

CUSTOMIZED DOSE PRESCRIPTION FOR PERMANENT PROSTATE BRACHYTHERAPY: INSIGHTS FROM A MULTICENTER ANALYSIS OF DOSIMETRY OUTCOMES

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Purpose: To investigate the biochemical control rate in patients undergoing permanent prostate brachytherapy as a function of the biologically effective dose (BED) and risk group.

Methods and Materials: Six centers provided data on 3,928 permanent brachytherapy patients with postimplant dosimetry results. The mean prostate-specific antigen level was 8.9 ng/mL. ¹²⁵I was used in 2,293 (58%), ¹⁰³Pd in 1,635, and supplemental external beam radiotherapy in 882 (22.5%) patients. The patients were stratified into low- (*n* = 2,188), intermediate- (*n* = 1,188), and high- (*n* = 552) risk groups and into three BED groups of < 140 Gy (*n* = 524), 140–200 Gy (*n* = 2284), and >200 Gy (*n* = 1,115). Freedom from biochemical disease progression (biochemical freedom from failure [bFFF]) was determined using the American Society for Therapeutic Radiology Oncology and Phoenix definitions and calculated using the Kaplan-Meier method, with factors compared using the log-rank test.

Results: The 10-year prostate-specific antigen bFFF rate for the American Society for Therapeutic Radiology Oncology and Phoenix definitions was 79.2% and 70%, respectively. The corresponding bFFF rates for the low-, intermediate-, and high-risk groups was 84.1% and 78.1%, 76.8% and 63.6%, and 64.4% and 58.2%, respectively (*p* < 0.0001). The corresponding bFFF rate for the three BED groups was 56.1% and 41.4%, 80% and 77.9%, and 91.1% and 82.9% (*p* < 0.0001). The corresponding bFFF rate for the low-risk patients by dose group was 69.8% and 49.8%, 86% and 85.2%, and 88.1% and 88.3% for the low-, intermediate, and high-dose group, respectively (*p* < 0.0001). The corresponding bFFF rate for the intermediate-risk patients by dose group was 52.9% and 23.1%, 74.1% and 77.7%, and 94.3% and 88.8% for the low-, intermediate-, and high-dose group, respectively (*p* < 0.0001). The corresponding bFFF rate for high-risk patients by dose group was 19.2% and 41.7%, 61.8% and 53.2%, and 90% and 69.6% for the low-, intermediate-, and high-dose group, respectively (*p* < 0.0001).

Conclusions: These data suggest that permanent brachytherapy dose prescriptions can be customized to risk status. In low-risk patients, achieving a BED of ≥140 Gy might be adequate for prostate-specific antigen control. However, high-risk disease might require a BED dose of ≥200 Gy. © 2007 Elsevier Inc.

Prostate cancer, Brachytherapy, External beam radiotherapy.

INTRODUCTION

Permanent prostate brachytherapy can be performed using different isotopes and in combination with hormonal therapy (HT) or external beam radiotherapy (EBRT). Controversy exists regarding the selection of the optimal regimen for a given risk group. For low-risk patients, monotherapy using ¹²⁵I with a prescription dose of 144 Gy or ¹⁰³Pd with a dose of 124 Gy has been advocated (1). Intermediate- and high-risk disease is often treated with the addition of HT and/or EBRT. Despite these general guidelines, several single-institution studies have found little or no benefit with additional

therapies compared with monotherapy (2, 3). In addition, the dosing recommendations have come into question. Some centers have routinely prescribed 160 Gy when using ¹²⁵I and others 144 Gy (4–6). Other brachytherapy sites exclusively use ¹⁰³Pd, believing that a radiobiologic advantage may exist for 124 Gy of this isotope in most clinical situations (7). Finally, the most appropriate dose for combination therapy (implantation plus EBRT) has come into question, prompting a randomized trial investigating different dosing regimens (8).

We elected to try and answer some of these difficult questions by analyzing the results of six large and experienced

brachytherapy centers. Because each center used their own treatment protocols involving different dosing regimens, isotopes, and indications for the addition of HT and EBRT, a common dose variable that equated the results from all the centers was chosen. Stock *et al.* (9) have identified that the biologically effective dose (BED) is one method to equate the different isotopes, doses, and the addition of EBRT.

In this study, we investigated whether a BED could be identified to correspond to disease risk that could be tailored to the patient's risk status.

