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CLINICAL INVESTIGATION **Prostate**

DOSE ESCALATION USING CONFORMAL HIGH-DOSE-RATE BRACHYTHERAPY IMPROVES OUTCOME IN UNFAVORABLE PROSTATE CANCER

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Purpose: To overcome radioresistance for patients with unfavorable prostate cancer, a prospective trial of pelvic external beam irradiation (EBRT) interdigitated with dose-escalating conformal high-dose-rate (HDR) prostate brachytherapy was performed.

Methods and Materials: Between November 1991 and August 2000, 207 patients were treated with 46 Gy pelvic EBRT and increasing HDR brachytherapy boost doses (5.50–11.5 Gy/fraction) during 5 weeks. The eligibility criteria were pretreatment prostate-specific antigen level ≥10.0 ng/mL, Gleason score ≥7, or clinical Stage T2b or higher. Patients were divided into 2 dose levels, low-dose biologically effective dose <93 Gy (58 patients) and high-dose biologically effective dose >93 Gy (149 patients). No patient received hormones. We used the American Society for Therapeutic Radiology and Oncology definition for biochemical failure.

Results: The median age was 69 years. The mean follow-up for the group was 4.4 years, and for the low and high-dose levels, it was 7.0 and 3.4 years, respectively. The actuarial 5-year biochemical control rate was 74%, and the overall, cause-specific, and disease-free survival rate was 92%, 98%, and 68%, respectively. The 5-year biochemical control rate for the low-dose group was 52%; the rate for the high-dose group was 87% ($p < 0.001$). Improvement occurred in the cause-specific survival in favor of the brachytherapy high-dose level ($p = 0.014$). On multivariate analysis, a low-dose level, higher Gleason score, and higher nadir value were associated with increased biochemical failure. The Radiation Therapy Oncology Group Grade 3 gastrointestinal/genitourinary complications ranged from 0.5% to 9%. The actuarial 5-year impotency rate was 51%.

Conclusion: Pelvic EBRT interdigitated with transrectal ultrasound-guided real-time conformal HDR prostate brachytherapy boost is both a precise dose delivery system and a very effective treatment for unfavorable prostate cancer. We demonstrated an incremental beneficial effect on biochemical control and cause-specific survival with higher doses. These results, coupled with the low risk of complications, the advantage of not being radioactive after implantation, and the real-time interactive planning, define a new standard for treatment.

Prostate cancer, Conformal radiotherapy, High-dose-rate brachytherapy, Outcome.

INTRODUCTION

External beam radiotherapy (EBRT) has been the reference standard treatment for patients with unfavorable prostate cancer, but the results have been suboptimal. The 5- and 10-year survival rates, ranging from 40% to 75% and 35% to 55%, respectively, are discouraging (1–4). In addition, patients with posttreatment persistence of the disease in the gland have been found to have an increased risk of symptomatic local failure and distant metastasis and a decrease in overall survival (5–8). From the above information, one may conclude that an improvement in local control may have an impact on biochemical control (BC), disease-free survival, and cause-specific survival. Consequently, therapeutic efforts are now concentrated toward this goal. The strategies tested to improve local control in the past decade have included hormonal ablation before, during, and after standard RT (9–11); particle beam therapy with either pro-

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tons or neutrons as a boost to EBRT (12, 13); a permanent seed low-dose-rate (LDR) implant as a boost to EBRT (14, 15); and dose-escalating conformal RT using one of the following two pathways: three-dimensional conformal RT (3D-CRT) (16, 17) or conformal high-dose-rate (HDR) brachytherapy (18, 19). Tumor dose escalation should hypothetically overcome the radioresistance of tumor clonogens seen at conventional dose levels. The question remains as to which of these two strategies best escalates the dose sufficiently to obtain a greater therapeutic gain.

With standard EBRT fields and traditional treatment planning, the true extent of the target volume may not receive the prescribed dose. Hence, the relatively low dose delivered to the tumor is the most likely explanation for the suboptimal results. In this setting, perhaps the benefit of adding hormonal treatment (9–11) relates to a local effect on the malignant cells (fixation of potentially lethal damage) such that cell death from adding hormonal therapy would be equivalent to having delivered an additional dose of radiation. Although with 3D-CRT, the target volume and surrounding normal structures are better delineated, resulting in planning the delivery of a higher dose, dose escalation may not always be safe or possible. This is the case for patients with geometrically unfavorable lesions, which may be undertreated. In addition, other drawbacks to this approach include the accuracy of target volume definition and uncertainties related to daily dose delivery. Systematic and random setup errors, internal organ motion, deformation, and organ changes related to treatment have been well documented and may limit the efficacy of 3D-CRT (20–23). At William Beaumont Hospital, we have developed a strategy, the adaptive radiotherapy process, which has been tested to overcome motion uncertainties (24–26).

As a result of the potential drawbacks of 3D-CRT, in 1991, we began the first sequential dose escalating, prospective clinical trial using transrectal ultrasound (TRUS)-guided conformal HDR brachytherapy as a means of delivering the boost dose (18, 19, 27, 28). The TRUS-guided transperineal implant technique allows direct and continuous visualization of the relationship between the rectal wall, urethra, bladder, and prostate contour (18, 19, 28, 29). Our interactive real-time optimization program "the HDR smart seed technique," selects the needle positions, allowing us to correlate intraoperatively the anatomic relationship of the organs with the needle placement and their spatial distribution (27–29).

To address the issues of target volume definition and uncertainties of dose delivery systems, we prospectively performed and reported our study on overcoming internal prostatic motion and setup inaccuracies with conformal image-guided interstitial HDR brachytherapy (30). We documented and quantified intraoperatively the magnitude of prostatic motion and distortion that takes place in all three dimensions during the implant procedure, as well as the movement of the prostate gland between two separate implant procedures. We demonstrated no shifting or displacement of the location of the prostate just before treatment (planning volume) to that of the position of the gland immediately after treatment was delivered (treated volume) (30). Consequently, the prescribed dose and delivered dose were the same.

From the patient and family perspective, a great advantage of HDR brachytherapy over LDR permanent seed prostate brachytherapy is that once the HDR dose is delivered, the patient is no longer radioactive. This approach avoids all the radiation safety and protection issues related to permanent seed implantation. From the healthcare payers perspective, a decrease in cost results because the permanent seeds do not have to be purchased for each patient.

