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CLINICAL INVESTIGATION **Prostate**

NATURAL HISTORY OF CLINICALLY STAGED LOW- AND INTERMEDIATE-RISK PROSTATE CANCER TREATED WITH MONOTHERAPEUTIC PERMANENT INTERSTITIAL BRACHYTHERAPY

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Purpose: To evaluate the natural history of clinically staged low- and intermediate-risk prostate cancer treated with permanent interstitial seed implants as monotherapy.

Methods and Materials: Between April 1995 and May 2005, 463 patients with clinically localized prostate cancer underwent brachytherapy as the sole definitive treatment. Men who received supplemental external beam radiotherapy or androgen deprivation therapy were excluded. Dosimetric implant quality was determined based on the minimum dose that covered 90% of the target volume and the volume of the prostate gland receiving 100% of the prescribed dose. Multiple parameters were evaluated as predictors of treatment outcomes.

Results: The 12-year biochemical progression-free survival (bPFS), cause-specific survival, and overall survival rates for the entire cohort were 97.1%, 99.7%, and 75.4%, respectively. Only pretreatment prostate-specific antigen level, percent positive biopsy cores, and minimum dose that covered 90% of the target volume were significant predictors of biochemical recurrence. The bPFS, cause-specific survival, and overall survival rates were 97.4%, 99.6%, and 76.2%, respectively, for low-risk patients and 96.4%, 100%, and 74.0%, respectively, for intermediate-risk patients. The bPFS rate was 98.8% for low-risk patients with high-quality implants versus 92.1% for those with less adequate implants ($p < 0.01$), and it was 98.3% for intermediate-risk patients with high-quality implants versus 86.4% for those with less adequate implants ($p < 0.01$).

Conclusions: High-quality brachytherapy implants as monotherapy can provide excellent outcomes for men with clinically staged low- and intermediate-risk prostate cancer. For these men, a high-quality implant can achieve results comparable to high-quality surgery in the most favorable pathologically staged patient subgroups.

Prostate cancer, Brachytherapy, Cause-specific survival, Biochemical progression-free survival.

INTRODUCTION

Permanent interstitial seed implants are used commonly as monotherapy for men with low-risk, clinically localized prostate cancer. Brachytherapy is used somewhat less frequently as the sole modality for men with intermediate-risk disease. In the larger series the biochemical progression-free survival (bPFS) rate ranges from 80% to 98% for low-risk patients (1–8) undergoing brachytherapy and from 70% to 97% for intermediate-risk patients (1–3, 5–9). However, many men in these series received supplemental external beam radiation and/or neoadjuvant or planned adjuvant androgen deprivation. These series also included men whose implants would be considered suboptimal by today's standards.

The purpose of this report is to explore the natural history of prostate cancer in men who receive brachytherapy as the sole modality. There are obvious short-term advantages to avoiding initial combined-modality treatment, including shorter duration of treatment, exposure to fewer side effects, and lower overall health care costs. However, these advantages disappear rapidly if a significant number of men treated with monotherapy require additional, increasingly morbid salvage therapy because of disease recurrence. Hence understanding the efficacy and durability of high-quality, sole-modality brachytherapy is important.

METHODS AND MATERIALS

Between April 1995 and May 2005, 463 patients with low- or intermediate-risk prostate cancer were treated with permanent interstitial seed implants as the sole definitive treatment. Men who received neoadjuvant or planned adjuvant androgen suppression for any reason were excluded from the analysis. In addition, men who received supplemental external beam radiotherapy were excluded. Patients

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were categorized as low risk if they met all of the following criteria: Gleason score of 6 or less, prostate-specific antigen (PSA) level of 10 ng/mL or less, and clinical stage of T1b to T2b. Patients were categorized as intermediate risk if they had one of the following adverse factors: Gleason score of 7, PSA level of 10.1 to 20.0 ng/mL, or clinical stage of T2c. The study population included a wide range of men of different ages (median, 65 years; range, 43–81 years), preimplant international prostate symptom score (median, 4.0; range, 0–25), and prostate gland volumes (median, 34.7 cm^3; range, 14.2–62.3 cm^3). Neither patient age, preimplant international prostate symptom score, nor prostate volume is used as an independent criterion for monotherapeutic brachytherapy.