METHODS AND MATERIALS

Six centers provided clinical data from 5,889 consecutively treated permanent brachytherapy patients, of whom 3,928 had post-implant dosimetry results. The institutional review board at each center approved the sharing of their raw patient data, which was entered into the Prostate Research Database (created by Fearn and Potters), an Access-based database with a corresponding data export and biochemical outcome calculator. No center analyzed the outcomes independent of the entire cohort.

¹²⁵I was used in 2,293 patients (58%) and ¹⁰³Pd in 1,635 (42%). Short-term HT was used for a median of 3.9 months (range, 3-9) in 1,540 (39.2%) and EBRT in 882 (22.5%). The patients were stratified by National Comprehensive Cancer Network (NCCN) criteria into low- (*n* = 2,188), intermediate- (*n* = 1,188), and high- (*n* = 552) risk groups (Table 1). Low risk was defined as Stage T1-T2a, Gleason score 2-6, and prostate-specific antigen (PSA) level < 10 mg/mL. Intermediate risk was defined as Stage T2b-T2c or Gleason score 7 or PSA level of 10-20 ng/mL (patients with multiple adverse

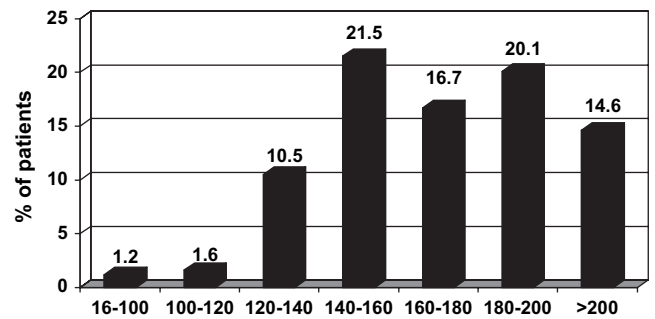


Fig. 1. Biologically effective dose (BED) distribution. Median BED was 179 Gy.

factors were considered high risk). Finally, high risk was defined as T3a or Gleason score 8-10 or PSA level >20 ng/mL.

Postimplant dosimetry was performed within 1 month of implantation, and the minimal dose received by 90% of target volume (D₉₀) was the postimplant variable analyzed. The BED was calculated from the implant D₉₀ and EBRT dose using an α/β ratio of 2 according to the formulas previously described by Stock *et al.* (9).

The median BED was 179 Gy (Fig. 1), and the results per center are given in Table 2. The BED data were divided into three dose groups: low, < 140 Gy (*n* = 527, 13.4%); intermediate, 140-200 Gy (*n* = 2,284, 58.2%); and high, >200 Gy (*n* = 1,117, 28.4%). The respective D₉₀ for the ¹²⁵I and ¹⁰³Pd groups for each BED dose group was as follows: low BED: ¹²⁵I, ≤134 Gy and ¹⁰³Pd, ≤122 Gy; intermediate: ¹²⁵I, 135-188 Gy and ¹⁰³Pd, 123-166 Gy; and high: ¹²⁵I, ≥189 Gy and ¹⁰³Pd, ≥167 Gy or ¹²⁵I, 110 Gy plus 45 Gy EBRT or ¹⁰³Pd, 102 Gy plus 45 Gy EBRT.

Disease progression was defined as any use of androgen deprivation after permanent brachytherapy, clinical relapse, or biochemical failure. Biochemical failure was defined as three PSA rises with two modifications: biochemical freedom from failure (bFFF) using the American Society for Therapeutic Radiology Oncology (ASTRO)-Kattan definition to account for backdating and as a 2-ng/mL increase greater than a nadir (the Phoenix definition) (10, 11). The requirement that the three increases had to be consecutive was relaxed and, in patients in whom the most recent PSA values were increasing at the last follow-up visit but in whom failure had not occurred, the follow-up time was truncated at the PSA level immediately before the first increase. Patients with fewer than three PSA rises were censored at the first PSA increase.

Table 1. Patient characteristics

Characteristic	<i>n</i> (%)
PSA (ng/mL)	
0-4	330 (8.4)
4.1-10	2,651 (67.5)
10.1-20	735 (18.7)
>20	212 (5.4)
Stage	
T1b-T1c	2,345 (59.8)
T2a	975 (24.8)
T2b	410 (10.4)
T2c	158 (4)
T3	40 (1)
Gleason score	
2-4	133 (3.4)
5-6	2,711 (69.1)
7	851 (21.7)
8-10	233 (5.8)
Risk group	
Low	2,188 (55.7)
Intermediate	1,188 (30.2)
High	552 (14.1)
Isotopes	
¹²⁵ I	2,293 (58)
¹⁰³ Pd	1,635 (42)
Supplemental EBRT	882 (22.5)
HT	1,540 (39.2)

Abbreviations: PSA = prostate-specific antigen; EBRT = external beam radiotherapy; HT = hormonal therapy.

