Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 1, pp. 67–74, 2008

0360-3016/08/$–see front matter

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doi:10.1016/j.ijrobp.2007.06.054

CLINICAL INVESTIGATION **Prostate**

LONG-TERM RESULTS OF THE M. D. ANDERSON RANDOMIZED DOSE-ESCALATION TRIAL FOR PROSTATE CANCER

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Purpose: To report the long-term results of a randomized radiotherapy dose escalation trial for prostate cancer.
Methods and Materials: From 1993 to 1998, a total of 301 patients with stage T1b to T3 prostate cancer were accrued to a randomized external beam dose escalation trial using 70 Gy versus 78 Gy. The median follow-up is now 8.7 years. Kaplan-Meier analysis was used to compute rates of prostate-specific antigen (PSA) failure (nadir + 2), clinical failure, distant metastasis, disease-specific, and overall survival as well as complication rates at 8 years post-treatment.
Results: For all patients, freedom from biochemical or clinical failure (FFF) was superior for the 78-Gy arm, 78%, as compared with 59% for the 70-Gy arm ($p = 0.004$, and an even greater benefit was seen in patients with initial PSA >10 ng/ml (78% vs. 39%, $p = 0.001$). The clinical failure rate was significantly reduced in the 78-Gy arm as well (7% vs. 15%, $p = 0.014$). Twice as many patients either died of prostate cancer or are currently alive with cancer in the 70-Gy arm. Gastrointestinal toxicity of grade 2 or greater occurred twice as often in the high dose patients (26% vs. 13%), although genitourinary toxicity of grade 2 or greater was less (13% vs. 8%) and not statistically significantly different. Dose–volume histogram analysis showed that the complication rate could be significantly decreased by reducing the amount of treated rectum.
Conclusions: Modest escalation in radiotherapy dose improved freedom from biochemical and clinical progression with the largest benefit in prostate cancer patients with PSA >10 ng/ml.

Prostate cancer, Radiotherapy, Dose, External beam, Randomized.

INTRODUCTION

With data emerging on prostate-specific antigen (PSA) failure rates after external beam radiation, which appeared higher than those previously documented clinically, and with mounting evidence for a dose–response relationship for prostate cancer, a dose-escalation trial was opened at The University of Texas M. D. Anderson Cancer Center in 1993. This was the first randomized trial in the PSA era that showed the benefit of higher radiation doses for prostate cancer. Previously reported results of this study supported dose escalation for patients with pretreatment PSA values >10 ng/ml (1). All patients have now been treated at least 8 years ago, and follow-up to 12 years is available. A more sensitive and specific PSA failure definition for patients treated by radiation has been tested and can now be applied (2), and the data on clinical failure have matured. Accordingly, this is an updated analysis confirming previous findings and also reporting additional risk group, clinical outcome, and survival data with the benefit of long-term follow-up.

METHODS AND MATERIALS

Protocol eligibility and goals

A clinical protocol was opened in 1993 to test the hypothesis that 78 Gy compared with 70 Gy (or an 8-Gy dose increase) would result in an absolute increase in freedom from failure, including biochemical failure, of 15% for patients treated with definitive external beam radiation for prostate cancer. The procedures followed were in accordance with the ethical standards of the Institutional Review Board. Eligibility criteria were as follows: stage T1 to T3 N0M0 based on the 1992 American Joint Commission on Cancer staging system (3), pathologic review by The University of Texas M. D. Anderson Cancer Center, a pretreatment serum PSA, no previous

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Presented at the 48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), Philadelphia, PA, November 5–9, 2006.

Conflict of interest: none.

Received Jan 2, 2007, and in revised form June 29, 2007. Accepted for publication June 30, 2007.

history of pelvic radiation, radical prostatectomy, or androgen ablation. Stratification was based on the pretreatment PSA level: PSA <10 ng/ml; >10 to 20 ng/ml; and >20 ng/ml. The trial met accrual and closed in 1998. A total of 305 patients were entered and 301 were assessable, 150 in the 70 Gy arm and 151 in the 78 Gy arm. Four patients were not included in the analysis: 2 withdrew before receiving radiation, 1 refused further radiation 3 weeks into treatment, and pathologic confirmation of prostate cancer at The University of Texas M. D. Anderson Cancer Center was lacking in 1 patient. In addition, 2 patients randomized to the 78 Gy arm received 70 Gy, 1 because of planning difficulties caused by obesity and 1 who withdrew consent for 78 Gy. The analysis presented is based on intent to treat.

