Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 4, pp. 980–988, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.02.073

CLINICAL INVESTIGATION **Prostate**

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

Abrahim Al-Mamgani, M.D.,* Wim L. J. van Putten, M.Sc.,* Wilma D. Heemsbergen, Ph.D.,† Geert J. L. H. van Leenders, M.D., Ph.D.,* Annerie Slot, M.D.,‡ Michel F. H. Dielwart, M.D.,§ Luca Incrocci, M.D., Ph.D.,* and Joos V. Lebesque, M.D., Ph.D.†

*Erasmus Medical Centre–Daniel den Hoed Cancer Center, Rotterdam, The Netherlands; †The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; ‡Radiotherapeutic Institute Friesland, Leeuwarden, The Netherlands; and §Zeeuws Radiotherapeutic Institute, Vlissingen, The Netherlands

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

Reprint requests to: Abrahim Al-Mamgani, M.D., Department of Radiation Oncology, Erasmus Medical Centre–Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA, Rotterdam, The Netherlands. Tel: (+31) 10-7040-704; Fax: (+31) 10-7041-013; E-mail: a.al-mamgani@erasmusmc.nl

Supported by the Dutch Cancer Society (NKB Grants NKI 98-1830 and CKTO 96-10).

Presented at the 49th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), October 28–November 1, 2007, Los Angeles, CA.

Conflict of interest: none.

Received Nov 14, 2007, and in revised form Dec 18, 2007. Accepted for publication Feb 20, 2008.

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.

Table 2. Patient, tumor, and treatment characteristics

Characteristic	68-Gy arm (n = 331)	78-Gy arm (n = 333)
Mean age (y)	68.6	68.8
Median follow-up (mo)	70.3	71
Radiation dose (Gy)		
68	100	
68–76		11
78		89
Hormonal therapy (total)	22	21
Short term	11	9
Long term	11	12
Institution		
A	61	61
B	26	26
C	10	10
D	3	3
Treatment group		
1	17	16
2	20	20
3	46	49
4	17	15
Risk group		
Low	17	19
Intermediate	27	27
High	56	54
Gleason score*		
2–6	49	51
7	34	35
8–10	17	14
Tumor stage		
T1	18	21
T2	45	41
T3	35	37
T4	2	1
PSA level (μg/L)		
0–10	36	41
10–20	38	38
20–60	26	21

Abbreviation: PSA = prostate-specific antigen.

Data presented as percentages, unless noted otherwise.

* For 46 patients, Gleason score was not available and score was assigned according to differentiation grade.

Toxicity

Late radiation side effects were assessed at each follow-up visit, using patient questionnaires and slightly modified Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer scoring criteria (17). We also scored more detailed gastrointestinal (GI) and genitourinary (GU) symptoms (17), designated indicators for RTOG/EORTC Grade 2 or greater toxicity (Table 3).

Endpoints

The primary endpoint was FFF, which was defined as BF or CF, whichever was first. BF was defined according to the ASTRO definition of three consecutive increases in PSA level with backdating to midway between the nadir and the first increase (18). Because of concerns that backdating might influence the timing and degree of BF (19), a second analysis was performed without backdating. In addition to the ASTRO definition, we used the Phoenix definition (increase of $\geq$2 μg/L greater than the PSA nadir after RT) (12). CF was defined as local relapse (palpable and/or biopsy proven), regional relapse, distant metastases (DMs), or the initiation of salvage HT because of an increasing PSA level. The other endpoints were OS and GI and GU toxicity. Cancer-related death was defined as death from locoregional failure or DMs. All other causes of death were considered as unrelated to prostate cancer.

Table 3. Cumulative incidence at 7 years (Kaplan-Meier estimates) for all late GI and GU endpoints, including Grade 2 or greater toxicity indicators

Endpoint	Cumulative incidence at 7 y (%) 68 Gy	78 Gy	p
GI			
RTOG/EORTC Grade $\geq$2	25	35	0.04*
RTOG/EORTC Grade $\geq$3	4	6	0.3
Rectal bleeding (laser/transfusion)	3	8	0.01*
Fecal incontinence (pads >2 d/wk)	7	13	0.02*
High stool frequency ($\geq$6/d)	7	10	0.2
Steroids for proctitis	5	6	0.5
Pain/cramps/tenesmus requiring medication	9	13	0.3
GU			
RTOG/EORTC Grade $\geq$2	41	40	0.6
RTOG/EORTC Grade $\geq$3	12	13	0.6
Haematuria (laser/transfusion)	0.7	0.4	0.5
Urinary incontinence (pads >2 d/wk)	7	7	0.9
High daytime urinary frequency ($\geq$16)	6	5	0.9
Nocturia ($\geq$4)	26	30	0.2
Dysuria requiring medication	12	16	0.3
Urinary obstruction requiring treatment	8	11	0.2

Abbreviations: GI = gastrointestinal; GU = genitourinary; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer.