Table 2. Mean BED per center with and without supplemental EBRT (implant only)

Center	All patients		Patients without EBRT*	
	<i>n</i>	Mean BED (95% CI)	<i>n</i>	Mean BED (95% CI)
1	1,115	172 (170-174)	853	158 (156-159)
2	1,548	197 (195-198)	994	188 (186-190)
3	516	149 (147-151)	516	149 (147-151)
4	310	170 (167-173)	290	166 (164-169)
5	249	185 (182-188)	246	185 (181-188)
6	190	167 (162-172)	147	154 (150-158)
Total	3,928	179 (178-180)	3,046	169 (168-170)

Abbreviations: BED = biologically effective dose; EBRT = external beam radiotherapy; CI = confidence interval.

* Monotherapy cases only (*p* < 0.001 between centers).

Freedom from progression was calculated using the Kaplan-Meier method, with factors compared using the log-rank test. Cox regression analysis was used for multivariate analysis of freedom from progression. The means were compared using one-way analysis of variance.

RESULTS

The median censored follow-up time was 42.5 months (range, 1.8–161). The median PSA level was 8.9 ng/mL (range, 0–300). The mean number of follow-up PSA values per patient was 6.3 (range, 2–22).

The 10-year bFFF rate for the entire cohort was 79.2% and 70% using the ASTRO-Kattan and Phoenix definitions, respectively. The corresponding bFFF rate by risk group was 84.1% and 78.1%, 76.8% and 63.6%, and 64.4% and 58.2% for the low-, intermediate, and high-risk groups, respectively ($p < 0.0001$). The corresponding bFFF rate for the three BED groups was 56.1% and 41.4%, 80% and 77.9%, and 91.1% and 82.9% ($p < 0.0001$). The corresponding bFFF rate for the low-risk patients by dose group was 69.8% and 49.8%, 86% and 85.2%, and 88.1% and 88.3% for the low-, intermediate, and high-dose group, respectively ($p < 0.0001$; Fig. 2). The corresponding bFFF rate for the intermediate-risk patients by dose group was 52.9% and 23.1%, 74.1% and 77.7%, and 94.3% and 88.8% for the low-, intermediate-, and high-dose group, respectively ($p < 0.0001$; Fig. 3). A separate analysis for the two higher dose groups in the intermediate-risk patients was also significant ($p < 0.0001$). The corresponding bFFF rate for high-risk

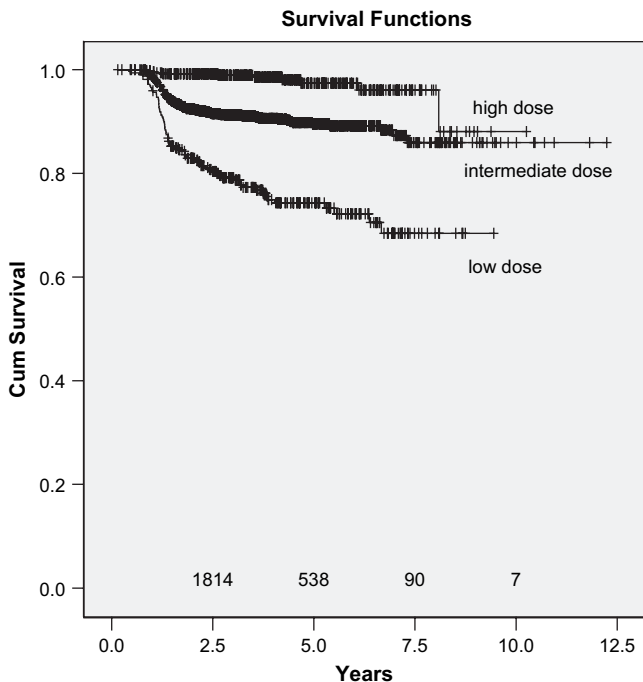


Fig. 2. Biochemical freedom from failure (bFFF) for low-risk patients by dose group. Low dose, 69.8%; intermediate dose, 86%; and high dose, 88.1% ($p < 0.0001$). Kaplan-Meier curves generated using American Society for Therapeutic Radiology Oncology-Kattan definition of prostate-specific antigen (PSA) failure.

