Int. J. Radiation Oncology Biol. Phys., Vol. 46, No. 4, pp. 839–850, 2000

0360-3016/00/$–see front matter

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PII S0360-3016(99)00499-X

CLINICAL INVESTIGATION **Prostate**

PALLADIUM-103 BRACHYTHERAPY FOR PROSTATE CARCINOMA

JOHN C. BLASKO, M.D.,* PETER D. GRIMM, D.O.,* JOHN E. SYLVESTER, M.D.,*§
KAS RAY BADIOZAMANI, M.D.,† DAVID HOAK, M.D.,‡ AND WILLIAM CAVANAGH, B.S.*

*Seattle Prostate Institute, Seattle, WA; †Department of Radiation Oncology, University of Washington School of Medicine, Seattle, WA; ‡Pathology Associates, Spokane, WA; and §Puget Sound Tumor Institute, Seattle, WA

Purpose: A report of biochemical outcomes for patients treated with palladium-103 (Pd-103) brachytherapy over a fixed time interval.

Methods and Materials: Two hundred thirty patients with clinical stage T1–T2 prostate cancer were treated with Pd-103 brachytherapy and followed with prostate-specific antigen (PSA) determinations. Kaplan-Meier estimates of biochemical failure on the basis of two consecutive elevations of PSA were utilized. Multivariate risk groups were constructed. Aggregate PSA response by time interval was assessed.

Results: The overall biochemical control rate achieved at 9 years was 83.5%. Failures were local 3.0%; distant 6.1%; PSA progression only 4.3%. Significant risk factors contributing to failure were serum PSA greater than 10 ng/ml and Gleason sum of 7 or greater. Five-year biochemical control for those exhibiting neither risk factor was 94%; one risk factor, 82%; both risk factors, 65%. When all 1354 PSA determinations obtained for this cohort were considered, the patients with a proportion of PSAs ≤ 0.5 ng/ml continued to increase until at least 48 months post-therapy. These data conformed to a median PSA half-life of 96.2 days.

Conclusions: Prostate brachytherapy with Pd-103 achieves a high rate of biochemical and clinical control in patients with clinically organ-confined disease. PSA response following brachytherapy with low-dose-rate isotopes is protracted. **© 2000 Elsevier Science Inc.**

Prostate cancer, Brachytherapy, Prostate-specific antigen, Radiotherapy.

INTRODUCTION

Radical prostatectomy and external beam radiotherapy are the most common curative modalities employed in the treatment of early-stage prostate carcinoma. Recently, transrectal ultrasound guided brachytherapy has gained popularity as an additional treatment option for patients with early-stage disease (1–3). Although reports of image-based brachytherapy with iodine-125 (I-125) have yielded promising results in patients with prognostically favorable disease, controversy remains regarding the role of prostate brachytherapy relative to that of radical prostatectomy and external beam radiotherapy in the overall management of prostate cancer (4–8).

Iodine-125 has been the most common permanent radioisotope used for prostate brachytherapy. Iodine-125 emits a low-energy (27 keV) photon and possesses a half-life of 60 days, which results in a relatively low initial dose-rate of 7 to 10 cGy/hr at the prescription isodose contour. Palladium-103 (Pd-103) was introduced in 1987 as an additional permanent radioisotope suitable for interstitial implantation. The characteristics of Pd-103 are similar to I-125 in that it emits a low-energy photon with an average energy of 21 KeV. It differs in that the half-life is 17 days with a resultant initial dose rate of 20–24 cGy/hr for a typical prescription dose. Whether these dose rate differentials significantly influence clinical outcomes has been the subject of theoretical speculation but little clinical data is available to date (9–12).

This series represents the Seattle experience with transperineal, ultrasound-guided Pd-103 brachytherapy in patients with clinically organ-confined prostate cancer.

METHODS AND MATERIALS

Of patients presenting for evaluation of newly diagnosed prostate carcinoma at our institution between 1 January 1988 and 31 December 1995, 233 received Pd-103 brachytherapy as the sole form of treatment. Three patients have been lost to follow-up with no postimplant serum prostate-specific antigen (PSA) determinations, and are excluded, leaving 230 available for PSA-based analysis.

Patients were staged clinically as the result of medical history, physical examination, digital rectal examination,

Reprint requests to: John C. Blasko, M.D., Seattle Prostate Institute, Suite 1101, 1101 Madison St., Seattle, WA 98104. E-mail: jcb@SeattleProstateInst.com

Acknowledgments—Thanks to Haakon Ragde, M.D. and all other urologists at Northwest Hospital for their support of this endeavor and their assistance in the management of these patients.

Accepted for publication 5 November 1999.

and serum PSA measurement. Chest X-ray, bone scan, and/or computed tomography (CT) of the pelvis were performed as clinically indicated. Pathological lymph node staging was not performed. Clinical stage was assigned retrospectively according to the 1992 American Joint Committee on Cancer (AJCC) staging system (13). T stage was assigned strictly by digital rectal examination findings. Diagnostic prostate biopsies were graded by the Gleason sum methodology. The median patient age was 69 years.

Patient selection

This study describes a subset of consecutively treated, prospectively followed patients who received Pd-103 as the sole modality of therapy. During the time period in which these patients were treated, the higher dose rate of Pd-103 relative to I-125 was considered a potential advantage to those patients presenting with moderately to poorly differentiated histology. For this reason, patients with higher grade disease were more likely to be selected for treatment with Pd-103 than I-125. No patient underwent medical or surgical intervention for the purpose of diminishing hormone levels. No form of radiotherapy other than the implant was employed. No other local or systemic treatment was prescribed. The intention of the seed implant was curative.

TREATMENT

The Seattle technique of transperineal prostate brachytherapy has been reported elsewhere in detail (3, 14–16). For radiation planning purposes, a volumetric study was performed using transrectal ultrasonography to define the prostate. The treatment volume included the ultrasonically defined prostate plus a discretionary margin of 2–5 mm. The seminal vesicles were not included in the treatment volume. Dedicated prostate brachytherapy treatment planning software running on a PC platform calculated a three-dimensional source matrix that would attain a minimum prescription dose of 115 Gy encompassing the treatment volume. The dosimetric philosophy of seed distribution within the prostate evolved with time. For patients treated early in this series, sources were distributed in a uniform pattern across the target volume. Later patients were treated with a modified peripheral source distribution so that the planned urethral dose was limited to less than 150% of the prescription dose.

The implant procedure was performed on an outpatient basis utilizing preloaded 18-gauge needles. Transrectal ultrasound was the primary imaging modality used for needle guidance.