Patient characteristics

Tumor stage, pretreatment PSA, Gleason score, and risk group for all patients are listed in Table 1. There was no statistically significant difference at a level of $p = 0.05$ between the 70-Gy and 78-Gy arms for any of these variables. Risk groups were determined by the National Comprehensive Cancer Network Guidelines (4). Groups were defined as follows: low-risk, stage <T2a and Gleason score ≤6 and PSA ≤10 ng/ml; high-risk, stage T3 or Gleason score ≥8 or PSA >20 ng/ml; intermediate-risk, all others. The median age was 69 years for each arm. Follow-up ranged from 0.4 to 12.5 years for the entire cohort, with a median follow-up of 8.7 years. Of the patients, 74% were alive at the time of this analysis. The median follow-up for surviving patients was 9.5 years.

Treatment

A full description of the radiation technique used in this study has been previously published (1). Briefly, in both arms the fractional dose was 2 Gy per day and prescribed to isocenter. All patients were initially treated with a conventional four-field box technique to 46 Gy. Typical field sizes were 11 × 11 cm for the anterior and posterior fields and 11 × 9 cm for the lateral fields with a small block over the anterior bladder and the posterior half of the rectum. Patients on the 70-Gy arm then had a small field reduction for both anterior/posterior and lateral dimensions, to approximately 9 × 9 cm. For patients on the 78-Gy arm, a three-dimensional, six-field conformal boost was used after the first 46 Gy. The clinical target volume (CTV) included the prostate and seminal vesicles for both study arms, and although the 70 Gy group underwent conventional treatment planning, a CT scan was done during the first week of treatment to confirm that the CTV was adequately covered. Margins from the CTV to the block edge were 1.25 to 1.5 cm in the anterior and inferior dimensions and 0.75 to 1.0 cm in the posterior and superior dimensions.

Table 1. Patient characteristics by treatment arm

Factor	70-Gy arm (n = 150)	78-Gy arm (n = 151)
T-stage		
T1−T2	125 (83%)	117 (77%)
T3	25 (17%)	34 (23%)
Gleason score		
2−6	70 (46%)	76 (50%)
7	55 (37%)	48 (32%)
8−10	25 (17%)	27 (18%)
Pre-Tx PSA		
<10 ng/ml	97 (65%)	98 (65%)
>10 ng/ml	53 (35%)	53 (35%)
Risk group		
Low	31 (21%)	30 (20%)
Intermediate	71 (47%)	68 (45%)
High	48 (32%)	53 (35%)

Abbreviation: Pre-tx PSA = pretreatment prostate-specific antigen.

Complication grading

Late bladder and rectal toxicity were graded using the Radiation Therapy Oncology Group (RTOG) (5) and Late Effects Normal Tissue Task Force scales (6) as modified by Hanlon *et al*. (7). A description of late toxicities by grade is contained in Table 2.

Endpoints and statistical analysis

The primary endpoint of the trial was freedom from clinical and/or biochemical failure (FFF). Although a standard definition of biochemical failure was not in practice when this trial was designed, the ASTRO definition (8) was used in the previous analysis (1). However, the recent Radiation Therapy Oncology Group–American Society for Therapeutic Radiology and Oncology Consensus Conference report points out the problems with this definition and advocates use of the nadir + 2 ng/ml failure definition, which is more sensitive and specific for eventual clinical failure, performs better in regression analysis comparing definitions, and eliminates backdating (2). Therefore, the nadir + 2 ng/ml failure definition was used to define PSA failure in this updated report. Additional failure definition criteria included local, distant, and nodal recurrence before PSA failure and the administration of salvage hormonal therapy. Secondary study endpoints were overall survival and distant metastasis; disease-specific survival was also analyzed. An event in the cause-specific survival analysis was defined as death due to prostate cancer or death with progressive metastatic disease. Local failure was defined as palpable evidence of disease confirmed by biopsy or positive biopsy performed because of a rising serum PSA. Although routine prostate biopsy at 2 years after treatment was done in 168 patients, this alone did not define local recurrence, since not all patients were biopsied and not all patients with positive biopsy showed evidence of disease progression either clinically or biochemically. These routine biopsy results have been presented in a separate report (9) and have also been updated (10).

All statistical analyses were performed using Stata statistical software, release 9 (StataCorp, College Station, TX). Differences in prognostic patient characteristics and stratification criteria between treatment groups were assessed using the χ^2 test. Kaplan-Meier analysis was used to determine freedom from failure, overall, cause-specific, and distant metastatic-free survival, and freedom from toxicity in each study arm as a function of time after the end of radiotherapy. Outcome generally was reported at 8 years post-treatment because the available number of patients in some subgroup analyses became small at 10 years. Comparisons between groups were made using the log-rank test. A Cox proportional hazards model was used for multivariate analysis. All reported p values are nominal values and not corrected for multiplicity of comparisons.

