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CLINICAL INVESTIGATION **Prostate**

UPDATE OF DUTCH MULTICENTER DOSE-ESCALATION TRIAL OF RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

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Purpose: To update the analysis of the Dutch dose-escalation trial of radiotherapy for prostate cancer.

Patients and Methods: A total of 669 patients with localized prostate cancer were randomly assigned to receive 68 or 78 Gy. The patients were stratified by age, institution, use of neoadjuvant or adjuvant hormonal therapy, and treatment group. The primary endpoint was freedom from failure (FFF), with failure defined as clinical or biochemical failure. Two definitions of biochemical failure were used: the American Society for Therapeutic Radiology and Oncology definition (three consecutive increases in prostate-specific antigen level) and the Phoenix definition (nadir plus 2 μg/L). The secondary endpoints were freedom from clinical failure, overall survival, and genitourinary and gastrointestinal toxicity.

Results: After a median follow-up of 70 months, the FFF using the American Society for Therapeutic Radiology and Oncology definition was significantly better in the 78-Gy arm than in the 68-Gy arm (7-year FFF rate, 54% vs. 47%, respectively; $p = 0.04$). The FFF using the Phoenix definition was also significantly better in the 78-Gy arm than in the 68-Gy arm (7-year FFF rate, 56% vs. 45%, respectively; $p = 0.03$). However, no differences in freedom from clinical failure or overall survival were observed. The incidence of late Grade 2 or greater genitourinary toxicity was similar in both arms (40% and 41% at 7 years; $p = 0.6$). However, the cumulative incidence of late Grade 2 or greater gastrointestinal toxicity was increased in the 78-Gy arm compared with the 68-Gy arm (35% vs. 25% at 7 years; $p = 0.04$).

Conclusion: The results of our study have shown a statistically significant improvement in FFF in prostate cancer patients treated with 78 Gy but with a greater rate of late gastrointestinal toxicity.

Prostate cancer, Randomized trial, External beam radiotherapy, Conformal, Dose escalation, Rectal toxicity.

INTRODUCTION

The incidence of prostate cancer is rapidly increasing in all industrialized countries. External beam radiotherapy (RT) is one of the options used to treat about 8,000 men diagnosed with prostate cancer annually in The Netherlands. The need for an increased radiation dose to greater than conventional levels has been suggested from the dose–response observations by Perez *et al*. (1) and Hanks (2). The past few decades have witnessed the development of new radiation techniques such as three-dimensional conformal RT and intensity-modulated RT (IMRT). These advanced techniques can result in improved conformality of high radiation dose levels to the target volume while sparing normal tissues, reducing complications and possibly permitting safe dose escalation, and thereby improve local control. Studies of dose escalation with three-dimensional conformal RT have been initiated by investigators in North America, the United Kingdom, France, and The Netherlands (3–8). These studies have consistently showed an improvement in freedom from failure (FFF), but no improvement in overall survival (OS), probably because of the competing risk of death from intercurrent illnesses, the short follow-up period, or the of lack of statistical power in these studies.

Because of the increasing need for a good definition for biochemical failure (BF) and recent publications demonstrating that the Phoenix definition (prostate-specific antigen [PSA] nadir plus 2 μg/L after RT) is a better approximation

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of eventual clinical failure (CF) (9–13) than the American Society for Therapeutic Radiology and Oncology (ASTRO) definition, we have compared the rate and pattern of failure using both definitions.

In our first reported outcome results, our trial showed that after a median follow-up of 51 months, a high radiation dose (78 Gy) was beneficial in terms of FFF, without significant differences in freedom from clinical failure (FFCF) or OS (4). In this report, we present the results on outcome and toxicity of the more mature trial with a median follow-up of 70 months.

PATIENTS AND METHODS

Study design

This Phase III multicenter randomized trial was designed to compare two different radiation doses delivered using conformal techniques for patients with localized prostate cancer and was performed in four Dutch institutions.

