Int. J. Radiation Oncology Biol. Phys., Vol. 53, No. 5, pp. 1097–1105, 2002

0360-3016/02/$–see front matter

ELSEVIER

PII S0360-3016(02)02829-8

CLINICAL INVESTIGATION **Prostate**

PROSTATE CANCER RADIATION DOSE RESPONSE: RESULTS OF THE M. D. ANDERSON PHASE III RANDOMIZED TRIAL

ALAN POLLACK, M.D., PH.D.,* GUNAR K. ZAGARS, M.D.,* GEORGE STARKSCHALL, PH.D.,†
JOHN A. ANTOLAK, PH.D.,† J. JACK LEE, PH.D.,‡ EUGENE HUANG, B.S.,*
ANDREW C. VON ESCHENBACH, M.D.,§ DEBORAH A. KUBAN, M.D., AND ISAAC ROSEN, PH.D.†

Departments of *Radiation Oncology, †Radiation Physics, ‡Biostatistics, and §Urology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

Purpose: A randomized radiotherapy dose escalation trial was undertaken between 1993 and 1998 to compare the efficacy of 70 vs. 78 Gy in controlling prostate cancer.

Methods and Materials: A total of 305 Stage T1–T3 patients were entered into the trial and, of these, 301 with a median follow-up of 60 months, were assessable. Of the 301 patients, 150 were in the 70 Gy arm and 151 were in the 78 Gy arm. The primary end point was freedom from failure (FFF), including biochemical failure, which was defined as 3 rises in the prostate-specific antigen (PSA) level. Kaplan–Meier survival analyses were calculated from the completion of radiotherapy. The log–rank test was used to compare the groups. Cox proportional hazard regression analysis was used to examine the independence of study randomization in multivariate analysis.

Results: There was an even distribution of patients by randomization arm and stage, Gleason score, and pretreatment PSA level. The FFF rates for the 70- and 78 Gy arms at 6 years were 64% and 70%, respectively ($p = 0.03$). Dose escalation to 78 Gy preferentially benefited those with a pretreatment PSA >10 ng/mL; the FFF rate was 62% for the 78 Gy arm vs. 43% for those who received 70 Gy ($p = 0.01$). For patients with a pretreatment PSA ≤10 ng/mL, no significant dose response was found, with an average 6-year FFF rate of about 75%. Although no difference occurred in overall survival, the freedom from distant metastasis rate was higher for those with PSA levels >10 ng/mL who were treated to 78 Gy (98% vs. 88% at 6 years, $p = 0.056$). Rectal side effects were also significantly greater in the 78 Gy group. Grade 2 or higher toxicity rates at 6 years were 12% and 26% for the 70 Gy and 78 Gy arms, respectively ($p = 0.001$). Grade 2 or higher bladder complications were similar at 10%. For patients in the 78 Gy arm, Grade 2 or higher rectal toxicity correlated highly with the proportion of the rectum treated to >70 Gy.

Conclusion: An increase of 8 Gy resulted in a highly significant improvement in FFF for patients at intermediate-to-high risk, although the rectal reactions were also increased. Dose escalation techniques that limit the rectal volume that receives ≥70 Gy to <25% should be used. © 2002 Elsevier Science Inc.

Radiotherapy, Dose, Prostate-specific antigen, Rectal toxicity.

INTRODUCTION

Since the use of prostate-specific antigen (PSA) has been introduced as a surrogate end point after radiotherapy (RT) for the treatment of prostate cancer, it has become apparent that the standard doses of 65–70 Gy result in far fewer cures than once believed. These data have provided the stimulus for dose escalation using conventional conformal and intensity-modulated RT techniques. In nearly every retrospective and prospective PSA era trial that has evaluated prostate cancer radiation dose response, an improvement in outcome has been substantiated for intermediate- and high-risk patients (1–7). To our knowledge, the M. D. Anderson Cancer Center (MDACC) randomized dose escalation trial initiated in 1993 is the most mature Phase III PSA era evidence published to date that supports dose escalation for prostate cancer. The preliminary MDACC report, based on an analysis with a median follow-up of 40 months, indicated that intermediate- and high-risk patients with a pretreatment PSA level >10 ng/mL significantly benefited from an increase in isocenter dose to 78 Gy from 70 Gy (7). No significant increase in bladder or rectal toxicity was ob-

Reprint requests to: Alan Pollack, M.D., Ph.D., Department of Radiation Oncology, Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA 19111. Tel: (215) 728-2940; Fax: (215) 728-2868; E-mail: A_Pollack@FCCC.edu

This study was supported in part by Grants CA 06294 and CA 16672 awarded by the National Cancer Institute, U.S. Department of Health and Human Services, DOD Grant DAMD 17-98-1-8483, and the Prostate Cancer Research Program at M. D. Anderson Cancer Center.

Acknowledgments—The authors thank Alecia Arciniega for assistance with database management.

Received Jan 8, 2002, and in revised form Mar 11, 2002. Accepted for publication Mar 20, 2002.

served (8, 9). The current report represents a scheduled analysis with extension of the median follow-up to 60 months.

METHODS AND MATERIALS

Protocol eligibility and goals

All patients entered into the trial signed an MDACC Institutional Review Board–approved consent form. Patients with Stage T1–3, Nx/N0, M0 were entered between 1993 and 1998. All patients had a pretreatment PSA measurement, were free of evidence of metastasis, and had no prior history of pelvic RT, radical prostatectomy, or androgen ablation, as described previously (7). The intent was to deliver RT without neoadjuvant or adjuvant androgen ablation. Stratification at protocol entry was based on the pretreatment PSA level: PSA $\leq$10, $>$10–20, and $>$20 ng/mL.