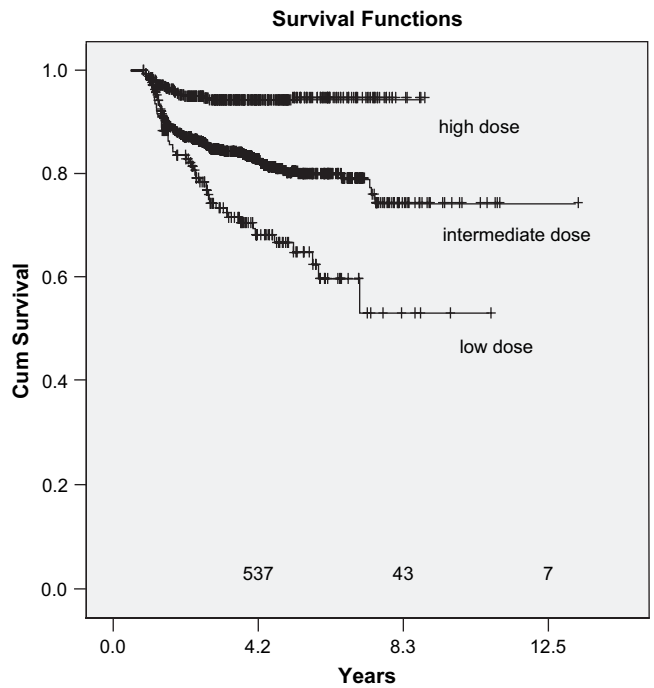


Fig. 3. Biochemical freedom from failure (bFFF) for intermediate-risk patients by dose group. Low dose, 52.9%; intermediate dose, 74.1%; and high dose, 94.3% ($p < 0.0001$). Kaplan-Meier curves generated using American Society for Therapeutic Radiology Oncology-Kattan definition of prostate-specific antigen (PSA) failure.

patients by dose group was 19.2% and 41.7%, 61.8% and 53.2%, and 90% and 69.6% for the low-, intermediate-, and high-dose group, respectively ($p < 0.0001$; Fig. 4). Cox

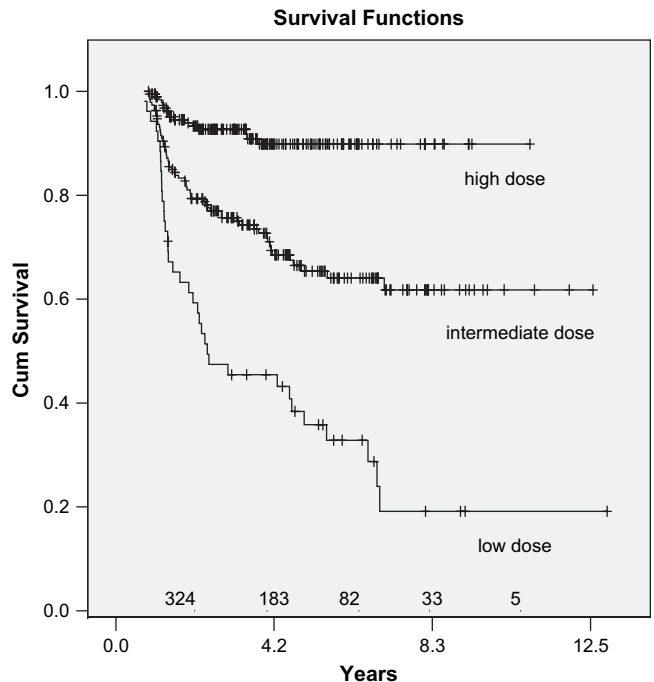


Fig. 4. Biochemical freedom from failure (bFFF) for high-risk patients by dose group. Low dose, 19.2%; intermediate dose, 61.8%; and high dose, 90% ($p < 0.0001$). Kaplan-Meier curves generated using American Society for Therapeutic Radiology Oncology-Kattan definition of prostate-specific antigen (PSA) failure.

