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CLINICAL INVESTIGATION **Prostate**

FIVE-YEAR BIOCHEMICAL OUTCOME FOLLOWING PERMANENT INTERSTITIAL BRACHYTHERAPY FOR CLINICAL T1–T3 PROSTATE CANCER

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Purpose: To evaluate 5-year biochemical disease-free outcome for men with clinical T1b–T3a NxM0 1977 American Joint Committee on Cancer (1997 AJCC) adenocarcinoma of the prostate gland who underwent transperineal ultrasound-guided permanent prostate brachytherapy.

Methods and Materials: Four hundred twenty-five patients underwent transperineal ultrasound-guided prostate brachytherapy using either ^{103}Pd or ^{125}I, for clinical T1b–T3a NxM0 (1997 AJCC) adenocarcinoma of the prostate gland, from April 1995 to October 1999. No patient underwent pathologic lymph-node staging. One hundred ninety patients were implanted with either ^{103}Pd or ^{125}I monotherapy; 235 patients received moderate-dose external beam radiation therapy (EBRT), followed by a prostate brachytherapy boost; 163 patients received neoadjuvant hormonal manipulation, in conjunction with either ^{103}Pd or ^{125}I monotherapy (77 patients) or in conjunction with moderate-dose EBRT and a prostate brachytherapy boost (86 patients). The median patient age was 68.0 years (range, 48.2–81.3 years). The median follow-up was 31 months (range, 11–69 months). Follow-up was calculated from the day of implantation. No patient was lost to follow-up. Biochemical disease-free survival was defined by the American Society of Therapeutic Radiation and Oncology (ASTRO) consensus definition.

Results: For the entire cohort, the 5-year actuarial biochemical no evidence of disease (bNED) survival rate was 94%. For patients with low-, intermediate-, and high-risk disease, the 5-year biochemical disease-free rates were 97.1%, 97.5%, and 84.4%, respectively. For hormone-naive patients, 95.7%, 96.4%, and 79.9% of patients with low-, intermediate-, and high-risk disease were free of biochemical failure. Clinical and treatment parameters predictive of biochemical outcome included: clinical stage, pretreatment prostate-specific antigen (PSA), Gleason score, risk group, age > 65 years, and neoadjuvant hormonal therapy. Isotope choice was not a statistically significant predictor of disease-free survival for any risk group. The median postimplant PSA was ≤ 0.2 for all risk groups, regardless of hormonal status. The mean posttreatment PSA, however, was significantly lower for men implanted with ^{103}Pd (0.14 ng/mL) than for those implanted with ^{125}I (0.25 ng/mL), $p \leq 0.001$.

Conclusion: With a median follow-up of 31 months, permanent prostate brachytherapy results in a high probability of actuarial 5-year biochemical disease-free survival (DFS) for patients with clinical T1b–T3a (1997 AJCC) adenocarcinoma of the prostate gland, with an apparent plateau on the PSA survival curve. © 2001 Elsevier Science Inc.

Prostate cancer, Brachytherapy, Biochemical outcome, ^{103}Pd, ^{125}I.

INTRODUCTION

Over the past decade, the field of prostate brachytherapy has experienced an unparalleled resurgence, secondary to several technologic advances, including the evolution of transrectal ultrasonography, the development of a closed transperineal approach, and the widespread availability of sophisticated treatment planning computers. These imaging and planning advances have significantly improved the accuracy of seed placement. In addition, CT-based postoperative dosimetry has provided a unique opportunity to evaluate quality and proactively predict outcome and complications.

Prostate brachytherapy represents the ultimate three-dimensional (3D) conformal therapy, permitting dose escalation far exceeding other modalities. The majority of the prostate brachytherapy literature has reported results as favorable as those of the most positive radical prostatectomy and EBRT series (1–9). These brachytherapy results have been obtained with a variety of planning and intraoperative techniques, of which no method has proven superior. Our planning philosophy and intraoperative techniques have resulted in the delivery of therapeutic doses of radiation to a generous periprostatic margin by the placement of multiple periprostatic seeds (10).

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Table 1. Distribution of patients among various treatment groups

Treatment group	Brachytherapy as monotherapy	External beam + brachytherapy boost	Overall
^{125}I mPD (Gy, TG-43)*	145	110	
^{103}Pd mPD (Gy, TG-43)*	115	90	
No. of ^{125}I patients	153	51	204
No. of ^{103}Pd patients	37	184	221
No. hormone naive	113	149	262
No. neoadjuvant hormones	77	86	163
Number overall patients	190	235	425
	Hormone naive	Neoadjuvant hormones	
No. of ^{125}I patients	125	79	204
No. of ^{103}Pd patients	137	84	221
Number overall patients	262	163	425

* mPD is the prescribed minimum peripheral dose in Gy based on AAPM TG-43 dosimetry.

In this study, we report 5-year biochemical disease-free outcome using the American Society of Therapeutic Radiation and Oncology (ASTRO) consensus definition (11) for the first 425 men with clinical T1b–T3a NxM0 (1997 American Joint Committee on Cancer [AJCC]) adenocarcinoma of the prostate gland undergoing transperineal ultrasound-guided permanent prostate brachytherapy at our institution.

METHODS AND MATERIALS

A total of 425 patients underwent transperineal ultrasound-guided permanent prostate brachytherapy, using either ^{103}Pd or ^{125}I, for clinical T1b–T3a NxM0 adenocarcinoma of the prostate gland from April 1995 to October 1999. Patients were clinically staged by medical history, physical examination, including digital rectal examination, and serum prostate-specific antigen (PSA). Bone scans, computerized tomography (CT) of the pelvis, and prostatic acid phosphatase (PAP) were obtained as clinically indicated. No patient underwent pathologic lymph-node staging. Clinical stage was assigned according to the 1997 AJCC staging system (12). No patient was lost to follow-up.