The brachytherapy planning treatment volume (PTV) consisted of the prostate gland with a 5-mm margin in all dimensions except posteriorly. In addition, the proximal 1.0 cm of the proximal seminal vesicles was included in the target volume (10). Calculations of the minimum dose that covered 90% of the target volume (D90) were based on Day 0 evaluation of postimplant coverage of this PTV. The minimal peripheral dose was prescribed as 125 Gy (American Brachytherapy Society, 2000) for ^{103}Pd and 145 Gy (Task Group 43) for ^{125}I. For purposes of the analysis, biologic effective doses (BEDs) for each isotope were determined by use of the consensus model of the American Association of Physicists in Medicine Task Group 137 (11, 12). With this method, for example, a ^{103}Pd dose of 125 Gy equates to a BED of 115 Gy and a ^{125}I dose of 145 Gy equates to a BED of 110 Gy. For this analysis, implants of either isotope with a BED of 116 Gy or higher were consider high quality.

The Task Group 137 approach differs from the D90-based approach of Stock *et al*. (13), which does not account for cell repopulation and assumes an α:β ratio of 2. The net effect of differences in approach is that the Task Group 137 method will estimate BEDs that are 25% to 35% lower than those determined by use of the method of Stock *et al*. For example, with the approach of Stock *et al*., a ^{103}Pd dose of 125 Gy translates into a BED of 144 Gy and a ^{125}I dose of 145 Gy translates to a BED of 152 Gy.

Patients were monitored by physical examination including digital rectal examination and serum PSA level determination at 3- and 6-month intervals. The endpoint of the analysis was cause-specific survival (CSS), bPFS (defined as a PSA level ≤0.40 ng/mL after nadir) (1), and overall survival (OS). Cause of death was determined for each deceased patient. Patients with metastatic prostate cancer or hormone refractory disease without obvious metastases who died of any cause were classified as dead of prostate cancer. All other deaths were attributed to the immediate cause of death. bPFS was defined as a PSA level remaining equal to or below 0.4 ng/mL after nadir, which has been shown to be a particularly sensitive definition for identifying patients in whom treatment has failed (14). Patients whose PSA level failed to fall below 0.4 ng/mL at nadir and those whose PSA level remained above that level after effective nadir were considered to have had biochemical failure. Multiple clinical, treatment, and dosimetric parameters were evaluated for impact on survival.

Clinical and treatment variables that were continuous were compared between low- and intermediate-risk patients by use of an independent *t* test. Categorical variables were compared by use of a χ^2 analysis. Kaplan-Meier analysis and curves were used to determine CSS, OS, and bPFS. BED was stratified into two groups: those with a value of less than 116 Gy and those with a value of greater than or equal to 116 Gy. The survival of patients in these two groups was compared by use of Kaplan-Meier analysis. Univariate Cox regression analysis was used to determine the variables that predicted biochemical failure. Those variables with $p < 0.10$ were entered into a forward conditional, multivariate Cox regression. For all analyses, $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS software, version 14.0 (SPSS, Chicago, IL).

RESULTS

Table 1 summarizes the clinical and treatment characteristics of men included in the analysis. Of the 463 men, 319 were low risk and 144 were intermediate risk. In addition to having a higher Gleason score, men in the intermediate-risk group had a higher pretreatment PSA level, higher percentage of positive biopsy cores, and higher clinical stage and were older.

At 12 years, the bPFS, CSS, and OS rates for the group as a whole were 97.1%, 99.7%, and 75.4%, respectively (Fig. 1). Table 2 presents univariate and multivariate analysis of predictors of bPFS, CSS, and OS. Only pretreatment PSA level, percent positive biopsy cores, and dosimetric coverage as defined by D90 were significant predictors of biochemical recurrence. None of the variables predicted for CSS. Age and smoking were most strongly associated with OS.

