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ORIGINAL REPORT

Randomized Trial Comparing Conventional-Dose With High-Dose Conformal Radiation Therapy in Early-Stage Adenocarcinoma of the Prostate: Long-Term Results From Proton Radiation Oncology Group/American College of Radiology 95-09

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ABSTRACT

Purpose
To test the hypothesis that increasing radiation dose delivered to men with early-stage prostate cancer improves clinical outcomes.

Patients and Methods
Men with T1b-T2b prostate cancer and prostate-specific antigen ≤ 15 ng/mL were randomly assigned to a total dose of either 70.2 Gray equivalents (GyE; conventional) or 79.2 GyE (high). No patient received androgen suppression therapy with radiation. Local failure (LF), biochemical failure (BF), and overall survival (OS) were outcomes.

Results
A total of 393 men were randomly assigned, and median follow-up was 8.9 years. Men receiving high-dose radiation therapy were significantly less likely to have LF, with a hazard ratio of 0.57. The 10-year American Society for Therapeutic Radiology and Oncology BF rates were 32.4% for conventional-dose and 16.7% for high-dose radiation therapy ($P < .0001$). This difference held when only those with low-risk disease (n = 227; 58% of total) were examined: 28.2% for conventional and 7.1% for high dose ($P < .0001$). There was a strong trend in the same direction for the intermediate-risk patients (n = 144; 37% of total; 42.1% *v* 30.4%, $P = .06$). Eleven percent of patients subsequently required androgen deprivation for recurrence after conventional dose compared with 6% after high dose ($P = .047$). There remains no difference in OS rates between the treatment arms (78.4% *v* 83.4%; $P = .41$). Two percent of patients in both arms experienced late grade ≥ 3 genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade ≥ 3 GI toxicity.

Conclusion
This randomized controlled trial shows superior long-term cancer control for men with localized prostate cancer receiving high-dose versus conventional-dose radiation. This was achieved without an increase in grade ≥ 3 late urinary or rectal morbidity.

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INTRODUCTION

The majority of cases of prostate cancer now diagnosed in the United States are detected at an early stage, and external-beam radiation is one of the principal treatment options.[1] There is concern that conventional-dose radiation therapy does not eradicate prostate cancer in a significant proportion of patients, with a resultant increase in prostate-specific antigen (PSA), need for secondary treatment, and ultimately clinical recurrence.[2,3] Increasing the radiation dose delivered may increase the probability of local tumor control but carries a risk of greater side effects unless the volume of normal tissue treated along with the tumor can be reduced. In the 1990s, a number of computed tomography (CT) –based techniques became available to deliver radiation more accurately. These are collectively known as conformal therapy and include three-dimensional conformal photon beam, intensity-modulated photon beam, and proton beam.

Several phase III studies have now demonstrated a consistent improvement in tumor control using radiation dose escalation,[4-6] but only one has reported with long follow-up.[6] This study focused on men with more advanced disease, men who now represent only a minority of the patients seen in contemporary US practice.

Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR) 95-09 was a randomized trial that used the technology of proton beam to conformally increase the radiation dose to the prostate. The study looked primarily at patients with the common presentation of low- and intermediate-risk disease. It compared conventional-dose radiation (70.2 Gy) with high-dose radiation (79.2 Gy) and was first reported with 5-year follow-up.[7] At that time it showed an advantage to dose escalation for low-risk patients without any increase in serious late rectal or urinary morbidity. It is recognized that prostate cancer failure and late normal tissue toxicity can occur well beyond the 5-year time point and that a more complete understanding of the benefits or hazards of dose escalation can only come from additional follow-up.[8,9] This report with long-term follow-up provides more definitive conclusions.

PATIENTS AND METHODS

Study Schema

This randomized controlled trial was designed to compare two different radiation doses delivered by conformal techniques. Patients were stratified at random assignment to ensure balanced groups with respect to serum PSA (<4 ng/mL *v* 4 to 15 ng/mL) and for nodal status (Nx *v* N0).