The key to the delivery of conformal HDR prostate brachytherapy was the development of an interactive real-time dose-optimization program in 1991 at William Beaumont Hospital (27). We termed this program "the HDR smart seed technique." This optimization program allows (*1*) real-time, computer selection of ideal needle location and determination of actual needle position, (*2*) direct visualization of isodose curves in relationship to real-time prostate gland boundaries, (*3*) determination of actual dose at multiple prostate levels with corresponding doses to the rectal wall and urethra, (*4*) detection and compensation for prostate motion during the procedure (30), (*5*) intraoperative dose volume analysis, and (*6*) intraoperative analysis of implant quality (18, 19, 28–33).

The William Beaumont Hospital HDR prostate brachytherapy boost trial is the first prospective dose-escalation brachytherapy trial ever performed. The study was undertaken to test the hypothesis that local failure for patients with prostate cancer harboring large-volume disease is related to both large cell mass and radioresistant cell clones, which require biologically higher radiation doses than conventionally delivered with EBRT. We report the results to date of this trial.

METHODS AND MATERIALS

Between November 1991 and August 2000, 311 patients with unfavorable and/or large-volume prostatic adenocarcinoma were prospectively enrolled into this dose-escalating trial. They were treated with pelvic EBRT interdigitated with a conformal HDR (C-HDR) brachytherapy boost at William Beaumont Hospital (Royal Oak, MI). Sequentially seen patients meeting the study criteria and with an expected survival of >5 years were offered participation in this dose-escalating trial. All patients signed an institutional review board–approved informed consent before protocol entry. Patients with any of the following characteristics were eligible for study entry: pretreatment prostate-specific antigen (PSA) level ≥ 10.0 ng/mL, Gleason score ≥ 7, or clinical Stage T2b or higher. One hundred four patients were excluded from this current analysis for the following reasons: neoadjuvant hormonal therapy for gland downsizing in 100 patients (gland volume >65 cm^3 or length >5.5 cm) and noncompletion of therapy in 4 patients. The remaining 207 patients comprised the study population. The

evaluation process before enrollment has been previously described (18, 31–33). Patients' upper age limit was 85 years. All patients enrolled were expected to have a life expectancy of >5 years. All patients were staged according to the 1993 American Joint Committee on Cancer (AJCC-93) clinical Stages I–III (T1–T3N0M0). In October 1995, an upper limit of 40 ng/mL for the pretreatment PSA level was established and Stage T1c-T2a was accepted providing the Gleason score was ≥7 and/or the PSA level was ≥10 ng/mL. It is important to recognize that if these patients underwent pathologic staging after prostatectomy, they would be upstaged by ≥60% in T stage and Gleason score.

Our treatment technique has been previously described (18, 19). The pelvis was treated to an isocentric dose of 46 Gy in 23 fractions using a 4-field technique. All patients underwent pretreatment pelvic CT with contrast to assist in defining the prostate and normal tissue volumes. Pelvic EBRT was interdigitated with TRUS-guided transperineal conformal interstitial ^{192}Ir implants. The overall treatment time was compressed to only 5 weeks. No EBRT was given on the day of the outpatient implant. After we established enough experience with patients' tolerance to HDR prostate brachytherapy and that their toxicity was acceptable, we decided to decrease the number of C-HDR implants from 3 to 2. From 1991 to 1995, all patients underwent 3 TRUS-guided C-HDR implants during the first, second, and third weeks of treatment. After October 1995, all patients underwent 2 HDR implants during the first and third weeks of pelvic EBRT. This change was implemented to eliminate administration of one spinal anesthesia and the surgical trauma of a third implant. Patients with a prostate gland volume >65 cm^3 or length >5.5 cm were initially ineligible for the protocol. These patients underwent downsizing with a short course of hormonal therapy (<6 months) and were the subject of a separate analysis (34). Brachytherapy dosimetry was never done using preplanning TRUS performed days before the actual HDR implant. Instead, using our "HDR smart seed technique program," the dosimetry was done in real time intraoperatively. The implant procedure was performed under spinal anesthesia with the patient in a lithotomy position with extreme pelvic flexion. A 7.5-MHz biplanar TRUS probe was fixed to the table to allow only longitudinal motion. The apex and base of the prostate gland were identified on-line using transverse and sagittal TRUS images. The probe was positioned as parallel as possible to the prostatic urethra. The length of the prostate and corresponding treatment length was considered the distance from the base to the apex. No margins were added. The prostate gland was scanned at 5-mm intervals from 1.0 cm above the base to 1.0 cm below the apex of the prostate gland on the transverse plane (only for intraoperatively planning purposes, not for treatment). The urethra was mapped on each 5-mm transverse image as well. The transverse image with the largest cross-sectional prostate area was considered the reference plane. This area was contoured with no planning margins added. Consequently, the CTV and planning target volume were the same. The optimal needle positions within the reference plane were determined intraoperatively using our real-time, interactive optimization program. The computer planning software gave the physician the needle coordinates with reference to the perineal template (27–29). Under TRUS guidance, and after the intraoperative treatment plan generated by the optimization program, the needles were placed parallel to the TRUS probe using a template mounted and fixed to the probe. After placement of all needles, cystoscopy was performed to reconfirm the prostate treatment length with adequate depth by virtue of bladder mucosa tenting. To reconfirm the gland apex during cystoscopy, the TRUS probe was placed in the sagittal plane at the apex. The verumontanum was used to correlate with the TRUS probe position in the longitudinal plane. After cystoscopy, contrast material was instilled in the bladder and fluoroscopy (by way of a C-arm) was performed before and after connecting the transfer tubes to verify and document the appropriate needle tip positions. Because the needle positions may have shifted slightly during cystoscopy, the final TRUS needle positions, as well as the final urethral locations before treatment, were recaptured to determine the actual treatment dwell positions and times. Intraoperatively, all dosimetric calculations were performed using real-time interactive optimization software (27–29). The treatment was optimized using standard geometric optimization (27). On each transverse TRUS image, the 100% isodose line encompassed the contoured prostate volume. The urethral dose was calculated on each 5-mm transverse image and was limited to ≤125% of the treatment dose in each transverse plane. The rectal dose was calculated at the anterior edge of the TRUS probe within the reference plane and was limited to ≤75% of the treatment dose. For those patients who underwent 3 initial implants, the dose to this treatment volume was subsequently escalated from 5.5 Gy for each initial implant to 6.0 Gy and finally 6.5 × 3 Gy. This group constituted the low-dose group. Patients who received 2 implants initially received 8.25 Gy during each implant, then 8.75 Gy, 9.50 Gy, 10.5 Gy, and 11.5 Gy. This was the high-dose group (Table 1).