RESULTS

Outcomes

Crude numbers of patients with biochemical, local, nodal, and distant failure by treatment arm are listed in Table 3. Only 2 patients received hormonal therapy before another type of failure was documented. Freedom from biochemical failure or clinical failure (FFF) was significantly different for patients treated to 78 Gy versus 70 Gy, $p = 0.004$ (Fig. 1). The

Table 2. Modified Radiation Therapy Oncology Group–Late Effects Normal Tissue (RTOG-LENT) late toxicity grading scale

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lower gastrointestinal	Excess bowel movements twice baseline. Slight rectal discharge or blood.	More than two antidiarrheals/week. Two or fewer coagulations for bleeding. Occasional steroids for ulceration. Occasional dilatation. Intermittent use of incontinence pads. Regular nonnarcotic or occasional narcotic for pain.	More than two antidiarrheals/day. At least one blood transfusion or more than two coagulations for bleeding. Prolonged daily steroid enemas. Hyperbaric oxygen for ulceration. Regular dilation. Daily use of pads for incontinence. Regular narcotic for pain.	Dysfunction requiring surgery. Perforation. Life- threatening bleeding.	Fatal toxicity
Genitourinary	Nocturia twice baseline. Microscopic hematuria. Light mucosal atrophy and minor telanglectasia.	Moderate frequency. Nocturia more than twice baseline. Generalized telanglectasia. Intermittent macroscopic hematuria. Two or fewer blood transfusions. Two or fewer coagulations. Regular nonnarcotic or occasional narcotic for pain.	Severe frequency and dysuria. Nocturia more frequent than once every hour. Reduction in bladder capacity (150 cc). Frequent hematuria. More than two transfusions. More than one coagulation for hematuria. Regular narcotic for pain.	Severe hemorrhagic cystitis. Ulceration. Requirement for urinary diversion and/or cystectomy.	Fatal toxicity

difference in FFF between the two study arms increased with time (85% vs. 78% at 5 years, 78% vs. 59% at 8 years, and 73% vs. 50% at 10 years). When patients were stratified by initial PSA level, those with PSA >10 ng/ml derived the greatest benefit from dose escalation (78% vs. 39% FFF at 8 years, $p < 0.001$; Fig. 2a). There were too few patients (16) with an initial PSA >20 ng/ml to analyze separately, and combining these patients with the group with the PSA of 10 to 20 ng/ml did not alter the results of the comparison between the two dose levels. In patients with an initial PSA level <10 ng/ml, there was no significant difference in FFF between treatment arms (78% vs. 66%), at 8 years post-therapy ($p = 0.237$, Fig. 2b).

When analyzed by risk group, at 8 years postradiation, patients with low-risk disease treated to 78 Gy had a FFF of 88% versus those treated to 70 Gy, who had an FFF of 63% ($p = 0.042$, Fig. 3). Interestingly, the intermediate-risk patients as an entire group showed no statistically significant difference in FFF based on dose level ($p = 0.36$) with 8-year FFF of 86% for patients treated to 78 Gy and 76% for those treated to 70 Gy (Fig. 4a). However, intermediate-risk patients with an initial PSA >10 ng/ml did show a greater difference in FFF when dose was escalated (94% vs. 65%), as well as a trend toward statistical significance ($p = 0.076$, Fig. 4b) Intermediate-risk patients with an initial PSA ≤10 ng/ml had similar FFF at both the 70-Gy and 78-Gy levels. Patients with high-risk disease showed a significant difference in FFF based on dose (63% vs. 26%, $p = 0.004$; Fig. 5). Of note however, is that when the high-risk group was divided by PSA level, only those patients with a PSA level >10 ng/ml showed a difference in FFF based on dose level, similar to the intermediate-risk patients. It should be noted that risk group

Table 3. Crude incidence of clinical and biochemical failure by treatment arm

Failure	70-Gy arm ($n = 150$)	78-Gy arm ($n = 151$)
PSA	36	25
Local	12	7
Nodal	6	2
Distant	8	2
Salvage+	0	2

Salvage+ indicates salvage hormonal therapy as first failure event.