For low-risk patients, the bPFS, CSS, and OS rates were 97.4%, 99.6%, and 76.2%, respectively, (Fig. 2). Low-risk patients with high-quality implants (BED ≥116 Gy) had a long-term bPFS rate of 98.8% versus 92.1% (p = 0.003) for patients with less adequate implants (Fig. 3).

For intermediate-risk patients, the bPFS, CSS, and OS rates were 96.4%, 100%, and 74.0%, respectively (Fig. 4). Intermediate-risk patients with high-quality implants (BED ≥116 Gy) had a long-term bPFS rate of 98.3% versus 86.4% (p = 0.006) for patients with less adequate implants (Fig. 5).

Cause of death is reported in Table 3. Cardiovascular disease was the leading cause of death overall, leading to 18 deaths in the low-risk group (5.6%) and 5 deaths in the intermediate-risk group (3.5%). Overall, 55 deaths were recorded, 54 of which were from causes other than prostate cancer. The lone death from prostate cancer was a patient in the low-risk group (with a BED <116 Gy), representing 0.2% of the entire study population.

DISCUSSION

The largest published series to date of sole-modality brachytherapy includes 1,444 low-risk men and 960 intermediate-risk men from 11 institutions (8). The 8-year PSA relapse-free survival rate was 82% for low-risk patients and 70% for intermediate-risk patients. Unfortunately, dosimetric analysis was available for only a subset of this cohort. In the cases when dosimetry information was available, men whose ^{125}I implants had a D90 of 130 Gy or greater (still below current recommendations) (15) had much better results.

Other brachytherapy series have shown better long-term outcomes for low- and intermediate-risk patients, with bPFS rates ranging from 86% to 94% for low-risk patients (2–4, 6, 7) and from 80% to 89% for intermediate-risk patients (2, 3, 6, 7, 9). Of note, most of these studies included supplemental external beam radiation and/or did not specify dosimetric

Table 1. Continuous clinical, treatment, and dosimetric parameters, stratified by radiation dose

	Low risk (n = 319)		Intermediate risk (n = 144)			Total (n = 463)	
	Median	Mean ± SD/count (%)	Median	Mean ± SD/count (%)	p Value	Median	Mean ± SD /count (%)
Continuous variables							
Age at implantation (y)	64.0	63.0 ± 7.6	67.0	66.8 ± 6.8	<0.001	65.0	64.2 ± 7.5
Follow-up (y)	6.2	6.6 ± 2.8	5.2	5.8 ± 2.6	0.003	5.8	6.4 ± 2.8
Pretreatment PSA	5.6	5.8 ± 1.9	5.9	6.8 ± 4.2	0.015	5.7	6.1 ± 2.9
Gleason score	6.0	5.9 ± 0.4	7.0	6.9 ± 0.4	<0.001	6.0	6.2 ± 0.6
% Positive biopsies	16.7	24.9 ± 16.6	32.1	37.1 ± 23.2	<0.001	25.0	28.7 ± 19.7
BMI (kg/m^2)	27.2	28.0 ± 4.3	27.6	28.4 ± 5.3	0.387	27.4	28.1 ± 4.6
Prostate volume (cm^3)	35.0	34.9 ± 7.3	33.4	33.8 ± 7.5	0.166	34.7	34.5 ± 7.3
V100 (% volume)	97.6	95.6 ± 5.8	97.5	96.2 ± 5.0	0.359	97.6	95.8 ± 5.6
V150 (% volume)	67.2	63.7 ± 15.0	69.6	66.9 ± 13.8	0.033	68.1	64.7 ± 14.7
V200 (% volume)	35.0	33.9 ± 12.6	39.2	37.5 ± 12.3	0.005	36.8	35.0 ± 12.6
D90 (% prescription dose)	116.0	115.2 ± 14.0	116.3	116.9 ± 13.0	0.219	116.2	115.7 ± 13.7
Most recent PSA	0.01	0.05 ± 0.11	0.00	0.05 ± 0.10	0.790	0.01	0.05 ± 0.11
Categorical variables							
Clinical stage*					0.038		
T1b		4 (1.3)		1 (0.7)			5 (1.1)
T1c		212 (66.5)		82 (56.9)			294 (63.5)
T2a		90 (28.2)		47 (32.6)			137 (29.6)
T2b		13 (4.1)		12 (8.3)			25 (5.4)
T2c		0 (0.0)		2 (1.4)			2 (0.4)
Hypertension					0.066		
No		180 (56.4)		68 (47.2)			248 (53.6)
Yes		139 (43.6)		76 (52.8)			215 (46.4)
Diabetes					0.150		
No		289 (90.6)		124 (86.1)			413 (89.2)
Yes		30 (9.4)		20 (13.9)			50 (10.8)
Tobacco					0.383		
Never		120 (37.6)		61 (42.4)			181 (39.1)
Former		147 (46.1)		66 (45.8)			213 (46.0)
Current		52 (16.3)		17 (11.8)			69 (14.9)