From 1988 through 1991, orthogonal X-rays were the only method available to evaluate implant quality at our institution. For these patients, implant quality was evaluated via a comparison of the preimplant ultrasound-determined prostate dimensions with the dimensions of the calculated 115 Gy isodose contour derived from film-based calculations. By this method, an adequate implant was defined as the volume encompassed by the 115 Gy isodose equaling or exceeding 80% of the ultrasound-determined volume. After 1992, all patients underwent postimplant CT-based dosimetric evaluation, but dose–volume histogram (DVH) technology was not available during this time. For these patients, the implant quality was evaluated by calculating isodose distributions on successive CT images of the prostate at 0.5-cm increments. The implant was judged to be adequate provided that the 90 Gy or greater isodose contour encompassed each CT cut of the prostate in its entirety. By these methods, all implants were judged by the treating physician to be adequate and no patient required reimplantation or supplemental external beam irradiation. The lack of CT-based postimplant dosimetry in the early patients and the lack of DVH capability precludes any meaningful analysis of outcome relative to the evolving dosimetric philosophies employed in these patients.

FOLLOW-UP

Patients were monitored by physical examination and serum PSA determinations at 3- to 6-month intervals during the first 5 years postimplant and yearly thereafter. Ten patients for whom follow-up PSAs were obtained at a maximum of less than 2 years are included. Of these 10, five expired with no evidence of disease (NED) within 3 years of implant. The remaining five (2%) have multiple PSA determinations available and are included in order to preserve the consecutive nature of the cohort.

Biopsy, bone scan, or other study was performed upon the occasion of a steadily rising PSA in order to define the location of putative tumor progression.

Biochemical outcomes are summarized in two ways. First, in order to describe biochemical success rates, cumulative survival functions are employed in which each patient in the cohort is represented as either a failure or as a censored observation. For the purposes of this analysis, failure is “PSA progression failure,” defined as two consecutive rises in serum PSA. Time to failure is defined as the midpoint between the lowest serum PSA attained and the first of the elevated values. Thus, the determination of biochemical failure in this series is similar to that of the ASTRO Consensus Conference (17) definition except that only two rises are required for failure instead of three. Censored observations are recorded at the time of last PSA follow-up.

Second, a series of cross-sectional analyses were performed for the purpose of quantifying actual cohort PSA response. Of special concern in examining the serum PSA data in toto were (a) a description of the effect of time upon response of the group as a whole, and (b) a description of the minimum PSA levels that may be reasonably expected following Pd-103 brachytherapy in this series.

For this latter analysis, discrete intervals were defined and all patient serum PSA data from that interval summarized. Intervals are defined as 6-month periods for the first 24 months from implant date and yearly thereafter. Each patient with available PSA data contributes only one PSA

measurement per interval; in cases where more than one determination is present, only the latest determination in the interval is included. For each interval, a hypothesis test is performed seeking to determine the likelihood of unequal sampling of patients ultimately defined as PSA progression failures per interval as opposed to the overall proportion of PSA failures. This testing seeks to ascertain the likelihood that the quantities (i.e., the median PSA over time) calculated represent the entire cohort, and are not restricted to the PSA "successes" only.

In the case of all data presented, serum PSA values subsequent to the documentation of clinical failure are excluded from analysis so that appropriate androgen deprivation for clinically evident recurrence does not influence the subsequent PSA profile of these patients. The PSA value and trend at the time of clinical relapse is maintained as the PSA of record for that patient.

Clinical failure was defined as either distant failure manifested as radiographically evident metastatic disease, or local failure defined as either a positive biopsy or a positive digital examination. An attempt was made to biopsy as many patients as possible post-treatment. Of the 230 patients, 107 underwent biopsy at a minimum of 1 year following the procedure. Biopsies were performed under transrectal ultrasound guidance by sextant or quadrant technique with additional cores taken of ultrasonically suspicious areas. Postimplant biopsies were classified as negative, indeterminate, or positive. The histopathologic characteristics of these categories have been previously described (18). In cases where uncertainty existed with hematoxylin and eosin stains, immunohistochemical testing was employed to distinguish between indeterminate and positive results as described by Crook *et al.* (19).

Cumulative survival functions were calculated by the method of Kaplan and Meier. Hypotheses regarding differences in biochemical relapse-free survival functions were evaluated using the log rank test. Linear confidence intervals were included where appropriate. Hypotheses regarding independence of proportions were evaluated using a two-tailed Fisher's exact test. The influence of multiple covariates on PSA progression-free survival was estimated by Cox regression; the influence of single covariates on PSA progression-free survival was evaluated using the log rank test.

RESULTS

The clinical, pathological, and biochemical characteristics of the patient population at the time of presentation are summarized in Table 1. The majority of patients (56%) presented with palpable T2a disease and 40% were classified as poorly differentiated with Gleason sum scores of 7 or greater. The median presenting PSA was 7.3 ng/ml, with the majority (63%) possessing an initial PSA of 4.0–10.0 ng/ml.

Ultrasound-determined prostate volumes at the time of implantation ranged from 11 to 69 cc (median: 30 cc). The average activity per seed was 1.4 mCi (range 1.0 to 1.8). The total number of seeds implanted in each case ranged from 50 to 152 (median: 91) and the median total activity was 122 mCi (range 68 to 198) to achieve the minimum prescription dose of 115 Gy.

Table 1. Clinical characteristics

		Number of patients	% of patients
Gleason grade			
3		1	0.4
4		9	3.9
5		42	18.3
6		87	37.8
7		77	33.5
8		13	5.7
9		0	0
10		1	0.4
Clinical stage			
T1b		4	1.7
T1c		65	28.3
T2a		129	56.1
T2b		27	11.7
T2c		2	0.9
Unk		3	1.3
Serum PSA			
0–4.0 ng/ml		28	12.2
4.1–10.0		146	63.5
10.1–20.0		47	20.4
20.1–30.0		6	2.6
>30.0		3	1.3
range	0.2–94		
median	7.3		
mean	8.9		

Clinical outcomes

No patient in this series has died from prostate cancer. The median follow-up for the entire series was 41.5 months. The status of the 230 patients at last follow-up is described in Table 2. No clinically evident disease was noted in 209/230 (90.9%). Twenty-one patients (9.1%) were diagnosed with clinical recurrence of carcinoma over the observation period. Local failure was noted in 7/230 (3.0%) and 14/230 (6.1%) developed distant or regional disease.

Postimplant biopsies were requested of all patients. One hundred and seven patients consented to biopsy 12 to 60 months postimplant. All patients who exhibited PSA progression underwent biopsy, except for four patients who

Table 2. Clinical status at last PSA follow-up

	Number (%)	Med. PSA
NED	199 (86.5)	0.3
PSA progression	10 (4.3)	4.5
Seminal vesicle disease	1 (0.4)	1.1
Local disease	7 (3.0)	6.5
Distant disease	13 (5.7)	16.0

NED = no evidence of disease.

