Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 2, pp. 348–352, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.10.011

CLINICAL INVESTIGATION **Prostate**

PROTON THERAPY FOR PROSTATE CANCER: THE INITIAL LOMA LINDA UNIVERSITY EXPERIENCE

JERRY D. SLATER, M.D., CARL J. ROSSI, JR., M.D., LES T. YONEMOTO, M.D., DAVID A. BUSH, M.D., B. RODNEY JABOLA, M.D., RICHARD P. LEVY, M.D., PH.D., ROGER I. GROVE, M.P.H., WILLIAM PRESTON, ED.D., AND JAMES M. SLATER, M.D., F.A.C.R.

Department of Radiation Medicine, Loma Linda University Medical Center, Loma Linda, CA

Purpose: We analyzed results of conformal proton radiation therapy for localized prostate cancer, with emphasis on biochemical freedom from relapse.

Methods and Materials: Analyses were performed for 1255 patients treated between October 1991 and December 1997. Outcomes were measured on primarily in terms of biochemical relapse and toxicity.

Results: The overall biochemical disease-free survival rate was 73%, and was 90% in patients with initial PSA ≤4.0; it was 87% in patients with posttreatment PSA nadirs ≤0.50. Rates dropped with rises in initial and nadir PSA values. Long-term survival outcomes were comparable with those reported for other modalities intended for cure.

Conclusions: Conformal proton radiation therapy at the reported dose levels yielded disease-free survival rates comparable with other forms of local therapy, and with minimal morbidity. Dose-escalation strategies are being implemented to further improve long-term results. © 2004 Elsevier Inc.

Prostate cancer, Proton beam therapy, Conformal radiotherapy.

INTRODUCTION

Proton radiation therapy (PRT) has been used since 1991 at Loma Linda University Medical Center (LLUMC) to treat prostate cancer. The ability of any form of radiation therapy to eradicate localized disease depends upon such factors as initial prostate-specific antigen (PSA) status, extent and virulence of disease, and the ability to deliver effective doses without causing unacceptable treatment-related complications. PRT has demonstrated the ability to do the latter, as LLUMC's earlier results have shown (1). Herein we update data offered in that previous report.

Conformal PRT exploits the physical depth-dose characteristics of heavy charged particles, enabling the physician to create three-dimensional high-dose regions that can be shaped to conform to irregular target volumes. In contrast to X-ray beams of any energy, a single proton beam has a low entrance dose, a maximal dose at a user-defined depth (the "Bragg peak"), and no exit dose. These characteristics make possible a substantial reduction in integral dose (i.e., dose delivered to normal tissue), and an inherent dose-distribution advantage over conformal photon therapy (2).

METHODS AND MATERIALS

Between October 1991 and December 1997, 1961 patients with localized prostate cancer (Stages Ia–III) were treated with conformal PRT alone or with a combination of proton- and photon-beam radiation therapy. This study reviews 1255 patients who had received no prior surgery or hormonal therapy and had no evidence of distant metastases at time of treatment. Before treatment, all patients received physical examinations; pretreatment serum PSA values were obtained and pathology slides were reviewed whenever possible. Additional imaging studies, such as bone scans and endorectal magnetic resonance imaging scans, were ordered only if judged to be appropriate (i.e., if bone pain was present or if physical examination demonstrated substantial extracapsular spread of disease).

Patient preparation for treatment was similar to that described previously (1, 3). In the early years of treatment, all patients were treated in a combined fashion with protons and photons. A conformal "boost" of 30 CGE in 15 fractions was delivered to the prostate and seminal vesicles, followed by 45 Gy of photon radiation therapy to a volume that included the first- and second-echelon lymphatics. All X-ray therapy was delivered via a three-dimensional con-

Reprint requests to: Jerry D. Slater, M.D., 11234 Anderson St., Loma Linda, CA 92354. Tel: (909) 558-4258; Fax: (909) 558-0295.

Supported by the Ken Venturi Endowed Chair for Proton Therapy Research.

Received Mar 6, 2003, and in revised form Oct 6, 2003. Accepted for publication Oct 15, 2003.

formal technique, using a four-field setup with all fields treated daily. Because treatment capacity increased during the first few years of operation, patients were put into two treatment groups. Based on the Partin nomogram, patients with a risk of 15% or greater for micrometastases in pelvic lymph nodes continued with the combined photon-proton treatment, whereas those at lesser risk were treated by protons alone.