* Statistically significant (log–rank test) difference (p <0.05).

Statistical analysis

We calculated the FFF, FFCF, and OS using the Kaplan-Meier method, and the differences were assessed with the log–rank test. To detect a clinically relevant difference of 10% in the primary endpoint (FFF), 600 patients were required with sufficiently long follow-up, using a two-sided test with α = 0.05 and power of 80%. The analysis was done according to the intention-to-treat principle. Multivariate analysis of prognostic factors was performed, using Cox proportional hazards regression model, to analyze differences between the two arms. All p values are based on two-sided tests, with $p < 0.05$ considered statistically significant. Retrospectively, we performed subgroup analyses according to risk group (15) and a test of interaction by risk group using odds ratios.

RESULTS

Between June 1997 and February 2003, 669 patients were enrolled in the study. Of these patients, 5 were excluded either because they were ineligible. Of the remaining 664 patients, 331 were randomly assigned to receive 68 Gy and 333 to receive 78 Gy. The median follow-up was 70 months (range, 10–115 months). All the patients in the 68-Gy arm

received the prescribed dose. In the 78-Gy arm, however, 11% received a dose <78 Gy: 6% received 68 Gy because of the dose constraints to the rectum and small bowel, and 3% and 1.8% received 74–76 Gy and 70–72 Gy, respectively, because of acute toxicity, technical problems, or patient request. One patient (0.3%) died during treatment of an unrelated cause and had received only 16 Gy. HT was prescribed to 143 patients; 73 in the low-dose arm and 70 in the high-dose arm. The patient, tumor, and treatment characteristics are listed in Table 2.

Outcome

The FFF rate was significantly better in the 78-Gy arm than in the 68-Gy arm using both the ASTRO definition and the Phoenix definition (7-year FFF rate with ASTRO definition, 54% and 47%, respectively, $p = 0.04$; and with Phoenix definition, 56% and 45%, respectively, $p = 0.03$). Because we knew that the ASTRO definition with backdating might influence the timing and rate of BF, we repeated the analysis without backdating. The FFF remained significantly different, in favor of the high-dose arm (49% and 37%, $p = 0.04$; Fig. 1). No difference was found between the high- and low-dose arms in FFCF rate (70% vs. 68% at 7 years, respectively; $p = 0.68$) or OS rate (75% vs. 75% at 7 years; $p = 0.45$).

Salvage HT was started in 22 patients (12 in low-dose arm and 10 in high-dose arm) because CF had occurred or because of an increasing PSA level but before the point of formal BF (ASTRO definition). Of 83 patients with clinical progression, 40 were in the low-dose arm and 43 in the high-dose arm. A total of 23, 12, and 56 patients developed local failure, regional failure, and DMs, respectively. No significant differences were seen between the two arms regarding the type of CF. In the high-dose arm, 68 patients died, with 45 of the deaths related to prostate cancer. In the low-dose arm, 75 patients died, with 42 deaths related to prostate cancer. The remaining patients died of intercurrent disease (mostly cardiovascular or pulmonary disease) or other malignancies. The type and number of failures, as well as the deaths by treatment arm, are listed in Table 4.

Retrospectively, we did a subgroup analysis using the three risk groups (15) and a test of interaction among these risk groups. The odds ratio of the total group was 0.75 ($p = 0.04$) in favor of the high-dose arm. The benefit of high-dose RT was most apparent in the intermediate-risk group, with an odds ratio of 0.6 (95% confidence interval, 0.33–0.87; $p = 0.01$). A clear trend was seen in the high-risk group, but not in the low-risk group. Furthermore, when this analysis was done with the dose actually given, instead of the dose at randomization, the difference in FFF in the high-risk group was statistically significant ($p = 0.03$).