Because of well-documented inaccuracies in Gleason grading, all cases originating from outside institutions were reviewed before the formulation of a treatment plan (13). Calculation algorithms and seed parameters used in preplans and postoperative dosimetry were those recommended by the American Association of Physicists in Medicine (AAPM) Task Group 43 (TG-43) (14). Our patient selection, preplanning philosophies, intraoperative techniques, and dosimetric evaluation have been described previously (10, 15–22). Specifically, the brachytherapy procedure was performed with preloaded 18-gauge needles using transverse and sagittal ultrasonography along with fluoroscopy. On average, 40% of the seeds were placed in periprostatic locations (10).

Table 1 summarizes the distribution of patients among various treatment groups: brachytherapy as monotherapy, brachytherapy boost following moderate-dose external beam radiation therapy (EBRT), and neoadjuvant hormonal manipulation status. EBRT consisted of 45 Gy to the prostate/periprostatic region/seminal vesicles/first echelon lymph nodes, in 1.8-Gy fractions, utilizing 15- to 18-MV photons delivered via a multifield technique, with shielding of the posterior one-half of the rectum via the lateral portals. The prescribed minimum peripheral doses (mPD), based on TG-43 dosimetry for ^{103}Pd monotherapy, ^{103}Pd boost, ^{125}I monotherapy, and ^{125}I boost, were 115 Gy, 90 Gy, 145 Gy, and 110 Gy, respectively. Those ^{125}I patients implanted before the implementation of the TG-43 formalism were recalculated. The number of patients implanted as monotherapy and boost were comparable, 190 patients and 235 patients, respectively, but ~80% of the monotherapy patients were implanted with ^{125}I, while nearly 80% of the boost patients were implanted with ^{103}Pd. The distribution of patients receiving neoadjuvant hormonal manipulation was comparable between mono- and boost therapy and between isotopes. Hormonal manipulation consisted of an LHRH agonist and an antiandrogen. Hormones were prescribed for either urinary obstructive symptomatology, unfavorable geometry, or multiple poor prognosticators.

Table 2 is a summary of patient clinical and implant characteristics stratified by risk group. Low-risk disease was defined as clinical T1c/T2a disease, Gleason score ≤ 6, and pretreatment PSA ≤ 10 ng/mL. Intermediate-risk patients presented with one unfavorable prognostic parameter, and high-risk patients presented with two or more unfavorable prognostic parameters (clinical stage T2b/T3a, PSA > 10, Gleason score ≥ 7). The median patient age was 68.0 years (range, 48.2–81.3 years). The mean follow-up was 32.8 $\pm$ 15.2 months, and the median follow-up was 31 months (range, 11–69 months). Follow-up was calculated from the day of implantation. Clinical parameters evaluated for biochemical disease-free survival (DFS) included patient age, clinical T stage, Gleason score, and pretreatment PSA. Treatment parameters evaluated included the utilization of neoadjuvant hormonal manipulation, the utilization of moderate-dose EBRT before implantation, and the choice of isotope.

Patients were monitored by physical examination, includ-

Table 2. Patient clinical and implant characteristics stratified by risk group

Parameter	Overall $n = 425$		Low risk $n = 160$	Intermediate $n = 165$	High risk $n = 100$	Risk group p value
	Median	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age at implant (years)	68.0	66.9 ± 6.8	65.3 ± 6.9	67.7 ± 6.3	68.1 ± 7.1	0.001
Pretreatment prostate-specific antigen (ng/mL)	7.5	9.4 ± 6.6	6.5 ± 1.9	8.8 ± 5.1	15.1 ± 9.5	<0.001
Gleason score	6	6.5 ± 1.0	5.7 ± 0.5	6.8 ± 0.9	7.3 ± 0.8	<0.001
Clinical stage	T2a	T1c–T2a	T1c–T2a	T1c–T2a	T2a–T2b	<0.001
Prostate US volume (cm^3)	35.4	36.5 ± 10.3	37.6 ± 9.9	36.4 ± 10.5	34.8 ± 10.4	0.107
Planning target vol. (cm^3)†	58.5	58.9 ± 13.6	62.0 ± 13.0	58.0 ± 13.7	54.1 ± 13.4	0.001
PTV/US vol†	1.69	1.71 ± 0.14	1.70 ± 0.14	1.70 ± 0.14	1.75 ± 0.15	0.077
No. of needles used	30	30.1 ± 3.3	31.2 ± 2.9	29.7 ± 3.4	29.1 ± 3.4	<0.001
No. of seeds used	134	134 ± 20	138 ± 19	132 ± 19	128 ± 20	<0.001
^{125}I activity/seed (mCi)* $n = 204$	0.284	0.289 ± 0.046	0.307 ± 0.042 $n = 126$	0.263 ± 0.037 $n = 61$	0.243 ± 0.027 $n = 17$	<0.001
^{103}Pd activity/seed (mCi)* $n = 221$	1.15	1.21 ± 0.18	1.47 ± 0.11 $n = 34$	1.19 ± 0.15 $n = 104$	1.12 ± 0.12 $n = 83$	<0.001

* ^{125}I activities are expressed in terms of the NIST 99 calibration standard, 1.27 U/mCi. ^{103}Pd activities are in terms of the manufacturer's calibration standard, 1.293 U/mCi.