The principal hypothesis of the trial was that an 8 Gy increase in radiation would result in a 15% long-term increase in freedom from failure (FFF), including biochemical failure. The accrual target was 300 patients, assuming direct causality from differences in local tumor control (10). A total of 305 patients were entered into the study and, of these, 301 were available for evaluation; 150 in the 70 Gy group and 151 in the 78 Gy group. As described previously (7), 4 patients were unassessable because 2 withdrew before RT was given, pathologic confirmation of prostate cancer at the MDACC was lacking in 1 patient, and 1 patient withdrew consent and stopped RT 3 weeks after beginning treatment. In addition, four assessable protocol violations occurred. Androgen ablation was given to 2 patients before failure after completing RT. Also, 2 patients in the 78 Gy arm were treated to 70 Gy, 1 because of planning difficulties owing to obesity and 1 because consent for 78 Gy was withdrawn. The analyses presented were based on intent to treat.

Patient characteristics

The distribution of patients by randomization group and pretreatment PSA, Gleason score, and stage was even, as described previously (7). The median PSA values for the entire cohort, 70 Gy arm, and 78 Gy arm were 7.8, 7.5, and 7.8 ng/mL, respectively. The median age was 69 years for the entire cohort and for the 70 Gy and 78 Gy arms. Median follow-up times for the entire cohort, 70 Gy arm, and 78 Gy arm were 60, 57, and 61 months.

Clinical staging was accomplished using the AJCC 1992 palpable staging system, as described in the prior report (7). Transrectal ultrasound staging was not used, nor was the extent or distribution of biopsy tumor involvement.

Grading of bladder and rectal late complications

Late bladder and rectal side effects were graded using modifications of the Radiation Therapy Oncology Group (11) and Late Effects Normal Tissue Task Force (12) scales, as modified by Hanlon *et al.* (13) and described by Storey *et al.* (9).

RT techniques

The 70 Gy and 78 Gy dose specifications were to the isocenter, and the fractional dose was 2 Gy. All patients were initially treated with a conventional four-field box to 46 Gy. The fields were typically 11 $\times$ 11 cm in the AP dimension and 11 $\times$ 9 cm laterally. Lateral shielding consisted of a small corner block over the anterior bladder and the posterior half of the rectum. For those in the 70 Gy group, treatment was continued with a small field reduction. The reduced fields were typically 9 $\times$ 9 cm in both the AP and lateral dimensions, with the inferior border at the ischial tuberosities (7). For those in the 78 Gy group, a six-field conformal field boost arrangement was implemented using three-dimensional conformal RT treatment planning based on a pretreatment pelvic CT scan. The clinical target volume (CTV) included the prostate and seminal vesicles. The mean CTV volume was 97.7 $\pm$ 2.3 cm^3 ($\pm$SEM). Margins from the CTV to the block edge were 1.25–1.5 cm in the anterior and inferior dimensions and 0.75–1.0 cm in the posterior and superior dimensions. It should be noted that although the 70 Gy group underwent conventionally planning, a pelvic CT scan was done during the first week of treatment to confirm that the prostate and seminal vesicles were in the field. Small adjustments were sometimes made on the basis of the CT scan for these conventionally planned patients.

End points and statistical analyses

The primary end point of the trial was freedom from clinical and/or biochemical failure (FFF). Biochemical failure was based on 3 rises in PSA per the American Society for Therapeutic Radiology and Oncology consensus guidelines (14) and was backdated to the midpoint between the first risen value and the preceding value. Every patient considered to have treatment failure had a rising PSA profile, except 1 who underwent radical prostatectomy when a planned prostate biopsy 2 years after treatment contained evidence of malignancy.

The significance of differences in proportions was assessed using the chi-square test. Kaplan–Meier survival calculations (15) were dated from the completion of RT. The log–rank test was used to determine differences in survival curve comparisons (16). Cox proportional hazards regression analysis was used to confirm the independence of the treatment stratification in multiple covariate analysis of FFF (16).

Three analyses of the FFF data were planned. The first two incorporated early stopping if a difference between the arms was $<$0.0005 or $<$0.014. The first analysis was performed while the trial was ongoing, but the second analysis was delayed until the summer of 1999, after accrual goals had been met. The second analysis was the subject of the prior preliminary report (7). The third scheduled analysis described here had a target FFF significance level between the randomization arms of $p < 0.045$.

Distant metastasis and overall survival were secondary study end points that were also tested. Prostate biopsy

Table 1. Biochemical and clinical failure and death by treatment arm

Failure	Total (n = 301)	70-Gy arm (n = 150)	78-Gy arm (n = 151)	p*
PSA†	80	48	32	0.03
Local‡	25	12	13	0.84
Nodal	4	3	1	0.31
Distant	8	6	2	0.15
Death	32	17	15	0.69

* Chi-square test.
† Pretreatment prostate-specific antigen–based biochemical failure.
‡ Biopsy proven.

positivity at 2 years after RT completion was also assessed and will be described in detail in another publication.

RESULTS

The crude numbers of patients with biochemical, local, regional, and distant failure are shown in Table 1. Also displayed are the number of deaths. The only statistically significant effect of dose on failure was for biochemical failure, which was 32% for the 70 Gy group and 21% for the 78 Gy group. These findings are reflected in the Kaplan–Meier survival analyses of FFF. It should be noted that only 1 patient was considered to have treatment failure without a rising PSA. Therefore, the FFF survival end point was basically freedom from a rising PSA.