All patients received conformal photon (x-ray) therapy to a fixed dose of 50.4 Gy. The difference between the arms was in the boost dose, which was delivered using proton beam (Fig 1). The unique physical characteristics of this beam allow the treatment of tumors with considerable sparing of normal tissues.[10,11] The boost dose was either 19.8 Gy or 28.8 Gy, for total doses of either 70.2 Gy (conventional dose) or 79.2 Gy (high dose). All patients received their radiation without the administration of any concurrent or adjuvant hormonal therapy.

Study Objective

The primary objective was to determine whether local failure (LF) at 5 years in the high-dose arm was reduced compared with the conventional-dose arm. The secondary objectives were biochemical failure (BF) defined by the American Society for Therapeutic Radiology and Oncology Consensus definition (ASTRO BF), BF by Phoenix definition (Phoenix BF), overall survival (OS), and genitourinary (GU) and GI toxicity.

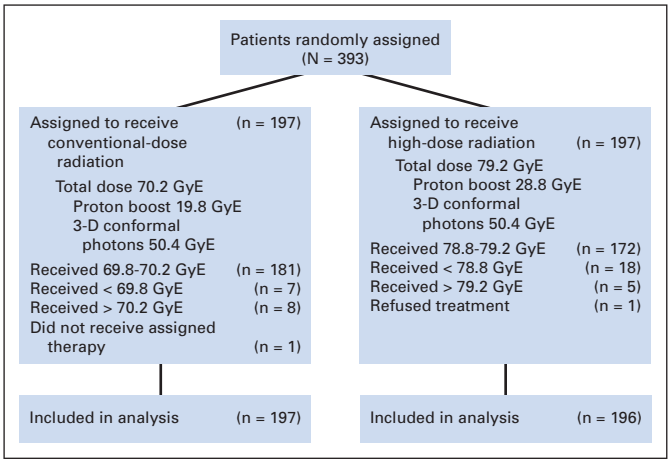

Fig 1. CONSORT diagram. GyE, Gray equivalents.

Patient Eligibility and Follow-Up

Eligible patients with early-stage adenocarcinoma of the prostate, as defined by criteria available in 1995, were offered entry onto this trial: T1b-T2b (1992 American Joint Committee on Cancer criteria) tumors, serum PSA of ≤ 15 ng/mL, and no evidence of metastatic disease by both bone scan (if PSA >10 ng/mL or T2b or Gleason ≥ 7) and abdominopelvic CT scan. There was no exclusion from entry on the basis of Gleason grade.

All participants gave informed consent, and the study had the approval of the institutional review board at both participating institutions and at the ACR. For LF, prostate rebiopsy was recommended for men whose postradiation PSA either did not decrease to 1 ng/mL by 2 years or increased above that level at some subsequent point. It was, however, recognized that it is difficult to encourage elderly men to undergo rebiopsy, and thus a biochemical surrogate for local control would be required.[12] All patients were seen every 3 months for the first year, every 6 months to 5 years, and annually after that.

Radiation Treatment

Conformal radiation therapy was given in two phases:

Phase I. In phase I, conformal proton beams were used to treat the prostate alone. The proton beam dose was corrected to a photon equivalent using a radiobiologic effectiveness ratio of 1.1. Dose is thus expressed as Gray equivalent (GyE). Either 19.8 GyE or 28.8 GyE was given, depending on random assignment, in either 11 or 16 1.8-GyE fractions. The clinical target volume was the prostate with a 5-mm margin. Planning was performed using three-dimensional CT-based techniques. Patient position and beam arrangement differed according to local experience. At Loma Linda University Medical Center, patients were treated supine using opposed lateral 250-MV proton beams. At Massachusetts General Hospital, patients were in the lithotomy position using a single 160-MV perineal proton beam.