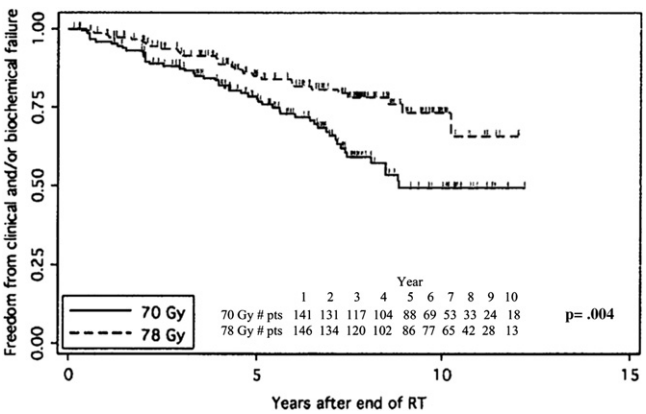

Fig. 1. Freedom from failure for all patients treated to 78 Gy versus 70 Gy.

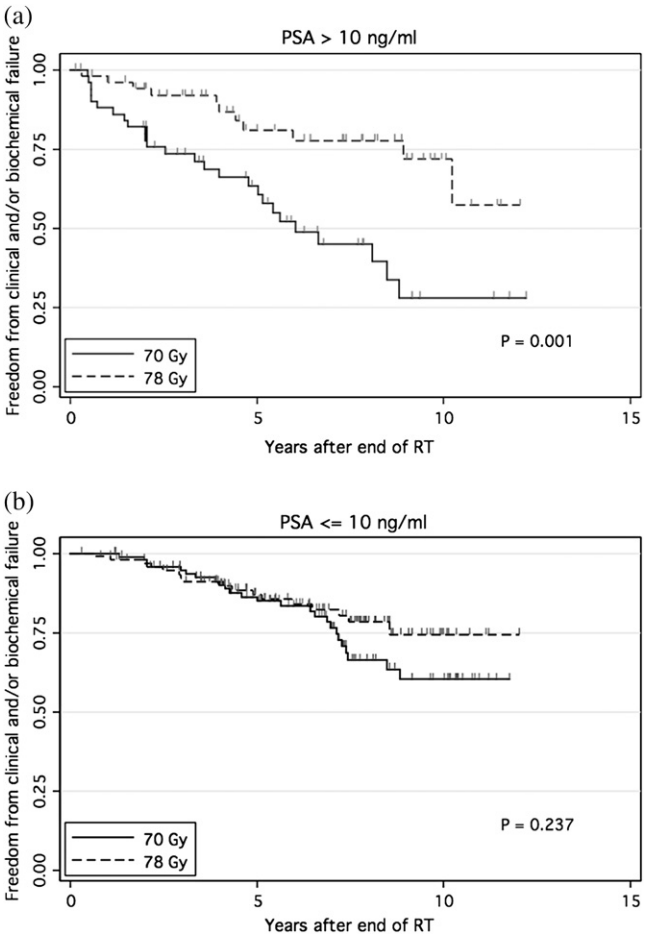

Fig. 2. Freedom from failure for patients with pretreatment prostate-specific antigen >10 ng/ml (a) and <10 ng/ml (b).

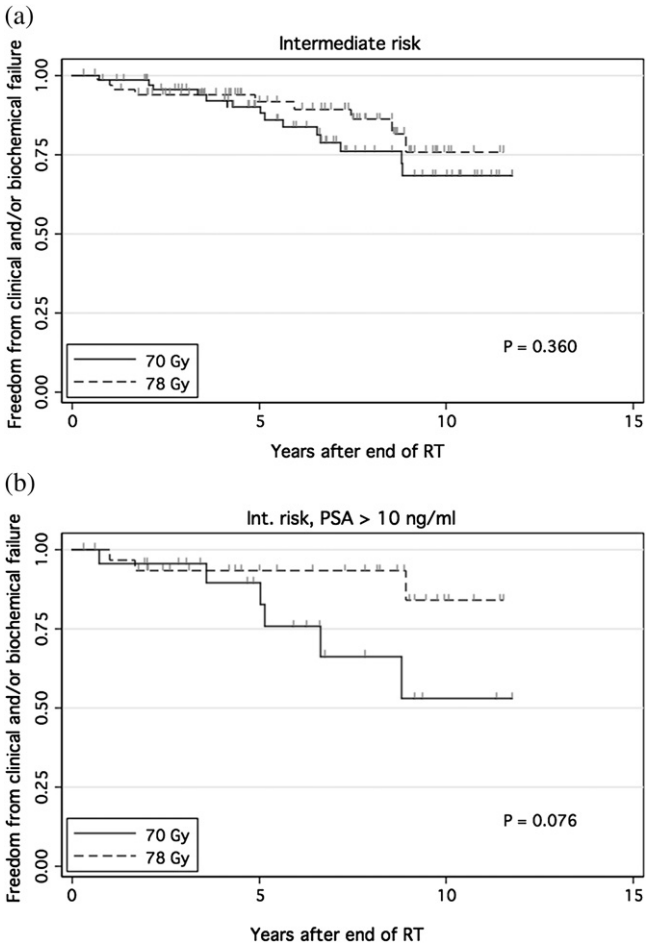

Fig. 4. Freedom from failure for all intermediate-risk patients (a) and those with prostate-specific antigen >10 ng/ml (b).

analysis was not reported in the original study, and although this was not a stratification factor, risk groups were evenly distributed between the two treatment arms.