When the trial began in 1991, the linear-quadratic formula was used to calculate the biologically equivalent dose (BED) (35). The α/β ratio for tumor control probability was 10 and 4 for normal tissues complications. The basic assumption was that EBRT of 46 Gy in 23 daily fractions to the pelvis followed by a prostate EBRT boost of 24 Gy in 12 fractions (total dose 70 Gy at 2-Gy increments) in 7 weeks will deliver a BED to 5.5 Gy × 3 in weekly HDR fractions interdigitated with 23 pelvic EBRT doses in 5 weeks. The expected biologic effect was a decrease in tumor control probability of 5% for the EBRT + HDR regimen. Similarly, when we eliminated one implant in 1995, the same formulation and biologic assumptions (α/β of 10) were used. There is evidence now that the α/β ratio for prostate cancer is much lower (36–38). Recently, we published the validation of this low α/β value. The value of 1.2 was derived from this EBRT + HDR clinical trial (39). For comparison, we have listed in Table 1 the BEDs for all levels of our

Table 1. Equivalent dose per brachytherapy dose level

Dose level	Brachytherapy dose	BED* (Gy) $\alpha/\beta = 10$	BED* (Gy) $\alpha/\beta = 5$	BED* (Gy) $\alpha/\beta = 1.2^{\dagger}$
Low dose	5.50 Gy × 3	67.1	70.7	80.2
	6.00 Gy × 3	70.0	74.3	86.1
	6.50 Gy × 3	72.6	78.1	92.5
High dose	8.25 Gy × 2	72.0	78.8	94.2
	8.75 Gy × 2	74.2	82.1	99.9
	9.50 Gy × 2	78.0	87.1	108.9
	10.50 Gy × 2	82.9	94.4	122.0
	11.50 Gy × 2	87.0	99.8	136.3

Abbreviation: BED = biologically equivalent dose.
* To 2 Gy per fraction, 70 Gy total external beam dose.
† α/β ratio of 1.2 derived from our clinical trial (39).

dose-escalation trial using α/β ratios of 10, 5, and 1.2. For this analysis, the low-dose group receiving 3 implants using an α/β of 1.2 had a BED of $<$93 Gy; for the high-dose group with two implants, the BED was $>$93 Gy. With an HDR dose of 11.5 Gy × 2, the BED using an α/β ratio of 1.2 was 136.3 Gy, a dose unlikely to be achieved with any EBRT delivery system.

No patients received hormonal therapy before, during, or after RT unless local or distant failure was documented or the post-RT PSA profile was indicative of biochemical failure. Patients were seen in follow-up 1 month after completion of RT and were evaluated every 3 months thereafter for the first 18 months. Beyond this, patients were seen in follow-up every 6 months. Patients alternated follow-up visits between their urologist and radiation oncologist. TRUS was performed at 6, 12, and 18 months. TRUS-guided multiple core biopsies were obtained at 18 months if the patient had not developed metastatic disease. No therapeutic intervention was allowed as a consequence of the repeat biopsy results. These data were obtained for study purposes only, analyzed prospectively for clinical relevance, and recently submitted for publication (40). For all patients, routine serial posttreatment PSA levels were obtained with each follow-up visit. Biochemical failure was defined according to the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus panel statement (41). Three consecutive rises in PSA after reaching nadir constituted biochemical failure. The date of failure was the midpoint between the nadir and the first of the 3 rises in PSA. If hormonal therapy was administered to patients before they met the criteria for failure, patients were considered to have biochemical failure at the time of hormonal therapy initiation. Overall survival reflected all deaths, cancer related or otherwise. Disease-free survival incorporated all biochemical failures (including patients taking hormones without meeting the ASTRO definition), clinical failure, or death from any cause. Cause-specific survival was based on deaths that could be attributed to prostate cancer.

The actuarial rates were calculated by the Kaplan–Meier method (42). The association of clinical, pathologic, and treatment-related variables with any given event was analyzed using Pearson's chi-square, Fisher's exact test, and Mann–Whitney test for categorical variables and logistic regression analysis for continuous variables. The Student unpaired *t* test was used to determine the significance of the difference between two sample means. The statistical significance of the difference between actuarial curves was calculated with the log–rank test (43). Multiple regression analysis was performed using the Cox proportional hazards model (44). A p value of $\leq$0.05 was considered statistically significant. All intervals were calculated from the date of RT completion. Follow-up was complete through November 2001. The relationship between variables was determined by Pearson's correlation. Statistical analysis was performed with SYSTAT, version 10.0, and Statistical Package for Social Sciences, version 10 (SPSS, Chicago, IL).

RESULTS

The clinicopathologic characteristics, including stage, Gleason score, pretreatment PSA, and age by brachytherapy dose level are listed in Table 2. According to the AJCC-93, Stages T1c-T2a were seen in 30%, T2b in 28%, T2c in 32%, and T3 in 10% (70% of these patients had bulky disease $\geq$T2b). Of the 207 patients, 35 patients had all 3 poor prognostic factors (pretreatment PSA $\geq$10 ng/mL, Gleason score $\geq$7, and clinical Stage T2b or higher), leaving 75 patients with 2 poor factors; the remaining 97 patients had 1 poor prognostic factor. To avoid double counting patients, the 35 patients with all 3 poor factors and the 75 patients with 2 factors were deleted from the 1-factor group, leaving only 97 patients in this group, although all 207 had at least 1 poor factor. Because of the change in the eligibility criteria in 1995 for which a limit of $\leq$40 ng/mL was placed on the PSA level and Stage T1c with either Gleason score $\geq$7 or PSA $\geq$10 ng/mL were accepted for enrollment, a stage shift occurred with all the T1c-T2a patients and fewer of those with PSA levels $>$20 ng/mL in the high-dose group. The mean pretreatment PSA was 11.5 ng/mL. Our patients were clinically staged. Considering the inaccuracies

Table 2. Clinical and pathologic characteristics by brachytherapy dose level

Characteristic	Low dose (n = 58)	High dose (n = 149)
1993 T stage		
T1c	0 (0.0)	36 (24.2)
T2a	0 (0.0)	34 (22.8)
T2b	18 (31.0)	35 (23.5)
T2c	25 (43.1)	40 (26.8)
T3a-c	15 (25.9)	4 (2.7)
Age at diagnosis (y)		
<65	16 (27.6)	52 (34.9)
≥65–75	32 (55.2)	76 (51.0)
>75	10 (17.2)	21 (14.1)
Gleason score		
≤6	24 (41.4)	57 (38.3)
7	16 (27.6)	69 (46.3)
≥8	18 (31.0)	23 (15.4)
Pretreatment PSA (ng/mL)		
<4.0	1 (1.7)	13 (8.7)
4.0–10.0	19 (32.8)	88 (59.1)
10.1–20.0	23 (39.7)	42 (28.2)
>20.0	15 (25.9)	6 (4.0)

Abbreviation: PSA = prostate-specific antigen.