Table 3. Cox regression analysis for entire cohort

Variable	<i>p</i>	Hazard ratio	95% CI for Exp(B)
Gleason score	0.001	1.191	1.076–1.317
PSA level	0.000	1.009	1.004–1.013
Stage	0.261	1.059	0.958–1.170
Supplemental EBRT	0.000	0.233	0.172–0.315
HT	0.351	0.910	0.747–1.109
Year of implant	0.229	1.000	1.000–1.000
BED	0.000	0.971	0.968–0.974

Abbreviations as in Tables 1 and 2.

regression analysis for bFFF using the ASTRO-Kattan definition for the entire cohort and for each risk group is shown in Tables 3–6. The only difference in the significance of the covariates in the Cox regression analysis between the two PSA failure definitions was for HT. The hazard ratio for patients not receiving HT was 1.817 (95% confidence interval, 1.42–2.32, $p < 0.001$) when the Phoenix definition was used.

DISCUSSION

This study represents a large cohort of prostate brachytherapy patients with postimplant dosimetry and a long follow-up period. This analysis has demonstrated the importance of implant dosimetry in predicting for biochemical freedom from recurrence for all risk groups of patients. Furthermore, our results suggest that the implant dose can be customized according to the prostate cancer disease risk status.

Patients who present with low-risk disease require intermediate-dose prescriptions (BED doses, 140–200 Gy), and patients with intermediate- and high-risk disease benefit most from the highest doses (>200 Gy). The typical prescription dose for prostate cancer patients receiving ^{125}I or ^{103}Pd as monotherapy has been 145 Gy and 124 Gy, respectively (American Association of Physicists in Medicine Task Group 43 and National Institute of Standards and Technology 1999). No distinction was made for risk status regarding the prescription doses. It is, however, reasonable to consider that patients with more advanced and aggressive local disease might require higher radiation doses. Such data are available from EBRT studies, in which randomized trials have demonstrated an advantage to higher doses that is clear for intermediate- and high-risk patients, but less clear for patients with low-risk disease (12).

Table 4. Cox regression analysis for low-risk patients

Variable	<i>p</i>	Hazard ratio	95% CI for Exp(B)
Gleason score	0.246	1.188	0.888–1.588
PSA level	0.644	1.012	0.961–1.066
Stage	0.215	1.180	0.908–1.532
Supplemental EBRT	0.034	2.256	1.063–4.787
HT	0.775	1.047	0.764–1.434
BED	0.000	0.314	0.249–0.396
Year of implant	0.156	1.000	1.000–1.000

Abbreviations as in Tables 1 and 2.

Table 5. Cox regression analysis for intermediate-risk patients

Variable	<i>p</i>	Hazard ratio	95% CI for Exp(B)
Gleason score	0.373	1.102	0.890–1.365
PSA level	0.227	1.005	0.997–1.012
Stage	0.223	1.102	0.943–1.289
Supplemental EBRT	0.000	2.346	1.571–3.502
HT	0.887	0.978	0.724–1.323
BED group	0.000	0.301	0.228–0.397
Year of implant	0.291	1.000	1.000–1.000

Abbreviations as in Tables 1 and 2.

A problem with the permanent brachytherapy data has been the difficulty in interpreting the results from centers using different isotopes and with or without EBRT. Recently, Stock *et al.* (9) described the use of the BED as a method of equating to a common dose the use of ^{125}I , ^{103}Pd and EBRT with clinical outcomes. A similar approach was used in the present study. By equating the different doses from the two isotopes, as well as the contribution from EBRT in patients receiving combination therapy, certain conclusions can be drawn. Patients with low-risk disease have an improved outcome with a BED of ≥ 140 Gy. Patients with a BED of < 140 Gy had a 10-year bFFF rate of 69.8% compared with those with an intermediate dose who had a bFFF rate of 86% and those with a high dose, who had a bFFF rate of 88.1%. In this low-risk group, it appears that an insignificant difference exists between the intermediate and high dose. Thus, patients demonstrated little benefit when receiving a BED dose of >200 Gy. Conversely, for patients with intermediate- or high-risk prostate cancer, BED doses of < 200 Gy resulted in inferior PSA control. If implant monotherapy is used in these patients, a D_{90} of ≥ 189 Gy for ^{125}I or ≥ 167 Gy of ^{103}Pd would be needed. Alternatively, the same BED (>200 Gy) could be achieved by a combination of ^{125}I at 110 Gy or ^{103}Pd at 100 Gy plus 45 Gy of EBRT, typically given in 1.8 Gy/fraction with 25 fractions.