In the univariate analyses (Table 2 and Fig. 1), the study randomization of 70 Gy vs. 78 Gy was predictive of FFF, with the 78 Gy patients having a significantly higher rate at 6 years. The FFF survival analysis shown in Fig. 1 illustrates that the largest separation in the curves was early and

Table 2. Single covariate survival analysis of freedom from failure

Factor	n	6-y % FFF (NR)	p*
All patients	301	67 (46)	—
Pre-Tx PSA (ng/mL)			
≤10	195	75 (30)	0.0002
>10	106	53 (16)	
T category			
T1-T2	241	72 (35)	<0.0001
T3	60	47 (11)	
Gleason score			
2–6	148	75 (22)	<0.0001
7–10	152	59 (24)	
Randomization (Gy)			
70	150	64 (22)	0.03
78	151	70 (24)	

Abbreviations: FFF = freedom from failure; Pre-Tx PSA = pretreatment prostate-specific antigen; NR = number at risk at time indicated;
* Log–rank test.

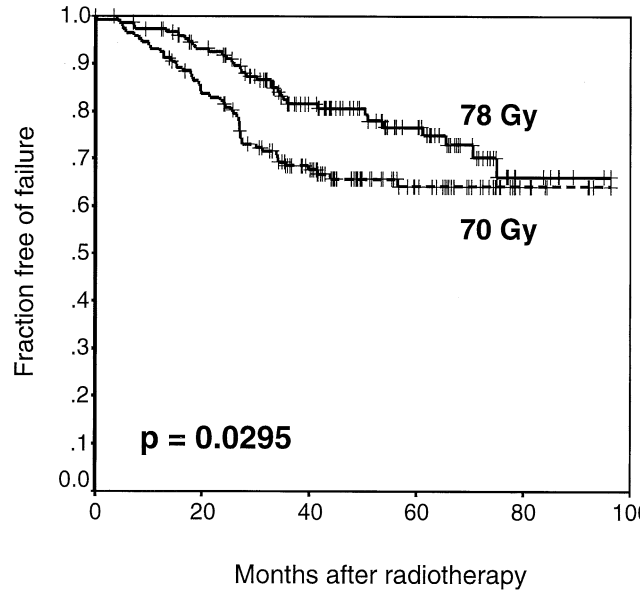

Fig. 1. Kaplan–Meier FFF curves for all patients by dose randomization (70 Gy vs. 78 Gy).

that late failures after 5 years in the 78 Gy group reduced this difference, although a superior FFF rate in the 78 Gy group was still maintained (the curves never crossed). Although the absolute difference at 6 years of 6% favoring the 78 Gy group (Table 2) appears slight, the overall difference between the arms was stronger than on the preliminary report (7). Other correlates of FFF in the univariate analyses were pretreatment PSA, Gleason score, and clinical T category (Table 2).

Cox proportional hazards regression analyses were performed to ensure that the study randomization was independent of the other correlates of FFF. The data in Table 3 demonstrate that the study randomization maintained significance (p = 0.018) when adjusting for the other prognostic covariates. Significance was sustained regardless of whether pretreatment PSA was included as a dichotomous or continuous variable. In fact, the significance of study randomization was stronger (p = 0.009) when pretreatment PSA was a continuous variable.

In prior retrospective series (2–6) and the preliminary analysis of the randomized trial reported previously (7), the patients demonstrating the greatest improvement from dose escalation had intermediate-to-high risk features. The data in Fig. 2 established that the dose-related improvement in FFF for patients at intermediate-to-high risk with a pretreatment PSA level >10 ng/mL was sustained with 60 months of follow-up. The 6-year FFF rate was 43% for the 70 Gy group and 62% for the 78 Gy group. In contrast, no dose-related effect on FFF was found for favorable patients with a pretreatment PSA ≤10 ng/mL (6-year FFF rate of about 75%). Of note, pretreatment PSA level was used in the stratification of the patients in the trial, which supports the validity of this subgroup analysis.

As depicted in Table 1, only 8 cases of distant metastasis

Table 3. Multiple covariate survival analyses of FFF by Cox proportional hazards regression analysis*

Factor	Grouping	RR	95% CI	*p*
Pretreatment PSA as a categorical variable				
Gleason score	2–6 vs. 7–10	2.40	1.48–3.91	<0.0001
Pre-Tx PSA	≤10 vs. >10 ng/mL	2.07	1.32–3.25	0.002
Randomization	70 Gy vs. 78 Gy	0.59	0.38–0.92	0.018
T category	T1-T2 vs. T3	1.81	1.11–2.93	0.020
Pretreatment PSA as a continuous variable				
Gleason score	2–6 vs. 7–10	2.35	1.44–3.82	<0.0001
Pre-Tx PSA	Continuous	1.06	1.04–1.09	<0.0001
Randomization	70 Gy vs. 78 Gy	0.55	0.35–0.87	0.009
T category	T1-T2 vs. T3	1.67	1.01–2.74	0.052

Abbreviations: RR = relative risk; CI = RR confidence interval; Pre-Tx PSA = pretreatment prostate specific antigen.
* Data of 299 patients were available for these analyses.