Abbreviations: PSA = prostate-specific antigen; % Positive biopsies = percent of prostate core biopsies that were involved with carcinoma; BMI = body mass index; V100 = percent of target volume receiving at least 100% of prescribed dose; V150 = percent of target volume receiving at least 150% of prescribed dose; V200 = percent of target volume receiving at least 200% of prescribed dose; D90 = minimum dose that covers 90% of target volume.

* The Fisher exact test was used because at least one cell had a count of less than 5.

quality. A recent study from the group from Mount Sinai School of Medicine (New York, NY) (5), where all patients received 180 Gy or greater with ^{125}I brachytherapy alone, reported 5-year bPFS rates of 97% and 93% for low-risk and intermediate-/high-risk patients, respectively. None of these patients received external beam radiation, but nearly one third received neoadjuvant and adjuvant hormonal therapy. Earlier reports from the same group (16–18) noted excellent results when D90 was 140 Gy or greater, although—as in the more recent study—a subset of these men received hormonal therapy.

Recently, investigators at Johns Hopkins Hospital (Baltimore, MD) reported excellent outcomes in highly selected low-risk patients who underwent high-quality surgery (19). This group examined long-term outcomes of men undergoing prostatectomy with truly low-risk disease (*i.e.*, reconfirmed pathologic Gleason score ≤6, lack of extracapsular extension, negative margins, and retrospective re-evaluation of pathology of each patient who failed to see if post hoc upgrading was warranted). Their purpose was to identify how frequently men in this very favorable subgroup would require subsequent salvage therapy for disease recurrence. They found extremely few biochemical failures and no clinical disease recurrence. They concluded that ''when PCa [prostate cancer] is treated by the anatomic approach to RP [radical prostatectomy] with negative surgical margins and the tumor is organ-confined and lacks high-grade elements, it is effectively cured.'' Other surgical series based on clinical rather than pathologic staging have also identified very good rates of freedom from failure in low-risk prostatectomy patients, ranging from 86% to 93% (20–22).

Patients treated with brachytherapy never receive full pathologic staging. Nonetheless, for clinically staged low- and intermediate-risk patients, seed implants alone can result in excellent rates of disease control—comparable to the best surgery in the most favorable patient subgroups. In our study men with high-quality implants (BED ≥116 Gy) achieved a rate of 10-year actuarial freedom from failure of 98.8% in the low-risk group and 98.3% in the intermediate-risk group. There were no prostate cancer–related deaths among these

