Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer

Anthony V. D'Amico, MD, PhD; Richard Whittington, MD; S. Bruce Malkowicz, MD; Delray Schultz, PhD; Kenneth Blank, MD; Gregory A. Broderick, MD; John E. Tomaszewski, MD; Andrew A. Renshaw, MD; Irving Kaplan, MD; Clair J. Beard, MD; Alan Wein, MD

Context.—Interstitial radiation (implant) therapy is used to treat clinically localized adenocarcinoma of the prostate, but how it compares with other treatments is not known.

Objective.—To estimate control of prostate-specific antigen (PSA) after radical prostatectomy (RP), external beam radiation (RT), or implant with or without neoadjuvant androgen deprivation therapy in patients with clinically localized prostate cancer.

Design.—Retrospective cohort study of outcome data compared using Cox regression multivariable analyses.

Setting and Patients.—A total of 1872 men treated between January 1989 and October 1997 with an RP (n = 888) or implant with or without neoadjuvant androgen deprivation therapy (n = 218) at the Hospital of the University of Pennsylvania, Philadelphia, or RT (n = 766) at the Joint Center for Radiation Therapy, Boston, Mass, were enrolled.

Main Outcome Measure.—Actuarial freedom from PSA failure (defined as PSA outcome).

Results.—The relative risk (RR) of PSA failure in low-risk patients (stage T1c, T2a and PSA level ≤10 ng/mL and Gleason score ≤6) treated using RT, implant plus androgen deprivation therapy, or implant therapy was 1.1 (95% confidence interval [CI], 0.5-2.7), 0.5 (95% CI, 0.1-1.9), and 1.1 (95% CI, 0.3-3.6), respectively, compared with those patients treated with RP. The RRs of PSA failure in the intermediate-risk patients (stage T2b or Gleason score of 7 or PSA level >10 and ≤20 ng/mL) and high-risk patients (stage T2c or PSA level >20 ng/mL or Gleason score ≥8) treated with implant compared with RP were 3.1 (95% CI, 1.5-6.1) and 3.0 (95% CI, 1.8-5.0), respectively. The addition of androgen deprivation to implant therapy did not improve PSA outcome in high-risk patients but resulted in a PSA outcome that was not statistically different compared with the results obtained using RP or RT in intermediate-risk patients. These results were unchanged when patients were stratified using the traditional rankings of biopsy Gleason scores of 2 through 4 vs 5 through 6 vs 7 vs 8 through 10.

Conclusions.—Low-risk patients had estimates of 5-year PSA outcome after treatment with RP, RT, or implant with or without neoadjuvant androgen deprivation that were not statistically different, whereas intermediate- and high-risk patients treated with RP or RT did better then those treated by implant. Prospective randomized trials are needed to verify these findings.

JAMA. 1998;280:969-974

From the Joint Center for Radiation Therapy, Harvard Medical School, Boston, Mass (Drs D'Amico, Kaplan, and Beard); Departments of Radiation Oncology (Drs Whittington and Blank), Urology (Drs Malkowicz, Broderick, and Wein), and Pathology (Dr Tomaszewski), Hospital of the University of Pennsylvania, Philadelphia; Department of Mathematics, University of Millersville (Dr Schultz), Millersville, Pa; and Department of Pathology, Brigham and Women's Hospital (Dr Renshaw), Boston, Mass.

Reprints: Anthony V. D'Amico, MD, PhD, Joint Center for Radiation Therapy, 330 Brookline Ave, Fifth Floor, Boston, MA 02215 (e-mail: ADAMICO@jcrt.harvard.edu).

THERE ARE no completed prospective randomized trials, to our knowledge, that compare definitive local treatment options for clinically localized adenocarcinoma of the prostate. Retrospective comparisons[1,2] stratified by the known prognostic factors and using actuarial analyses have been published comparing radical prostatectomy (RP) with external beam radiation therapy (RT). However, a direct comparison of the results of ultrasound-guided interstitial prostate radiation (implant) therapy with RP or RT stratified by the pretreatment prognostic factors has not been previously reported.

See also pp 975 and 1008.

The utility of the pretreatment prostate-specific antigen (PSA),[3] biopsy Gleason score,[4] and American Joint Commission on Cancer Staging (AJCC) T stage[5] in predicting postradiation[6-10] and postoperative[11-16] PSA outcome has been previously published by several investigators.

The purpose of this study is to provide PSA outcome data stratified by the pretreatment PSA, biopsy Gleason score, and AJCC T stage in men treated with RP, RT, or implant therapy with or without the addition of neoadjuvant androgen deprivation for clinically localized prostate cancer.

METHODS

Patient Population

Between January 1989 and October 1997, 1872 men with clinically localized prostate cancer underwent definitive local therapy. Local therapy received was RP (n = 888) or implant with or without neoadjuvant androgen deprivation therapy (n = 218) at the Hospital of the

University of Pennsylvania (HUP), Philadelphia, or conformal RT (n = 766) at the Joint Center for Radiation Therapy, Boston, Mass.