† The planning target volume (PTV) and the ratio of PTV to ultrasound (US) volume was determined for 304 patients planned on a computer system capable of performing three-dimensional volumetric analyses.

ing digital rectal examination and PSA determinations at 3- to 6-month intervals. The endpoint of this analysis was disease-free survival with biochemical no evidence of disease (bNED), as defined by the ASTRO consensus definition (11). An abnormal digital rectal examination and/or the development of distant metastases in the absence of PSA progression were also scored as failures. No patient underwent routine postimplant prostate biopsy.

Biochemical DFS functions and comparisons of failure rates between patients across risk groups, hormonal therapy status, and the use of EBRT were calculated by Kaplan–Meier analysis using SPSS 10.0 software (SPSS, Inc., Chicago, IL). Pearson's correlation coefficient, t tests, and χ^2 analysis techniques were used to determine the strengths of the relationships between biochemical outcome and clinical/treatment parameters. Statistical significance was set at $p \leq 0.05$ for all analyses.

RESULTS

Table 2 outlines the clinical and treatment parameters and statistical analyses of the evaluated patient population in terms of risk group. Increasing risk was significantly correlated with increasing patient age. All other significant differences based on risk group are an expected consequence of either risk-group selection criteria (clinical stage, Gleason score, PSA) or planning target volume (PTV) definition (number of seeds and needles used). The PTV and the ratio of PTV to ultrasound volume was determined only for the 304 patients planned on a computer system capable of performing 3D volumetric analyses. The isotope activity was inversely related to risk group, because low-risk patients usually received monotherapy with an attendant higher mPD and higher seed strength, whereas high-risk patients usually received a lower-dose, lower-seed-strength brachytherapy boost.

Eighteen of 425 patients have failed treatment. Five of 18 have failed with distant metastases, including 2 men who died with prostate cancer, and 13 were classified as biochemical failure. To date, no patient has developed a clinically detectable local failure. There have been 12 deaths in the disease-free patient population, 3 of cancer other than prostate, and 9 of non–cancer-related causes.

Figure 1 displays a Kaplan–Meier analysis of all 425 patients with an overall bNED rate of 94%. Figure 2 illustrates biochemical outcome when stratified by risk group.

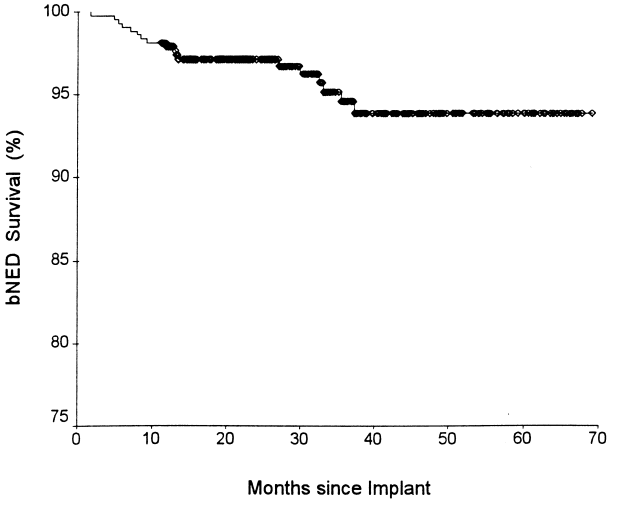

Fig. 1. Kaplan–Meier biochemical no evidence of disease (bNED) survival curve for the 425 consecutive patients in the study population. Diamonds indicate the follow-up time for the patients in the series.

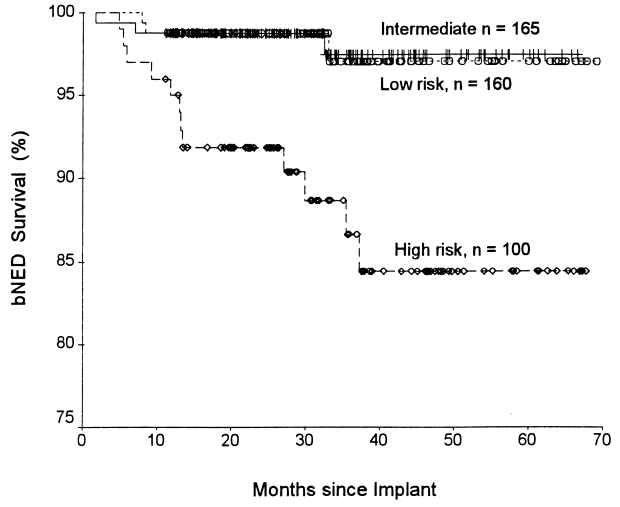

Fig. 2. Kaplan–Meier biochemical no evidence of disease (bNED) survival curves for the three risk groups. Dotted line and open circle markers = low risk, $n = 160$. Solid line and plus sign markers = intermediate risk, $n = 165$. Dashed line and diamond markers = high risk, $n = 100$. Markers indicate the follow-up time for the patients in the series. The difference between risk groups is significant, $p < 0.001$.

Although the low- and intermediate-risk curves are virtually superimposed with plateaus at 97.1% and 97.5%, respectively, the disease-free survival (DFS) curve of the high-risk patients, 84.4% at 5 years, is statistically different, $p < 0.001$. The risk groups were further dissected into isotope status in Fig. 3. There was no statistically significant difference in DFS due to isotope choice in any risk group. When the risk groups were merged, there was also no overall differences in DFS due to isotope choice, $p = 0.102$.