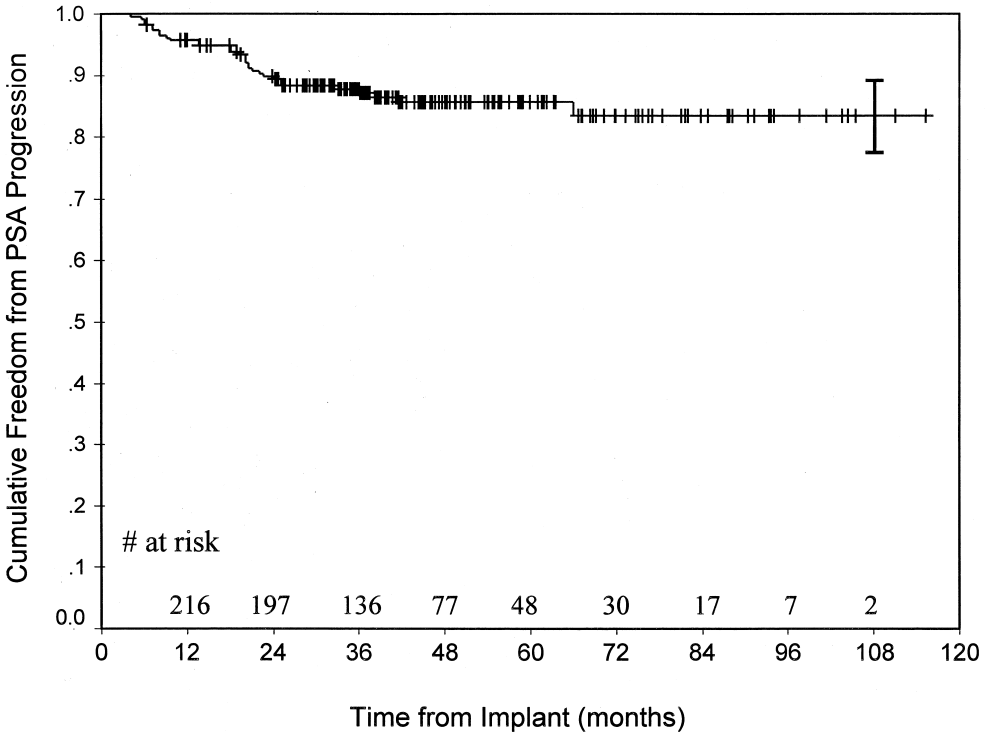

Fig. 1. PSA progression-free survival for entire cohort.

refused biopsy but were documented with metastatic recurrence. Negative biopsies were obtained in 100/107 (93%) and 7/107 (3%) were positive, accounting for the local failures.

Biochemical outcomes

In all cases of clinical disease recurrence (21 patients), PSA progression failure preceded the definitive diagnosis of clinical failure. Ten additional patients exhibit PSA progression without establishment of disease site in spite of clinical investigation (Table 2). Thus, a total of 31 patients (13.5%) qualify as PSA progression failures in this series.

A total of 1354 serum PSA measurements were compiled on the 230 patients, an average of 5.9 PSA determinations per patient. Figure 1 depicts the PSA progression-free survival function as observed for the entire 230-patient cohort. The function is defined at 108 months (9 years) as 83.5% (95% confidence interval 78.3–88.7%) and at 5 years as 85.6% (95% confidence interval 81.4–89.8%).

No statistically significant difference in outcome was demonstrated by univariate analysis of clinical stage (Fig. 2). Outcomes stratified by Gleason score categories are depicted in Fig. 3. The 5-year progression-free rates were: Gleason 3–4, 89%; Gleason 5–6, 92%; Gleason 7, 75%; Gleason 8–10, 86%. A significant difference ($p = 0.001$) was noted for Gleason 3–6 versus 7–10 (Fig. 3). Figure 4 demonstrates biochemical outcomes stratified by initial PSA levels. The 5-year PSA progression-free rate was: PSA 0–4, 90%; >4–10, 88%; >10–20, 80%; >20, 67%. A statistically significant difference was seen between 0–10 vs. >10 ($p = 0.041$).

PSA response by time interval

The overall proportion of patients attaining arbitrary PSA levels at the time of last follow-up is presented in Table 3.

Table 4 depicts the number of patients per time interval who attained a serum PSA level of 0.5, 1.0, or 2.0, as well as the median PSA of all patients within each interval. The data in Table 4 are plotted in Figs. 5 and 6 and demonstrate graphically the protracted time required for a stable PSA minimum to be reached in the group as a whole. Figure 5 illustrates that a median minimum PSA value of 0.2 ng/ml can be expected in a treated group, but two or more years may pass before it is observed. Figure 6 illustrates the observation that while the proportion of serum PSA values less than or equal to 2.0 ng/ml reaches a maximum within a year of treatment, the proportion reaching 0.5 ng/ml or less continues to increase to at least 48 months.

Table 5 contains a series of probability values indicating that no time interval referenced in Table 4 is biased by underrepresentation of PSA progression failures (as compared to the overall proportion of PSA progression failures: all $p > 0.05$). Thus, the PSA data tabulated would appear to represent a sufficiently unbiased sample over the time intervals summarized to yield an accurate reflection of PSA response in this cohort, given the observation times for this cohort.

For the 199 patients not exhibiting biochemical progression (i.e., those whose PSA trends would be expected to obey first-order kinetics) a median half-life of 96.2 days was observed. Half-lives were calculated from initial PSA (time 0) to either 1.0 ng/ml or lowest PSA obtained if greater than 1.0 ng/ml.