Staging

In all cases, staging evaluation included a history and physical examination including a digital rectal examination, serum PSA, computed tomographic scan of the pelvis or an endorectal and pelvic coil magnetic resonance imaging scan of the prostate and pelvis, bone scan, and a transrectal ultrasound-guided needle biopsy of the prostate with Gleason score histologic grading.[4] A sextant biopsy was performed using a 18-gauge Tru-Cut needle (Travenol Laboratories, Deerfield, Ill) via a transrectal approach. The clinical stage was obtained from the digital rectal examination findings using the 1992 AJCC staging system.[5] Radiologic and biopsy information was not used to determine clinical stage. The PSA level was obtained on an ambulatory basis prior to radiologic studies and the biopsy procedure. All PSA measurements[3] were made using the Hybritech (San Diego, Calif), Tosoh (Foster City, Calif), or Abbott assays (Chicago, Ill).

Treatment

A referee genitourinary pathologist reviewed the diagnostic biopsy specimens for all patients undergoing surgery or implant at the HUP (J.E.T.) and RT at the Joint Center for Radiation Therapy (A.A.R.). Surgical treatment consisted of a radical retropubic prostatectomy and bilateral pelvic lymph node sampling.

All patients managed with definitive RT were treated using at least 10-MV photons and a conformal shaped 4-field technique. Those patients with AJCC clinical stage T1c, T2a disease who also had a PSA level of 10 ng/mL or less and biopsy Gleason score of 2 to 6 were treated to the prostate only with a 1.5-cm margin. The median prescription dose was 66 Gy (66-70 Gy) and was delivered using 2-Gy fractions. All other patients with clinically localized disease received a median prescription dose of 45 Gy (45-50.4 Gy) in 1.8-Gy fractions to the prostate and seminal vesicles plus a 1.5-cm margin. This was followed by treatment to the prostate alone using a shrinking field technique with a 1.5-cm margin to a median prescription dose of 22 Gy (18-22 Gy) in 1.8- to 2.0-Gy fractions. A 95% normalization was used.

Implant therapy was performed using palladium 103 (^{103}Pd) seeds, a perineal template-guided, peripheral-loading technique, and a Bruel & Kjaer 8551 transrectal ultrasound unit (Naerum, Denmark). The minimum peripheral dose to the prostatic capsule was 115 Gy. A transrectal ultrasound probe was used to image the prostate at 5-mm intervals preoperatively to ascertain the optimal number and location of seeds needed to deliver the minimum peripheral dose to the entire prostate gland volume. Individual seed strength ranged from 58 to 61 MBq. The total amount implanted ranged from 1306 to 7189 MBq. Postimplant dosimetry was performed on all patients based on films obtained at 4 weeks after the implant. For the first 143 patients this consisted of orthogonal films, and for the latter 75 patients, computed tomography was used. Of the 218 patients who received implant therapy, 152 (70%) received neoadjuvant androgen deprivation for a median of 3 months (2-10 months). Hormonal therapy consisted of a luteinizing hormone-releasing hormone agonist that was preceded by the use of a nonsteroidal antiandrogen for 7 to 10 days. Ninety-six (63%) of 152 patients received 3 months of neoadjuvant androgen deprivation therapy. The remaining 2 (1.33%), 15 (10%), 14 (9%), 20 (13%), 1 (1%), 2 (1.33%), and 2 (1.33%) received 2, 4, 5, 6, 7, 9, or 10 months of neoadjuvant androgen deprivation therapy, respectively.

Follow-up

The median follow-up of the 888 surgically managed patients at HUP was 38 months (8-100 months). The median follow-up for the 766 and 218 radiation-managed patients at the Joint Center for Radiation Therapy and HUP was 38 months (8-75 months) and 41 months (3-72 months), respectively. The patients were seen 1 month postoperatively or after the end of radiation therapy, then at 3-month intervals for 2 years, every 6 months for 5 years, and annually thereafter. At each follow-up a serum PSA was obtained prior to performing the digital rectal examination. All pretreatment PSA values were obtained within 1 month of the date of surgery or start of radiation. No patient was lost to follow-up and all patients were alive at the time of this analysis.

Statistical Analyses

In order to have the multivariable analysis results of the Cox proportional

Table 1.—Clinical Pretreatment Characteristics of the 1872 Patients Used in the Time to Prostate-Specific Antigen (PSA) Failure Analyses Are Shown Stratified by Type of Treatment