Disease-free survival as a function of risk group and hormonal status is shown in Figs. 4 and 5. For men receiving hormonal therapy, the DFS plateaus for low-, intermediate-, and high-risk groups are at 100%, 100%, and 97.1%, respectively. Of the 34 hormonally treated high-risk patients without evidence of biochemical failure, 29 (85.3%) had completed hormonal therapy, on average, 24.3 months (range, 5–61 months; median, 20 months) before data analysis. For hormone-naive patients, the DFS plateaus are at 95.7%, 96.4%, and 79.9% for low-, intermediate-, and high-risk groups, respectively. Hormonal status was not predictive of failure in any risk group, but in the overall population, patients receiving hormones were significantly less likely to fail, $p = 0.012$. Kaplan–Meier analyses were also run for various Gleason score groups and PSA groups. For patients with Gleason score 2–4, 5–6, 7, and 8–10 histology, 100%, 97.9%, 93.6%, and 91.2% were free of biochemical failure at 5 years. For those patients with pretreatment PSAs of 0–4, 4–10, 10–20, and > 20, 100%, 98.6%, 90.3%, and 83.3% were free of biochemical failure at 5 years.

Table 3 documents treatment outcome by risk group in terms of follow-up, posttreatment PSA, the duration of hormonal manipulation (where appropriate), and the dosi-

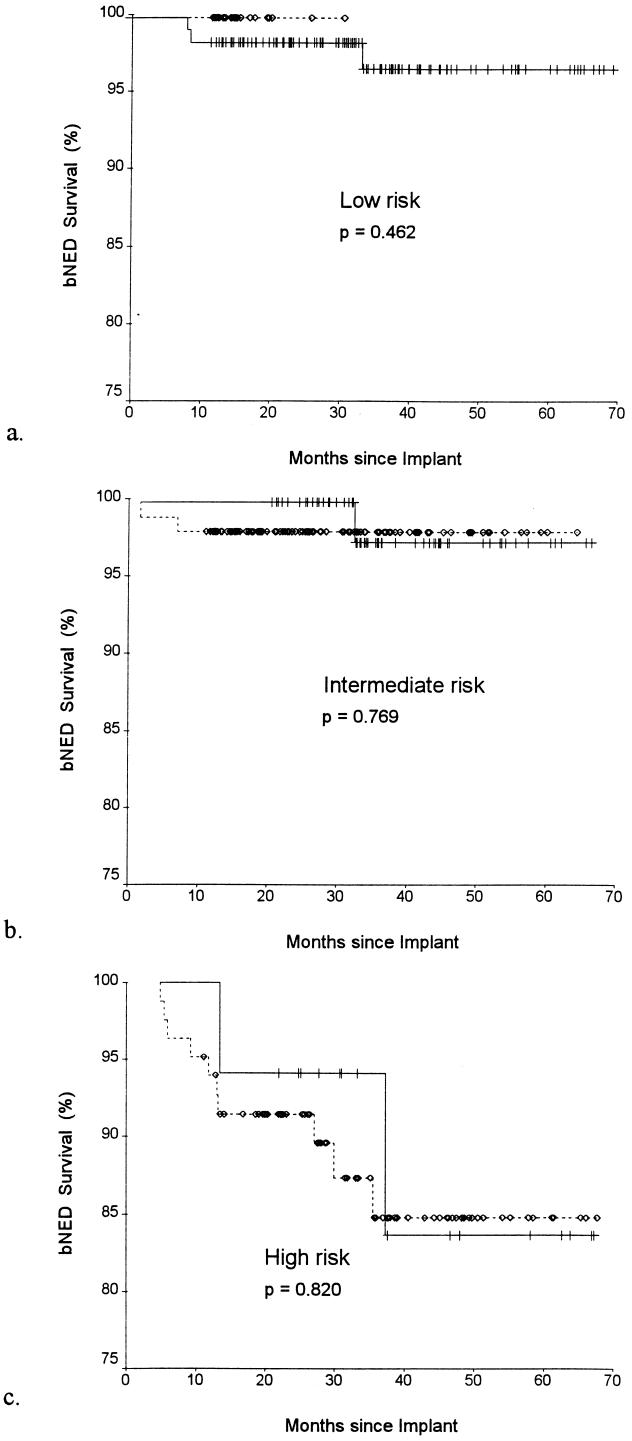

Fig. 3. Kaplan–Meier biochemical no evidence of disease (bNED) survival curves for the three risk groups stratified by isotope implanted. a. Low risk. b. Intermediate risk. c. High risk. The dotted lines and diamond markers are for patients who were hormone naive. The solid lines and plus sign markers are for patients who were implanted with ^{125}I. The bNED differences due to isotope in each risk group are not significant.

metric parameters, V_{100} and D_{90}. V_{100} is the percentage of the evaluated target volume (prostate plus margin) receiving 100% of the prescribed mPD, using CT-based dosimetry obtained on the day of the implant (Day 0). D_{90} is the