All patients were treated with protons using the LLUMC 70-250 MeV synchrotron (4). PRT was delivered by means of opposed lateral beams; in most cases one field was treated each day with energies ranging from 225–250 MeV. The planning target volume included the prostate, seminal vesicles with a 5-mm margin for setup uncertainty. The prescribed dose for patients receiving protons only was 74 CGE to the isocenter (cobalt-gray equivalent, using a relative biologic equivalence factor of 1.1), given in daily fractions of 2 CGE. A water balloon was inserted into the rectum, as described previously (1, 3). Patient position was verified before each treatment, by means of digital images.

Patients were monitored weekly during treatment to assess acute effects. Posttherapy monitoring included serum PSA determinations and rectal examination 4 months after therapy, then every 3 to 6 months thereafter until 5 years had elapsed after treatment, then annually. Additional studies were obtained for patients who subsequently developed rising PSA, a clinically palpable prostate nodule, or signs or symptoms of metastasis.

Biochemical measurements were the primary means of assessing patient response. Freedom from biochemical evidence of disease (bNED) was estimated using the consensus definition of the American Society for Therapeutic Radiology and Oncology: failure was defined as three consecutive rises in PSA levels with the date of failure being midway between the nadir and first rise (5).

Estimates of bNED were made using the Kaplan-Meier methodology with multivariate analysis using the Cox regression model. bNED was assessed in terms of initial PSA, stage, Gleason grade, and PSA nadir. Kaplan-Meier estimates were not extended beyond the time when fewer than 9 patients were at risk (6, 7).

RESULTS

The mean duration of follow-up was 63 months; median duration was 62 months (range, 1–132 months). Patient age ranged from 44 to 90 years (median, 69 years). Pretreatment patient characteristics are shown in Table 1. A total of 731 patients received a combination of protons and photons to the prostate and pelvic lymph nodes, and 524 received all of their treatment with protons to the prostate and seminal vesicle only.

The overall 5-year and 8-year actuarial biochemical disease-free survival rates were 75% and 73%, respectively (Fig. 1).

Table 1. Stage, initial prostate-specific antigen, and Gleason grade characteristics of studied population

	Patients	% of Total
TNM Stage		
T1a/b	35	3
T1c	314	26
T2a	291	24
T2b	248	20
T2c	283	23
T3	50	4
Initial PSA		
0–4.0	106	9
4.1–10.0	606	51
10.1–20.0	339	29
>20.0	133	11
Gleason		
2–4	204	18
5–7	868	75
8–10	86	7

Effect of initial PSA on biochemical freedom from relapse

The effect of initial PSA on actuarial bNED is illustrated (Fig. 2). Pretreatment PSA strongly predicted ultimate biochemical success or failure; patients whose initial PSA was ≤4.0 exhibited a 90% chance of being biochemically free of disease at 5 years. This contrasts with rates of 84% (4.1–10.0), 65% (10.1–20.0), and 48% (>20.0) for patients with higher PSA values ($p = 0.0001$).

Effect of grade on biochemical freedom from relapse

Gleason grade (Fig. 3) was related to bNED outcome. Patients whose Gleason scores were 8 or higher had a significantly poorer outcome ($p < 0.0001$), but low (2–4) and moderate (5–7) scores did not differentiate outcome in terms of bNED survival ($p = 0.08$).

Effect of PSA nadir on biochemical freedom from relapse

PSA nadir was employed as a surrogate endpoint for treatment success or failure. The impact of PSA nadir on bNED survival was evaluated in 1143 patients who had been followed for at least 24 months. The influence of PSA nadir on ultimate disease-free survival is shown (Fig. 4). Patients whose PSA levels reached a nadir at or below 0.50 ng/mL exhibited the highest 5-year and 8-year survival rates of 88% and 87%, respectively. This contrasts with rates of 72% at 5 years in those whose nadir levels were between 0.51 and 1.00, and 31% at 5 years for those nadirs above 1.00 ng/mL ($p = 0.0001$).

Summation of significant outcomes

Multivariate analyses indicate that initial PSA ($p = 0.0001$), Gleason grade ($p = 0.001$), and PSA nadir ($p = 0.0001$) were all independent predictors of treatment outcome.