Data presented as the number of patients, with the percentage in parentheses.

of clinical staging, if these patients had been pathologically staged (after prostatectomy), they would have been upstaged by ≥60% in both T stage and Gleason score. Because 70% of the patients had bulky Stage T2b or higher and >55% had 2 or 3 poor prognostic factors, we considered these patients to have large-volume disease. Fifty-eight patients (28%) underwent 3 interstitial implants during the course of EBRT, and 149 (72%) underwent 2 implants. Minor pubic arch interference occurred rarely (<2%). Because of our smart seed technique with intraoperative optimization, no implant was abandoned owing to pubic arch interference.

Age

Patients were subdivided into 3 age groups: <65 years, 68 patients; 65–75 years, 108 patients; and >75 years, 31 patients (Table 2). The median age of the patients was 69 years (range 48–85), an older population typical of a RT series. The analysis of BC and overall, disease-free, and cause-specific survival by the 3 age groups demonstrated no significant difference by age group. Whether analyzed by these subgroups or as a continuous variable, age was not a significant predictor of outcome. Younger and older patients benefited equally.

Follow-up

The median follow-up for the entire group was 4.4 years (range 0.6–9.8). A total of 139 patients (67%) have been followed for a minimum of 3 years, and 61 (30%) have been followed for ≥5 years. The median follow-up for the low-dose group (BED <93 Gy) was 7.0 years (range 2.0–9. 8) and 3.4 years (range 0.6–6.0) for the high-dose group (BED >93 Gy). Follow-up and dose characteristics for the various implant groups are summarized in Table 3.

Table 3. Follow-up characteristics and number of patients per brachytherapy dose escalation

Brachytherapy dose	Patients (n)	Follow-up (y)		
		Mean	Median	Range
5.50 Gy × 3	18	8.3	8.8	2.1–9.8
6.00 Gy × 3	15	7.6	7.9	5.8–8.7
6.50 Gy × 3	25	5.7	6.1	1.9–7.7
8.25 Gy × 2	26	4.3	4.5	1.4–6.0
8.75 Gy × 2	26	3.9	4.2	1.5–4.8
9.50 Gy × 2	37	3.6	3.7	2.0–4.3
10.50 Gy × 2	45	2.4	2.4	0.9–3.7
11.50 Gy × 2	15	1.2	1.3	0.6–2.0
All patients (n)	207	4.4	3.8	0.6–9.8

Biochemical outcome and factors associated with failure

The actuarial analysis of BC and survival for the entire population is shown in Fig. 1. On the basis of the ASTRO consensus panel definition of biochemical failure (41), the actuarial BC rate was 74% at 5 years. Only 1 patient had failure after 4 years, with 61 of 207 patients followed for ≥5 years. A total of 43 patients (21%) experienced biochemical failure by the ASTRO definition at a median interval of 1.8 years (range 0.1–6.3 from treatment completion). The 5-year actuarial BC rate for all patients by brachytherapy dose level was 52% for the low-dose level and 87% for the high-dose level, with a highly significant difference (p <0.001; Fig. 2). The characteristics used for the univariate and multiple regression analyses to correlate with biochemical failure were T stage, Gleason score, pretreatment PSA, age, brachytherapy dose level, gland volume at implant 1, length of follow-up, number of poor prognostic factors present, and nadir PSA value. Table 4 illustrates the univariate analysis with the p values and corresponding odd ratios of the above variables obtained using the logistic regression model for continuous variables and chi-square test for categorical variables. A lower brachytherapy dose, higher Gleason score, higher pretreatment PSA, longer follow-up time, and higher nadir value were significant in correlating with biochemical failure. In addition, to account for time as a variable the Cox proportional hazards model was used (Table 4). The same variables remained statistically significant. For multivariate regression analysis, the Cox proportional hazards full model and reduced model, as derived for selecting the optimal subset for prediction by the forward selection method, are depicted in Table 5. Although pretreatment PSA, number of prognostic factors, and longer follow-up time lost (in both models) significance, the brachytherapy dose level, Gleason score, and nadir PSA value remained statistically significant in predicting biochemical failure. The model itself (full and reduced model in Table 4) was significant (p <0.001, Wald's test).

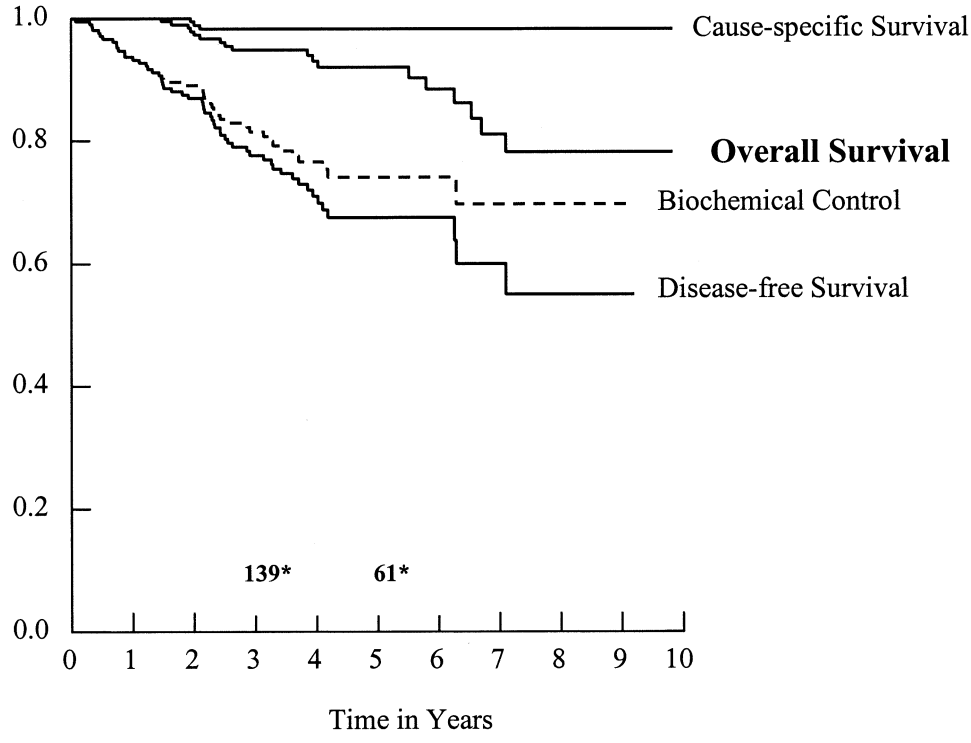

Fig. 1. Actuarial analysis of all 207 patients for cause-specific, overall, and disease-free survival and BC.