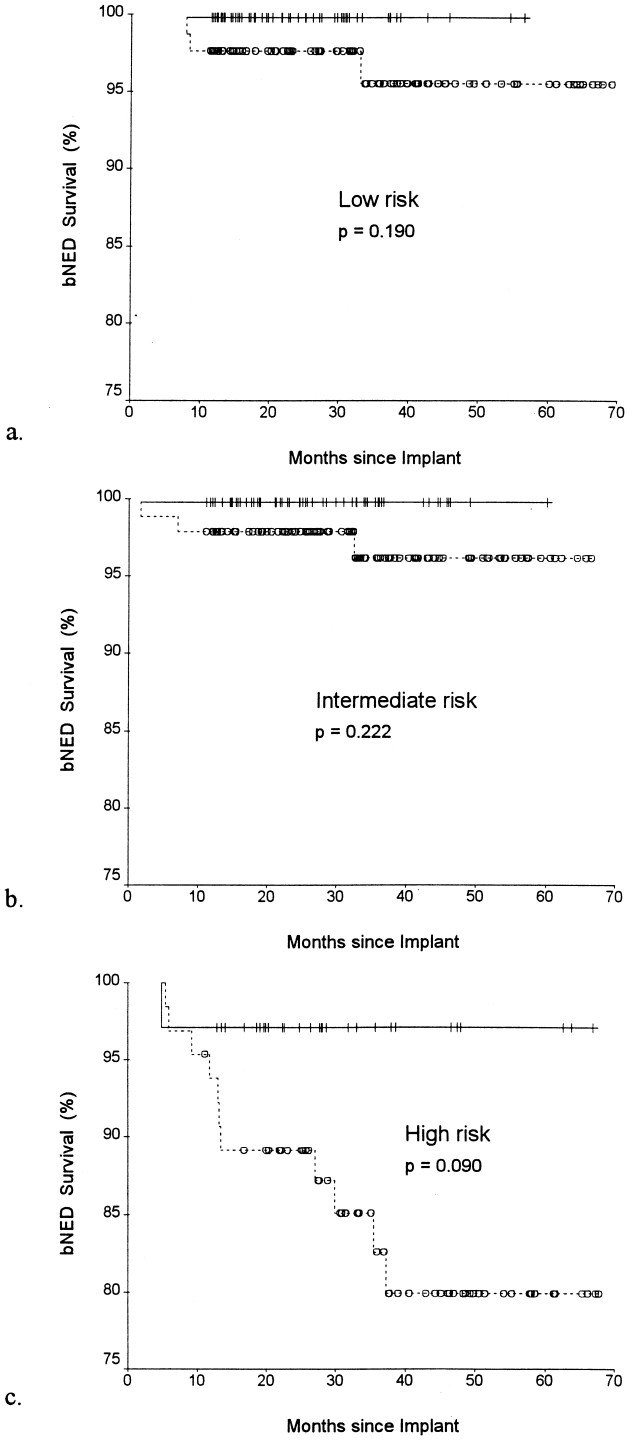

Fig. 4. Kaplan–Meier biochemical no evidence of disease (bNED) survival curves for the three risk groups stratified by neoadjuvant hormone status. a. Low risk. b. Intermediate risk. c. High risk. The dotted lines and open circles markers are for patients who were hormone naive. The solid lines and plus sign markers are for patients who used neoadjuvant hormones. The bNED differences due to hormone status in each risk group are not significant.

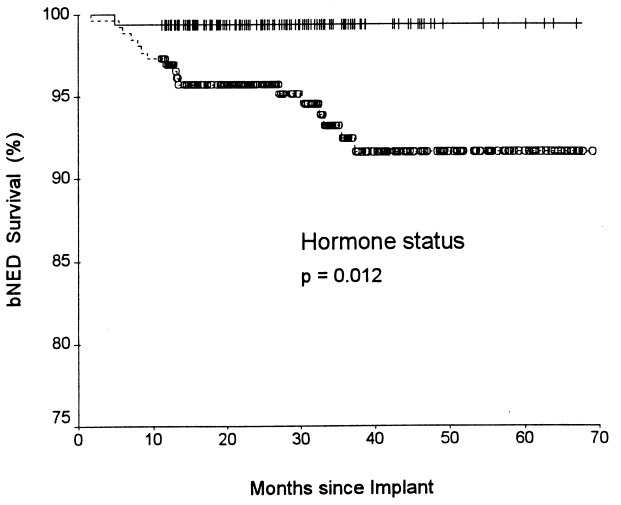

Fig. 5. Kaplan–Meier biochemical no evidence of disease (bNED) survival curves as a function of neoadjuvant hormone use. The dotted line and open circle markers are for the 262 patients who were hormone naive. The solid line and plus sign markers are for the 163 patients who used neoadjuvant hormones for a median duration of 4 months and a mean of 6.2 ± 5.9 months. The bNED difference due to hormone status is significant, $p = 0.012$.

minimum dose received by 90% of the evaluated target volume. All implants were evaluated by CT-based dosimetry, but the V_{100} and D_{90} data reported in Table 3 are from 304 patients whose Day 0 dosimetry was performed on a computer system capable of calculating dose–volume histograms. The mean V_{100} was 93.8% ± 5.3%, and the mean D_{90} was 111% ± 12% of mPD. Neither showed significant variation across risk groups; the variation between isotopes, although statistically significant for V_{100}, 94.6 ± 5.0 for ^{125}I vs. 93.1 ± 5.5 for ^{103}Pd, is not considered to be clinically significant (17, 20). Total months of follow-up from the time of implant was significantly greater as a function of increasing risk group, and, within each risk group, patients implanted with ^{125}I were followed significantly longer than were those implanted with ^{103}Pd. For those men receiving neoadjuvant hormones, the total duration of hormone treatment also increased significantly with increasing risk group.

The mean posttreatment PSAs decreased significantly with increasing risk group. This decrease across risk groups was significant not only overall, but also for patients stratified into hormone-naive and hormone-treated groups, but not when stratified by isotope used. Patients who received neoadjuvant hormones had significantly lower PSAs than their hormone-naive counterparts in each risk group cohort, and also when the risk groups were merged: 0.13 ± 0.21 ng/mL for hormone patients vs. 0.25 ± 0.32 ng/mL for hormone-naive men, $p < 0.001$. Although insufficient time has elapsed for all patients to have reached their PSA nadir, the mean posttreatment PSA was significantly lower for men implanted with ^{103}Pd (0.14 ± 0.22 ng/mL) than for those with ^{125}I (0.25 ± 0.33 ng/mL), $p < 0.001$. The mean follow-up for the ^{103}Pd patients was about 6.8 months less than that of the ^{125}I patients. Although the mean PSAs in each risk group were consistently lower for ^{103}Pd patients, the isotope difference was only significant in the low-risk group.