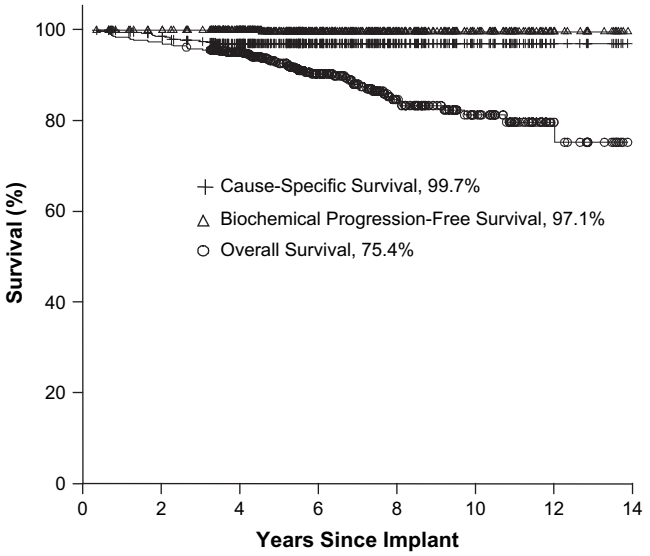

Fig. 1. Kaplan-Meier curves for cause-specific, biochemical progression-free, and overall survival for entire study cohort of men treated with monotherapeutic brachytherapy.

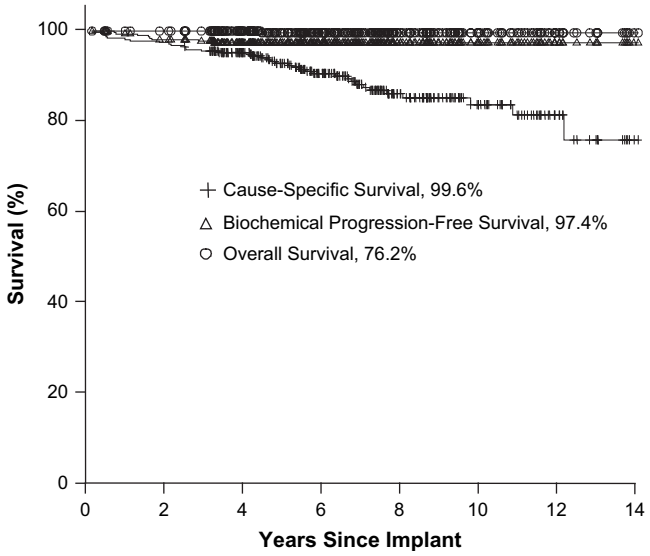

Fig. 2. Kaplan-Meier curves for cause-specific, biochemical progression-free, and overall survival for low-risk patients.

men. This was achieved without supplemental beam radiation or androgen deprivation.

Avoiding supplemental beam radiation and androgen deprivation, if possible, has several benefits. Supplemental external beam radiation adds several weeks of daily treatments, as opposed to a single day for an implant. Additional treatments add to the total cost of care and patient inconvenience (23). Androgen deprivation commonly causes weight

Table 2. Univariate and multivariate predictors for cause-specific, biochemical progression-free and overall survival

	Cause-specific survival				Biochemical progression-free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	p Value	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR
Age	0.803				0.721				<0.001	1.085	<0.001	1.092
Pretreatment PSA	0.357				0.002	1.112	<0.001	1.161	0.479			
Gleason score	0.825				0.106				0.660			
% Positive biopsies	0.845				0.010	1.026	0.003	1.031	0.406			
BMI	0.598				0.305				0.162			
Prostate volume	0.410				0.187				0.591			
V100	0.511				0.004	0.943	0.186		0.106			
V150	0.186				0.002	0.955	0.242		0.990			
V200	0.282				0.004	0.939	0.723		0.101			
%D90	0.170				<0.001	0.941	<0.001	0.941	0.150			
BED (cut point of 116 Gy)	0.626				<0.001	0.144	0.427		0.054	0.283		
Clinical stage	0.990				0.233				0.714			
Risk group	0.708				0.564				0.366			
Isotope	0.581				0.015	0.250	0.663		0.023	1.925	0.013	0.491
Hypertension	0.630				0.999				0.365			
Diabetes	0.890				0.721				0.865			
Tobacco	0.866				0.195				<0.001	—	<0.001	
Current vs. never									<0.001	5.810	0.001	4.693
Current vs. former									<0.001	7.568	<0.001	8.278

Abbreviations: HR = hazard ratio; PSA = prostate-specific antigen; % Positive biopsies = percent of prostate core biopsies that were involved with carcinoma; BMI = body mass index (in kilograms per square meter); V100 = percent of target volume receiving at least 100% of prescribed dose; V150 = percent of target volume receiving at least 150% of prescribed dose; V200 = percent of target volume receiving at least 200% of prescribed dose; %D90 = minimum dose that covers 90% of target volume; BED = biologic effective dose.