Toxicity

The cumulative incidence of late GU Grade 2 or greater toxicity was 40% in the high-dose arm and 41% in the low-dose arm at 7 years ($p = 0.6$), and the cumulative incidence of late GI Grade 2 or greater toxicity was increased in the 78-Gy arm (35% vs. 25%, respectively, at 7 years; $p = 0.04$;

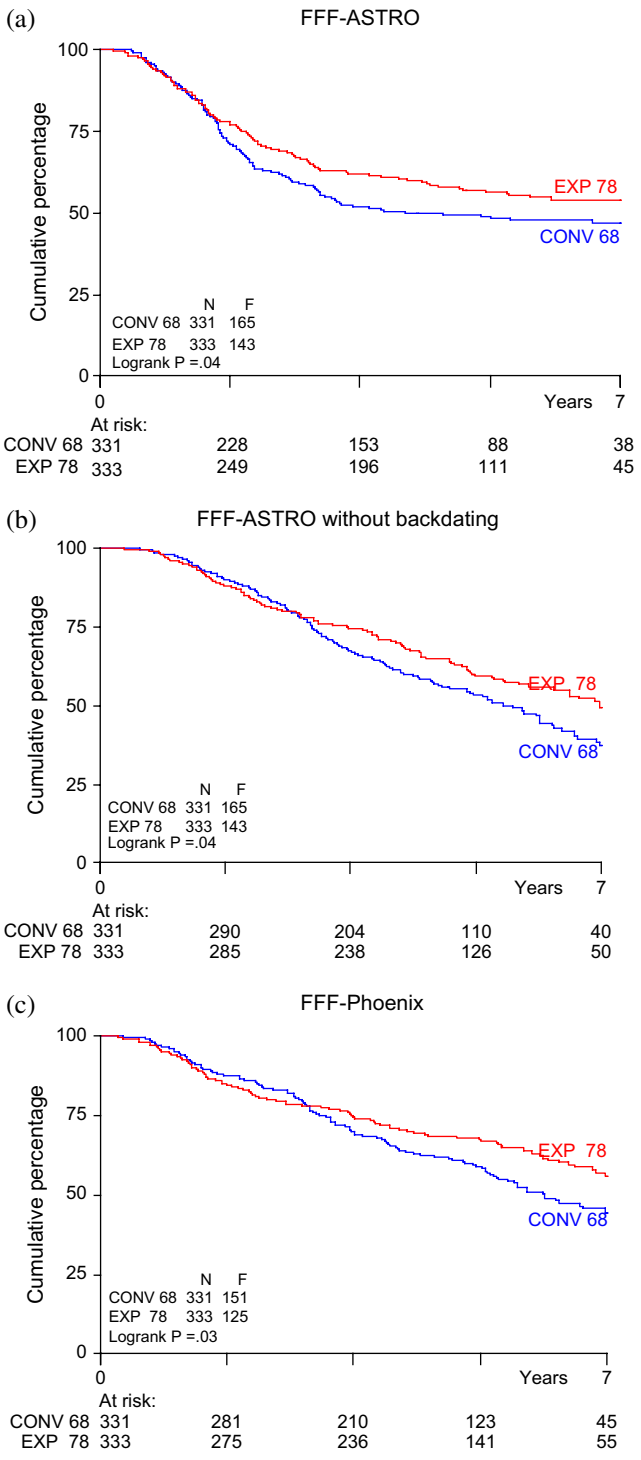

Fig. 1. (a) Kaplan-Meier curve of 7-year rates of freedom from failure (FFF) by dose randomization (68 vs. 78 Gy), defined according to American Society for Therapeutic Radiology Oncology (ASTRO) definition (three consecutive increases in prostate-specific antigen level, backdated to midway between nadir and first increase). (b) Kaplan-Meier curve of 7-year rates of FFF by dose randomization (68 vs. 78 Gy), defined according to ASTRO definition without backdating. (c) Kaplan-Meier curve of 7-year rates of FFF by dose randomization defined according to Phoenix definition (nadir plus 2 μg/L after radiotherapy). CONV = conventional; EXP = experimental.

Table 4. Biochemical failure, clinical failure and death by treatment arm

Variable	Total (n = 664)	68-Gy arm (n = 331)	78-Gy arm (n = 333)
BF (ASTRO)*	244	135	109
BF (Phoenix)*	238	131	107
CF (total)	83	40	43
Local	21	15	6
Regional	5	1	4
DMs	49	21	28
Local and DMs	1	0	1
Local and regional	1	1	0
Regional and DMs	6	2	4
Salvage HT†	22	12	10
Death (total)	143	75	68
Cancer related	87	42	45
Not cancer related	56	33	23

Abbreviations: BF = biochemical failure; CF = clinical failure; DMs = distant metastases; HT = hormonal therapy.