Clinical outcome

The analysis of clinical failure revealed that only 22 patients (11%) experienced clinical failure (by digital rectal examination [DRE] or radiography) after completing RT. Of these 22 patients, 12 patients had local recurrence by DRE and 9 distant recurrence by radiography. One patient experienced both local and distant recurrence. The 13 local failures detected by DRE occurred at a median interval of

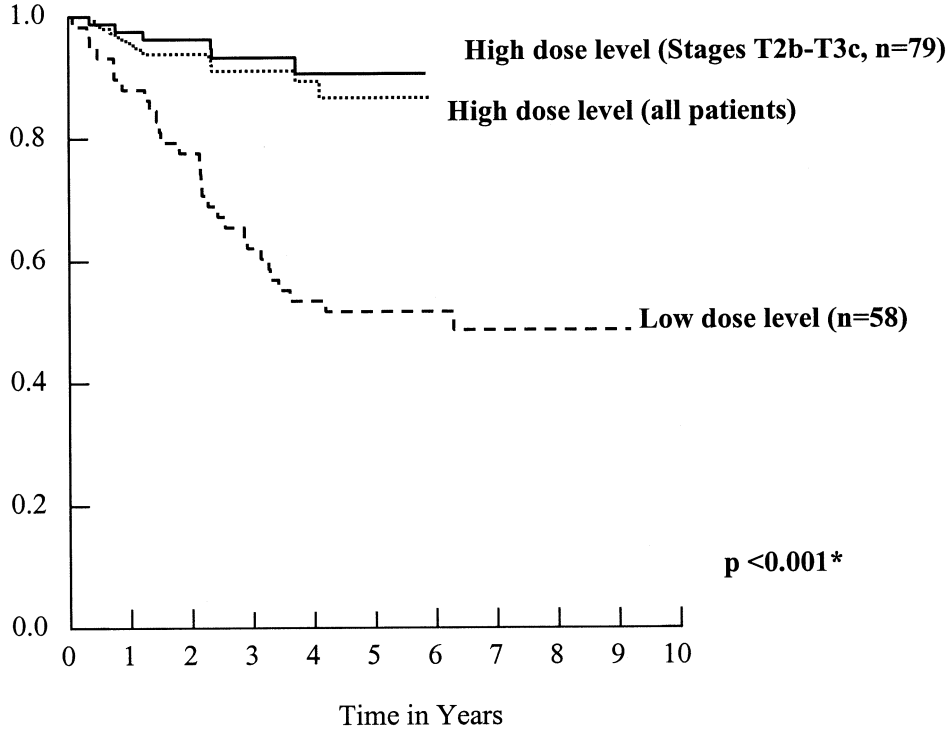

Fig. 2. Actuarial analysis of BC by brachytherapy dose level and clinical stage: All stages and only Stage T2b-T3c. *Generated from log–rank test.

Table 4. Univariate analysis of factors associated with biochemical failure

	Logistic regression/chi-square		Cox proportional hazards	
Factor	*p*	Odds ratio	*p*	Odds ratio
1993 T stage	0.005	1.409	0.065	1.204
Age (ys)	0.562	0.987	0.633	0.990
Brachytherapy dose level (low vs. high)	<0.001		<0.001	0.221
Gland volume (cm^3)	0.361	1.014	0.390	1.011
Gleason score	<0.001	1.946	<0.001	1.740
Pretreatment PSA (ng/mL)	<0.001	1.078	<0.001	1.040
PSA nadir (ng/mL)	<0.001	5.056	<0.001	1.511
Follow-up (y)	<0.001	1.041	<0.001	1.024
Prognostic factors*	<0.001		0.001	1.966

Abbreviation: PSA: prostate-specific antigen.
All but age and gland volume were statistically significant.
* Number of prognostic factors 1 vs. 2 vs. 3.

3.0 years (range 1.0–9.2) after treatment. Ten patients experienced distant metastasis at a median interval of 0.8 year (range 0.2–3.8). The 5-year actuarial rate of local failure and distant metastasis was 8% and 6%, respectively. Table 6 lists the 5-year actuarial analysis of overall survival, cause-specific survival, disease-free survival, and BC for patients stratified by brachytherapy dose level, with the corresponding *p* values. A statistically significant difference was noted at 5 years in favor of the high-dose group in BC ($p < 0.001$), disease-free survival ($p < 0.001$), and cause-specific survival ($p = 0.014$).

Figure 3 reveals that the overall survival rates by brachytherapy dose level are very high, despite the population median age of 69 years. Because one of the study entry criteria was an expected survival >5 years, the cancer death rate became a significant issue, a risk that should be measured. This risk of prostate cancer death was measured and correlated to treatment in Figure 4. In Fig. 4, one can see the actuarial analysis of cause-specific survival by brachytherapy dose level, demonstrating a statistically significant improvement in cause-specific survival for the high-dose group ($p = 0.014$).

Table 5. Multiple Cox proportional hazard regression analysis of factors associated with biochemical failure

	Full model		Reduced model*	
Factor	*p*	Odds ratio	*p*	Odds ratio
1993 T-stage	0.905	1.017		
Age at diagnosis	0.091	0.958		
Brachytherapy dose level	<0.034	0.252	<0.001	0.282
Gland volume	0.218	1.020		
Gleason score	<0.001	1.781	0.002	1.547
Nadir value	<0.001	1.505	<0.001	1.358
Pretreatment PSA	0.551	0.990		
Follow-up time	0.402	1.009		
Prognostic factors†	<0.225	0.658		
Model significance‡	<0.001			<0.001

Abbreviation: PSA = prostate-specific antigen.
Brachytherapy dose, Gleason score, nadir value, and model significance were statistically significant.
* Factor selected by the forward stepwise Cox proportional hazard regression with the likelihood ratio method.
† Number of prognostic factors 1 vs. 2 vs. 3.
‡ *p* values generated by Wald's test.