Phase II. All men, regardless of trial arm, received 50.4 Gy delivered with photons in 1.8-Gy fractions to the prostate and seminal vesicles. Patients were treated supine using a combination of four high-energy (10 to 23 MV) beams (anterior, posterior, right lateral, and left lateral). The clinical target volume included the prostate and seminal vesicles, with a margin of 10 mm.

Patient immobilization and treatment target imaging. Patients were immobilized daily using casts of thermal setting plastic or body foam. During proton treatments, a balloon was inserted into the rectum and inflated with 25 to 50 mL of saline as described previously.[11,13] This immobilized the prostate and displaced the posterior rectal wall from the beam path. Daily portal images were performed throughout the first phase of treatment and weekly during the second phase.

Design

This study required 390 eligible patients to detect a 20% increase in the proportion of men free from LF at 5 years with at least 80% statistical power.

Study End Points

LF. The failure event was defined as either: (1) a failure to achieve a complete response of palpable disease to protocol therapy, (2) a positive biopsy (backdated to date of equivocal disease), (3) clinical evidence of progression, or (4) PSA greater than 1 ng/mL more than 2 years after the completion of radiation therapy.[12]

BF by ASTRO Consensus. The failure event is the earlier one of the following two: (1) Three successive increases in PSA level, with the failure backdated to a point halfway between the first increase and the last nonincreasing value (PSA nadir), or (2) initiation of salvage therapy.[14]

BF by Phoenix Consensus. The failure event is defined as the PSA value $\geq$ PSA nadir + 2 ng/mL after radiation therapy.[15]

OS. The failure event is defined as death due to any cause.

Toxicity. Acute and late GU and GI toxicities were scored using the Radiation Therapy Oncology Group (RTOG) criteria.[16] This is a 0 to 5 scale in which lower scores equate with fewer symptoms.

Statistical Methods

χ^2 test statistics were used to compare pretreatment characteristics of cases. Time to failure was measured from the date of random assignment to the

date of a failure event. The Kaplan-Meier method[17] was used to estimate the OS, and the log-rank test[18] was used to test the difference between the treatments or categories in the univariate analysis. The cumulative incidence method[19] was used to estimate the LF rate and two BF rates, and Gray's test[20] was used to test the difference between the treatments or categories in the univariate analysis. A Cox proportional hazards regression model [21] was used for OS, and Fine and Gray's regression model [22] was used for LF and the two different BFs. Unadjusted and adjusted hazard ratios were calculated for all covariates using either Cox proportional hazards model or Fine and Gray's regression model with associated 95% CIs and *P* values. All outcomes were modeled using multivariate proportional hazards regression with the following covariates: Treatment arm (70.2 GyE [reference level {RL}] *v* 79.2 GyE), age (continuous), PSA (< 4 [RL] *v* 4 to 15 ng/mL]), Gleason score (2 to 6 [RL] *v* 7 *v* 8 to 10), and clinical stage (T1b or T1c [RL] *v* T2a or T2b). The patients were divided into three risk groups: low risk (T1-2a, PSA < 10 ng/mL, and Gleason ≤ 6), intermediate risk (PSA 10 to 15 ng/mL or Gleason 7 or T2b), and high risk (Gleason 8 to 10). All statistical tests were two-sided, and a *P* value less than .05 was considered statistically significant.

RESULTS

A total of 393 patients were enrolled at two centers: Loma Linda University Medical Center and the Massachusetts General Hospital. Three hundred ninety-one patients were eligible: one withdrew consent and one refused to participate after random assignment. Patients were randomly assigned by the ACR on protocol 95-09 of the PROG between January 1996 and December 1999. In total, only two patients underwent a formal node sampling. Median follow-up for surviving patients was 8.9 years (range, 0.8 to 12.5 years). A median of 10 PSA values were available per patient. Table 1 shows that distribution of patients by pretreatment and prognostic factors were balanced between the two arms (*P* values > .05).