* As first failure before CF.

† Only salvage HT without previous formal ASTRO BF or CF on basis of increasing PSA included.

Fig. 2 and Table 3). No differences were found between the high- and low-dose arms regarding late Grade 3 or greater GU toxicity (13% vs. 12%, respectively; p = 0.6) and late Grade 3 or greater GI toxicity (6% vs. 4%, respectively; p = 0.3). Three patients each (1%) in both treatment arms developed late Grade 4 GU toxicity. Late Grade 4 GI toxicity developed in 3 patients in the high-dose arm (1%) but none in the low-dose arm. All five GI indicators were greater for the high-dose arm. The incidence of rectal bleeding requiring laser treatment or transfusion was significantly increased in the high-dose arm (8% vs. 3%; Table 3 and Fig. 3a). The incidence of rectal bleeding stabilized after 5 years, with no new cases observed after 5 years. The incidence of fecal incontinence was greater by a factor of 2 in the high-dose arm (13% vs. 7%; Table 3 and Fig. 3b), but this did not stabilize.

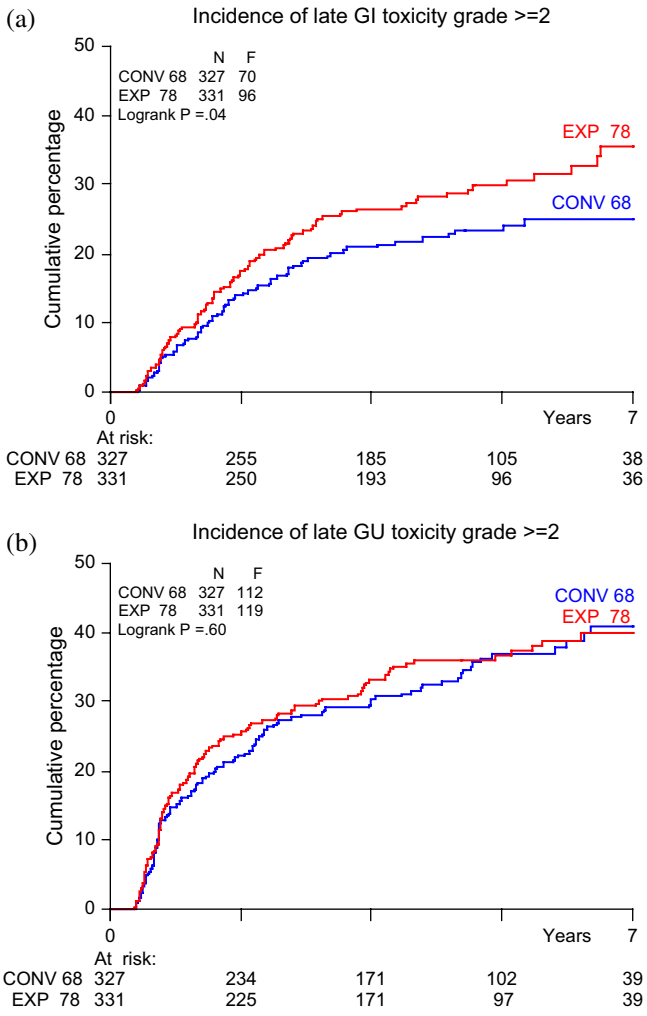

Fig. 2. Kaplan-Meier curves of 7-year cumulative incidence of (a) late Grade 2 or greater gastrointestinal (GI) toxicity and (b) late Grade 2 or greater genitourinary (GU) toxicity by randomization arm. CONV = conventional; EXP = experimental.

DISCUSSION

Outcome

The development of more accurate RT techniques has considerably altered the practice of radiation oncology, allowing for a greater dose to the prostate while limiting the dose to the bladder and rectum. Pollack *et al.* (5) published the first randomized trial, performed at the M.D. Anderson Cancer Center. The long-term results of their trial showed a significant improvement in FFF with high dose RT (8-year FFF rate, 59% for the 70-Gy arm and 78% for the 78-Gy arm, p = 0.004) (20) and also an improvement in FFCF. Dearnaley *et al.* (21) reported a significant improvement in biochemical progression-free survival in the escalated group (74 Gy) compared with the standard group (64 Gy). The 5-year biochemical progression-free survival rate in the escalated and standard group was 71% vs. 60%, respectively (p = 0.007). The hazard ratio for clinical progression-free survival was 0.69 (p = 0.064).