Participants

Patients with histologically proven Stage T1a-T4 adenocarcinoma of the prostate with an initial PSA (iPSA) level of <60 μg/L were eligible, provided they had no distant metastases and no cytologically or histologically proven positive regional lymph nodes. However, patients with Stage T1a and well-differentiated (or Gleason score <5) Stage T1b-T1c with an iPSA ≤4 μg/L were not included. Also, patients using anticoagulants, who had undergone previous radical prostatectomy or pelvic RT, with previous malignant disease (other than basal cell carcinoma), and with a Karnofsky performance score of ≤70 were excluded. The TNM classification was done according to the American Joint Committee on Cancer 1997 guidelines. All participants provided written informed consent. This study entered 669 patients between June 1997 and February 2003. Patients were randomly assigned to receive either 68 or 78 Gy. Stratification was performed at randomization to ensure balanced groups. Patients were stratified by age (≤70 vs. >70 years), institution (A, B, C, or D), use of neoadjuvant or adjuvant hormonal therapy (HT) (yes vs. no), and treatment group (1, 2, 3, or 4). Patients were stratified into four treatment groups, defined according to the estimated risk of the seminal vesicle (SV) involvement, according to Partin *et al.* (14) (Table 1). Patients who belonged to treatment group 1 had an estimated risk of SV involvement of <10%, those in group 2 had an estimated risk of 10–25%, and patients in Groups 3 and 4 had an estimated risk of >25%.

Retrospectively, patients were also divided into three prognostic risk groups (low, intermediate, and high risk) according to the single-factor model of Chism *et al.* (15). Patients with Stage T1-T2 and Gleason score 2-6 and PSA level of ≤10 μg/L were at low risk, and patients with Stage T3-T4 or Gleason score 8–10 or PSA level >20 μg/L were at high risk. All other patients were at intermediate risk.

Neoadjuvant or adjuvant HT was allowed and prescribed in two institutions (n = 143), mostly to high-risk patients (n= 125) and rarely to intermediate- or low-risk patients (n= 18). The use of HT was well balanced between both treatment arms (Table 2). Institution A used long-term HT (3 years), and Institution B used short-term HT (6 months). Androgen deprivation was achieved using 3-month depot injection of a luteinizing hormone-releasing hormone analog preceded by a short course of cyproterone acetate to prevent testosterone flare.

Radiotherapy

Simulation and treatment were performed with the patient in the supine position with a comfortably full bladder and without specific immobilization. All patients underwent computed tomography scanning of the pelvis in the treatment position. For both treatment arms, the fraction size was 2 Gy prescribed to the isocenter (the International Commission on Radiation Units and Measurements reference point). The mean dose to the planning target volume (PTV) was between –5% and +7% of the prescribed dose, and 99% of the PTV received ≥95% of the prescribed dose. The rectum was defined from the anal verge to the inferior border of the sacroiliac joints or to the point at which the rectum was no longer close to the sacrum. The percentage of the rectum receiving ≥74 Gy was limited to 40%, and the small bowel dose was limited to ≤68 Gy. The PTV included the prostate with or without the SVs as the clinical target volume (CTV), with a margin of 10 mm during the first 68 Gy and 5 mm (except toward the rectum for which it was 0 mm) for the last 10 Gy in the high-dose arm. The CTV for Group 1 was defined as the prostate only, and for Group 4, it was the prostate and SVs. For Groups 2 and 3, the CTV also included the prostate and SVs, but the SVs were excluded from the CTV after 50 and 68 Gy, respectively.

Institutions A, B, and D used a three-field technique (n = 594) and Institution C, a four-field technique (n = 70). For 41 patients in the high-dose arm, an IMRT technique was used for the simultaneous integrated boost in Institution B. For these patients, the boost was irradiated to 78 Gy with a 2-Gy fraction size. The PTV minus the boost region was defined by the 5–10-mm shell formed by the PTV from which the boost region was subtracted. This shell was irradiated to ≥95% of 68 Gy (or 64.6 Gy) in 39 fractions, resulting in a dose per fraction in this shell of 1.9 Gy (95% of 2 Gy) to 1.66 Gy (16).

Follow-up

All patients were scheduled to be seen every 3 months for the first year, every 4 months for the second year, every 6 months for the next 3 years, and annually thereafter. The assessment of disease status included history, clinical examination, and PSA measurement.

Table 1. Treatment group according to risk of involvement of seminal vesicles, as defined by Partin *et al.* (14)

		Stage T1b, T1c, T2a*				Stage T2b–T3a*	Stage T3b–T4*
Gleason score	Differentiation	PSA 0–4 μg/L	PSA 4–10 μg/L	PSA 10–20 μg/L	PSA 20–60 μg/L	PSA 0–60 μg/L	PSA 0–60 μg/L
2–4	Good	1	1	1	2	3	4
5–7	Moderate	1	2	2	3	3	4
8–10	Poor	2	3	3	3	3	4

Abbreviation: PSA = prostate-specific antigen.
* According to American Joint Committee on Cancer 1997 guidelines.