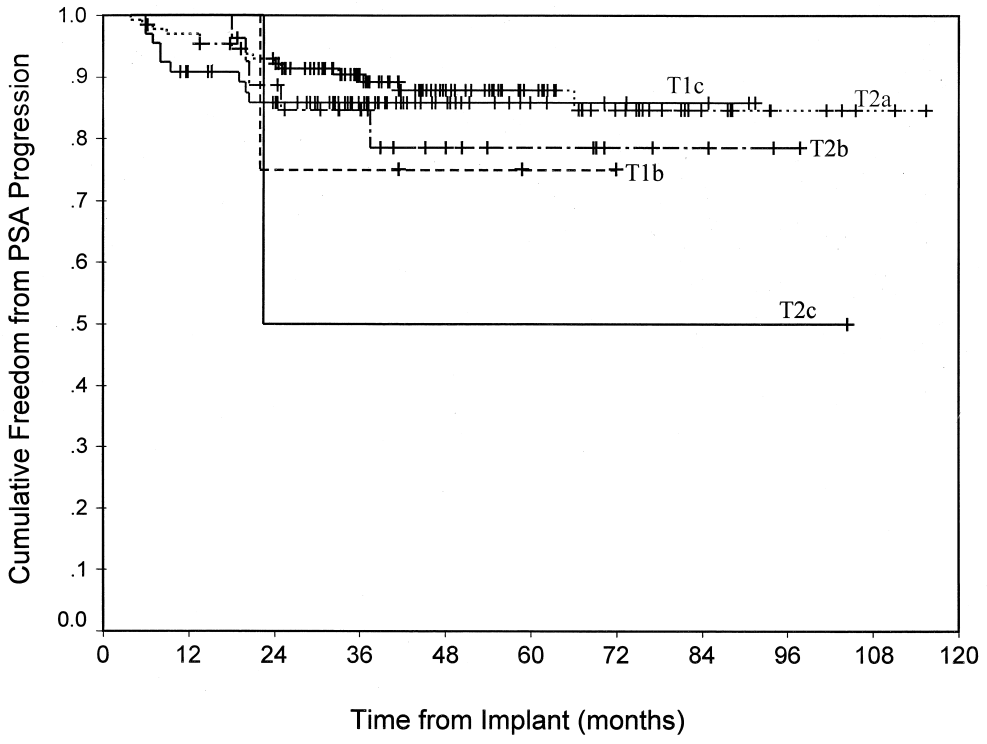

Fig. 2. PSA progression-free survival by clinical stage.

Prognostic categories

Clinical stage, Gleason score, and serum PSA at presentation were evaluated across all available cut-points. The univariate stratification models yielding the largest significant differences are plotted in Figs. 7 and 8. No model using clinical stage alone demonstrated a significant difference in PSA progression-free survival. The most significant differences were demonstrated in biochemical outcomes for patients presenting with Gleason scores 3–6 versus 7–10 ($p = 0.001$), and for presenting PSA $<$10.0 ng/ml versus $>$10.0 ($p = 0.041$).

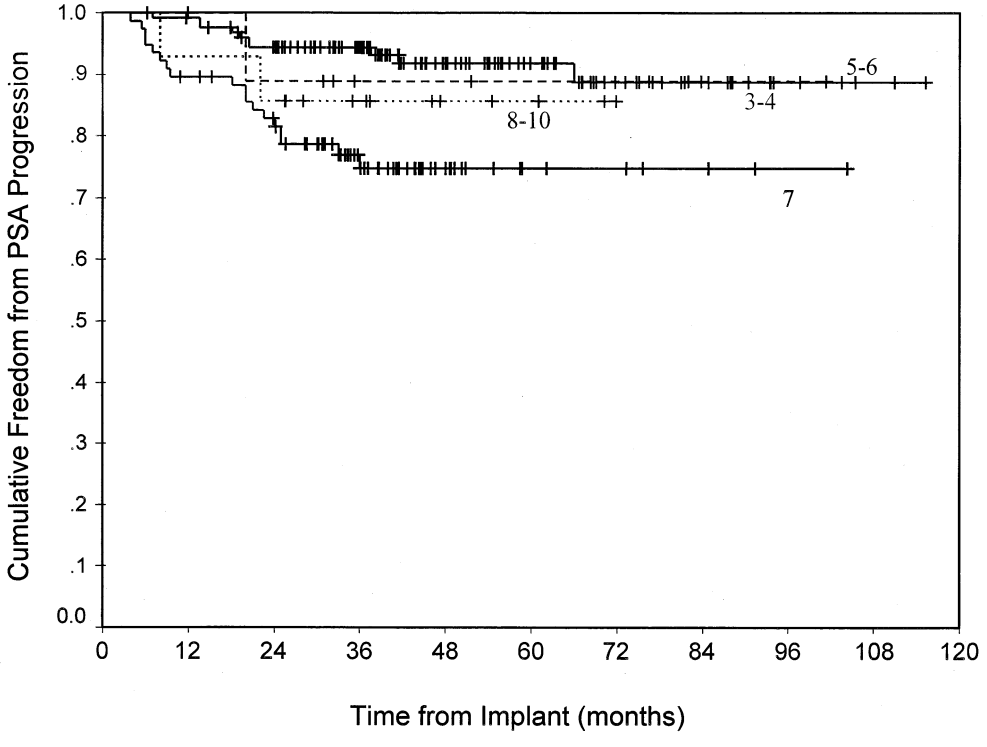

Fig. 3. PSA progression-free survival by Gleason score.

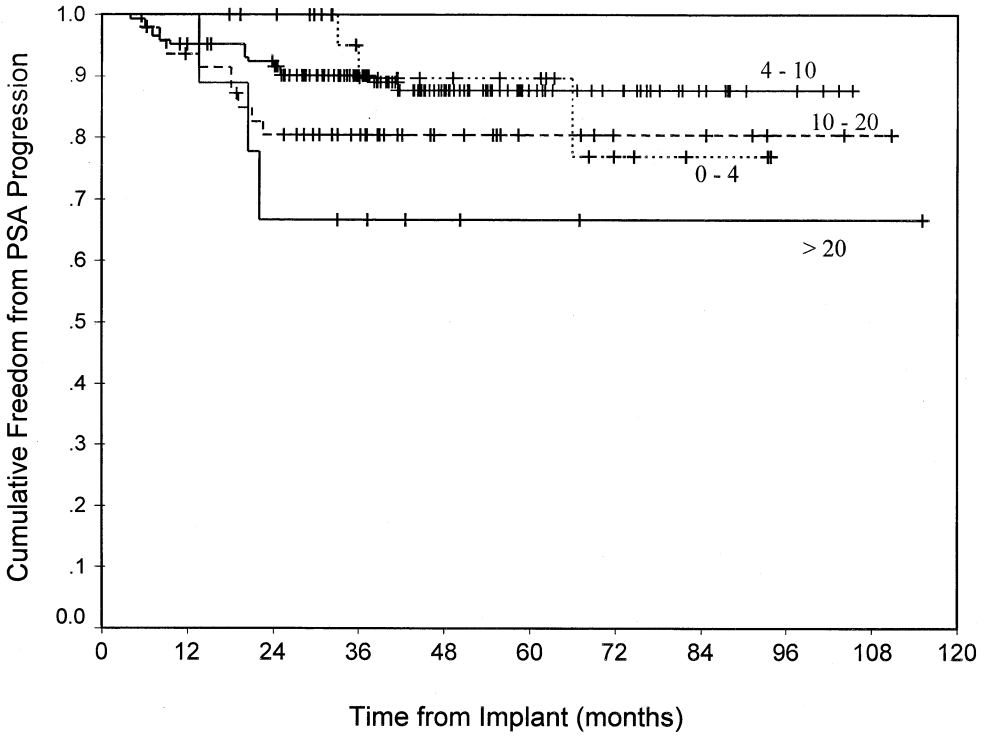

Fig. 4. PSA progression-free survival by PSA (ng/ml) at presentation.