	No. (%) of Patients Receiving Treatment*			
Clinical Factor	Radical Prostatectomy at the Hospital of the University of Pennsylvania (N = 888)	External Beam Radiation Therapy at the Joint Center for Radiation Therapy (N = 766)	Interstitial Radiation (Implant) (N = 66)	Interstitial Radiation (Implant) Plus Neoadjuvant Androgen Deprivation Therapy (N = 152)
PSA, ng/mL				
>0 – 4	85 (10)	77 (10)	5 (8)	16 (10.5)
4.1-10	510 (57)	329 (43)	37 (56)	111 (73)
10.1-20	210 (24)	198 (26)	16 (24)	24 (16)
>20	83 (9)*	162 (21)†	8 (12)‡	1 (0.5)§
Gleason score				
2-4	164 (19)	109 (14)	6 (9)	10 (7)
5-6	517 (58)	376 (49)	47 (71)	110 (72)
7	133 (15)	192 (25)	10 (15)	29 (19)
8-10	74 (8)	89 (12)	3 (5)	3 (2)
American Joint Commission on Cancer Staging T stage				
T1c	256 (29)	222 (29)	15 (23)	57 (37.5)
T2a	388 (44)	246 (32)	35 (53)	68 (45)
T2b	93 (10)	141 (18)	5 (7)	7 (4.5)
T2c	151 (17)	157 (21)	11 (17)	20 (13)

*PSA range of 20.3 to 243 ng/mL and median of 29.8 ng/mL.
†PSA range of 20.1 to 561 ng/mL and median of 32.6 ng/mL.
‡PSA range of 20.4 to 96.7 ng/mL and median of 26 ng/mL.
§PSA value of 26.9 ng/mL and median of 26.9 ng/mL.

Table 2.—Detailed Description of the Clinical Pretreatment Characteristics of the 1872 Patients Used in the Time to Prostate-Specific Antigen (PSA) Failure Analyses Stratified by Risk Group and the Type of Treatment

Level of Risk	No. (%) of Patients Receiving Treatment*			
	Radical Prostatectomy at the Hospital of the University of Pennsylvania	External Beam Radiation Therapy at the Joint Center for Radiation Therapy	Interstitial Radiation (Implant)	Interstitial Radiation (Implant) Plus Neoadjuvant Androgen Deprivation Therapy
Low	(n = 402)	(n = 225)	(n = 32)	(n = 91)
PSA >0-4	68 (17)	42 (19)	4 (13)	12 (13)
PSA 4.1-10	334 (83)	183 (81)	28 (87)	79 (87)
Biopsy Gleason score 2-4	104 (26)	53 (24)	4 (12)	7 (8)
Biopsy Gleason score 5-6	298 (74)	172 (76)	28 (88)	84 (92)
American Joint Commission on Cancer Staging (AJCC) T1c, T2a	402 (100)	225 (100)	32 (100)	91 (100)
Intermediate	(n = 247)	(n = 232)	(n = 15)	(n = 38)
PSA >0-4	9 (4)	23 (10)	1 (7)	1 (3)
PSA 4.1-10	100 (40)	82 (35)	4 (27)	19 (50)
PSA 10.1-20	138 (56)	127 (55)	10 (66)	18 (47)
Biopsy Gleason score 2-4	31 (13)	31 (13)	3 (20)	3 (8)
Biopsy Gleason score 5-6	126 (51)	91 (39)	6 (40)	12 (32)
Biopsy Gleason score 7	90 (36)	110 (48)	6 (40)	23 (60)
AJCC T1c, T2a	179 (72)	138 (59)	12 (80)	31 (82)
AJCC T2b	68 (28)	94 (41)	3 (20)	7 (18)
High	(n = 239)	(n = 309)	(n = 19)	(n = 23)
PSA >0-4	8 (3)	12 (4)	0 (0)	3 (13)
PSA 4.1-10	76 (32)	64 (21)	5 (26)	13 (57)
PSA 10.1-20	72 (30)	71 (23)	6 (32)	6 (26)
PSA >20	83 (35)	162 (52)	8 (42)	1 (4)
Biopsy Gleason score 2-4	29 (12)	25 (8)	0 (0)	0 (0)
Biopsy Gleason score 5-6	93 (39)	113 (36)	12 (63)	14 (61)
Biopsy Gleason score 7	43 (18)	82 (27)	4 (21)	6 (26)
Biopsy Gleason score 8-10	74 (31)	89 (29)	3 (16)	3 (13)
AJCC T1c, T2a	63 (26)	105 (34)	6 (31)	3 (13)
AJCC T2b	25 (11)	47 (15)	2 (11)	0 (0)
AJCC T2c	151 (63)	157 (51)	11 (58)	20 (87)

*n indicates sample sizes stratified by risk and treatment.

hazards regression model be applicable in the clinical setting for an individual patient,[3] risk groups were defined. These risk groups were established from a review of the literature[6-19] and were based on the known prognostic factors: PSA level, biopsy Gleason score, and 1992 AJCC T stage. Patients with AJCC clinical T stage T1c, T2a and PSA level of 10 ng/mL or less and biopsy Gleason score of 6 or less have been identified to be at low risk (<25% at 5 years) for posttherapy PSA failure. Conversely, patients with AJCC stage T2c disease or a PSA level of more than 20 ng/mL or a biopsy Gleason score of 8 or more have a risk higher than 50% at 5 years of posttherapy PSA failure. The remaining patients with PSA levels higher than 10 and 20 ng/mL or lower, a biopsy Gleason score of 7, or AJCC clinical stage T2b have been found to have an intermediate risk (25%-50% at 5 years of posttherapy PSA failure). Patients with AJCC clinical stage T1a, T1b were not managed using implant therapy because of the significant rate or urinary incontinence noted[17] using this approach in patients with a history of a transurethral resection of the prostate. Therefore, patients with AJCC clinical stage T1a, T1b disease managed with RP or RT were excluded from the study to ensure statistically valid comparisons.