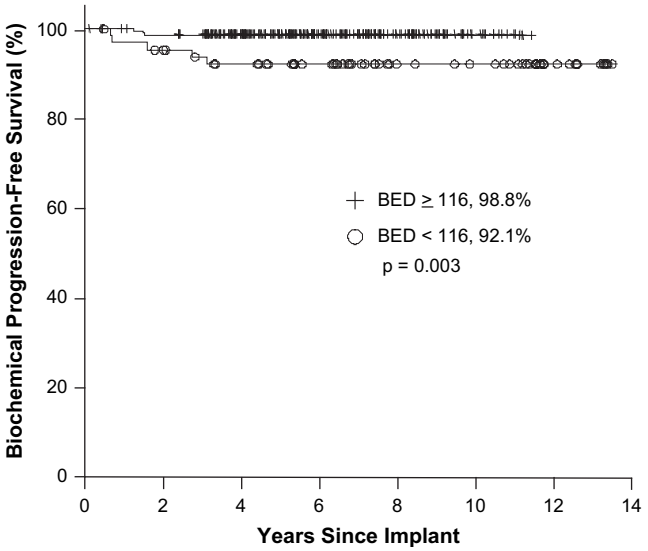

Fig. 3. Kaplan-Meier curves for biochemical progression-free survival for low-risk patients, stratified by biologic effective dose (BED) (cut point of 116 Gy).

gain, loss of libido, lethargy, and hot flashes. Therefore identifying the subset of patients who are appropriately treated without multimodality therapy has benefits for patients and the health care system overall.

Our study is limited by its retrospective nature. Our clinically staged population included a large number of men who would no doubt have been excluded in the retrospective prostatectomy series of Hernandez *et al.* (19). The bPFS rate and, more importantly, the CSS rate of our unselected group were very similar to those of the most favorable, retrospectively selected prostatectomy patients. This suggests that for a broad range of men, sole-modality brachytherapy offers an excellent opportunity for long-term disease control. In addition, it suggests that the lack of pathologic staging does not meaningfully influence the prognosis of clinically staged men treated with high-quality implants.

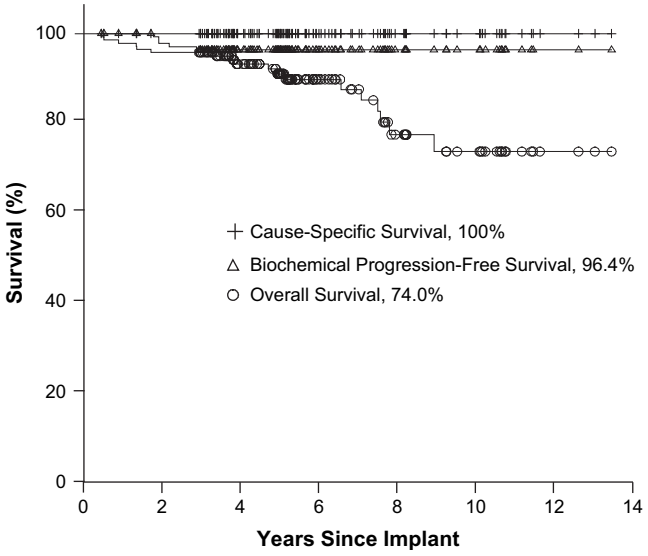

Fig. 4. Kaplan-Meier curves for cause-specific, biochemical progression-free, and overall survival for intermediate-risk patients.