developed, although 75% were in the 70 Gy arm. Kaplan–Meier survival analysis of distant metastasis did not reveal any significant dose effect, with freedom from distant metastasis rates at 6 years of 96% in the 70 Gy group and 99% in the 78 Gy group ($p = 0.16$). Likewise, the freedom from distant metastasis rates were similar for the study randomization groups when the pretreatment PSA was ≤10 ng/mL. In this relatively favorable subset, only 1 patient developed distant metastasis and he was in the 78 Gy group. However, a significant impact of dose on distant metastasis is suggested for those with a pretreatment PSA >10 ng/mL. Freedom from distant metastasis at 6 years for this subgroup (Fig. 3) was seen in 88% for the 70 Gy arm and 98% for the 78 Gy arm ($p = 0.056$). In terms of overall survival, 32 deaths occurred that were evenly distributed between the treatment arms (Table 1). The overall survival rate at 6 years was 83% for the 70 Gy group and 90% for the 78 Gy group ($p = 0.67$).

Side effects as a consequence of dose escalation for prostate cancer have not been insignificant (6, 17, 18). Although in the previous preliminary report (7) of this trial, significant side effects related to dose were not observed, in the current analysis, late rectal toxicity was substantially greater in the 78 Gy arm. Table 4 shows that considerably more Grade 2 or higher rectal complications resulted ($p = 0.006$) for those randomized to 78 Gy. Most striking was that for the 11 patients identified as having Grade 3 rectal toxicity, 10 received 78 Gy. No significant increase in

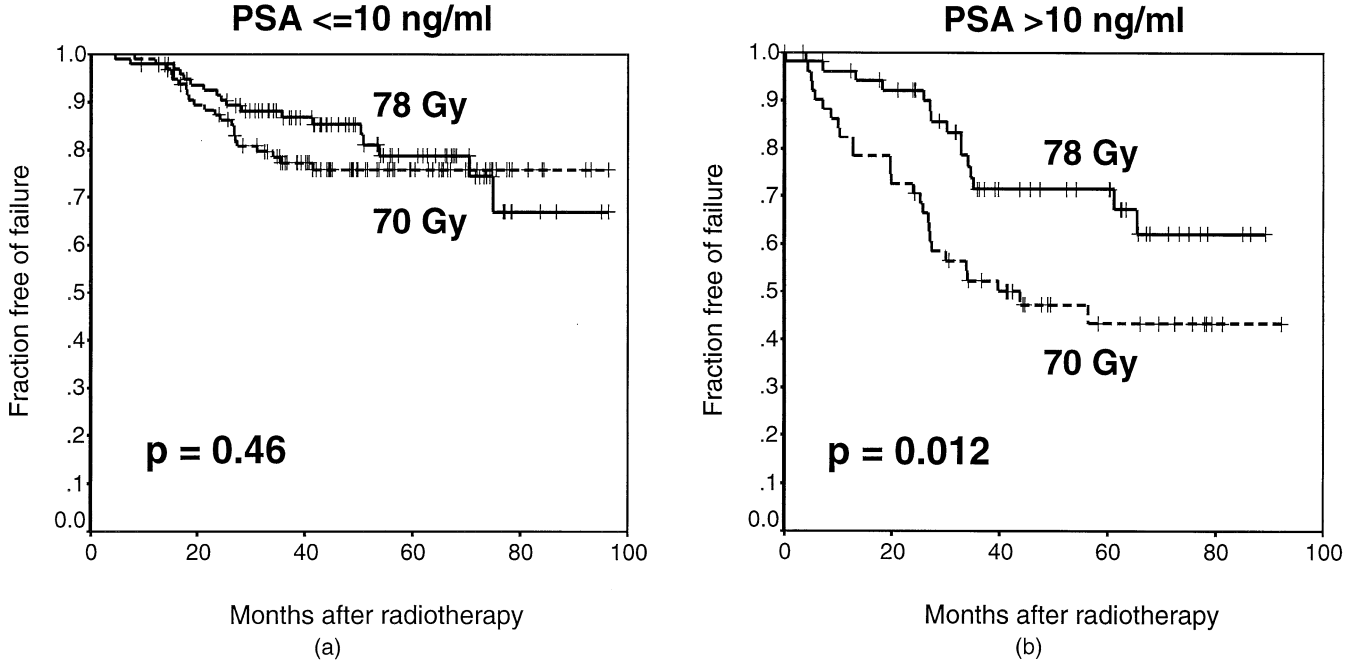

Fig. 2. Kaplan–Meier FFF curves for patients with pretreatment PSA (a) ≤10 ng/mL and (b) >10 ng/mL by dose randomization (70 Gy vs. 78 Gy).

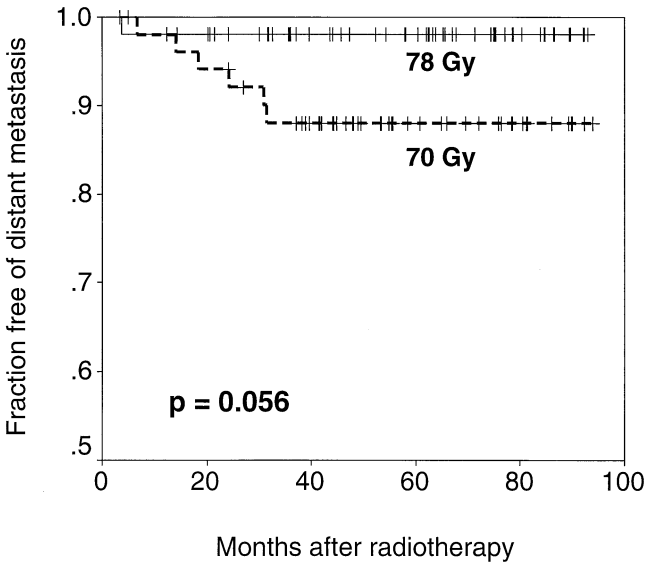

Fig. 3. Kaplan–Meier freedom from distant metastasis curves for patients with PSA >10 ng/mL by dose randomization (70 Gy vs. 78 Gy).

bladder toxicity was appreciated. Kaplan–Meier survival analyses of Grade 2 and higher rectal and bladder complications subdivided by treatment arm are shown in Fig. 4. Treatment to 78 Gy was associated with a 6-year rate of rectal complications that was 117% greater than that for 70 Gy (relative increase from 12% to 26%). No significant dose-related bladder complications were observed.