A Cox regression multivariable analysis[20] was used to compare PSA outcome among the therapies within each risk group. For each analysis the assumptions of the Cox model were tested and satisfied. Coefficients from the Cox regression model were used to calculate the overall relative risk of PSA failure for patients managed with RT or implant with or without neoadjuvant androgen suppression as compared with patients managed with RP. For the purposes of the multivariable analysis, the type of therapy was treated as a categorical variable indicating RP at HUP, RT, implant, or implant plus neoadjuvant androgen deprivation. Radical prostatectomy at HUP was defined as the baseline group for the purposes of the multivariable analyses. Patients were also stratified and analyzed with the traditional rankings of a biopsy Gleason score of 2 through 4, 5 through 6, 7, and 8 through 10.

Prostate-specific antigen failure was defined according to the American Society of Therapeutic Radiation and Oncology 1996 consensus statement[21] for all study patients. The definition required that a patient have 3 consecutive rising PSA values each obtained at least 3 months apart before PSA failure was scored. The time of PSA failure was defined as the midpoint between the time of the PSA nadir value and the time of the first rising PSA value. Time zero was defined as the date of diagnosis for all study patients.

Pairwise comparisons were made using the log-rank test. In the case where a number of comparisons were made, the level of significance in order to be called statistically significant was lowered from the convention of .05 to .05 divided by the number of comparisons following the Bonferonni adjustment.[22] For the purpose of illustration, estimates of PSA outcome were calculated using the Kaplan-Meier[23] actuarial method and graphically displayed. In the low-, intermediate-, and high-risk patient groups the sample size and the number of events in this study was sufficient to detect a 12%, 17%, and 15% difference in PSA survival, respectively, with 80% power at a .05 level of significance. This was calculated for a baseline PSA survival of 85%, 60%, and 30% at 5 years in the low-, intermediate-, and high-risk patients, respectively.

Table 3.—Pairwise *P* Values Comparing the Proportion of Patients With the Given Pretreatment Clinical Characteristic Shown in Table 2 Across Treatment Modalities*

Level of Risk	Prostate-Specific Antigen	Gleason Score	Clinical Stage
Low			
Radical prostatectomy (RP) vs external beam radiation therapy (RT)	.58	.52	.99
RP vs interstitial radiation (implant)	.58	.09	.99
RP vs implant and neoadjuvant androgen deprivation therapy (H)	.38	.009	.99
RT vs implant	.39	.16	.99
RT vs implant plus H	.24	.01	.99
Implant vs implant plus H	.92	.80	.99
Intermediate			
RP vs RT	.19	.27	.009
RP vs implant	.48	.56	.57
RP vs implant plus H	.60	.02	.23
RT vs implant	.69	.77	.11
RT vs implant plus H	.13	.30	.009
Implant vs implant plus H	.28	.34	.99
High			
RP vs RT	.003	.09	.01
RP vs implant	.78	.97	.94
RP vs implant plus H	.003	.04	.05
RT vs implant	.55	.09	.85
RT vs implant plus H	.0002	.69	.009
Implant vs implant plus H	.006	.99	.06

*Because of the multiple comparisons, the level of significance as per Bonferonni method[22] was defined as <.05 divided by 6 or <.008.

Table 4.—*P* Values From the Cox Regression Analyses Evaluating the Ability of a Treatment Modality to Predict the Time to Posttherapy Prostate-Specific Antigen (PSA) Failure Stratified by Risk Group*

	RR (95% CI) [*P* Value]		
Treatment	Low Risk	Intermediate Risk	High Risk
External beam radiation therapy at the Joint Center for Radiation Therapy	1.1 (0.5-2.7) [.79]	0.8 (0.5-1.2) [.26]	0.9 (0.7-1.1) [.26]
Interstitial radiation (implant)	1.1 (0.3-3.6) [.91]	3.1 (1.5-6.1) [.006]	3.0 (1.8-5.0) [.0002]
Implant plus neoadjuvant androgen deprivation therapy	0.5 (0.1-1.9) [.21]	1.6 (0.8-3.3) [.22]	2.2 (1.2-4.0) [.02]

*Radical prostatectomy at the Hospital of the University of Pennsylvania is the baseline group. RR indicates relative risk; CI, confidence interval. RR is defined as the proportional increase in PSA failure expected with a given treatment modality when compared with radical prostatectomy.