To date, at least five randomized trials have investigated the effect of dose escalation (3, 4, 6–8). All these trials, with the exception of the study by Shipley *et al.* (7), have decisively demonstrated improved biochemical control with an increased dose to the primary prostate tumor.

Biochemical failure

Our trial showed a statistically significant improvement in FFF in prostate cancer patients treated with 78 Gy compared with those treated with 68 Gy using the ASTRO definition (with and without backdating) and the Phoenix definition. In our earlier analysis (median follow-up, 51 months), the 5-year FFF rate using the Phoenix definition was better in the high- than in the low-dose arm (67% vs. 61%, respectively), but this difference was not statistically significant (p = 0.2) (4). At that time, we had already realized that a backdating censoring artifact occurs using the ASTRO definition. Repeating the analysis without backdating also yielded a significant difference (p = 0.02) between the two treatment arms (4). Therefore, it might be possible that in a randomized trial,

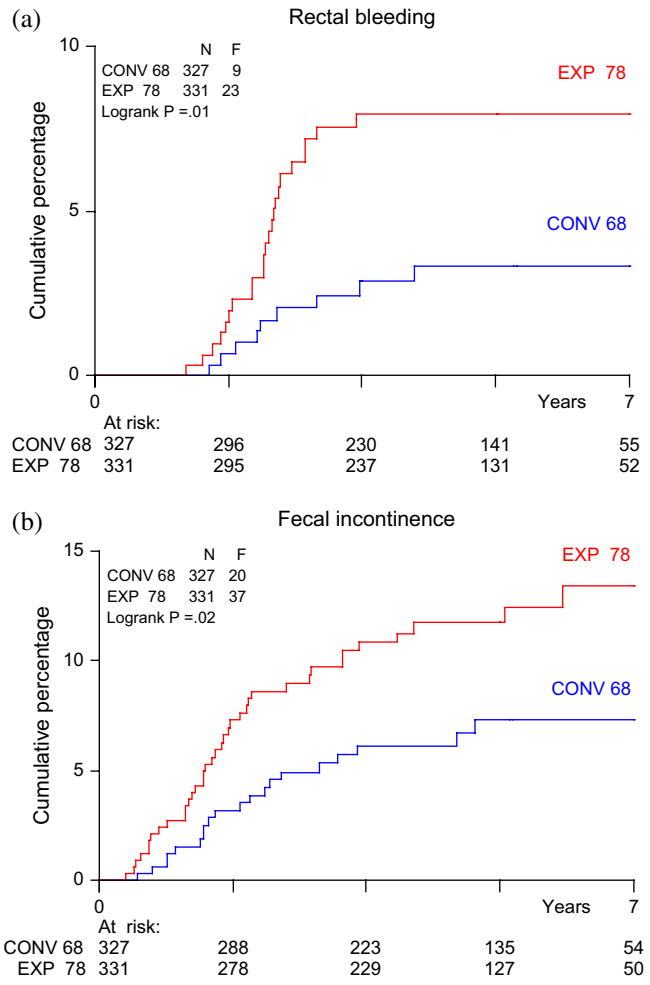

Fig. 3. Kaplan-Meier curve of 7-year cumulative incidence of (a) rectal bleeding requiring laser or transfusion and (b) fecal incontinence by treatment arm. CONV = conventional; EXP = experimental.

the ASTRO definition (with and without backdating) could demonstrate a significant difference between the randomization arms earlier than could be demonstrated using the Phoenix definition.

Definitions of BF

Despite the known shortcomings of the ASTRO definition, it is still used widely as an indication of BF. Because of the recent recommendations (9–13, 22), one should use the Phoenix definition in addition to the ASTRO definition after RT for prostate cancer. The lack of specificity of the ASTRO definition when HT is used is one of its weaknesses. These patients might have a transient increase in the PSA level when the HT is stopped. Thus, false-positive results were possible secondary to such a benign PSA bounce; however, these false-positive results would have been present in both treatment arms. The second problem with the ASTRO definition is the backdating, which was reasonably solved by performing the analysis without backdating. Another reason for using both definitions (ASTRO with and without backdating and Phoenix) is that the ASTRO definition (with backdating) systematically underestimates the occurrence of late BF. Using the Phoenix definition and the ASTRO definition (without backdating), the occurrence of BFs was spread more evenly among Years 0–10 (12, 23). We also have observed the same pattern of failure using these three definitions. Early control rates seemed better using the Phoenix definition, and the later results favor the ASTRO definition with backdating (Fig. 1). The Phoenix definition of BF has been more strongly related to clinical failure than the ASTRO definition and less frequently influenced by the use of HT or the length of follow-up. Vicini *et al.* (10) studied 19 different definitions for BF and their correlation with CF and cause-specific survival and found that the PSA nadir plus 2 μg/L is highly specific and very accurate for identifying BF and also correlates better with CF than do other definitions that use a specific number of consecutive increases in PSA level, such as the ASTRO definition.