For the purpose of multivariate analysis, clinical stage, Gleason score, and initial PSA were established as dichotomous variables across all available cut-points and entered into a forward, step-wise Cox regression model. The results of the values with the largest coefficients (relative risks) are tabulated in Table 6. The resulting stratified survival function is plotted in Fig. 9. The three derived groups stratified by risk might thus be considered "risk groups" as follows: 1) "Low-risk": Gleason 3–6/10, PSA ≤10.0 ng/ml, any T1–T2 stage. 2) "Intermediate-risk": either Gleason 7–10, or PSA >10.0 ng/ml, any T1–T2 stage. 3) "High-risk": Both Gleason 7–10 and PSA >10 ng/ml, any T1–T2 stage. At 5 years the biochemical disease-free progression rate for the "low-risk" subgroup (103 patients) was 94% with a median follow-up of 48.9 months. For the "intermediate-risk" subgroup (107 patients) with a median follow-up of 39.5 months, 82% were disease-free. In the "high-risk" subgroup (20 patients), 65% were disease-free with a median follow-up of 45.5 months. The differences between all subgroups are significant as defined by log rank $p < 0.05$ (Fig. 9).

Of the 107 biopsied patients, 49 (46%) were considered "low-risk," 47 (44%) were "intermediate-risk," and 11 (10%) were "high-risk."

Table 3. Last serum PSA (median follow-up 41.5 mo)

≤0.5 ng/ml	157 (68.3%)
≤1.0 ng/ml	188 (81.7%)
≤2.0 ng/ml	200 (87.0%)
>2.0 ng/ml	30 (13.0%)

To illustrate the outcomes of patients with high-grade malignancy, the results of 91 patients with Gleason sum score ≥ 7, stratified by initial PSA, are demonstrated in Fig. 10. For patients with Gleason score of 7–10 whose PSA was ≤ 10 ng/ml, the 5-year actuarial PSA relapse-free survival was 80%. For patients who presented with a PSA greater than 10 ng/ml, the result declines to 65%.

DISCUSSION

The conceptual advantage of brachytherapy resides in the ability to deliver high doses of radiation to a limited volume. This report describes a prospectively followed cohort treated for clinically localized prostate carcinoma with Pd-

Table 4. PSA data by postimplant interval

Interval	Months postimplant	Median PSA	≤ 0.5	≤ 1.0	≤ 2.0	*n*
0	0	7.3	1	3	9	230
1	0.1–6.0	1.4	23	50	83	131
2	6.1–12.0	0.9	47	107	152	171
3	12.1–18.0	0.7	59	103	133	156
4	18.1–24.0	0.5	61	88	103	118
5	24.1–36.0	0.3	113	142	156	168
6	36.1–48.0	0.2	97	114	120	128
7	48.1–60.0	0.2	61	70	73	78
8	60.1–72.0	0.2	32	36	40	42
9	72.1–84.0	0.2	23	26	27	30
10	84.1–96.0	0.2	12	12	14	16
11	96.1–115.0	0.25	6	7	7	8

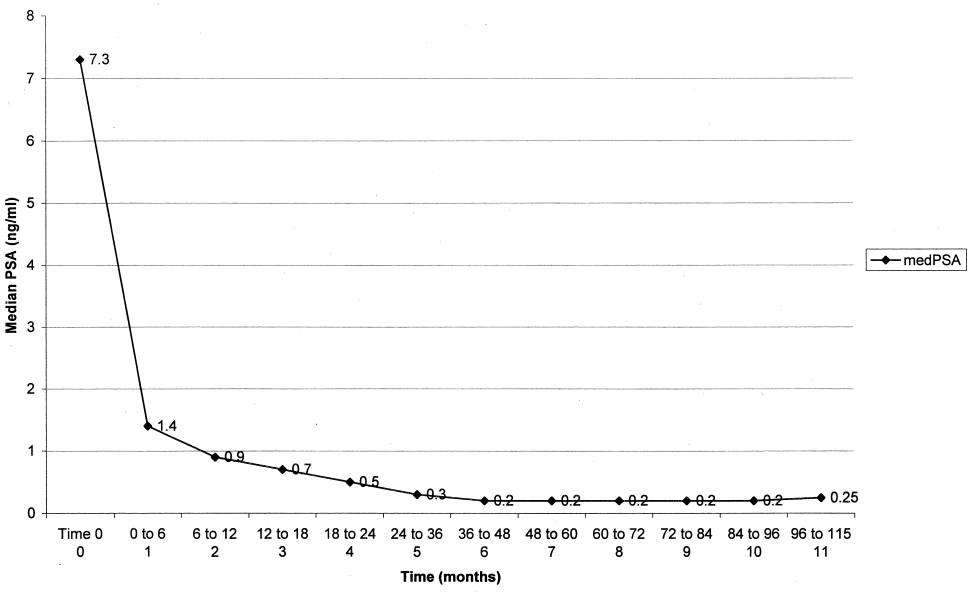

Fig. 5. Median PSA by interval postimplant.

103 brachytherapy as the sole treatment modality. These outcomes demonstrate a high rate of biochemical and clinical tumor control to 9 years. Given the relatively low hazard to survival presented by early-stage prostate cancer, the conclusions to be drawn from this study derive primarily from a description of observed PSA-based endpoints.

A universal definition of PSA, or biochemical, failure has been extensively debated, especially as such a definition may necessarily vary among treatment strategies. Following surgery (which by definition should immediately remove all PSA-producing tissue), serum PSA is expected to ablate rapidly, and has been reported to obey first-order kinetics with a median half-life of 3.8 days (20). Post-treatment serum PSA profiles have been reported to obey a more gradual pattern following external beam irradiation, declining with median half-lives of 50–78 days (21–25). The PSA response following Pd-103 brachytherapy demonstrates an even more protracted course (median half-life 92 days) of biochemical response as is demonstrated in this series. As a result, the notion of failure or success following radiotherapeutic regimes tends to resist definitions that take into account only absolute levels of serum PSA without considering time elapsed following therapy. Figure 6 illustrates the difficulty associated with positing criteria for failing patients on the basis of an absolute serum PSA value in this series, demonstrating that 3 to 4 years may be required