RESULTS

Risk Group Analysis

The clinical pretreatment characteristics of the 1872 patients used in the time to PSA-failure analyses are listed in Table 1 and are stratified by the type of treatment. Table 2 lists the clinical characteristics of the study patients within each risk group. The pairwise *P* values from the comparative analyses of the proportion of patients having a specific pretreatment clinical characteristic between the treatment groups are shown in Table 3. After adjustment for the multiple comparisons,[22] no significant differences were noted in low-risk and intermediate-risk patients. High-risk patients managed with implant plus neoadjuvant androgen deprivation had an increased proportion of patients with PSA levels lower than 10 ng/mL and decreased proportion of patients with a PSA level of more than 20 ng/mL compared with patients managed with RP ($P = .003$) or RT ($P = .0002$). Both of these differences could bias the comparisons of PSA survival in favor of the implant plus neoadjuvant androgen suppression patient cohort. The use of multiple comparisons between treatment modalities (n = 6) required that the level of statistical significance as per Bonferonni adjustment[22] be redefined as lower than .008.

Time to PSA Failure Analyses

Table 4 lists the *P* values from the Cox regression multivariable analyses evaluating the effect of the treatment type on time to posttherapy PSA failure stratified by risk group. The relative risks of PSA failure with a 95% confidence interval are also listed. No significant difference ($P \geq .25$) in outcome was noted in low-risk patients (T1c, T2a and PSA level ≤10 ng/mL and Gleason score ≤6) across all treatment modalities. The 95% confidence intervals for the relative risk of PSA failure relative to RP for all patients included 1.0. High-risk patients (T2c, PSA level >20 ng/mL, or Gleason score ≥8), however, treated using a RP or RT did significantly better ($P \leq .01$) then those managed with implant with or without neoadjuvant androgen deprivation. Specifically, high-risk patients managed with implant therapy had at least a 2.2-fold increased risk of PSA failure compared with those treated with RP even if neoadjuvant androgen deprivation therapy was used. Intermediate-risk patients (T2b, Gleason score of 7, or PSA level >10 and ≤20 ng/mL) did significantly worse ($P \leq .003$) if managed by implant alone, but fared equivalently ($P = .18$) to those patients managed with RP if androgen deprivation was also administered. Intermediate-risk patients managed with implant therapy alone had a 3.1-fold increased risk of PSA failure compared with those patients managed with RP. These results remained unchanged when patients were stratified using the traditional groups of biopsy Gleason score. Specifically, patients with biopsy Gleason score of 2 through 6 had no statistical difference in their estimates of PSA failure-free survival across all the treatment modalities evaluated in this study. However, patients with biopsy Gleason scores of 8 through 10 who were managed with implant with or without neoadjuvant androgen deprivation therapy had a lower PSA failure-free survival that approached statistical significance ($P \leq .07$) when compared with those patients managed with RP or RT. Patients with biopsy Gleason scores of 7 did not have statistically different PSA failure-free survival when managed with RP, RT, or implant plus neoadjuvant androgen deprivation therapy ($P \geq .59$). However these patients did statistically worse ($P \leq .003$) if managed by implant alone. This analysis was repeated using the traditional Gleason score groupings for patients with PSA levels lower than 20 ng/mL and the results remained unchanged.

For the purpose of illustration, estimates of PSA outcome with pairwise *P* values evaluating the comparisons between treatment types were calculated using the Kaplan-Meier[23] actuarial method and are graphically displayed by risk group in Figures 1 through 3 and by biopsy Gleason score in Figures 4 through 7.

COMMENT

Several studies from the urologic[12-16] and oncologic[6-11,17-19] literature support that the combination of the AJCC clinical T stage, pretreatment PSA, and biopsy Gleason score can predict the pathologic organ confinement rate, biochemical failure rate, and subsequent metastatic rates in patients managed with definitive local therapy for clinically localized prostate

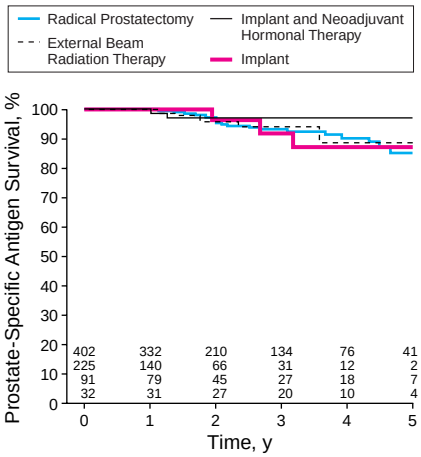

Figure 1.—Estimated prostate-specific antigen outcome for low-risk patients stratified by treatment modality. All pairwise *P* values are more than .25.