There were 227 patients (58%) in the low-risk group, 144 patients (37%) in the intermediate-risk group, and 17 patients (4%) in the high-risk group.

Table 1. Pretreatment Characteristics

Characteristic	Assigned Dose: 70.2 GyE (n = 196) No.	%	79.2 GyE (n = 195) No.	%
Age, years				
45-59	43	22	34	17
60-69	92	47	106	54
70-79	61	31	55	28
≥ 80	1	0.5	0	
Median	67		66	
Range	45-91		47-78	
Race				
White	175	89	178	91
Hispanic	4	2	7	3
Black	12	6	5	3
Other	5	3	5	3
PSA, ng/mL				
< 5	54	28	47	24
5 to < 10	114	58	119	61
10-15	28	14	29	15
Median	6.3		6.2	
Range	1.24-14.68		0.67-14.30	
Karnofsky performance status				
80	8	4	9	5
90	52	27	47	24
100	136	69	139	71
Combined Gleason				
2-6	148	75	147	75
7	29	15	30	15
8-10	18	9	15	8
Unknown	1	1	3	2
T stage				
T1b	1	1	0	
T1c	120	61	120	61
T2a	43	22	50	26
T2b	32	16	25	13
N stage				
N0	0		2	1
NX	196	100	193	99
Risk groups*				
Low	111	57	116	59
Intermediate	75	38	69	35
High	10	5	7	4
Not classified	0		3	2

Abbreviations: GyE, Gray equivalents; PSA, prostate-specific antigen.
*Risk groups according to D'Amico et al.[23]

Radiation Dose Delivered

Of the 197 patients randomly assigned to 70.2 GyE, 180 patients (92%) received this dose (Fig 1). Seven patients (3.6%) received lower doses, and eight patients (4.0%) received higher doses. One patient refused treatment. Of the 196 patients assigned to 79.2 GyE, 172 patients (88.2%) received this dose, five patients (2.5%) received higher doses, and 18 patients (9.2%) received lower doses. Of these, only two patients received lower doses because of toxicity. Four patients received lower doses because of new medical issues; others did so for a mixture of anxiety, refusal to accept random assignment to the higher dose, and convenience.

LF

There was a statistically significant difference in LF rate between the two arms. Men treated with 79.2 GyE were less likely to have LF than those treated with 70.2 GyE, with a hazard ratio of 0.57 ($P < .0001$; 95% CI, 0.43 to 0.74). This result held when adjusted for other covariates. There was a statistically significant difference in LF for the low-risk group and the intermediate-risk group ($P = .01$ and .002, respectively).

BF

In the conventional-dose arm, 81.0% had a PSA nadir of less than 1.0 ng/mL, and 44.7% had a nadir less than 0.5 ng/mL. In the high-dose arm, these proportions were 86.6% and 59.8%, respectively. The difference between the nadirs less than 0.5 ng/mL was significant ($P = .003$). Median time to nadir was 28.0 months after conventional-dose and 39.6 months after high-dose radiation.

The 10-year ASTRO BF rates were 32.3% (95% CI, 25.7% to 39.0%) for the conventional dose arm and 16.7% (95% CI, 10.8% to 22.7%) for the high-dose arm ($P = .0001$; Fig 2A). This difference held when only those with low-risk disease were examined: 10-year ASTRO BF rate was 28.2% (95% CI, 19.4% to 37.1%) in the conventional-dose arm and only 7.1% (95% CI, 2.3% to 11.9%) in the high-dose arm ($P < .0001$; Fig 3A). There was a strong trend in the same direction for the smaller group of 144 intermediate-risk patients: 42.1% (95% CI,