In multivariate Cox proportional hazards analysis, tumor stage, Gleason score, dose, and initial PSA as a categorical variable, were all significant in predicting FFF. To more fully investigate which patients benefited most from dose escalation, these factors were explored particularly in regard to their interaction with dose. The only interaction retained as being significant in the Cox model was the interaction of dose with PSA >10 ng/ml, indicating that these are the patients who benefited most from dose escalation.

There was a significant difference in clinical failure based on dose as well ($p = 0.014$). Of the patients, 93% treated to

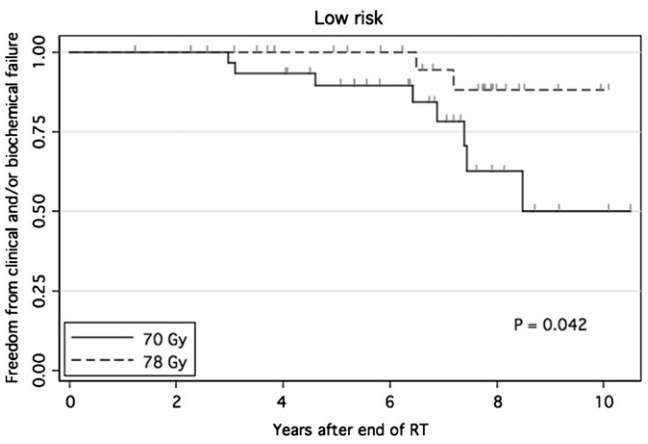

Fig. 3. Freedom from failure for low-risk patients.

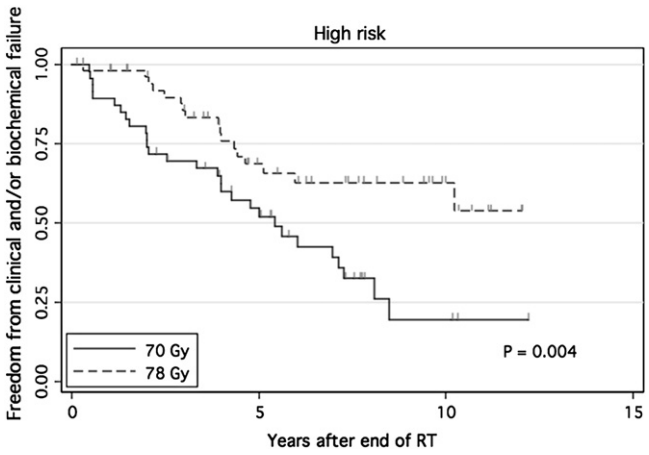

Fig. 5. Freedom from failure for high-risk patients.

78 Gy were clinically disease-free at 8 years post-treatment as compared with 85% of patients who were treated to 70 Gy. Although distant metastasis has been documented in only 10 patients to date, 8 of these were in the 70-Gy arm. For the entire cohort, freedom from distant metastasis after 70 Gy versus 78 Gy was 95% versus 99%, and the p value was marginally significant ($p = 0.059$; Fig. 6). However, all 10 patients had high-risk disease, and among the high-risk patients, the difference reached statistical significance at $p = 0.035$, with 83% versus 96% of patients distant disease-free at 8 years.

Although a difference in overall survival has not been seen, 78% versus 79% at 8 years (Fig. 7), twice as many patients either died of their cancer or are alive with disease in the 70-Gy arm, 43 patients versus 21 patients (Table 4). More patients died of other causes without detectable prostate cancer in the 78-Gy arm, and there was no evidence that the cause of death was treatment-related. Less than 10% of patients (equal numbers in both arms) had a cause of death which is unknown. The cause-specific survival difference was marginally significant in favor of the 78-Gy arm at 99% versus 95% ($p = 0.063$; Fig. 8), but four times as many patients died of prostate cancer in the 70 Gy arm (8 vs. 2).