The data from this study may undoubtedly create some controversy. Anytime higher radiation doses are suggested, an understanding of the potential for adverse effects also needs to be considered. This study did not address morbidity or whether these higher doses can be delivered without additional risks. However, with intraoperative planning, the potential to minimize rectal doses while delivering higher prostate doses has been established (13–16). Li *et al.* (17)

Table 6. Cox regression analysis for high-risk patients

Variable	<i>p</i>	Hazard ratio	95% CI for Exp(B)
Gleason score	0.003	1.236	1.073–1.424
PSA level	0.000	1.012	1.006–1.019
Stage	0.673	0.965	0.819–1.137
Supplemental EBRT	0.017	2.082	1.138–3.812
HT	0.743	0.927	0.591–1.455
BED	0.000	0.218	0.145–0.328
Year of implant	0.647	1.000	1.000–1.000

Abbreviations as in Tables 1 and 2.

proposed using the concept of the equivalent uniform dose, that it is dosimetrically possible to increase dose to the prostate without a substantial increase in the dose to the rectum and urethra. However, some centers have reported increased morbidity when combination therapy has been used to treat high-risk patients (18).

One question this study did not adequately answer is the need for supplemental EBRT or whether higher implant doses are enough to control intermediate- and high-risk disease. The Cox regression analysis for the entire cohort suggested that supplemental EBRT is a contributory variable in bFFF for all three risk categories. Although it was less significant than the BED in the low-risk group compared with the intermediate- and high-risk groups, it still remained in the equation. One possible explanation is that the supplemental EBRT improved the results (by increasing the BED) of patients who had a low-dose implant. Of the low-risk patients, 13% had a BED of < 140 Gy and the failure rate in this group was 30.2%. Also, the use of EBRT could provide an advantage in the intermediate- and high-risk patients that is independent of the BED. The extra margin provided with EBRT might have a direct beneficial effect on extracapsular disease extension.

We elected to calculate the BED for our patients using an α/β of 2. The decision was based on the recent publication by Stock *et al.* (9). Chen and Nath (19) suggested caution when using the BED as a qualitative predictor of clinical outcome. Increasing the α/β to 3 in the calculations would result in a substantial decrease in the corresponding D_{90} values we have suggested for ^{125}I and ^{103}Pd (20, 21). However, increasing evidence has shown that higher radiation doses are required for permanent implants when local control, bFFF, and distant metastases are considered (22, 23). As more data are accumulated with longer follow-up, the most appropriate relationship between the isotope D_{90} and BED, as well as the total BED recommended, should become standardized.

The use of HT in patients undergoing permanent prostate brachytherapy has also been controversial. Of our cohort, 39.2% received a median of 3.9 months of HT. None of the analyses showed that short-term HT affected bFFF. For the low-risk patients, these results come as no surprise. However,

data from randomized EBRT studies of intermediate- and high-risk patients have shown a benefit to short-term HT (24). We could find no benefit in these same patients, which could suggest that the delivered dose is far more important than the addition of short-term HT. However, when the Phoenix definition was used, the use of HT was significant in the Cox analysis. It remains unclear how to resolve this discrepancy other than to note that with longer follow-up these differences could disappear. Stock *et al.* (9), using the ASTRO definition, also found HT not to be significant on multivariate analysis of bFFF.

Recently, the Radiation Therapy Oncology Group-ASTRO Phoenix Consensus Conference recommended replacing the biochemical failure definition of three consecutive PSA increases (formerly ASTRO definition) with a failure definition defined as an increase of 2 ng/mL greater than a nadir (Phoenix definition) (11). Although this recommendation was developed for patients treated with EBRT, with or without HT, the panel also suggested reporting brachytherapy with HT results similarly. We elected to report our results using both definitions and noted identical trends for all the analyzed parameters, except for HT. Although the bFFF rates differed slightly at each endpoint for the two definitions, the impact of the independent variables, especially the BEDs, remained highly significant.

CONCLUSIONS

The data from six large prostate brachytherapy centers have suggested that radiation doses can be prescribed based on disease characteristics. Low-risk patients demonstrated excellent bFFF at doses that have typically been recommended in published studies (140 Gy for ^{125}I and 124 Gy for ^{103}Pd) and did not seem to benefit from high doses of ^{125}I (≥ 189 Gy or $^{103}\text{Pd} \geq 167$ Gy). According to our results, patients with intermediate- and high-risk disease have improved bFFF when treated with doses greater than those routinely recommended. These higher doses can be achieved by boosting the implant dose or by the addition of supplemental EBRT.

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