Clinical failure

Biochemical control has been shown to correlate not only with local failure, but also with DMs, cause-specific survival, and disease-free survival (9, 10). Morgan *et al.* (23) have shown that the 5-year actuarial DM rates decreased from 8% to 2% with an increasing radiation dose ($p = 0.01$). However, our trial did not show a significant difference between the two treatment arms in terms of FFCF ($p = 0.68$). We believe this was because most of the patients with CF developed an increasing PSA value long before their CF clinically manifested and some of them (n = 22) started salvage HT before their CF was documented. The use of HT is a potential confounding factor in the analysis of the effect of high-dose RT on the rate of DMs and local failure, because HT could destroy micrometastases and subsequently postpone, or even definitively eliminate, the appearance of DM or local recurrence. Our study did not find a lower DM rate in patients treated with higher dose RT. The likely explanations are that our study was underpowered for this purpose and/or because of the use of HT. Morgan *et al.* (23) reported a reduction in the DM rate in two waves. In patients receiving a dose of $\geq$74 Gy, the late occurrence of DMs appeared to be reduced to a greater degree. The reduction in the DM rate in the high-dose arm of our trial might, therefore, become manifest much later than BF. Another factor that made the assessment of CF difficult is that we did not systematically perform prostate repeat biopsy for men with a post-RT increase in PSA, because it was difficult to encourage elderly men to undergo rebiopsy as a surrogate endpoint for local control.

Overall survival

Another critical, but much more complicated, issue is whether improved biochemical control will eventually lead to significantly better OS. The effect of high-dose RT on OS has been reviewed. Mathematical studies by Kuban *et al.* (24) and Yorke *et al.* (25) have predicted an increase in survival of 16–30% if 100% local control could be reached. A retrospective analysis from the RTOG suggested improved survival in patients who received high-dose RT. In contrast to patients who received <66 Gy, high-grade cancer

patients who received radiation doses of ≥66 Gy had a 20% lower risk of death from prostate cancer and a 27% reduction in overall mortality (26). A clear OS benefit from dose escalation was also demonstrated in the systemic review by van Tol-Geerdink *et al*. (27). An estimated increase in 5-year survival of 10–11% was reported when the equivalent dose was increased from 70 Gy to 80 Gy. No single randomized trial, including our own, has yet demonstrated a significant survival benefit from dose escalation. In our trial, the 7-year OS rate was 75% for both treatment arms ($p = 0.45$), probably because our trial was underpowered for this endpoint. Also, no differences were observed in cause-specific mortality between the two arms. However, using this metric might have overestimated the percentage of men who actually died of prostate cancer because competing mortality was substantial. This bias is more pronounced in older men and in patients with low-risk disease, and it increases with each year of follow-up (28).

The already reported and the ongoing dose-escalation trials are going to recruit, in total, >4,500 patients. When the data from all these trials are completely available, a meta-analysis of all these randomized trials should give the answer to this critical issue. The ongoing RTOG 0126 trial, in which OS is the primary endpoint, will probably help us to resolve this problem further.

In the subgroup analysis, the odds ratios for these subgroups were not significantly different from the odds ratio for the total group, because of the overlapping confidence intervals. Therefore, we could not exclude the possibility that low-risk patients, or perhaps a subgroup of them, might also benefit from dose escalation in terms of outcome. Our study was not designed to detect differences between the two treatment arms.

Toxicity

In this study, late morbidity after high-dose RT for localized prostate cancer was in line with the experience from other dose-escalation trials (3, 5, 7, 8). The cumulative incidence of late Grade 2 or greater GU toxicity was the same in both arms, and the cumulative incidence of late Grade 2 or greater GI toxicity was increased in the high-dose arm. No differences were found in the rate of late Grade 3 or greater GI and GU toxicity between the two arms. In an already-reported analysis of toxicity from our group, Peeters *et al*. (17) have shown an increased incidence of Grade 2 or greater late GI toxicity in the high-dose arm, especially in patients with a history of abdominal surgery and in patients with GI symptoms before RT. However, even after excluding these patients from our analysis, we found a significant increase in Grade 2 or greater late GI toxicity in the high-dose arm (data not shown).