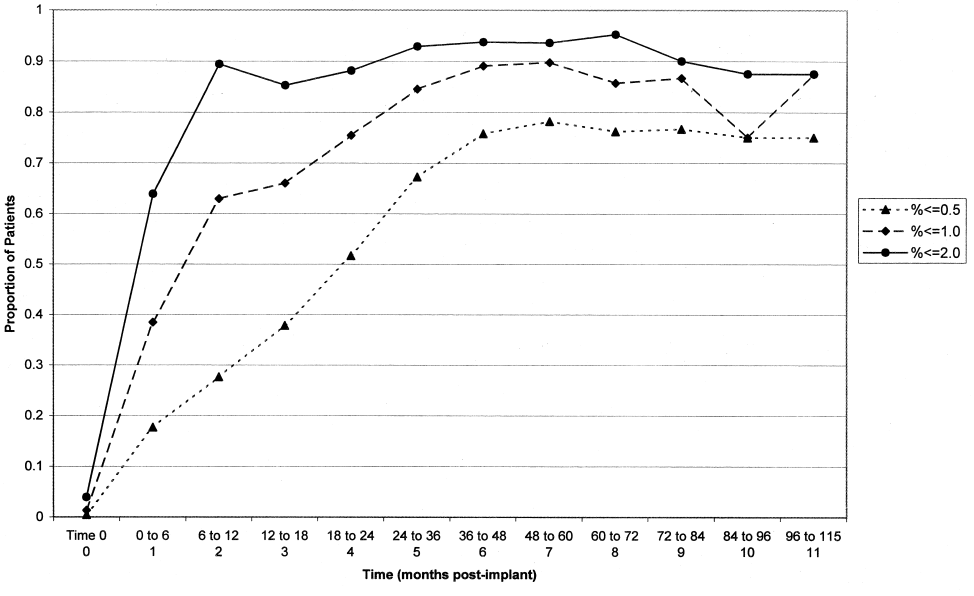

Fig. 6. Percentage of patients achieving designated PSA by interval postimplant.

Table 5. Sampling bias in interval analysis

Interval	PSA progression failures	Total patients	% Failures	*p* (Exact)
All patients	31(total)	230	13.5(total)	
1	23	131	17.6	0.4
2	25	171	14.6	0.8
3	22	156	14.1	0.9
4	18	118	15.3	0.7
5	17	168	10.1	0.4
6	14	128	10.9	0.6
7	10	78	12.8	1.0
8	5	42	11.9	1.0
9	4	30	13.3	1.0
10	2	16	12.5	1.0
11	1	8	12.5	1.0

before the group as a whole stabilizes at levels of PSA less than 0.5 ng/ml.

We have chosen a definition of biochemical failure as two consecutive rises in serum PSA, a definition that—if anything—would appear to overestimate the rate of failure relative to the ASTRO consensus definition of three consecutive rises (26). Serum PSA progression of at least two rises occurred in the event of all 21 patients who developed clinically evident disease, as well as in 10 additional patients in whom no clinical, radiographic, or biopsy evidence for recurrent disease was found. On this basis the biochemical relapse-free survival for the entire cohort stands at 83.5%.

We have summarized the serum PSA experience of this patient population as a cross-sectional summary contained in Table 4 and Figs. 5 and 6. This analysis attempts to portray the entire PSA experience, as opposed to condensing all sequential PSA data to one data point per patient. The difficulty in reporting all PSA data points resides in the potential of overrepresenting patients who ultimately succeeded with therapy at the expense of those who failed. In other words, such data may be subject to a number of biases which would tend to result in an unfair sample. Table 5 represents an attempt to address this possibility, by using Fisher's exact method to test the hypothesis that patients who were graded as PSA progression failures in each interval were represented significantly differently from the overall proportion of PSA progression failures.

As demonstrated, no significant underrepresentation was found for any interval, and the percentage of PSA progression failures per interval is relatively uniform. All PSA data points recorded (except those following intervention for recurrent disease) are included. While this particular analysis provides a noncumulative quantification of the PSA response observed in this series, it does depict the nature of the PSA response that can reasonably be expected in the patient with localized prostate cancer following palladium brachytherapy.

The experience of this cohort also illustrates the influence of the variables of presentation PSA and Gleason score on biochemical outcome (Figs. 7 and 8). In both univariate and multivariate models, patients presenting with a PSA greater than 10 or a Gleason score greater than 6 fared significantly

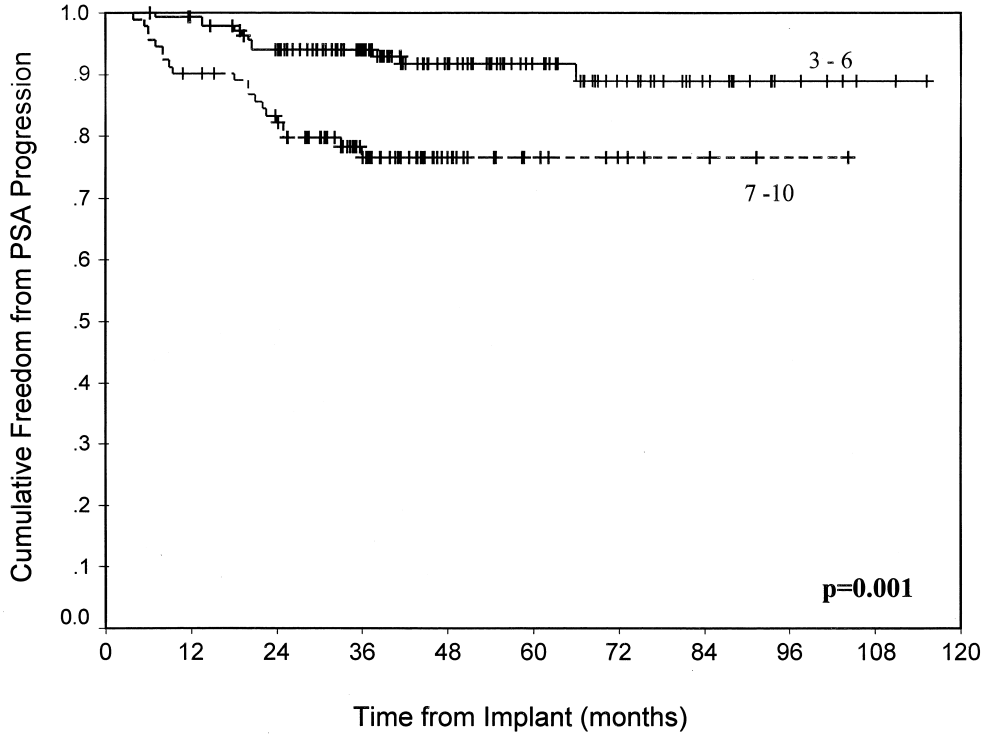

Fig. 7. PSA progression-free survival by Gleason score grouping.