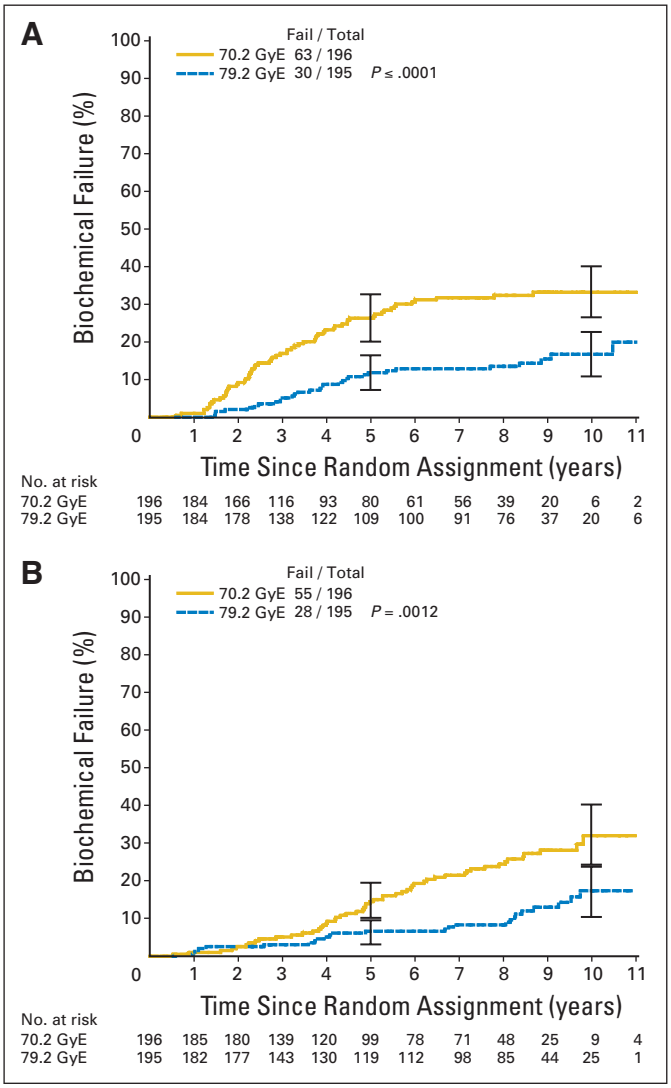

Fig 2. Biochemical failure after either conventional-dose or high-dose conformal radiation therapy. (A) Biochemical failure by American Society for Therapeutic Radiology and Oncology consensus.[14] (B) Biochemical failure by Phoenix criteria.[15] GyE, Gray equivalents.