Previously, Storey *et al.* (9) found a highly significant correlation between the extent of the rectal volume treated to ≥70 Gy and Grade 2 or higher rectal toxicity. With longer follow-up of patients in the 78 Gy arm, in whom this dose–volume histogram (DVH) relationship has been explored, the findings have been strengthened. Table 5 displays the number of patients by late rectal reaction grade and the percentage of rectum that received ≥70 Gy. Of the 144 patients for whom DVH data were available, 8 of the 9 Grade 3 reactions were in patients in whom the rectal volume treated to ≥70 Gy was >25%. Moreover, >50% of Grade 2 or higher rectal reactions were observed when >25% of the rectum received ≥70 Gy. For Grade 0–1 rectal reactions, 73% were recorded when ≤25% of the rectum received ≥70 Gy. Kaplan–Meier survival estimates confirmed these associations in that the 6-year rates of freedom from Grade 2 or higher rectal reactions were 84% and 54% when the proportion of the rectum treated to ≥70 Gy was ≤25% and >25%, respectively (Fig. 5).

DISCUSSION

Prostate cancer radiation dose response

Reports of a radiation dose response for prostate cancer date to articles by Hanks *et al.* (19, 20) and Perez *et al.* (21, 22) in the 1980s. These early descriptions provided incentive for treating the prostate to ≥70 Gy, but the concern of untoward toxicity restrained additional efforts. With the development of new methods for limiting doses to the rectum and bladder, and the disclosure of higher failure rates than expected using PSA as an end point, there has been a resurgence in the exploration of the impact of dose on prostate cancer control (1–7).

Along with a number of convincing retrospective studies (2–6), there have been prospective sequential (6, 23, 24) trials and a randomized dose escalation trial (1), in addition to the MDACC trial reported here. Of the sequential trials, the Memorial Sloan-Kettering experience (6) is by far the most established. The Memorial Sloan-Kettering results disclosed a significant dose-related reduction in biochemical failure. Although the retrospective and prospective sequential dose–response data have been positive, stage migration (25–27) in prostate cancer during the past 10 years has been pronounced and therefore may have a profound confounding influence on the interpretation of such studies. Randomized trials are required to delineate the true impact of dose on prostate cancer patient outcome.

A Phase III trial from Massachusetts General Hospital (1) used a proton boost to increase the dose to the prostate from 67.2 to 75.6 cobalt Gray equivalent. No difference in overall survival or local control for the entire cohort was identified; however, an improvement in local control was noted for those with high-grade tumors who were treated to 75.6 cobalt Gray equivalent. In our series, patients were stratified by pretreatment PSA level, and the greatest effect of dose escalation was for those with a pretreatment PSA >10 ng/mL. A similar relationship was not noted for Gleason score (not shown), although dose was independent of Gleason score as a correlate of FFF in the multivariate analysis. The patients

Table 4. Distribution of patients by late complication grade

Group	Grade 0	Grade 1	Grade 2	Grade 3	*p**
Rectal complications					
70-Gy arm	53 (78)	36 (53)	11 (16)	1 (1)	
78-Gy arm	46 (69)	28 (42)	19 (28)	7 (10)	0.006
Bladder complications					
70-Gy arm	72 (106)	20 (29)	7 (11)	1 (2)	
78-Gy arm	66 (98)	22 (32)	10 (15)	3 (4)	0.63

Data presented as the percentage of patients, with the number in parentheses.
* Chi-square test.