PSA nadir and gland volume

The PSA nadir achieved by dose level is depicted in Table 7. A PSA level ≤0.5 ng/mL was achieved in 60% of the low-dose group and in 73% of the high-dose group. The overall mean time to PSA nadir was 2.0 years. The mean time to nadir was 2.3 years for the low-dose group and 1.9 years for the high-dose group ($p = 0.167$). To look at the possible dependency or influence on PSA nadir value or time to nadir and initial gland volume, we determined their correlation as continuous variables. We used Pearson's correlation *t* test of gland volume at the time of the first implant and the PSA nadir value in relationship to the brachytherapy dose level. The distribution of gland volume at the first implant with the brachytherapy dose level is also shown in Table 7. No correlation was seen between the initial prostate gland volume and the PSA nadir value or time to nadir (i.e., larger gland volumes did not have a higher PSA nadir nor did it take longer to achieve nadir). In Table 7, we can see that, at present, no statistically significant difference results from achieving a given nadir value ($p = 0.257$) or time to nadir ($p = 0.220$) by brachytherapy dose level.

Table 6. 5-Year actuarial analysis of outcome by brachytherapy dose level

Dose level	Overall survival (%)	Cause-specific survival (%)	Disease-free survival (%)	Biochemical control (%)
Low	93	95	50	52
High	91	100	77	87
p	0.745	0.014*	<0.001*	<0.001*

* Statistically significant.

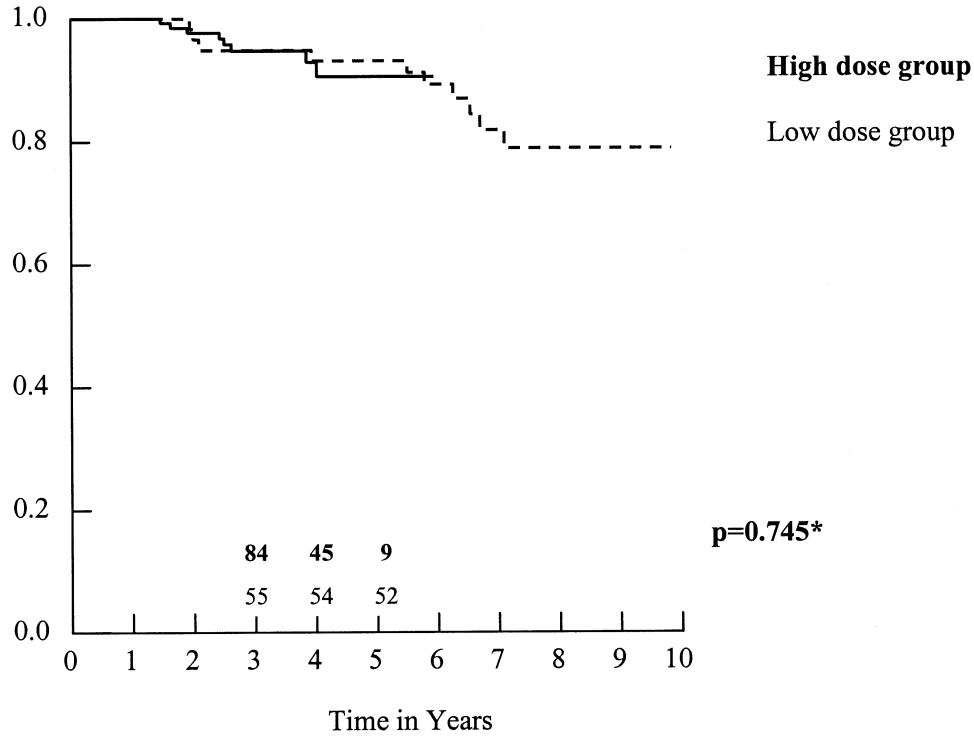

Fig. 3. Actuarial analysis of overall survival by brachytherapy dose level. *Generated from log–rank test.

Toxicity

The Radiation Therapy Oncology Group (RTOG) glossary was used to assess complications and was expanded to include toxicities common to brachytherapy. Grade 3 late urinary complications, mostly urinary strictures, were seen in 7 of 58 treated with 3 separate implants or the low-dose level and 3 of 149 treated with 2 implants or the high-dose level (Pearson chi-square 0.006). In the multivariate analy-

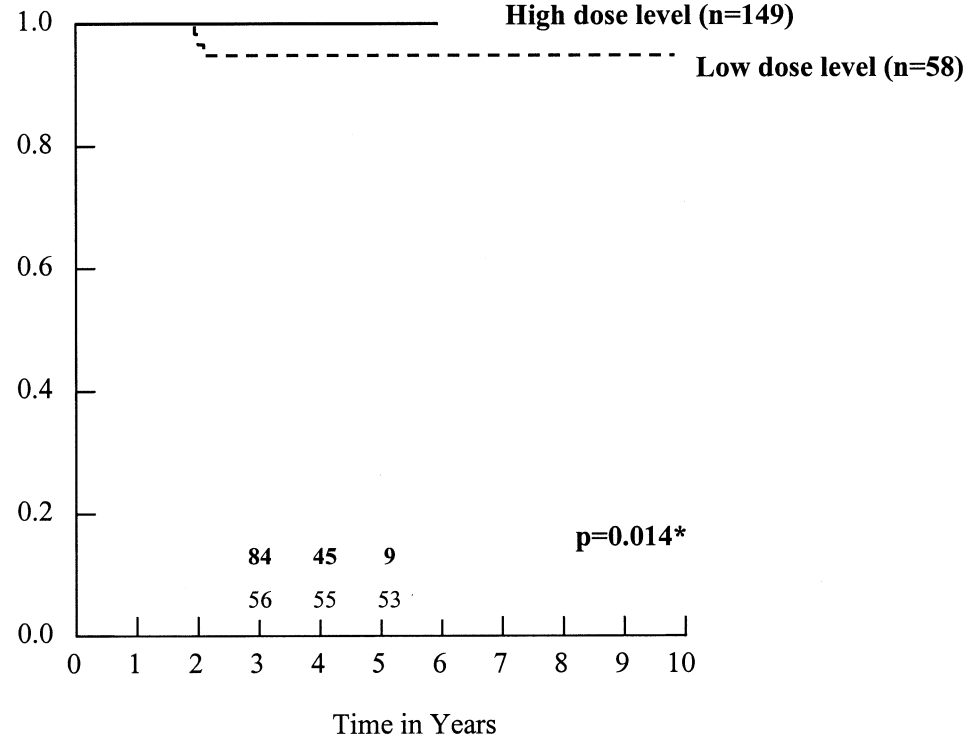

Fig. 4. Actuarial analysis of cause-specific survival by brachytherapy dose level. *Generated from log–rank test.