The influence of hormonal manipulation status is further delineated in Table 4 in terms of median PSAs. The median

Table 3. Comparison of dosimetric and outcome parameters in terms of isotope and risk group

Parameter	Isotope or hormone status	Low risk		Intermediate risk		High risk		Overall		Risk group p value
		n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	
V_{100} (% vol)	overall	120	94.3 ± 5.3	116	93.3 ± 5.6	68	93.8 ± 4.7	304	93.8 ± 5.3	0.308
	^{125}I	90	94.5 ± 5.6	39	94.9 ± 3.6	11	94.8 ± 3.9	140	94.6 ± 5.0	0.914
	^{103}Pd	30	94.0 ± 4.5	77	92.5 ± 6.3	57	93.6 ± 4.8	164	93.1 ± 5.5	0.337
	(Isotope p value)		(0.661)		(0.031)		(0.400)		(0.016)	
D_{90} (% mPD)	overall	120	111 ± 10	116	110 ± 11	68	113 ± 18	304	111 ± 12	0.324
	^{125}I	90	112 ± 9	39	111 ± 9	11	109 ± 17	140	111 ± 9	0.332
	^{103}Pd	30	111 ± 12	77	109 ± 12	57	113 ± 18	164	111 ± 14	0.811
	(Isotope p value)		(0.723)		(0.415)		(0.615)		(0.718)	
Last PSA (bNED patients)	overall	157	0.25 ± 0.29	162	0.19 ± 0.30	88	0.13 ± 0.23	407	0.20 ± 0.29	0.003
	^{125}I	123	0.28 ± 0.31	60	0.25 ± 0.38	15	0.20 ± 0.34	198	0.26 ± 0.33	0.661
	^{103}Pd	34	0.17 ± 0.19	102	0.16 ± 0.24	73	0.11 ± 0.20	209	0.14 ± 0.22	0.236
	(Isotope p value)		(0.011)		(0.084)		(0.152)		(<0.001)	
Last PSA (bNED patients)	hormone naive	89	0.30 ± 0.32	102	0.24 ± 0.33	54	0.18 ± 0.28	245	0.25 ± 0.32	0.068
	neoadj. hormones	68	0.19 ± 0.23	60	0.13 ± 0.23	34	<0.1 ± 0.08	162	0.13 ± 0.21	0.004
	(Hormone p value)		(0.015)		(0.024)		(0.007)		(<0.001)	
Months follow-up	overall	160	30.2 ± 15.4	165	32.5 ± 13.9	100	37.6 ± 16.0	425	32.8 ± 15.2	0.001
	^{125}I	126	34.1 ± 15.0	61	38.9 ± 12.4	17	44.4 ± 16.6	204	36.4 ± 14.7	0.007
	^{103}Pd	34	15.7 ± 4.3	104	28.7 ± 13.5	83	36.2 ± 15.6	221	29.6 ± 15.0	<0.001
	(Isotope p value)		(<0.001)		(<0.001)		(0.077)		(<0.001)	
Months hormones	overall	68	4.1 ± 1.8	60	4.7 ± 2.5	34	12.9 ± 9.7	162	6.2 ± 5.9	<0.001

Abbreviations: SD = standard deviation; PSA = prostate-specific antigen; bNED = biochemical no evidence of disease.

posttreatment PSAs for patients with low-, intermediate-, and high-risk disease were 0.2, 0.1, and < 0.1, respectively. The median postimplant PSA was ≤ 0.2 for all risk groups, regardless of hormonal status. Overall, with a median follow-up of 31 months, 97.1% of patients had a posttreatment PSA ≤ 1.0 and 89.2% had a PSA ≤ 0.5. A slightly larger percentage of patients receiving neoadjuvant hormones achieved PSAs < 1.0 ng/mL, when compared with those without hormonal therapy (98.8% vs. 95.9%) and < 0.5 ng/mL (94.4% vs. 85.7%).

The clinical and treatment parameters in Table 5 were evaluated in *t* tests to determine their impact on outcome. The same factors in Table 2 that classified patients into risk groups—clinical stage, Gleason score, and pretreatment PSA—were likewise predictors of failure. Using a cutoff point of 65 years produced a significant difference in DFS status, $p = 0.010$, indicating that patients older than 65 years are at significantly greater risk of failure. Other factors that differed by risk group, such as planning volume and number of seeds and needles, were not predictive of failure. The dosimetric quality variables V_{100} and D_{90}, which did not differ significantly by risk group, were not predictive of failure in this population.