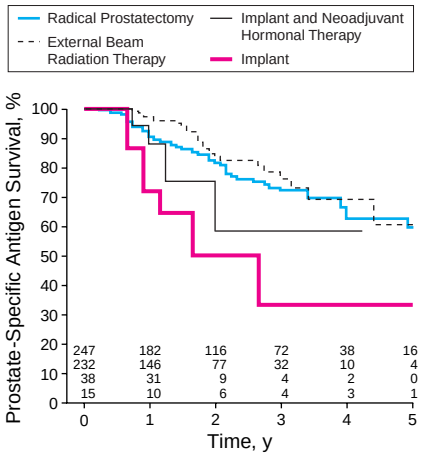

Figure 2.—Estimated prostate-specific antigen outcome for intermediate-risk patients. Pairwise *P* values are as follows: radical prostatectomy (RP) vs external beam radiation therapy (RT), .26; RP vs implant plus androgen ablation, .18; RP vs implant, .003; RT vs implant plus androgen ablation, .009; RT vs implant, .002; and implant plus androgen ablation vs implant, .14.

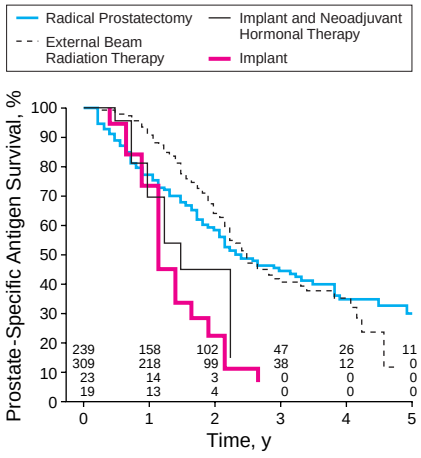

Figure 3.—Estimated prostate-specific antigen outcome for high-risk patients. Pairwise *P* values are as follows: radical prostatectomy (RP) vs external beam radiation therapy (RT), .25; RP vs implant plus androgen ablation, .01; RP vs implant, .005; RT vs implant plus androgen ablation, .007; RT vs implant, less than .001; and implant plus androgen ablation vs implant, .41.

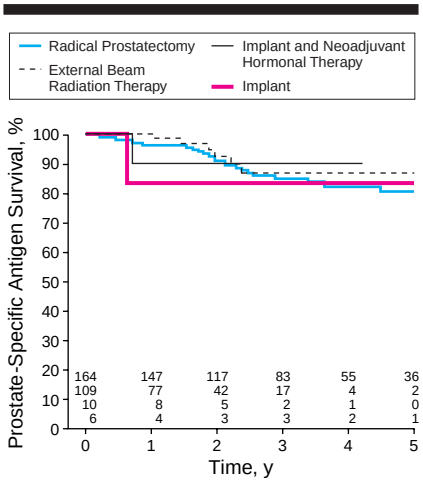

Figure 4.—Estimated prostate-specific antigen outcome for patients with biopsy Gleason score 2 through 4. All pairwise *P* values are more than .46.

cancer. Therefore, when attempting to compare PSA outcome across different treatment modalities, it is important to control for the values of these 3 prognostic factors. Using the results of the published literature,[6-19] the risk of postradiation and postoperative PSA failure was classified into 3 groups based on the pretreatment prognostic factors.

Using a multivariable time-to-PSA-failure analysis to compare PSA outcome after RP, RT, or implant with or without neoadjuvant androgen deprivation therapy for patients stratified by the defined pretreatment risk groups, several observations were noted. First, the group of patients defined to be at low risk for posttherapy PSA failure were estimated to derive equal benefit from treatment with RP, RT, or implant (Figure 1) at 5 years. Moreover, the addition of neoadjuvant androgen deprivation to implant therapy in low-risk patients provided no further benefit in the estimated 5-year PSA outcome. Second, patients at high risk for posttherapy PSA failure did significantly worse with implant therapy despite the addition of neoadjuvant hormonal deprivation when compared with patients treated with RP or RT (Figure 3). A statistically significant increase in favorable prognostic factors was present in the high-risk patients managed with implant plus neoadjuvant androgen suppression (ie, PSA level <10 ng/mL) compared with patients managed with RP or RT (Tables 2 and 3). Despite this potential bias in favor of the patients managed with implant plus neoadjuvant androgen suppression, the PSA outcome of these patients was still inferior to those patients managed with RP or RT. Finally, patients in the intermediate category for posttherapy PSA failure did significantly worse when managed with implant alone as compared with patients managed with RP, RT, or implant plus neoadjuvant androgen deprivation (Figure 2). While a statistical difference may exist for intermediate-risk patients managed with implant plus neoadjuvant androgen deprivation therapy vs RP or RT, this study was not adequately powered to detect this difference.

Further follow-up is needed to ascertain if these results are maintained. In particular, low-risk patients can sustain late PSA failures (ie, beyond 5 years). Moreover, men with low-grade or low-risk disease have a relatively low rate of PSA progression requiring numbers of patients much larger than presented in this study in order to prove a statistical difference. Therefore, while small differences may exist, they are unlikely to reach statistical significance. In addition, the intermediate-risk patients managed with a median of 3 months of neoadjuvant androgen deprivation and implant therapy may be experiencing a hormone-induced delay in PSA failure and not a true therapeutic gain. With only 9 patients at risk after 2 years in the implant plus androgen deprivation group compared with 116 and 77 in the RP and RT managed groups, respectively, it is too soon to make conclusions regarding the relative efficacy of these 3 treatments. Therefore, because of the small numbers and relatively short follow-up, particularly in the patients receiving neoadjuvant androgen deprivation, the results must be viewed as preliminary. However, these early data suggest that in high-risk patients, who are in greater need of treatment and who have the most to lose by ineffective therapy, implant therapy with or without the addition of a median of 3 months of neoadjuvant androgen deprivation was less effective than RP or RT at maintaining PSA-based survival. When examining the PSA failure-free survival using the traditional groupings of biopsy Gleason score, the exact results were found as those noted when the data were analyzed according to the risk groups lending further support to this study's findings.