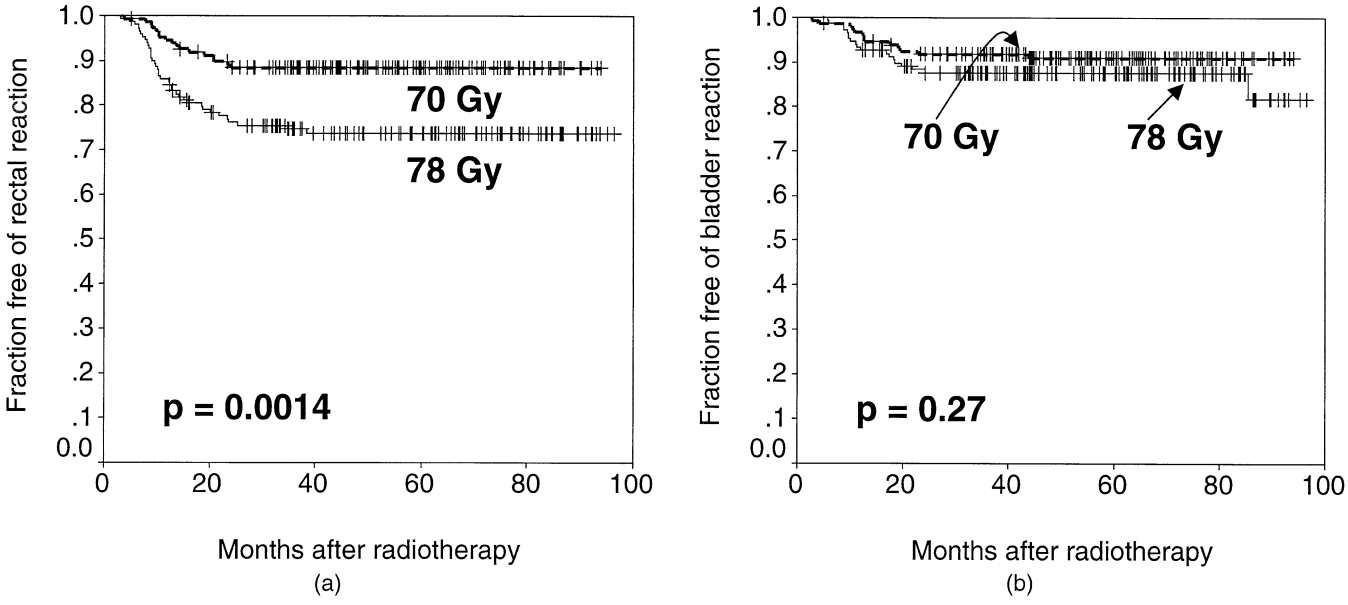

Fig. 4. Kaplan–Meier freedom from Grade 2 or higher late complications for (a) rectal reactions and (b) bladder reactions by dose randomization group.

in the Massachusetts General Hospital trial had pre-PSA era Stage T3-T4 disease, which is considerably more locally advanced than the contemporary prostate cancer patient. While in most retrospective series of such high-risk patients a small but significant gain in freedom from biochemical failure has been found, high-risk patients appear to require androgen ablation to satisfactorily reduce the risk of recurrence further. The patients in the MDACC randomized study were more favorable-to-intermediate risk, and the results are the most conclusive, thus far supporting dose escalation for prostate cancer.

In this scheduled analysis of the MDACC randomized trial, a significant gain in FFF was documented for the entire cohort. The current results, therefore, are more convincing than the original preliminary report (7). The Kaplan–Meier curves in Fig. 1 show that the largest difference between the 78 Gy and 70 Gy curves was before 5 years and that after 5 years, proportionally more failures occurred in the 78 Gy am, bringing the curves closer together. It should be emphasized that fewer patients are at risk at these later points and that a single failure may drop the curve significantly. More importantly, the overall significance has strengthened during the past 20 months of additional follow-up. In addition, no reduction was apparent in the difference in FFF based on dose for patients with a pretreatment PSA >10 ng/mL.

An underlying theme for retrospective and prospective dose–response studies is that the greatest reduction in biochemical and clinical failure has been in patients with intermediate-risk characteristics. The data presented here more firmly verify that it is the patients at intermediate-to-high risk who respond most visibly to an increase in dose >70 Gy. As shown in Fig. 2, no alteration in FFF occurred when the radiation dose was increased from 70 to 78 Gy for the more favorable patients with a pretreatment PSA of ≤ 10 ng/mL. Patients with a pretreatment PSA >10 ng/mL manifested absolute and relative increases in FFF of 19% and 44%, respectively. Clearly, intermediate-to-high risk patients should be targeted in the community for dose escalation. To our knowledge, no retrospective or randomized data are available that demonstrate a prostate cancer dose response with >70 Gy for favorable patients. In every case

Table 5. Distribution of 78-Gy patients by rectal late complication grade and percentage of rectal volume treated to 70 Gy or higher

	Rectum receiving ≥70 Gy				
Rectal toxicity	0–15%	>15–20%	>20–25%	>25–30%	>30%
Grade 0	54 (15)†	60 (18)	56 (19)	30 (10)	16 (3)
Grade 1	29 (8)	27 (8)	29 (10)	39 (13)	16 (3)
Grade 2	18 (5)	10 (3)	15 (5)	21 (7)	42 (8)
Grade 3	0 (0)	3 (1)	0 (0)	9 (3)	26 (5)*

* Chi-square linear-by-linear association $p < 0.0001$.
† Data presented as the percentage of patients, with the number in parentheses.

in which a dose response for favorable patients has been reported (6, 28–30), doses <70 Gy were used.

Controversy remains concerning the role of pelvic nodal irradiation for high-risk patients. The results with radiation alone have not conclusively shown a benefit to whole pelvic treatment (31, 32). In this randomized trial, whole pelvic fields were not used, although the rather generous initial fields irradiated the periprostatic lymph nodes to 46 Gy in all patients. Such initial fields are probably unnecessary for intermediate-risk patients, in whom the lymph node metastasis risk is low. Zelefsky and colleagues (6) have shown a dose response in patients at intermediate-to-high risk using conformal or intensity modulated RT fields, without nodal treatment, from the first day of treatment. Likewise, our leaning has been to reduce the initial fields to reduce toxicity. However, there may be a subset that benefits from nodal irradiation when combined with androgen ablation (33).