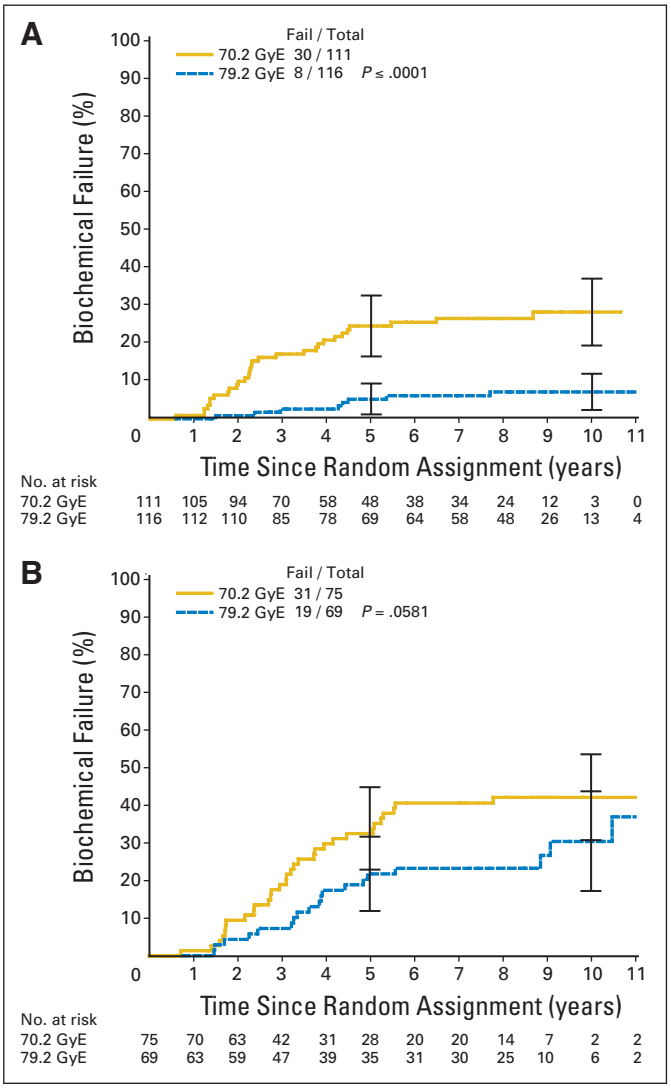

Fig 3. Biochemical failure by American Society for Therapeutic Radiology and Oncology Consensus definition after either conventional-dose or high-dose conformal radiation therapy. (A) Biochemical failure for the low-risk group; (B) biochemical failure for the intermediate-risk group. GyE, Gray equivalents.

30.6% to 53.5%) versus 30.4% (95% CI, 17.1% to 43.6%; $P = .06$; Fig 3B). The hazard ratios after adjusting for other covariates show the same results (hazard ratio was 0.22 [95% CI, 0.1 to 0.5] for the low-risk group and 0.58 [95% CI, 0.3 to 1.0] for intermediate-risk group). The smaller numbers in the intermediate-risk group limited the power to observe a significant difference in that group to only 54%. Because backdating used in the ASTRO definition of BF may affect the timing and rate of failure,[14] it has been superseded since PROG-9509 was initiated by the Phoenix Consensus definition.[15] The differences in Phoenix BF between the arms were similarly highly significant (Fig 2B). At 10 years, the Phoenix BF rates were 32.0% (95% CI, 23.8% to 40.2%) versus 17.4% (95% CI, 10.5% to 24.3%) for conventional- and high-dose radiation, respectively ($P < .001$). In the conventional-dose arm, 22 patients have received secondary treatment with androgen deprivation compared with 11 patients in the high-dose arm ($P = .47$). Treatment was started at the discretion of the physician and usually for an increasing PSA.

OS

At this time, there is no difference in the overall survival rates between the treatment arms (78.4% and 83.4%; $P = .41$). There were 34 deaths in the conventional-dose arm (four related to prostate cancer) and 27 deaths in the high-dose arm (two related to prostate cancer).

Toxicity

Table 2 shows morbidity associated with treatment and randomization group. Only 3% of patients receiving conventional-dose and 2% receiving high-dose radiation experienced acute GU toxicity of RTOG grade ≥ 3. Fifty-four percent and 62% of conventional-dose and high-dose patients, respectively, experienced grade 2 acute GU toxicity. The proportions for grade 2 or worse acute GI toxicity were 45% and 64%, respectively. So far, only 2% of patients in both arms have experienced late GU toxicity of RTOG grade ≥ 3, and 1% have experienced late GI toxicity of grade ≥ 3. For late grade ≥ 2 GU

Table 2. Acute and Late GU and GI Toxicity

	Assigned Dose																
	70.2 GyE (n = 196)								79.2 GyE (n = 195)								
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 1		Grade 2		Grade 3		Grade 4		
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P*
Acute																	
GU	72	37	100	51	5	3	0	0	56	29	117	60	4	2	1	1	.0745
GI	76	39	87*	44	2	1	0	0	50	26	123*	63	2	1	0	0	.0006*
Late																	
GU	82	42	44	22	4	2	0	0	88	45	52	27	3	2	0	0	.7934
GI	68	35	25	13	0	0	0	0	79	41	46	24	2	1	0	0	.0895

Abbreviations: GU, genitourinary; GyE, Gray equivalents.
*Testing grade 1 versus others using χ^2 test.

toxicity, these proportions were 25% and 29% ($P = .79$), respectively, and for grade ≥ 2 GI toxicity, these proportions were 13% and 24%, respectively ($P = .09$).