Rectal bleeding and fecal incontinence occurred in the high-dose arm about twice as often as in the low-dose arm. However, the incidence of rectal bleeding stabilized at 5 year, with no new patients diagnosed with bleeding. The incidence of fecal incontinence did not stabilize, and, therefore, the overall GI toxicity did not stabilize. In most available dose-escalation studies, however, late GI toxicity seems to stabilize after a follow-up of 5 years. A possible explanation for this difference is that in our study the scoring of fecal incontinence was done by the patients themselves using questionnaires. It is quite possible that in the other studies, this complication was underscored. As reported by other investigators, the incidence of late GI toxicity can be significantly lowered using IMRT. In a study by Zelefsky *et al*. (29), the 3-year actuarial incidence of late GI Grade 2 or greater toxicity in patients treated to 81 Gy with IMRT was 2% compared with 14% in those treated with three-dimensional conformal RT at the same dose ($p = 0.005$).

Although the incidence of late GU toxicity was greater than that of late GI toxicity, no dose-escalation trial has shown a significant difference in late GU toxicity with higher dose RT. However, it is well known that GU symptoms tend to accumulate and continue to emerge during the next 15 years after treatment. Gardner *et al*. (30) showed that a short follow-up period could underestimate urinary problems. In their long-term analysis of toxicity after 77.4 Gy in patients with prostate cancer, they reported a 15-year incidence of Grade 2 or greater GU toxicity of 59%. Despite improved conformality of the high-dose levels of RT, all of the prostatic urethra receives a full dose. Therefore, we share the concerns of the investigators at the Massachusetts General Hospital about the possibility of increasing late GU toxicity with a lengthening follow-up period. We have, therefore, scheduled the next analysis after a median follow-up of about 12 years. However, we also recognize the possible shortcomings of a longer follow-up time, including the high death rate of this already elderly population of patients from other cancers and intercurrent diseases and the usual increase in urinary symptoms with advancing age. These factors make it impossible to distinguish between GU symptoms resulting from the aging process and those due to late radiation effects.

Future research

Even with the substantial gains realized in external beam RT for prostate cancer, further improvement is still possible. In addition to dose escalation, another approach that has received attention is the hypofractionated technique (31). The disparity between an α/β ratio of about 3–4 Gy for late complications and an α/β ratio of ≤ 2 for prostate cancer raises the prospect that one might improve outcomes after conformal RT for prostate cancer with hypofractionation. These schedules might lead to improvement of the therapeutic ratio and could achieve economic and logistic advantages. Therefore, a randomized multicenter Phase III study has been started in The Netherlands to compare the relapse-free survival and toxicity after 78 Gy in daily fractions of 2 Gy with a hypofractionated schedule of 19 fractions of 3.4 Gy, three times weekly to a total dose of 64.6 Gy.

CONCLUSION

The data we have presented have confirmed our earlier findings that dose escalation of RT in patients with localized

prostate cancer is feasible and associated with a statistically significant improvement in FFF, but without differences in FFCF and OS. These findings further substantiate the conclusions of other investigators that dose escalation is strongly recommended for the treatment of patients with prostate cancer, especially for intermediate- and high-risk groups. However, we could not exclude the possibility that patients with low-risk, or at least a subgroup of low-risk patients, might also benefit from high-dose RT. Dose escalation was also associated with a statistically significant increase in late GI toxicity without an increase in late GU toxicity. We believe that the greater rate of late GI toxicity could be dramatically lowered with the use of innovative RT techniques such as IMRT and image-guided RT.