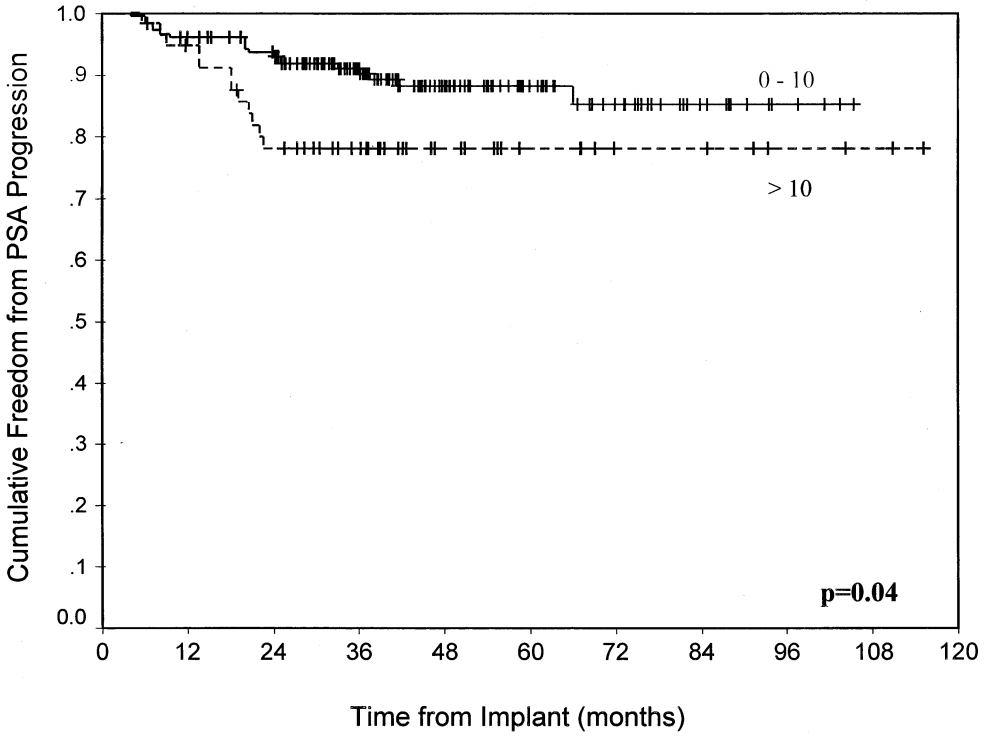

Fig. 8. PSA progression-free survival by serum PSA grouping.

worse than those absent these characteristics (Table 6). Regressing the data on the Cox model, the dichotomous variables PSA $>$ 10 and Gleason score $>$ 6 returned coefficients of 2.6 and 3.2, respectively. Stratified Kaplan-Meier survival functions employing these variables as "risk factors" of identical magnitude are depicted in Fig. 9.

The biochemical and clinical outcomes for the entire cohort (Fig. 1, Tables 2 and 3) compare favorably to contemporary reports of radical prostatectomy (27–29) and 3D conformal, dose-escalated external beam radiotherapy for T1–T2 disease (30–33). Although the single-institution, retrospective nature of currently reported experiences precludes definitive conclusions regarding the superiority or inferiority of a specific treatment approach, when our data are stratified by clinical stage, initial PSA, and Gleason score (Figs. 2–4), the results continue to be competitive with those of surgery and external beam radiotherapy across a broad spectrum of PSA ranges and Gleason scores (27–30, 34–37).

An increasingly popular strategy to achieve parity of risk factors in comparative patient groups is the collation of stage, initial PSA, and Gleason grade into arbitrary "risk groups" (30, 38, 39). By the use of multivariate analysis we were able to derive "low," "intermediate," and "high" risk groups based on stage, Gleason grade, and presenting PSA (Fig. 9). Our groupings are identical to those used by Zelefsky *et al.* (30) in reporting their results. Using a three-rise definition of biochemical failure, Zelefsky reported a 5-year actuarial PSA relapse-free survival of 85% for low-risk, 65% for intermediate-risk, and 35% for high-risk patients when treated with three-dimensional conformal radiation therapy. When their analysis was limited to those patients who received $>$75.6 Gy, the 4-year results improved to 95%, 79%, and 60%, respectively. Our 5-year outcomes of 94%, 82%, and 65% for low, intermediate, and high-risk categories reveal a remarkable similarity to the dose escalated subgroup of Zelefsky.

Table 6. Significance of covariates

Covariate	Values	Univariate *p*	Multivariate *p*
Gleason score	3–6 vs. 7–10	0.001	0.002
Serum PSA	0–10 vs. $>$10	0.041	0.035
Clinical stage	any	n.s.	n.s.

These results with Pd-103 monotherapy also compare favorably to previously published reports of image-guided, transperineal brachytherapy. Biochemical disease-free rates of 63–93% have been reported for I-125, Pd-103, and combinations of external beam irradiation and brachytherapy boost (4, 5, 7, 8, 40–46). When differing initial PSA and Gleason score profiles are taken into consideration, our result of 83.5% freedom from PSA failure appears at least equivalent.

An evolving issue in prostate brachytherapy is the question of isotope selection. Based on conceptual models of theoretical cell cycle time versus dose rate of the radioisotope, a common recommendation has been to limit the use of I-125 to patients with Gleason 2–6/10 histology, and reserve Pd-103 for Gleason 7 and above. We have previ-

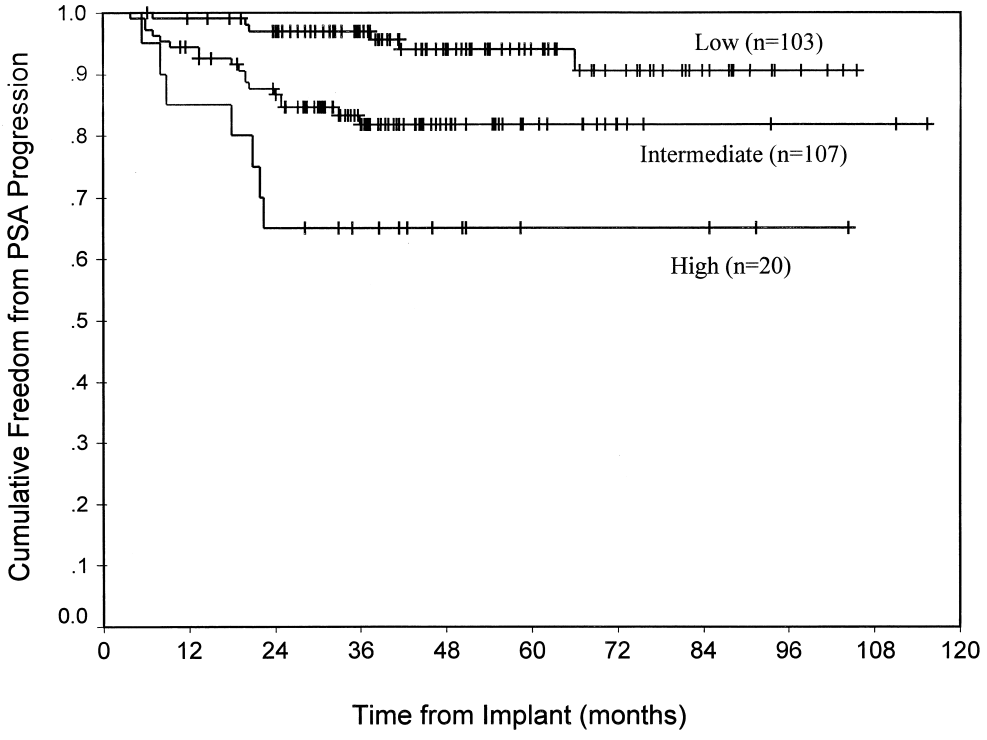

Fig. 9. PSA progression-free survival by risk profile.