DISCUSSION

This randomized trial shows that when men with early-stage prostate cancer are treated with high-dose rather than conventional-dose external radiation therapy, they are more likely to be free from an increasing PSA 10 years later and less likely to have required additional cancer therapy. It also shows that when highly conformal radiation techniques are used, dose escalation to 79.2 Gy can be safely achieved without an increase in serious (grade ≥ 3) acute or late morbidity. This study therefore provides Level 1 evidence to justify trends already well established in the United States toward conformal technology and higher doses in early-stage disease.

In 1995, when this trial was designed, early-stage disease was largely defined by T stage and PSA. Since then, predictive risk groups have been developed. The lowest risk are those with T1-2a tumors, Gleason grades of ≤ 6, and PSA of less than 10 ng/mL.[23] Such patients comprised 227 (58%) of 393 of those entered onto this trial. Intermediate-risk men comprised the majority of the remainder. The long-term advantage to higher radiation dose was clearer for those with low-risk disease than it was for those with higher risk, and this represents the novel finding of the trial. The greater advantage for the low-risk group perhaps reflects the fact that these men are more likely to have locally confined disease and thus are more likely to benefit from an improved local therapy.

Median follow-up was 8.9 years, and this, therefore, represents one of only two prospective studies in the literature documenting long-term outcome after conventional-dose or high-dose radiation in the contemporary era. It is also the only such study in which proton beam has been used. It demonstrates that conventional-dose radiation is already sufficient to render the majority of men with low-risk prostate cancer free but that this proportion may be increased even further with dose escalation. The choice of dose may therefore be made by the physician based on other patient considerations, such as life expectancy and concern about normal tissue injury. Although there was no survival advantage shown in this study, it may be presumed that those who have persistent disease as indicated by an increasing PSA are at greater risk of requiring additional therapy and ultimately of a prostate cancer death. Of the three other randomized trials examining this issue, all have shown a similar advantage to higher doses of radiation.[4-6] Two of these trials allowed the additional use of androgen deprivation therapy, which confounds the interpretation of radiation efficacy, and neither reports follow-up beyond 5 years.[4,5] The only other radiation monotherapy trial has reported 10-year data, but it concentrated on patients with higher-risk disease.[6] It too showed that improvements in freedom from PSA failure are associated with a reduction in the risk of having recurrent disease, requiring future salvage therapies, and dying from disease.

It is most likely that the improvement in biochemical disease-free outcome seen in this trial is due to improved local control, and this was suggested by the reduced hazard rate using a biochemical surrogate. Prostate rebiopsy would have been more definitive but, although this was encouraged, it was not done routinely for two reasons. First, interpretation of prostate biopsies in the first 3 post-treatment years is unreliable.[24] Second, it is ethically difficult to recommend routine prostate rebiopsy, an uncomfortable procedure, when the results are unlikely to influence subsequent management.

The randomized trials of radiation dose reported by Kuban et al,[6] Al-Mamgani et al,[5] and Dearnaley et al[4] all showed higher levels of late rectal morbidity, particularly bleeding, in the higher dose arms at 5 years. We have also seen a small increase in grade ≥ 2 rectal morbidity in the high-dose arm of our trial, though not grade ≥ 3. Surprisingly, a cross-sectional survey of long-term survivors on this study using a more sensitive quality-of-life instrument did not detect more morbidity than the physician-reported morbidity scales used.[25] Satisfaction scores were equal and high in both arms of the trial, even when physician-reported morbidity was present. This implies that patients adapt well with time to chronic morbidity such that this becomes a new "normality." Questions regarding sexual function were asked, but these are now recognized to be so prone to bias that the available data have not been presented here.