Several issues remain that are not addressed by the data in this study. First, the comparison of PSA outcome for expectant management vs treatment is lacking. This comparison would be particularly relevant in the low-risk patients

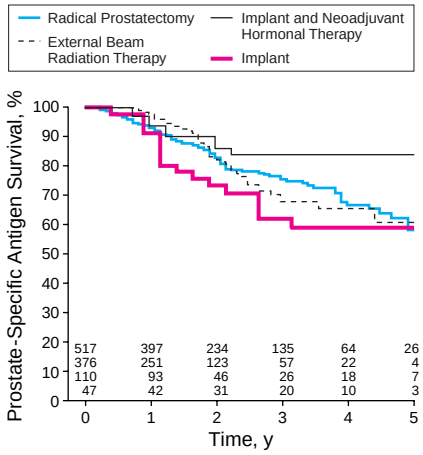

Figure 5.—Estimated prostate-specific antigen outcome for patients with biopsy Gleason score 5 through 6. All pairwise *P* values are more than .06.

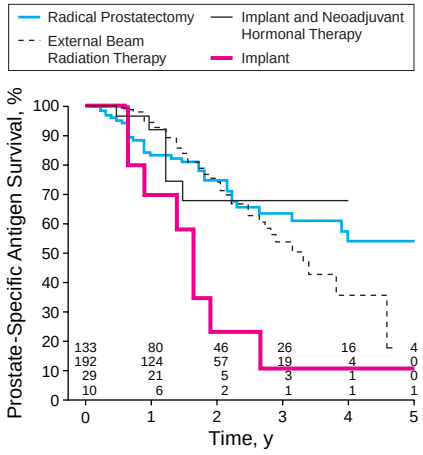

Figure 6.—Estimated prostate-specific antigen outcome for patients with biopsy Gleason score 7. Pairwise *P* values are as follows: radical prostatectomy (RP) vs external beam radiation therapy (RT), .59; RP vs implant plus androgen ablation, .95; RP vs implant, .002; RT vs implant plus androgen ablation, .79; RT vs implant, .003; and implant plus androgen ablation vs implant, .03.

where 5-year PSA-progression rates numerically approximate the 10-year clinical-progression rates noted from expectant management series.[24,25] Second, the PSA outcomes of the now widely practiced combination therapies of RT plus implant with or without neoadjuvant androgen deprivation therapy need to be prospectively compared with the PSA outcomes achieved after RP, RT, or implant. These comparisons would be particularly relevant in the high-risk and intermediate-risk groups where implant therapy alone may be insufficient. A final unanswered question remains. That is whether the use of ^{103}Pd as opposed to the conventional iodine 125 (^{125}I) affected the PSA outcome data reported in this study. The physical characteristics of these 2 radionuclides differ in that the half life and mean photon energy are 60 days, 27 keV and 17 days, 21 keV for ^{125}I and ^{103}Pd, respectively. These differences result in an initial dose rate of 0.0772 Gy/h and 0.197 Gy/h for ^{125}I and ^{103}Pd, respectively. It is therefore conceivable that the higher dose rate of palladium could have affected the results. Further investigations of these issues are needed.

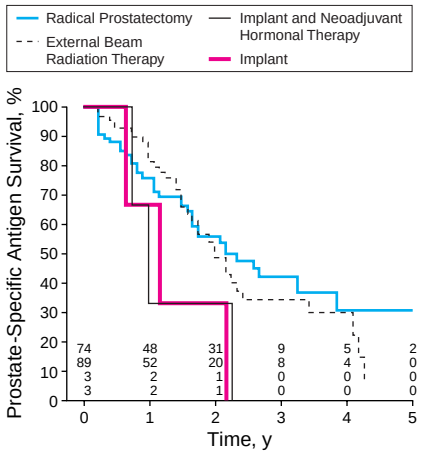

Figure 7.—Estimated prostate-specific antigen outcome for patients with biopsy Gleason score 8 through 10. Pairwise *P* values are as follows: radical prostatectomy (RP) vs external beam radiation therapy (RT), .71; RP vs implant plus androgen ablation, .07; RP vs implant, .06; RT vs implant plus androgen ablation, .06; RT vs implant, .05; and implant plus androgen ablation vs implant, .69.