ously published the results of I-125 monotherapy in a favorable group of patients with T1–T2 disease, median PSA of 5.0 ng/ml, and Gleason 2–6/10 histology who demonstrated a 7-year biochemical control rate of 89% (8). The patients with Gleason 3–6/10 histology treated with Pd-103 in this series achieved an equivalent biochemical control of

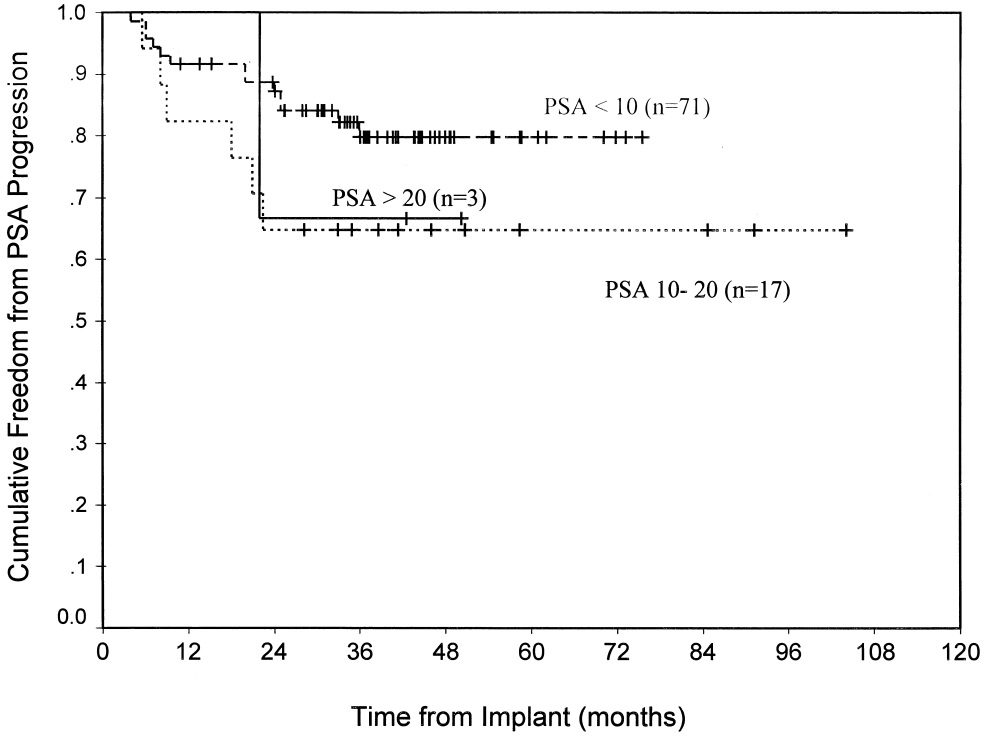

Fig. 10. PSA progression-free survival by Gleason score ≥ 7 by initial PSA grouping.

88%. Beyer *et al.* (4) have recently reported on 489 T1–T2 patients, PSA median of 7.3 ng/ml, treated with I-125 monotherapy. The 4-year biochemical disease-free rate was 88% for patients with Gleason 2–4/10, and 60% for those with Gleason 5–6/10. Our 5-year Pd-103 result for Gleason 3–4/10 was 89% and 92% for Gleason 5–6/10. Other authors have reported brachytherapy experiences in which patients were treated with either I-125 or Pd-103 monotherapy (7, 43). No difference in outcome was found based on radioisotope employed when the results were stratified for risk factors. Recently, Cha *et al.*(12) compared I-125 and Pd-103 results by matched pair analysis and were unable to demonstrate a statistically significant difference in outcomes for Gleason scores of 2–8. Based on the results of this series and the current literature, it appears that either source is effective in well to moderately differentiated prostate carcinoma.

The role of brachytherapy as monotherapy for high-grade disease is controversial. Patients with Gleason score 7–10 disease experience a higher relapse rate regardless of the treatment approach. In the Johns Hopkins radical prostatectomy experience (47), patients with Gleason 7 malignancies and negative surgical margins demonstrated a 10-year biochemical control rate of only 68%. Because of the greater probability of extracapsular disease associated with Gleason score 7–10 malignancies, it is common radiotherapeutic practice in brachytherapy circles to treat these patients with a combination of brachytherapy and external beam radiotherapy rather than brachytherapy alone. The intent of this combination therapy is to treat periprostatic tissues, which may be beyond the reach of an implant alone (1–3, 6, 14). In this series, 91 patients presented with Gleason 7 or greater disease and were treated with Pd-103 alone. Provided that the initial PSA was $\leq$10.0 ng/ml, the 5-year rate of no biochemical evidence of disease (bNED) was 80%. Wallner *et al.* (48), using I-125 monotherapy have demonstrated a 5-year biochemical control rate of 70% in 20 patients with Gleason score 7 histology whose PSA was $<$10.0 ng/ml. Although these single-institution experiences do not provide a definitive answer, it is suggestive that brachytherapy alone may achieve acceptable results in patients with Gleason score 7 malignancies provided the PSA is less than 10.0 ng/ml and the tumor burden is low.

Brachytherapy is an increasingly popular treatment option among both patients and physicians because of treatment convenience and the perception of minimal long-term morbidity (1, 49, 50). However, most published data have been of short follow-up and utilized the radioisotope I-125. The 9-year results using Pd-103 in this series add to the growing body of knowledge that brachytherapy can achieve a high rate of biochemical and clinical control for patients with clinically organ-confined disease. Further, this series contains patients who exhibit a spectrum of risk profiles and whose outcomes appear consistent with those of competing treatment approaches. Final answers regarding the effectiveness of brachytherapy relative to other treatment modalities and the resolution of patient selection issues will await prospective trials.

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