Dose escalation and rectal and bladder morbidity

Although the prior preliminary analysis of the MDACC randomized trial with a median of 40 months of follow-up did not disclose a dose effect for bladder or rectal complications, the current findings with 60 months' follow-up raise concerns regarding rectal toxicity. With an additional 20 months of follow-up, the 6-year Grade 2 or higher rectal complication risk in the 78 Gy group was double that of the 70 Gy group (Fig. 4). Both Grade 2 and Grade 3 complications were higher in the 78 Gy group. At this juncture, it is unlikely that the curves will change considerably, because no events were recorded after 40 months. Of note, the complication scoring system used was much more sensitive than the Radiation Therapy Oncology Group system (9, 13), and the complications were, in general, mild. Most of the Grade 3 complications were classified as such because of three laser coagulations. As others have reported in retrospective (17) and prospective (6, 18, 34) series, rectal complications are a consequence of dose and volume. This premise was confirmed in the DVH analyses presented in Table 5 and Fig. 5. When the percentage of rectum treated to ≥70 Gy was limited to ≤25%, only one Grade 3 event occurred and the overall Grade 2 or higher complication risk at 6 years was 16%. Treatment of >25% of the rectal volume to ≥70 Gy was associated with a 46% incidence of Grade 2 or higher complications.

Bladder complications were no different for the 70 Gy and 78 Gy arms (Fig. 4). The time course for bladder complications may be longer (35), and it is possible that longer follow-up may reveal differences. No DVH criteria have yet been identified to assist with treatment planning.

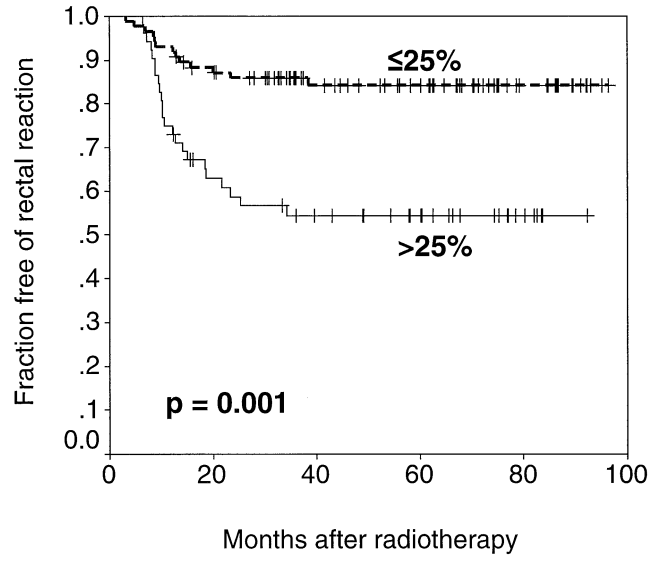

Fig. 5. Kaplan–Meier freedom from Grade 2 or higher late rectal complications by patients in whom ≤25% vs. >25% of the rectal volume received ≥70 Gy.

CONCLUSIONS

Although the weight of the available dose escalation data sanctions the adoption of treatment to higher doses for patients at intermediate-to-high risk, there is no conclusive proof that survival will be affected. A possible explanation for the findings described is that the number of tumor clonogens has been reduced substantially without complete tumor eradication and/or tumor growth has been slowed, thereby delaying detection of failure using a rising PSA as an end point. In either case, one should consider that the goal is prolongation of disease freedom, freedom from distant metastasis, and subsequently survival. Although decisive survival results are lacking in the MDACC trial, there is a suggestion that radiation dose does enhance survival in one case-control study (36), and the relationship between biochemical failure and distant metastasis is well-established. Because the presented response data indicate that most intermediate-risk patients harbor local disease that responds to raising the dose a modest 8 Gy, there is every reason to believe that additional dose escalation will garner added reductions in clonogen survival and solidify the responses observed.

There are two reasons why the MDACC trial results should be taken as a lower limit to what can be achieved with more modern dose escalation techniques. First, the planning and treatment delivery techniques used were antiquated compared with modern conformal and intensity modulated methods. The dose prescription was to the isocenter and not to the planning target volume. By prescribing to the planning target volume (minimum dose to the planning target volume), there is greater assurance that setup error and target motion will be accounted for. Also, the margins from the CTV to the block edge used were probably too small. Without some means of correcting for prostate interfraction motion, it is unlikely that the CTV was covered as consistently as needed to optimize the response. Second, rectal side effects were relatively high because, at the time, DVH criteria were not recognized. Using confor-

mal or IMRT techniques from the beginning of treatment and minimizing exposure of the bladder and rectum appropriately should dramatically reduce side effects. Dose escalation may be accomplished safely with adherence to the guidelines recommended and should be implemented for patients at intermediate-to-high risk.