Treatment-related morbidity

In general, conformal proton beam radiation therapy was well tolerated; the rate of Radiation Therapy Oncology

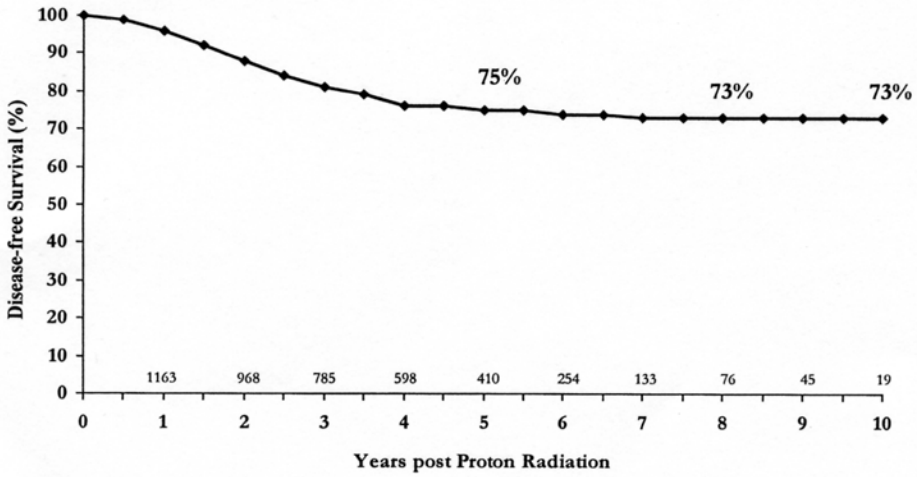

Fig. 1. Biochemical disease-free survival. The numbers represent number of patients at risk.

Group Grade 3 or greater acute gastrointestinal (GI) or genitourinary (GU) morbidity was less than 1%. Radiation Therapy Oncology Group Grade 3 late morbidity was seen in 16 patients (1%) and Grade 4 in 2 patients (0.2%). Late gastrointestinal toxicity included Grade 3 bleeding and pain in 2 patients, and a bowel obstruction requiring diverting colostomy in 1 patient. All severe GI toxicity initially presented within the first 2.5 years after treatment. The actuarial 5-year and 10-year rates for freedom from Grade 3 and 4 GI toxicity were both 99%.

Late GU morbidity was seen more frequently than GI morbidity. Fourteen patients developed Grade 3 late toxicity, with 8 of them having urethral strictures, followed by hematuria (4 patients) and dysuria (2 patients). The actuarial 5- and 10-year rates for freedom from Grade 3 and 4 GU toxicity were both 99%. One other patient developed necrosis of the symphysis, which was partially included in the treatment field.

No difference was seen in toxicity between those treated with combined protons and photons (11 of 731) and those with protons alone (6 of 524; $p = 0.52$). Because of the very small incidence of Grade 3 and 4 side effects, no statistically significant prognostic variables for toxicity could be found. These results, when accounting for length of follow-up, compare favorably with conformal photon therapy and intensity-modulated photon therapy (8, 9).

DISCUSSION

This series represents one of the largest groups of individuals treated with a three-dimensional conformal technique for prostate cancer at a single institution. All patients received essentially the same radiation dose and were treated with identical margins around the tumor, providing a large standardized database with which to assess treatment response and treatment-related morbidity. These data demon-

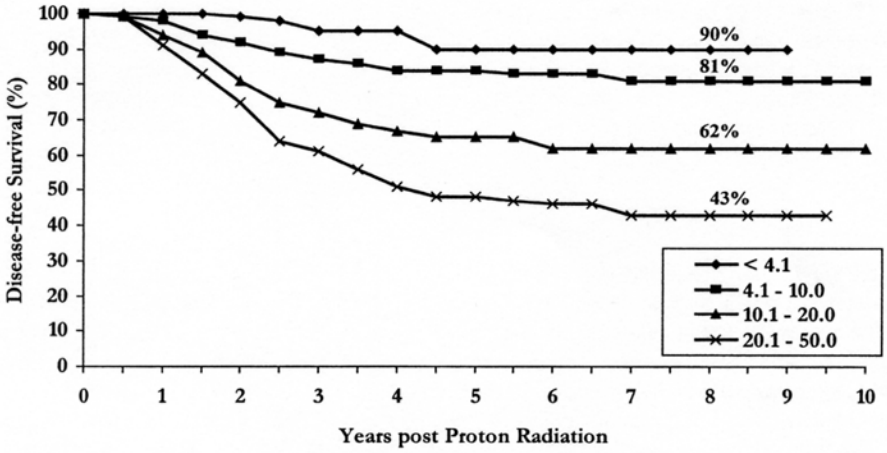

Fig. 2. Effect of initial prostate-specific antigen on biochemical disease-free survival.