Toxicity

Crude gastrointestinal (GI) and genitourinary (GU) complications are reported by treatment arm in Table 5, and freedom from complications greater than grade 2 are compared actuarially in Figures 9a and 9b. The 10-year incidence of GI toxicity greater than grade 2 was 13% for patients treated to 70 Gy as compared with 26% for those on the 78-Gy arm ($p = 0.013$). Grade 3 GI toxicity occurred in 1% of patients treated to the lower dose and in 7% of those treated to the higher dose level ($p = 0.018$). Of note is that normal tissue dose–volume guidelines were not yet defined nor followed during the study period. GU toxicity of grade 2 or greater was 8% for the 70-Gy arm and 13% for the 78-Gy arm at 10 years post-treatment, whereas grade 3 GU toxicity was 5% versus 4%, respectively, and neither comparison showed

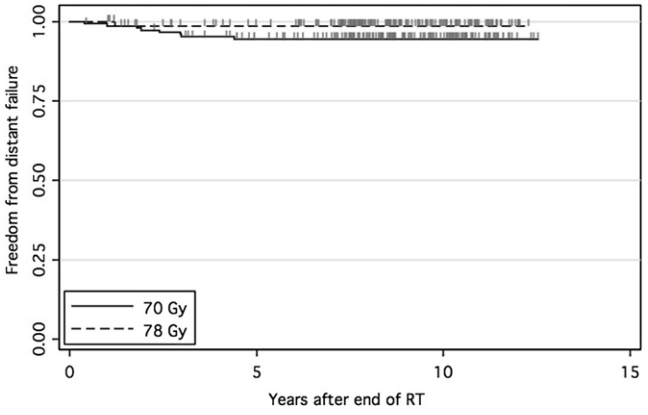

Fig. 6. Freedom from distant metastasis for all patients.

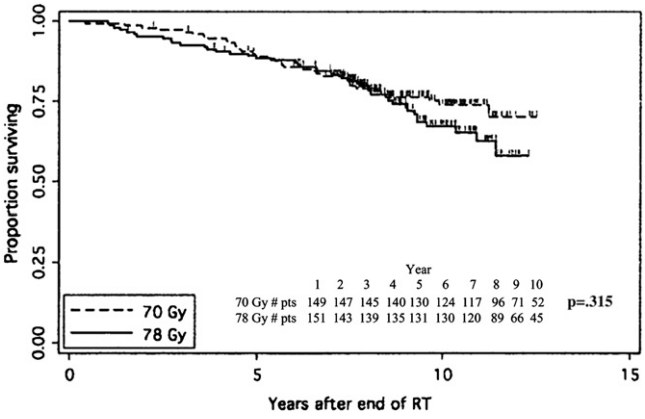

Fig. 7. Overall survival for all patients.

a statistically significant difference. There were no grade 4 or grade 5 GI or GU complications.

As shown in our previous randomized trial report (1) and in the report by Storey *et al.* (11), the amount of rectum treated can significantly affect the GI complication rate. Dose–volume histograms were available for patients treated with the conformal boost to 78 Gy. As reported previously, when <25% of the rectum was treated to >70 Gy, the grade 2 or greater complication rate at 6 years post-treatment was much reduced, 16% as compared with 46% when this dose–volume cutpoint was exceeded (1). We have since found that dose–volume parameters appear to be a continuous variable, and that lower dose points, in fact, may be even more significant in predicting rectal morbidity (Fig. 10). Our previous publications using normal tissue complication probability modeling support this premise as well (12, 13).

DISCUSSION

When published in 2000, the M. D. Anderson dose-escalation trial was the first PSA era randomized trial to show the anticipated benefit of higher dose in tumor control (14). For the preceding 10 to 15 years, there was a growing body of evidence to support higher radiation doses for localized prostate cancer from both prospective and retrospective trials (15–17) as well as from the randomized trial from Massachusetts General Hospital, which compared 67.2 Gy with photons to 75.6

Table 4. Disease status of study patients

Category	70-Gy arm ($n = 150$)	78-Gy arm ($n = 151$)
Alive, NED	79	88
Alive, WD	35	19
Dead, NED	12	20
Dead, OC	2	6
Dead, WD	1	3
Dead, CAP	8	2
Dead, UNK	13	13

Abbreviations: CAP = carcinoma of the prostate; NED = no evidence disease; OC = died of other cause and no prostate-specific antigen (PSA) within 1 year of death; UNK = unknown; WD = with disease (clinical or biochemical).