REFERENCES

1. 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.
2. Pollack A, Zagars GK. External beam radiotherapy for stage T1/T2 prostate cancer: How does it stack up? *Urology* 1998; 51:258–264.
3. Hanks GE, Hanlon AL, Schultheiss TE, *et al.* Dose escalation with 3D conformal treatment: Five year outcomes, treatment optimization, and future directions. *Int J Radiat Oncol Biol Phys* 1998;41:501–510.
4. Pollack A, Smith LG, von Eschenbach AC. External beam radiotherapy dose-response characteristics of 1127 men with prostate cancer treated in the PSA era. *Int J Radiat Oncol Biol Phys* 2000;48:507–512.
5. Lyons JA, Kupelian PA, Mohan DS, *et al.* Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1-T3 adenocarcinoma of the prostate. *Urology* 2000;55:85–90.
6. 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.
7. Pollack A, Zagars GK, Smith LG, *et al.* Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. *J Clin Oncol* 2000;18: 3904–3911.
8. Nguyen LN, Pollack A, Zagars GK. Late effects after radiotherapy for prostate cancer in a randomized dose-response study: Results of a self-assessment questionnaire. *Urology* 1998;51:991–997.
9. Storey MR, Pollack A, Zagars GK, *et al.* Complications from dose escalation in prostate cancer: Preliminary results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2000;48:635–642.
10. Peterson B, George SL. Sample size requirements and length of study for testing interaction in a $2 \times k$ factorial design when time-to-failure is the outcome. *Control Clin Trails* 1993;14: 511–522.
11. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
12. Pavy JJ, Denekamp J, Letschert J, *et al.* Late effects toxicity scoring: The SOMA scale. *Int J Radiat Oncol Biol Phys* 1995;31:1043–1049.
13. Hanlon AL, Schultheiss TE, Hunt MA, *et al.* Chronic rectal bleeding after high-dose conformal treatment of prostate cancer warrants modification of existing morbidity scales. *Int J Radiat Oncol Biol Phys* 1997;38:59–63.
14. American Society for Therapeutic Radiology, and Oncology Consensus Panel. Consensus statement: Guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1035–1041.
15. Harris EK, Albert A. Survivorship analysis for clinical studies. New York: Marcel Dekker; 1991. p. 5–125.
16. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall; 1984. p. 110–120.
17. Lee WR, Hanks GE, Hanlon AL, *et al.* Lateral rectal shielding reduces late rectal morbidity following high dose three-dimensional conformal radiation therapy for clinically localized prostate cancer: Further evidence for a significant dose effect. *Int J Radiat Oncol Biol Phys* 1996;35:251–257.
18. Hartford AC, Nienierko A, Adams JA, *et al.* Conformal irradiation of the prostate: Estimating long-term rectal bleeding risk using dose-volume histograms. *Int J Radiat Oncol Biol Phys* 1996;36:721–730.
19. Hanks GE, Leibel SA, Krall JM, *et al.* Patterns of care studies: Dose-response observations for local control of adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1985;11: 153–157.
20. Hanks GE, Martz KL, Diamond JJ. The effect of dose on local control of prostate cancer. *Int J Radiat Oncol Biol Phys* 1988;15:1299–1305.
21. Perez CA, Walz BJ, Zivnuska FR, *et al.* Irradiation of carcinoma of the prostate localized to the pelvis: Analysis of tumor response and prognosis. *Int J Radiat Oncol Biol Phys* 1980; 6:555–563.
22. Perez CA, Pilepich MV, Garcia D, *et al.* Definitive radiation therapy in carcinoma of the prostate localized to the pelvis: Experience at the Mallinckrodt Institute of Radiology. *NCI Monogr* 1988;7:85–94.
23. Michalski JM, Purdy JA, Winter K, *et al.* Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *Int J Radiat Oncol Biol Phys* 2000;46: 391–402.
24. Bey P, Carrie C, Beckendorf V, *et al.* Dose escalation with 3D-CRT in prostate cancer: French study of dose escalation with conformal 3D radiotherapy in prostate cancer—Preliminary results. *Int J Radiat Oncol Biol Phys* 2000;48:513–517.
25. Hankey BF, Feuer EJ, Clegg LX, *et al.* Cancer surveillance series: Interpreting trends in prostate cancer incidence, mortality and survival rates. *J Natl Cancer Inst* 1999;91:1017–1024.
26. Amling CL, Blute ML, Lerner SE, *et al.* Influence of prostate-specific antigen testing on the spectrum of patients with prostate cancer undergoing radical prostatectomy at a large referral practice. *Mayo Clin Proc* 1998;73:401–406.
27. Jhaveri FM, Klein EA, Kupelian PA, *et al.* Declining rates of extracapsular extension after radical prostatectomy: evidence for continued stage migration. *J Clin Oncol* 1999;17:3167–3172.
28. Pollack A, Zagars GK. External beam radiotherapy dose response of prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;39:1011–1018.
29. Kupelian PA, Buchsbaum JC, Reddy CA, *et al.* Radiation dose response in patients with favorable localized prostate cancer (stage T1-T2, biopsy Gleason $<$ or $=$ 6, and pretreatment prostate-specific antigen $<$ or $=$ 10). *Int J Radiat Oncol Biol Phys* 2001;50:621–625.
30. Pinover WH, Hanlon AL, Horwitz EM, *et al.* Defining the appropriate radiation dose for pretreatment PSA $<$ or $=$ 10 ng/mL prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;47: 649–654.
31. Seaward SA, Weinberg V, Lewis P, *et al.* Improved freedom from PSA failure with whole pelvic irradiation for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 1998;42:1055–1062.
32. Stock RG, Ferrari AC, Stone NN. Does pelvic irradiation play a role in the management of prostate cancer? *Oncology (Huntingt)* 1998;12:1467–1472.

33. Roach M III, Lu JD, Lawton C, *et al.* A phase III trial comparing whole pelvis (WP) to prostate only (PO) radiotherapy, and neoadjuvant to adjuvant total androgen suppression (TAS): Preliminary analysis of RTOG 9413. *Int J Radiat Oncol Biol Phys* 2001;51:3.
34. Dearnaley DP, Khoo VS, Norman AR, *et al.* Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: A randomised trial. *Lancet* 1999; 353:267–272.
35. 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.
36. Hanks GE, Hanlon AL, Pinover WH, *et al.* Survival advantage for prostate cancer patients treated with high-dose three-dimensional conformal radiotherapy. *Cancer J Sci Am* 1999;5: 152–158.