DISCUSSION

Prostate brachytherapy represents the ultimate 3D conformal therapy, permitting dose escalation far exceeding other radiation modalities. In addition, the periprostatic region can be much more aggressively treated with brachytherapy than with radical prostatectomy because of the ability to place periprostatic seeds safely and accurately (10). The majority of the prostate brachytherapy literature has reported results as favorable as those of the most pos-

Table 4. Postimplant prostate-specific antigen (PSA) in disease-free men stratified by hormonal manipulation status and risk group

Parameter	Hormonal status	Low risk n = 157	Intermediate risk n = 162	High risk n = 88	Overall n = 407
Median last postimplant PSA	overall	0.2	0.1	<0.1	0.1
	no	0.2 (n = 89)	0.1 (n = 102)	0.1 (n = 54)	0.1 (n = 245)
	yes	0.1 (n = 68)	<0.1 (n = 60)	<0.1 (n = 34)	<0.1 (n = 162)
Percent of men with last PSA ≤1.0	overall	97.5	95.7	98.9	97.1
	no	96.6	94.1	98.1	95.9
	yes	98.5	98.3	100.0	98.8
Percent of men with last PSA ≤0.5	overall	85.4	90.1	94.3	89.2
	no	80.9	87.3	90.7	85.7
	yes	91.2	95.0	100.0	94.4
Median months duration of hormones	yes	4	4	12	4

Table 5. Clinical and treatment parameters tested for effect on outcome in univariate analysis

Significant parameters	*p* value	Parameters not significant	*p* value
Clinical stage	0.019	Ultrasound volume	0.232
Pretreatment PSA	0.024	Planning volume	0.789
Gleason score	0.006	No. of needles used	0.621
Risk group	<0.001	No. of seeds implanted	0.326
Age at implant ≥65 years	0.010	V_{100}	0.251
External beam therapy	0.036	D_{90}	0.327
Neoadjuvant hormonal therapy	<0.001		

PSA = prostate-specific antigen.

itive radical prostatectomy and EBRT series (1–9). Our results compare favorably with those reports. For patients undergoing palladium monotherapy, Blasko and colleagues (2) reported 5-year biochemical control rates of 94%, 82%, and 65% for patients with low-, intermediate-, and high-risk disease. In our series, patients undergoing prostate brachytherapy with or without EBRT, who did not receive hormonal manipulation and were classified as low-, intermediate-, and high-risk disease, had actuarial biochemical disease-free rates at 5 years of 95.7%, 96.4%, and 79.9%, respectively. For patients managed with dose-escalated 3D conformal EBRT, Zelefsky *et al.* (23) reported 4-year biochemical disease-free survival rates of approximately 95%, 80%, and 55% for low-, intermediate-, and high-risk patients who received 75.6–81.0 Gy.

Critz and colleagues (4) managed all patients with ^{125}I brachytherapy followed by supplemental radiation therapy, with a 5-year disease-free survival rate of 88%. For patients with Gleason score 2–4, 5–6, 7, and 8–10 histology, 93%, 89%, 82%, and 67% were free of biochemical failure at 5 years. Our results for these Gleason score groups were 100%, 97.9%, 93.6%, and 91.2% at 5 years. For those patients with pretreatment PSAs of 0–4, 4–10, 10–20, and > 20, Critz *et al.* reported that 94%, 93%, 75%, and 69% were free of biochemical failure at 5 years. Our results for these PSA groups were 100%, 98.6%, 90.3%, and 83.3% freedom from biochemical failure at 5 years.

Our 5-year biochemical disease-free survival compares favorably with previous reports (1–8). In addition, our absolute PSA values also compare favorably with a previous report (2). Blasko and colleagues (2) reported a median PSA of 0.3 for patients with a median follow-up of 41.5 months, and 82% of those patients had a PSA ≤ 1.0 and 68% had a PSA ≤ 0.5. In the Seattle experience, posttreatment PSAs continued to decline for 48 months following brachytherapy. In our study population, 95.9% of men not receiving hormonal manipulation had a posttreatment PSA ≤ 1.0, and 85.7% had a posttreatment PSA ≤ 0.5, with a median follow-up of 31 months. It is probable that our mean and median PSA values will continue to decline for at least another year.

In multivariate analysis, age greater than 65 years predicted for biochemical failure. Although not all studies have reported age to be a predictor of recurrence (24), age has been reported to be of prognostic significance in both the radical prostatectomy (25, 26) and EBRT (27) literature. Smith and colleagues (26) recently reported a statistically significant reduction in biochemical failures for men 59 years of age or younger undergoing prostatectomy. The mean follow-up of those young patients (32 months) is comparable to our mean follow-up of 32.8 ± 15.2 months and our median follow-up of 31 months.

We are especially encouraged by the 79.9% 5-year freedom from biochemical failure rate (median posttreatment PSA, 0.1) for the 65 hormone-naive high-risk patients. Although some patients with high Gleason scores may have subclinical distant metastatic disease at diagnosis, a recent analysis of Radiation Therapy Oncology Group (RTOG) trials reported improved survival for patients with high Gleason scores who received higher doses of EBRT (28). This finding does not support the hypothesis that the majority of high Gleason score patients have subclinical distant metastases at diagnosis, and it supports an aggressive locoregional approach. We believe that our favorable results for all risk groups may be a result of delivering therapeutic doses of radiation to a generous periprostatic margin by the placement of multiple periprostatic seeds (10).

Stock and colleagues (29) have shown a dose–response for biochemical failures based on Day 30 D_{90} dosimetry of ^{125}I implants exceeding 97% mPD. In our study population, the mean dosimetric quality variables V_{100} and D_{90} were 93.8% ± 5.3% volume and 111% ± 12% mPD, respectively, on Day 0, and were not predictive of failure. The values of these implant parameters are expected to increase with time as operative edema resolves (30). Because the mean D_{90} of the failures was 115% ± 28% of mPD, we believe that the number of inadequate implants is too small in the relatively small failure group for statistical analysis to detect a dose response.

Our 5-year actuarial biochemical results add additional support to the literature (1–9) regarding the effectiveness of permanent prostate brachytherapy for patients with carcinoma of the prostate gland. Additional follow-up of our patient cohort will be mandatory to confirm the durability of these results.

CONCLUSION

With a median follow-up of 31 months, permanent prostate brachytherapy results in a high probability of actuarial 5-year biochemical disease-free survival, with an apparent plateau on the freedom-from-PSA failure curve.