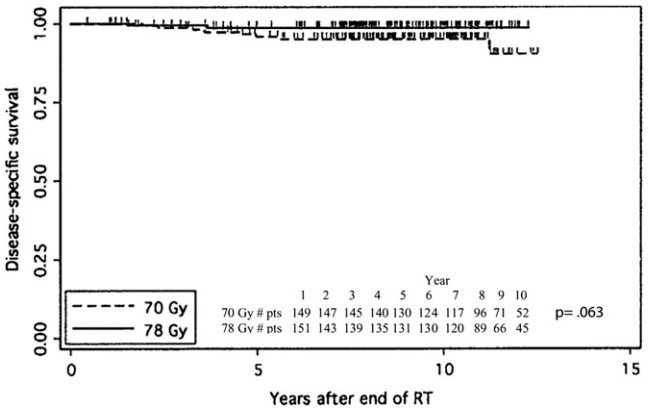

Fig. 8. Disease-specific survival for all patients.

Cobalt Gray Equivalent (GyE) delivered through a combination of photon and proton therapy (18). The M. D. Anderson trial was updated in 2002, and since that time two additional randomized trials have reported positive results with regard to dose escalation (19, 20). Zietman *et al*. randomized 393 patients with stage T1b to T2b prostate cancer to either 70.2 GyE or 79.2 GyE. There was a 19% absolute difference in PSA disease-free survival at 5 years post-treatment using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition, 61% versus 80% (19). The advantage in the higher dose group was seen nearly equally in the low-risk and the intermediate- to high-risk groups. Although a previous retrospective analysis from Memorial Sloan-Kettering Cancer Center showed a dose benefit in the low-risk group (16), the Zietman *et al*. study was the first randomized trial to show these results (19). Our current update, with longer follow-up, now shows the same. However, it should be noted that the original stratification in the M. D. Anderson trial was by initial PSA (<10 ng/ml vs. >10 ng/ml) and not by risk group, and only the group with PSA >10 ng/ml showed a significant dose response. Of note is that very few patients with PSA >20 ng/ml were included in this trial, such that the proven benefit is mainly in patients with a PSA in the range of 10 to 20 ng/ml.

The recently reported study by Peeters *et al*. compared 664 patients with stage T1b to T4 who were randomized to receive either 68 or 78 Gy (20). In this trial there was a 10% absolute difference in PSA failure-free survival favoring the high dose arm using the ASTRO definition (64% vs. 54%), at 5 years post-treatment. In risk group analysis, there was a significant difference in PSA failure (15% absolute)

Table 5. Crude incidence of complications by grade

	Complication grade			
Group	0	1	2	3
GI complications				
70-Gy arm	77	55	15	2
78-Gy arm	71	42	28	10
GU complications				
70-Gy arm	100	35	7	7
78-Gy arm	114	21	11	5

Complications are listed as events; a given patient may have had more than one event.

Abbreviations: GI = gastrointestinal; GU = genitourinary.

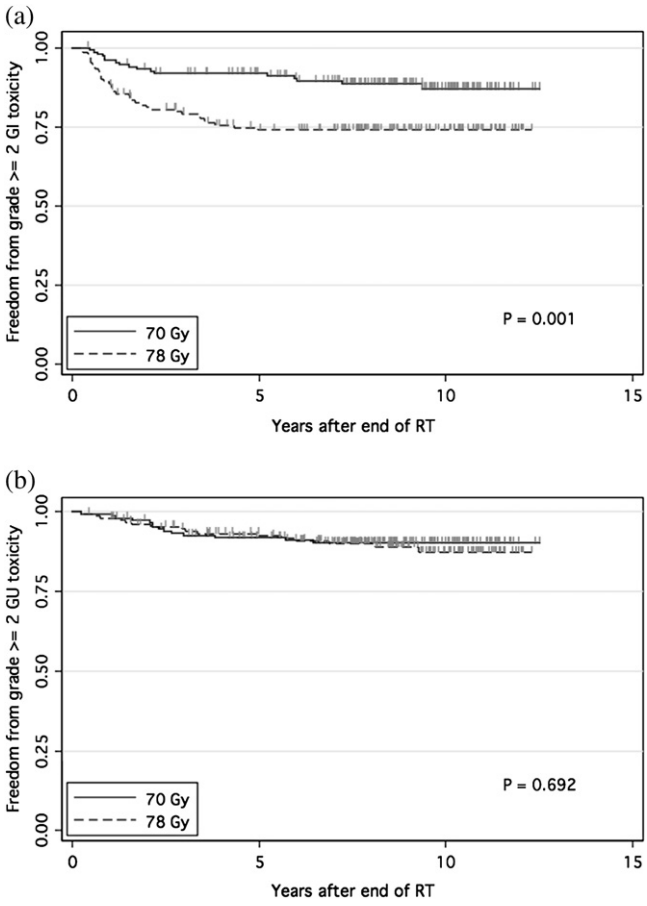

Fig. 9. Freedom from gastrointestinal (a) and genitourinary (b) complications of grade 2 or greater.