Table 7. Gland volume and nadir value by brachytherapy dose level

Characteristic	Low-dose level	High-dose level	p*
Nadir value (ng/mL)			0.257
≤0.5	35 (61)	109 (73)	
0.51–1.0	14 (25)	25 (17)	
1.1–1.9	5 (9)	9 (6)	
≥ 2.0	3 (5)	6 (4)	
Gland volume (cm^3)			0.496
< 30	20 (35)	38 (25)	
30–40	20 (35)	68 (46)	
>40	18 (30)	43 (29)	
Time to nadir (y)			0.220
<1.0	10 (17)	33 (22)	
1.0–1.9	17 (30)	46 (31)	
2.0–2.9	13 (23)	36 (24)	
≥ 3.0	17 (30)	34 (23)	

* *t* test analysis of continuous variable between dose levels; all statistically significant.

Data presented as the number of patients, with the percentage in parentheses.

sis of total urethral dose, dose per fraction, segment of the urethra, highest dose level, length of follow-up, and number of implants (2 vs. 3), only 3 implants correlated with an increased risk of stricture. The median time for late Grade 3 genitourinary stricture was 2.7 years for the low-dose group (3 implants) and 1.8 years for the high-dose group (2 implants). The 5-year actuarial rate of RTOG late genitourinary complications was 8% for Grade 3 and 0% for Grade 4. Only 1 patient developed Grade 3 urinary incontinence after transurethral resection of the prostate performed 3.8 years after RT. The corresponding 5-year actuarial rate for RTOG gastrointestinal complications was 0.5% for Grade 3 and 0.5% Grade 4 (1 patient developed an asymptomatic rectal ulcer). No patients experienced Grade 5 acute or late toxicity. Of the 100 patients who reported sexually potency before treatment, 46 of them developed impotence. The 5-year actuarial impotence rate was 51%, with impotence occurring at a median interval of 2.3 years (range 0.0–9.2). No difference in impotency rate was observed on the basis of the dose level (Pearson's chi-square $p = 0.475$).

DISCUSSION

The optimal treatment for patients with unfavorable prostate cancer remains undefined. During the past decade, several strategies directed to overcome radioresistance and/or large cell mass have been tested for tolerance and possible beneficial outcome. They include the addition of hormonal ablation before standard EBRT (9–11), EBRT with a particle beam boost (12–13), EBRT with a LDR permanent seed boost (14–15), 3D-conformal EBRT (16–17), and conformal HDR brachytherapy combined with EBRT (31, 32, 45–48). In the first two strategies, traditional treatment planning is hampered by the difficulty in defining the true extent of the target volume. As a result, it is difficult to deliver a high radiation dose to the prostate without potentially damaging the surrounding normal structures. Hormonal therapy was added to moderate doses of EBRT with the hope of an additive or synergistic effect to improve local control. Defining the target volume and surrounding structures is improved with 3D conformal planning, because this allows for the potential delivery of higher doses. Dose escalation is not always possible as a result of geometrically unfavorable lesions, inaccuracy of the target volume definition, and uncertainties related to dose delivery. Setup errors, both systematic and random, and internal organ motion and deformation are known to occur during an EBRT treatment course, which may decrease the ability to deliver the 3D conformal planned dose.

In 1991, a prospective clinical trial using EBRT combined with dose-escalating conformal HDR brachytherapy was started in an effort to overcome the drawbacks noted above with 3D-CRT and assess whether escalating radiation doses produces a better outcome. The smart seed technique, our TRUS-guided approach, offers continuous visualization of the prostate, rectum, bladder, and urethra during needle placement. This makes it possible to know the exact location of each needle relative to the target and surrounding structures. Our real-time optimization program selects the optimal needle positions, thereby guiding the physician on spatial needle location. Hence, the arbitrary decision-making process of where to place the needles is no longer determined be the operator's prior experience. Because the needle spatial selection and optimization is computer generated, we have termed this process the "HDR smart seed technique." We have demonstrated that during dose delivery, no shifting or displacement of the prostate takes place (30). As a result, accurate dose delivery to the planned target volume occurs. This provides a means not only to plan but also to deliver a highly conformal dose to the prostate.

In reference to dose escalation, we were able to dose escalate to very high doses. The improvement seen in BC by the higher dose group (87% at 5 years) has translated into a significant statistical benefit in cause-specific survival ($p = 0.014$). Although we recognize the imbalance of the 2 dose groups in terms of stage and pretreatment PSA and the shorter follow-up time for the high-dose group, in the multivariate Cox proportional hazards analysis of factors associated with biochemical failure (Table 5), none of these variables (stage, pretreatment PSA, number of prognostic factors, and follow-up time) were predictors of failure. On the other hand, the brachytherapy dose level was a strong predictor of failure in both the full model and the reduced model.