REFERENCES

1. Merrick GS, Butler WM, Lief JH, *et al*. Is brachytherapy comparable with radical prostatectomy and external beam radiation for clinically localized prostate cancer? *Tech Urol* 2001;7:12–19.
2. Blasko JC, Grimm PD, Sylvester JE, *et al*. Palladium-103 brachytherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2000;46:839–850.
3. Ragde H, Korb LJ, Elgamal AA, *et al*. Modern prostate brachytherapy: Prostate specific antigen results in 219 patients with up to 12 years of observed follow-up. *Cancer* 2000;89: 135–141.
4. Critz FA, Williams WH, Levinson AK, *et al*. Simultaneous irradiation for prostate cancer: Intermediate results with modern techniques. *J Urol* 2000;164:738–743.
5. Blasko JC, Wallner K, Grimm PD, *et al*. Prostate specific antigen based disease control following ultrasound guided 125iodine implantation for stage T1/T2 prostatic carcinoma. *J Urol* 1995;154:1096–1099.
6. Dattoli M, Wallner K, True L, *et al*. Prognostic role of serum prostatic acid phosphatase for 103Pd-based radiation for prostatic carcinoma. *Int J Radiat Oncol Biol Phys* 1999;45:853–856.
7. Zelefsky MJ, Hollister T, Raben A, *et al*. Five-year biochemical outcome, and toxicity with transperineal CT-planned permanent I-125 prostate implantation for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;47:1261–1266.
8. Potters L, Cha C, Oshinsky G, *et al*. Risk profiles to predict PSA relapse-free survival for patients undergoing permanent prostate brachytherapy. *Cancer J Sci Am* 1999;5:301–306.
9. Merrick GS, Butler WM, Lief JH, *et al*. Five-year biochemical outcome after prostate brachytherapy for hormone-naive men $\leq$ 62 years of age. *Int J Radiat Oncol Biol Phys* In press.
10. Merrick GS, Butler WM, Dorsey AT, *et al*. Seed fixity in the prostate/periprostatic region following brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;46:215–220.
11. 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.
12. Fleming ID, Cooper JS, Henson DE, *et al*. AJCC cancer staging handbook. 5th ed. Philadelphia: Lippincott-Raven Press; 1998.
13. Merrick GS, Butler WM, Farthing WH, *et al*. The impact of Gleason score accuracy as a criterion for prostate brachytherapy patient selection. *J Brachytherapy Int* 1998;14:113–121.
14. Nath R, Anderson LL, Luxton G, *et al*. Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy CommitteeTask Group No. 43. *Med Phys* 1995;22:209–234.
15. Butler WM, Merrick GS, Lief JH, *et al*. Comparison of seed loading approaches in prostate brachytherapy. *Med Phys* 2000;27:381–392.
16. Merrick GS, Butler WM. Modified uniform seed loading for prostate brachytherapy: Rationale, design, and evaluation. –2000;6:78–84.
17. Merrick GS, Butler WM, Dorsey AT, *et al*. Potential role of various dosimetric quality indicators in prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;44:717–724.
18. Merrick GS, Butler WM, Dorsey AT, *et al*. Rectal dosimetric analysis following prostatic conformal brachytherapy. *Int J Radiat Oncol Biol Phys* 1999;43:1021–1027.
19. Merrick GS, Butler WM, Dorsey AT, *et al*. The influence of timing on the dosimetric analysis of transperineal ultrasound guided prostatic conformal brachytherapy. *Rad Oncol Invest* 1998;6:182–190.
20. Merrick GS, Butler WM, Dorsey AT, *et al*. The effect of prostate size and isotope selection on dosimetric quality following permanent seed implantation. *Tech Urol* In press.
21. Merrick GS, Butler WM, Dorsey AT, *et al*. The influence of prophylactic dexamethasone on edema following prostate brachytherapy. *Tech Urol* 2000;6:117–122.
22. Butler WM, Dorsey AT, Nelson KR, *et al*. Quality assurance calibration of I-125 rapid strand in a sterile environment. *Int J Radiat Oncol Biol Phys* 1998;41:217–222.
23. Zelefsky MJ, Leibel SA, Gaudin PB, *et al*. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998;41:491–500.
24. Catalona WJ, Smith D. Five-year tumor recurrence rates after anatomical radical retropubic prostatectomy for prostate cancer. *J Urol* 1998;160:2428–2434.
25. Carter HB, Epstein JI, and Partin AW. Influence of age and prostate-specific antigen on the chance of curable prostate cancer among men with nonpalpable disease. *Urol* 1999;53: 126–130.
26. Smith CV, Bauer JJ, Connelly RR, *et al*. Prostate cancer in men age 50 years or younger: A review of the department of defense center for prostate disease research multi-center prostate cancer database. *J Urol* 2000;164:1964–1967.
27. Herold DM, Hanlon AL, Movsas B, *et al*. Age related prostate cancer metastases. *Urology* 1998;51:985–990.
28. Valicenti R, Lu J, Pilepich M, *et al*. Survival advantage from higher-dose radiation therapy for clinically localized prostate cancer treated in the Radiation Therapy Oncology Group trials. *J Clin Oncol* 2000;18:2740–2746.
29. Stock RG, Stone NN, Tabert A, *et al*. A dose response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101–108.
30. Waterman FM, Yue N, Corn BW, *et al*. Edema associated with I-125 or Pd-103 prostate brachytherapy and its impact on post-implant dosimetry: An analysis based on serial CT acquisition. *Int J Radiat Oncol Biol Phys* 1999;41:1069–1077.