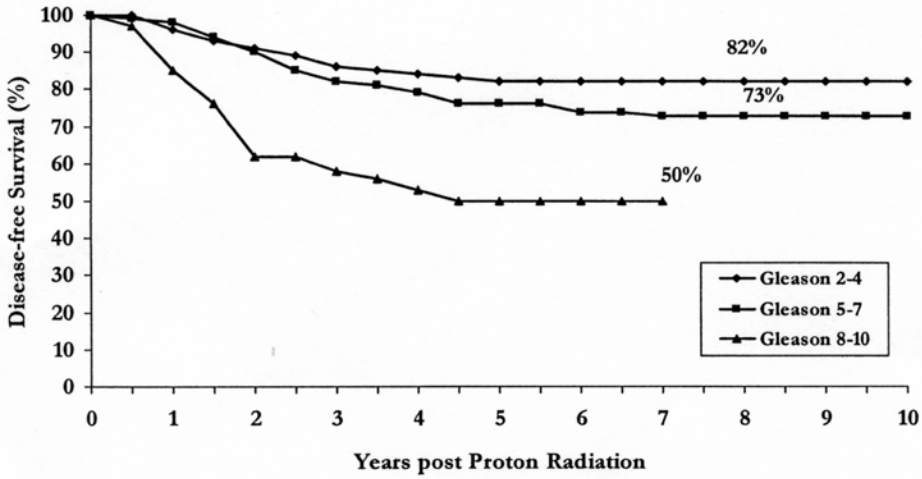

Fig. 3. Gleason grade in relation to biochemical disease-free survival.

strate that conformal proton beam radiation therapy at the reported dose levels can achieve bNED rates equivalent to those obtained with other treatment methods (10–13). As others have reported, pretreatment prognostic factors were significant for late treatment outcome, and posttreatment nadir was also shown to be associated with long-term PSA control.

These data also support the concept that PSA nadir is a useful "early endpoint" for prostate cancer treatment. In our series, patients whose PSA nadirs were <1.00 ng/mL had a statistically significant difference in their bNED rate as compared with those whose PSA nadirs never dropped to such levels. Whether PSA nadir will eventually supplant the current consensus definition of biochemical failure remains to be seen; however, our results suggest that it should be considered as a tool to assess patient response.

Although many patients continue to do well, further investigations are under way to continue to improve the outcomes of patients treated for localized prostate cancer. Numerous studies have shown that by localizing the dose to the target and minimizing normal tissues irradiated, higher doses can be delivered without a significant increase in toxicity (14–16). New trials have been completed; these trials evaluate the effects of higher doses on patients with early prostate cancer. One such trial, undertaken by LLUMC and Massachusetts General Hospital, was a randomized dose-escalation study using protons with photons for early prostate cancer. The trial began in 1995; it randomized 390 patients with T1-T2N0-XM0 prostate cancer and a pretreatment PSA level <15 ng/mL to receive a dose of 70.2 or 79.2 Gy. Accrual was completed in 1999; preliminary analysis of toxicity revealed that combined Grade 3 GU and GI toxicity was seen in 6.6% of those receiving 70.2 Gy and 2.5% of those randomized to 79.2 Gy (unpublished data).

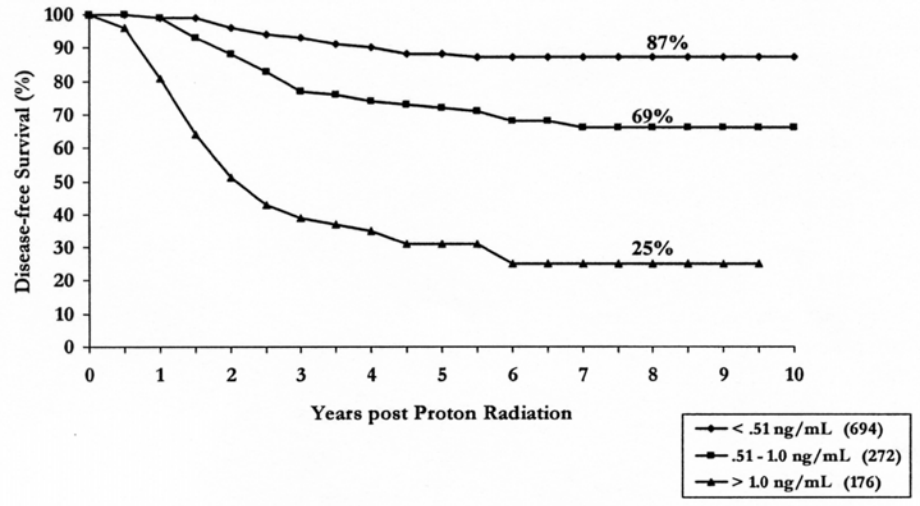

Fig. 4. Effect of prostate-specific antigen nadir levels on biochemical disease-free survival.