Another significant advantage is the radiobiologic benefit of HDR brachytherapy with respect to either LDR permanent seeds or 3D-CRT. The currently accepted low α/β ratios make our hypofractionated HDR boost ideal. With values for α/β as low as 1.2–1.5 for tumor control proba-

Table 8. Comparison of 5-year biochemical control rates for locally advanced prostate cancer with various forms of treatment

Study	Patients (*n*)	Mean PSA (ng/mL)	Median Gleason score	Median T stage	Follow-up (y)	Biochemical control (%)
EBRT + HDR						
William Beaumont Hospital	207	11.5	7	T2c	4.4	74
Swedish Hospital	29	10–20	6	T2a	3.8	84
	20	≥20	6	T2a	3.8	50
Götenborg University	50	4–20	WHO	T2b	3.7	78
Berlin University	82	14	WHO	T2	2.0	53*
EBRT + seeds						
Northwest Hospital	54	4–10	5–6	T2b	9.9	80
University Community	73	12	7	T2b	2.0	79*
Dekalb Medical Center	536	8.4	WHO	T2	3.3	76
3-D conformal EBRT						
Fox Chase ≥ 76 Gy	28	10–20	≤6	T2	4.9	75
Fox Chase ≥ 76 Gy	26	≥20	≤6	T2	4.9	30
University of Michigan, 69 Gy	>380	10–20	NR	NR	3.0	37
EBRT + neutrons						
Wayne State University	150	24.0	≥8	T3	NR	41*
EBRT + androgen deprivation						
EORTC	203	5–10	WHO	T3	3.8	81
RTOG 8531	477	NR	6–7	T3	4.5	53
Radical prostatectomy						
Northwestern University	116	31		T2b	7.0	46
Multiple institutions	298	10–20	5–7	T3	2.2	16*
University of Pennsylvania	239	10–20	5–6	T2c	3.2	36*

Abbreviations: PSA = prostate-specific antigen; EBRT = external beam radiotherapy; HDR = high dose rate; 3D = three-dimensional; EORTC = European Organization for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group; WHO = World Health Organization; NR = not reported.

* <5 years.

bility (36–39), the BED with our brachytherapy hypofractionation is considerably higher, in the range of 136.3 Gy (Table 1). This BED would be extremely difficult to achieve even with intensity-modulated radiotherapy (IMRT) (26). No experience exists with LDR permanent seeds in a dose-escalation setting. The current LDR-boost dose used in the United States was empirically derived from past experience. It is not known whether higher LDR doses are more effective and/or can be safely delivered. Our data demonstrate an incremental beneficial effect on BC, disease-free survival, and, most importantly, cause-specific survival at the higher dose levels with low morbidity. Although it is unlikely that with intensity-modulated radiotherapy one can deliver BEDs of the order of 136.3 Gy or that dose-escalation trials with permanent seeds will be activated, our dose-escalation trial will continue until we reach the goal of the study. We have currently treated 38 patients with 11.5 Gy × 2, which has a BED of 136.3 Gy (39).

With respect to LDR permanent seed implantation as a boost, the accuracy of spatial individual seed placement (as determined by preimplant planning) is decreased compared with HDR brachytherapy. The rigid conduit of the stainless steel HDR needle provides a more robust system to place and move the HDR seed inside the tissues. Spatial HDR seed position and orientation are identical to the computer plan. This is not the case for LDR seed placement for which the operator loses control once the seed is deposited in the tissue, thereby downgrading the intended original plan. Because the treatment is delivered in a few minutes, the issues of swelling owing to trauma, hematoma, and/or edema and their impact on dose distribution with time are irrelevant to the HDR technique whether used as a boost or as monotherapy (49). The same can be said for the effective radiobiologic dose. No changes in dose rate or volume, nor repopulation effects or recovery of sublethal damage, occur during the short HDR treatment time. Last but not least is the advantage of not leaving the patient radioactive after brachytherapy. As documented in our report on HDR monotherapy (46), the most significant factor for the patient, spouse, or family in selecting this therapy over LDR permanent seed therapy was that once the treatment was completed, the patient was no longer radioactive, avoiding the need to comply with radiation safety rules and regulations.

Despite the poor prognostic factors in our patients, the overall actuarial BC rate achieved at 5 years was 74%. Additional improvement, up to 87% in BC at 5 years, was seen for those patients in the high-dose group. The mean dose for patients with BC was 83.2 Gy vs. 75.6 Gy for those with biochemical failure. In addition, the 5-year rate of local failure (by DRE) and metastatic disease (by radiography) was 8% and 6%, respectively. These findings confirm that the "smart seed technique" is an effective method of delivering high doses of radiation and that higher radiation doses

do indeed appear to improve outcome. This is in agreement with our original hypothesis.

Several institutions have published encouraging results using EBRT with a brachytherapy boost for patients with good to poor prognostic factors (Table 8). Table 8 also lists 16 selected series that used other treatment techniques for locally advanced prostate cancer. They included EBRT+HDR boost, EBRT+seeds, EBRT+neutrons, EBRT+androgen deprivation, 3D conformal EBRT, and radical prostatectomy. The 5-year BC rates varied markedly among these 16 series. The wide variation in results was partially due to the selection of different risk groups and different biochemical failure definitions. When examining the larger series in Table 8 (containing >100 patients), only the study from the European Organization for Research and Treatment of Cancer by Bolla *et al.* (10) demonstrated a higher 5-year BC rate than did our trial with EBRT and a hypofractionated HDR brachytherapy boost. Considering that the total number of patients and the mean follow-up time in our study and that of Bolla *et al.* were the same and that the study by Bolla *et al.* (10) used hormonal therapy (goserelin) for 3 years, the 5-year interval might not be as representative, because many of their patients were still receiving treatment during this follow-up period. From the patients' perspective, their treatment time took 3 years with the Bolla program vs. 5 weeks in our study. In addition, the 100% impotency rate and other significant side effects, as well as the financial impact of 3 years of hormonal therapy, should not be underestimated.

This treatment approach has been well tolerated. When compared with other series, particularly dose-escalation studies with 3D-CRT, the toxicity has been acceptable (16, 17). The most common toxicity was sexual impotence followed by urethral strictures. Of the 207 patients, 10 developed urethral strictures, 3 patients with Grade 1 and 7 patients with Grade 3. Of these 10 strictures, 7 were in the 3-implant group ($n = 58$) and 3 in the 2-implant group ($n = 149$). On multivariate analysis for factors predicting for stricture, only 3 vs. 2 implants correlated with an increased risk of stricture. No Grade 5 acute or late toxicities occurred. Of the 100 patients with known potency status before treatment, 46 (51% actuarial rate) developed impotence at a median interval of 2.3 years. No difference in impotency was observed according to dose level (Pearson's chi-square $p = 0.475$).

CONCLUSION

Pelvic EBRT interdigitated with TRUS-guided real-time conformal HDR brachytherapy boost is both a precise dose delivery system and an effective treatment modality for patients with large-volume prostate cancer. An incremental beneficial effect on BC and, most importantly, in cause-specific survival according to the brachytherapy dose level was demonstrated in this report. When coupled with the advantage that the patient is not radioactive after brachytherapy and the low risk of complications, these results make this approach most appealing. Patient accrual at 11.5 Gy × 2 will continue at William Beaumont Hospital.

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