REFERENCES

1. Perez CA, Hanks GE, Leibel SA, *et al*. Localized carcinoma of the prostate (stages T1b, T1c, T2, and T3). *Int J Radiat Oncol Biol Phys* 1993;72:3156–3173.
2. Hanks GE. Optimizing the radiation treatment and outcome of prostate cancer. *Int J Radiat Oncol Biol Phys* 1985;11: 1235–1245.
3. Dearnaley DP, Hall E, Lawrence D, *et al*. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *B J Cancer* 2005;92:488–498.
4. Peeters STH, Heemsbergen WD, Koper PCM, *et al*. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24: 1990–1996.
5. Pollack A, Zagars GK, Starkschall G, *et al*. Prostate cancer radiation dose response: Results of the M.D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53: 1097–1105.
6. Sathya JR, Davis IR, Julian JA, *et al*. Randomized trial comparing iridium implant plus external beam radiation therapy with external beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23: 1192–1199.
7. Shipley WU, Verhey LJ, Munzenrider JE, *et al*. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone. *Int J Radiat Oncol Biol Phys* 1995;32:3–12.
8. Zietman AL, DeSilvio ML, Slater JD, *et al*. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. *JAMA* 2005;294:1233–1239.
9. Horwitz EM, Thames HD, Kuban DA, *et al*. Definition of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation alone: A multi-institutional pooled analysis. *J Urol* 2005; 173:797–802.
10. Vicini FA, Kestin LL, Martinez AA. The correlation of serial prostate specific antigen measurements with clinical outcome after external beam radiation therapy of patients for prostate carcinoma. *Cancer* 2000;88:2305–2318.
11. Kestin LL, Vicini FA, Martinez AA, *et al*. Practical application of biochemical failure definitions: What to do and when to do it. *Int J Radiat Oncol Biol Phys* 2002;53:304–315.
12. Roach M III, Hanks G, Thames H Jr., *et al*. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965–974.
13. Thames H, Kuban D, Levy L, *et al*. Comparison of alternative biochemical failure definitions based on clinical outcome in 4839 prostate cancer patients treated by external beam radiotherapy between 1986 and 1995. *Int J Radiat Oncol Biol Phys* 2003;57:929–943.
14. Partin AW, Yoo J, Carter HB, *et al*. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol* 1993;150: 110–114.
15. Chism DB, Hanlon AL, Horwitz EM, *et al*. A comparison of the single and double factor high-risk models for risk assignment of prostate cancer treated with 3D conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;59:380–385.
16. Bos LJ, Damen EMF, de Boer RW, *et al*. Reduction of rectal dose by integration of the boost in the large-field treatment plan for prostate irradiation. *Int J Radiat Oncol Biol Phys* 2002;52:254–265.
17. Peeters ST, Heemsbergen WD, van Putten WL, *et al*. Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005;61:1019–1034.
18. Cox J, Grignon D, Kaplan R, *et al*. Consensus statement: Guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1035–1041.
19. Gretzer MB, Trock BJ, Han M, *et al*. A critical analysis of the interpretation of biochemical failure in surgically treated patients using the American Society for Therapeutic Radiology and Oncology criteria. *J Urol* 2002;168:1419–1422.
20. Kuban DA, Tucker SL, Dong L, *et al*. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67–74.
21. Dearnaley DP, Sydes MR, Graham JD, *et al*. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;6:459–460.
22. Buyyounouski MK, Hanlon AL, Pollack A, *et al*. Defining biochemical failure after radiotherapy with and without androgen deprivation for prostate cancer. *Int J Radiat Oncol Biol Phys* 2005;63:1455–1462.
23. Morgan PB, Hanlon AL, Horwitz EM, *et al*. Radiation dose and late failures in prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;67:1074–1081.
24. Kuban DA, El Mahdi AM, Schellhammer PF. Potential benefit of improved local tumor control in patients with prostate carcinoma. *Cancer* 1995;75:2373–2382.
25. Yorke ED, Fuks Z, Norton L, *et al*. Modeling the development of metastases from primary and locally recurrent tumors: Comparison with clinical data base for prostate cancer. *Cancer Res* 1993;53:2987–2993.
26. Valicenti R, Lu J, Pilepich M, *et al*. Survival advantage from higher-dose radiation therapy for clinically localized prostate cancer treated on the Radiation Therapy Oncology Group trials. *J Clin Oncol* 2000;18:2740–2746.
27. van Tol-Geerdink JJ, Stalmeier PF, Pasker-de Jong PC, *et al*. Systematic review of the effect of radiation dose on tumor control and morbidity in the treatment of prostate cancer by 3D-CRT. *Int J Radiat Oncol Biol Phys* 2006; 64:5343–5345.
28. Albersten PC, Hanley JA, Murphy-Setzko M. Statistical considerations when assessing outcomes following treatment for prostate cancer. *J Urol* 1999;162:439–444.

29. Zelefsky MJ, Fuks Z, Hunt M, *et al*. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 2001;166: 876–881.
30. Gardner BG, Zietman AL, Shipley WU, *et al*. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. *J Urol* 2002;167: 123–126.
31. Lukka H, Hayter C, Julian JA, *et al*. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 2005;23:6132–6138.