Other dose-escalation Phase I/II protocols using protons are presently being activated at LLUMC and Massachusetts General Hospital. One study will be delivering 84.6 Gy with protons alone for early prostate cancer, whereas patients with locally advanced prostate carcinoma will be treated with in a Phase I/II dose-escalation trial with protons to the prostate in conjunction with irradiation to the pelvic lymph nodes and androgen deprivation therapy.

The use of topical radiation protectors as a means of protecting the anterior rectal wall holds potential significance for minimizing late rectal injury. Biologic studies are presently under way at LLUMC to evaluate the use of topical radiation protectors in conjunction with a rectal balloon to move the posterior rectum out of the treatment field. The combined use of rectal distention and topical protectors may increase the tolerance of the rectal mucosa as well as minimizing the volume of rectum treated.

Recent technological developments in proton therapy will allow the use of intensity-modulated protons in the very near future. Cella *et al.* have reported on the potential benefit of this modality in prostate cancer. They found that intensity-modulated protons reduced the integral dose to nontarget tissue by a factor of 1.7 compared with intensity-modulated photons (17).

CONCLUSION

Conformal proton beam radiation therapy of prostate cancer can achieve excellent biochemical freedom-from-relapse rates with minimal treatment-related morbidity at the doses reported. Additional studies of dose escalation are under way to define further the role of proton therapy in management of this disease.

REFERENCES

1. Slater JD, Yonemoto LT, Rossi CJ Jr, *et al.* Conformal proton therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1998;42:299–304.
2. Archambeau JO, Bennett GW, Levine GS, *et al.* Proton radiation therapy. *Radiology* 1974;110:445–457.
3. Slater JD, Rossi CJ Jr., Yonemoto LT, *et al.* Conformal proton therapy for early-stage prostate cancer. *Urology* 1999;53:978–984.
4. Slater JM, Archambeau JO, Miller DW, *et al.* The proton treatment center at Loma Linda University Medical Center: Rationale for and description of its development. *Int J Radiat Oncol Biol Phys* 1992;22:383–389.
5. 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.
6. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
7. Cox D. Regression models and life tables (with discussion). *J R Stat Soc* 1972;B34:187–220.
8. Ryu JK, Winter K, Michalski JM, *et al.* Interim report of toxicity from 3D conformal radiation therapy (3D-CRT) for prostate cancer on 3DOG/RTOG 9406, level III (79.2 Gy). *Int J Radiat Oncol Biol Phys* 2002;54:1036–1046.
9. Zelefsky MJ, Fuks Z, Hunt M, *et al.* High-dose intensity modulated radiation therapy for prostate cancer: Early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002;53:1111–1116.
10. Han M, Partin AW, Pound CR, *et al.* Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28:555–565.
11. Zagars GK, Pollack A, von Eschenbach AC. Prognostic factors for clinically localized prostate carcinoma: Analysis of 938 patients irradiated in the prostate specific antigen era. *Cancer* 1997;79:1370–1380.
12. Pollack A, Zagars GK, Antolak JA, *et al.* Prostate biopsy status and PSA nadir level as early surrogates for treatment failure: Analysis of a prostate cancer randomized radiation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2002;54:677–685.
13. Hanlon AL, Diratzouiann H, Hanks GE. Posttreatment prostate-specific antigen nadir highly predictive of distant failure and death from prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;53:297–303.
14. Zelefsky MJ, Leibel SA, Gaudin PB, *et al.* Dose escalation with 3-D conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998;41:491–500.
15. Hanks GE, Hanlon AL, Schultheiss TE, *et al.* Dose escalation with 3-D conformal treatment: 5 year outcomes, treatment optimization, and future directions. *Int J Radiat Oncol Biol Phys* 1998;41:501–510.
16. Huang EH, Pollack A, Levy L, *et al.* Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1314–1321.
17. Cella L, Lomax A, Miralbell R. Potential role of intensity modulated proton beams in prostate cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;49:217–223.