Although this trial strongly validates the use of proton beam as effective therapy, it was not designed to test whether this modality is more or less efficacious than other conformal techniques or, for that matter, brachytherapy or surgery. Nor does it justify using doses above 79 Gy outside a clinical trial.

In summary, this randomized, controlled trial shows a significant and durable advantage to high-dose over conventional-dose conformal radiation in terms of freedom from BF for men with low- and intermediate-risk prostate cancer. This advantage was achieved without any associated increase in either acute or late severe urinary or rectal morbidity by the use of highly conformal radiation techniques that included three-dimensional photon and proton beams.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

1. Cooperberg MR, Broering JM, Litwin MS, et al: The contemporary management of prostate cancer in the United States: Lessons from the cancer of the prostate strategic urologic research endeavor (CapSURE), a national disease registry. J Urol 171: 1393-1401, 2004

2. Kupelian PA, Potters L, Khuntia D, et al: Radical prostatectomy, external beam radiotherapy < 72G y or > 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-2 prostate cancer. Int J Radiat Oncol Biol Phys 58:25-33, 2004

3. Zietman AL, Chung CS, Coen JJ, et al: 10-year outcome for men with localized prostate cancer treated with external radiation therapy: Results of a cohort study. J Urol 171:210-214, 2004

4. Dearnaley DP, Sydes M, 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 8:475-487, 2007

5. Al-Mamgani A, van Putten WLJ, Heemsbergen WD, et al: Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 72:980-988, 2008

6. 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 70:67-74, 2008

7. 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 294:1233-1239, 2005 [Erratum: JAMA 299:899-900, 2008]

8. Vicini FA, Kestin LL, Martinez AA: The importance of adequate follow-up in defining treatment success after external beam irradiation for prostate cancer. Int J Radiat Oncol Biol Phys 45:553-561, 1999

9. Gardner BG, Zietman AL, Shipley WU, et al: Late normal tissue sequelae in the second decade following high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. J Urol 167:123-126, 2002

10. Shipley WU, Tepper JE, Pront GR, et al: Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 241:1912-1915, 1979

11. 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 32:3-12, 1995

12. Dugan TC, Shipley WU, Young RH, et al: Biopsy after external beam radiation therapy for adenocarcinoma of the prostate: Correlation with original histologic grade and current PSA levels. J Urol 146:1313-1316, 1991

13. Slater JD, Yonemoto LT, Rossi CJ, et al: Conformal proton therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 42:299-304, 1998

14. American Society for Therapeutic Radiology and Oncology Consensus Panel: Consensus statement: Guidelines for PSA following radiotherapy. Int J Radiat Oncol Biol Phys 37:1035-1041, 1997

15. Roach M, Hanks G, Thames H, 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 65:965-974, 2006

16. Lawton CA, Won M, Pilepich M: Long-term treatment sequelae following external beam radiation for adenocarcinoma of the prostate: Analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 21:935-939, 1991

17. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:447-457, 1958

18. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

19. Kim K, Tsiatis AA: Study duration for clinical trials with survival response and early stopping rule. Biometrics 46:81-92, 1990

20. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1143, 1988

21. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

22. Fine J, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509, 1999

23. D'Amico AV, Chen MH, Oh-Ung J, et al: Changing prostate-specific antigen outcome after surgery or radiotherapy for localized prostate cancer during the PSA-era. Int J Radiat Oncol Biol Phys 54:436-441, 2002

24. Crook JM, Bahadur YA, Robertson S: Evaluation of radiation effect, tumor differentiation, and prostate specific antigen staining in sequential prostate biopsies after external beam radiotherapy for patients with prostate carcinoma. Cancer 79:81-89, 1997

25. Talcott J, Zietman A, Rossi C, et al: Long-term quality of life after conventional-dose versus high-dose radiation for prostate cancer: Results from a randomized trial PROG 9509. J Clin Oncol 26:264s, 2008 (suppl; abstr 5058)