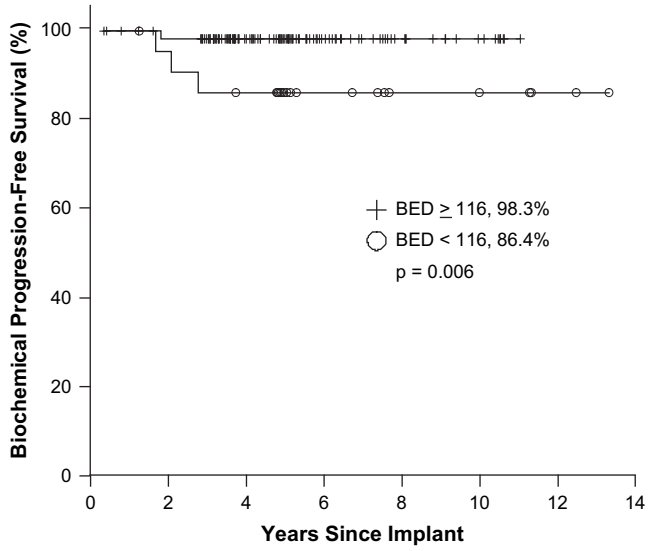

Fig. 5. Kaplan-Meier curves for biochemical progression-free survival for intermediate-risk patients, stratified by biologic effective dose (BED) (cut point of 116 Gy).

Our exclusion of men who received androgen deprivation for prostate downsizing should be noted. There is a strong consensus that androgen deprivation increases the efficacy of conventional-dose external beam radiotherapy (24–26). To test the true monotherapeutic efficacy of brachytherapy, it was necessary to exclude these patients. Our results strongly support monotherapeutic ^{103}Pd or ^{125}I in this patient cohort.

The BED calculations used in this study differ somewhat from those of the Mount Sinai group (5, 27, 28). As described in the ''Methods and Materials'' section, the Task Group 137 method will estimate BEDs that are 25% to 35% lower than those determined with the Mount Sinai approach. In addition, the target volumes for which D90s are calculated, we believe, are different. Our D90 calculations are based on a PTV (prostate plus a 5-mm margin in all directions except posteriorly) that extends beyond the prostate itself to cover potential extracapsular extension, which is not the case with the Mount Sinai group. In addition, our D90 calculations are based on Day 0 dosimetry as opposed to Day 30 dosimetry (29, 30). For the same implant, Day 30 dosimetry typically has a higher

Table 3. Cause of death for low- and intermediate-risk patients

Cause of death	Low risk (n = 319) [No. (%)]	Intermediate risk (n = 144) [No. (%)]	Total (N = 463) [No. (%)]
Prostate cancer	1 (0.3)	0 (0)	1 (0.2)
Diseases of heart	18 (5.6)	5 (3.5)	23 (5.0)
Gastrointestinal malignancies	3 (0.9)	3 (2.1)	6 (1.3)
Lung cancer	5 (1.6)	4 (2.8)	9 (1.9)
Other cancers	1 (0.3)	2 (1.4)	3 (0.6)
Pulmonary	3 (0.9)	1 (0.7)	4 (0.9)
Neurologic	3 (0.9)	2 (1.4)	5 (1.1)
Other	3 (0.9)	1 (0.7)	4 (0.9)
Total	37 (11.6)	18 (12.5)	55 (11.9)

calculated D90, because of resolution of implant-associated edema. These differences in BED calculations are important to note so that comparisons across the different studies can be made more readily.

CONCLUSIONS

Disease recurrence is very uncommon in clinically staged low- and intermediate-risk prostate cancer patients treated with high-quality brachytherapy monotherapy. For these men, a high-quality implant can achieve results comparable to high-quality surgery in the most favorable pathologically staged patient subgroups. As brachytherapy implant techniques continue to improve and the importance of appropriate dosimetric target coverage continues to disseminate, these results should become increasingly commonplace.

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