Nevertheless, considering the widespread increase in the use of implant therapy throughout the United States, these data serve to heighten awareness to the possibility that this form of prostate cancer therapy may only be clinically efficacious in a select subgroup of patients and possibly inadequate in others. While no definitive conclusions can be reached using nonrandomized retrospective data, these analyses can provide the basis on which to design prospective randomized clinical trials that could definitively compare PSA, cause-specific, and overall survival outcomes among treatment modalities.

References

1. Kupelian P, Katcher J, Levin HS, Klein EA. Stage T1-2 prostate cancer. *Int J Radiat Oncol Biol Phys*. 1997;37:1043-1052.
2. D'Amico AV, Whittington R, Kaplan I, et al. Equivalent biochemical failure free survival after external beam radiation therapy or radical prostatectomy in patients with a pretreatment prostate specific antigen of >4-20 ng/mL. *Int J Radiat Oncol Biol Phys*. 1997;37:1053-1058.
3. Oesterling JE, Jacobsen SJ, Klee GG, et al. Free, complexed and total serum prostate specific antigen. *J Urol*. 1995;154:1090-1095.
4. Gleason DF and the Veterans Administration Cooperative Urological Research Group. Histologic grading and staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urologic Pathology*. Philadelphia, Pa: Lea & Febiger; 1977:171-187.
5. Beahrs OH, Henson DE, Hutter RVP. *American Joint Committee on Cancer: Manual for Staging Cancer*. 4th ed. Philadelphia, Pa: JB Lippincott; 1992.
6. Zagars GK, Pollack A, Kavadi VS, von Eschenbach AC. Prostate specific antigen and radiation therapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 1995;32:293-306.
7. Pisansky TM, Kahn MJ, Rasp GM, Cha SS, Haddock MG, Bostwick DG. A multiple prognostic index predictive of disease outcome after irradiation for clinically localized prostate cancer. *Cancer*. 1997;79:337-344.
8. Lee WR, Hanks GE, Schultheiss TE, Corn BW, Hunt MA. Localized prostate cancer treated by external beam radiotherapy alone: serum prostate specific antigen driven outcome analysis. *J Clin Oncol*. 1995;13:464-469.
9. Pisansky TM, Cha SS, Earle JD, Durr ED, Kozelsky TF, Wie HS. Prostate specific antigen as a pretherapy prognostic factor in patients treated with radiation therapy for clinically localized prostate cancer. *J Clin Oncol*. 1993;11:2158-2166.
10. Zietman AL, Coen JJ, Shipley WU, Willett CG, Efird JT. Radical radiation therapy in the management of prostatic adenocarcinoma. *J Urol*. 1994;151:640-645.
11. Hanks GE, Lee WR, Schultheiss TE. Clinical and biochemical evidence of control of prostate cancer at 5 years after external beam radiation. *J Urol*. 1995;154:456-459.
12. Partin AW, Piantadosi S, Sanda MG, Epstein JI, Marshall FF, Mohler JL. Selection of men at high risk for disease recurrence for experimental adjuvant therapy following radical prostatectomy. *Urology*. 1995;45:831-838.
13. Lerner SE, Blute ML, Bergstralh EJ, Bostwick DG, Eickholt JT, Zincke H. Analysis of risk factors for progression in patients with pathologically organ confined prostate cancers after radical retropubic prostatectomy. *J Urol*. 1996;156:137-143.
14. Zietman AL, Edelstein RA, Coen JJ, Babayan RK, Krane RJ. Radical prostatectomy for adenocarcinoma of the prostate. *Urology*. 1994;43:828-833.
15. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Tomaszewski JE, Wein A. PSA failure despite pathologically organ confined and margin negative disease. *J Clin Oncol*. 1997;15:1465-1469.
16. D'Amico AV, Whittington R, Malkowicz SB, Tomaszewski JE, Schultz D, Wein A. Outcome based staging for clinically localized adenocarcinoma of the prostate. *J Urol*. 1997;158:1422-1426.
17. Ragde H, Blasko JC, Grimm PD, et al. Interstitial iodine 125 radiation without adjuvant therapy in the treatment of clinically localized prostate carcinoma. *Cancer*. 1997;80:442-453.
18. Blasko JC, Wallner K, Grimm PD, Ragde H. Prostate specific antigen based disease control following ultrasound guided I^{125} implantation for stage T_1/T_2 prostatic carcinoma. *J Urol*. 1995;154:1096-1099.
19. Wallner K, Roy J, Harrison L. Tumor control and morbidity following transperineal iodine 125 implantation for stage T_1/T_2 prostatic carcinoma. *J Clin Oncol*. 1996;14:449-453.
20. Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972;34:187-189.
21. Cox JD for the 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.
22. Neter J, Wasserman W, Kutner M, eds. Simultaneous inferences and other topics in regression analysis-1. In: *Applied Linear Regression Models*. Homewood, Ill: Richard D Irwin Inc; 1983:150-153.
23. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-500.
24. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med*. 1994;330:242-248.
25. Adolfsson J, Steineck G, Hedlund PO. Deferred treatment of clinically localized prostate cancer. *Urology*. 1997;50:722-726.