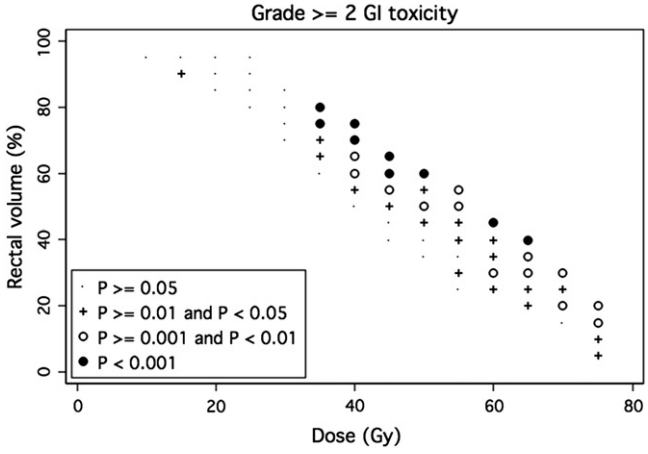

Fig. 10. Gastrointestinal toxicity of grade 2 or greater and the significance of various dose–volume cutpoints considered in increments of 5 Gy (dose) and 5% (volume). Symbols show comparisons for which there at least 10 patients in each of the two cohorts defined by the corresponding dose–volume cutpoint. The plotted symbol indicates the resulting level of statistical significance, as detailed in the legend.

between dose groups only for intermediate-risk patients (20). Perhaps as the data mature a greater difference between treatment arms will be seen. Differences in outcome between studies may also be caused by the failure definition applied, especially with shorter follow-up. One must also wonder whether the results of the Peeters *et al*. study (20) were affected by the administration of hormone therapy (for as long as 3 years in some patients), and the mixture of radiation techniques that were allowed. As might be expected with a median follow-up of 51 months, no difference in clinical failure or overall survival was seen.

To date, no randomized trial has documented a survival advantage attributable to higher radiation dose, including our study in which all patients were treated at least 8 years ago. As shown by others, prostate cancer is a somewhat unique malignant disease in that living with it and actually expiring of another cause is, in fact, quite common, even in patients with documented recurrence (21). In the update reported here, there were more patients alive with disease in the 70-Gy arm at the time of reporting. If a significant proportion of this group dies of their disease, a survival difference might be expected. There were more deaths due to other causes in the 78-Gy arm, and it would follow logically that if prostate cancer did not cause a patient's death, in this age group, some other disease would. This illustrates the dilemma of competing comorbidities that can affect assessment of treatment efficacy and outcomes in this particular malignancy. There was no indication that the excess noncancer deaths were related to higher radiation dose.

Also important are the therapeutic ratio and the complication risk associated with higher doses. In the Zietman *et al*. study, late grade 2 GI morbidity was doubled (17% vs. 8%) in patients treated to the higher dose level of 79.2 GyE (19). This is much the same as the rectal complication comparison in the M. D. Anderson study. In the Peeters *et al*. study, a slightly higher rate of late GI toxicity greater than grade 2 was seen in the high-dose, 78-Gy arm (32% vs. 27% at 5 years), but the difference was not statistically significant ($p = 0.2$) (20). Although there was also a higher grade 3 complication rate in the higher-dose arm in our study, no difference in grade 3 GI toxicity based on dose was seen in the studies by Zietman *et al*. and Peeters *et al*. (19, 20). There has been no significant difference in GU toxicity greater than grade 2 or grade 3 between dose levels in any of the randomized studies (19, 20). Since the design of the available randomized studies, however, it has become well known that close attention to dose–volume constraints, especially for the rectum, can substantially decrease the complication rate such that the therapeutic ratio and the benefit of applying higher doses is not compromised (11–13, 22, 23).

CONCLUSIONS

The update of the M. D. Anderson randomized dose escalation trial with long-term follow-up shows the benefit of higher dose in patients with localized prostate cancer treated by external beam radiotherapy alone. The greatest advantage appears to be in those patients with an initial PSA >10 ng/ml. This is tempered by the fact that androgen ablation therapy has also been shown to be beneficial in the same patient group (24). Further study may help to clarify whether at least a subset of patients with PSA >10 ng/ml might be treated just as effectively with radiation alone if a higher dose is used. Rectal complication rates clearly show that a price is paid for higher dose if dose–volume constraints are not adhered to, although this relationship for the bladder is less well-defined. An additional remaining question would seem to be whether even higher doses might provide even more benefit, for whom, and at what cost.

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