessed by the physicians (Table 1). The questionnaires were also suitable to be used in combination with the more recent CTCAE v3.0 criteria. For each questionnaire, we determined whether the assessments resulted in Grade 2 or worse rectal toxicity according to each of the three grading systems. The