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# Long-term outcomes and prognostic factors in patients treated with intraoperatively planned prostate brachytherapy

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**ABSTRACT**

**PURPOSE:** Evaluate outcomes and prognostic factors in men with localized prostate cancer.
**METHODS AND MATERIALS:** A total of 3760 patients have undergone prostate seed implantation at our institution. This review is of our initial 304 consecutive patients treated before January 30, 2001. A total of 124 patients were treated with $^{125}$I implant monotherapy and 180 with $^{103}$Pd implant combined with 45-Gy external beam radiation therapy.
**RESULTS:** The median followup was 10.3 years. A 10-year biochemical control for low risk (LR) was 98% , intermediate risk (IR) 94%, high risk (HR) 78%, and HR with one HR factor 88% ($p < 0.001$); cause-specific survival was 99%, 98%, and 84% for LR, IR, and HR, respectively ($p < 0.001$); No significant difference in outcome was seen for LR and IR patients ($p > 0.3$). On multivariate analysis, only pretreatment PSA, Gleason score, and T-stage were significant for biochemical control. Most biochemical failures occurred within 5 years (93%).
**CONCLUSIONS:** With a minimum followup of 10 years, results are excellent and do not differ for LR or IR prostate cancer patients. HR patients are a very heterogeneous group, and excellent results can still be achieved for HR patients with only one HR feature. 

*Keywords:* External beam radiation therapy; Brachytherapy; Prostate-specific antigen; Biochemical control; Overall survival; Toxicity; Outcomes; Prostate cancer

## Introduction

Randomized studies comparing different treatment modalities in the management of prostate cancer are limited. Most published experience with low-dose-rate (LDR) prostate brachytherapy relies on the retrospective analysis from select institutions (1–7). This is one of the largest brachytherapy series with a median followup longer than 10 years.

The purpose of this analysis was to analyze a single institution's long-term brachytherapy outcomes in patients treated a minimum of 10 years ago and further define prognostic risk factors for localized prostate cancer treated with intraoperative brachytherapy alone or combined with external beam radiation therapy (EBRT).

## Methods and materials

A total of 3760 patients have undergone an intraoperative LDR prostate seed implant by a Florida Radiation Oncology Group physician at our institution. Patient and treatment data were prospectively collected in our institutional review board–approved database. Patients received brachytherapy with or without EBRT and/or androgen suppression (AS). Patients who had radiologic or pathologic evidence of metastatic or lymph node–positive diseases were not included in this database. For this analysis, only patients treated before January 10, 2001 were selected. Patients lost to followup ($n = 34$) or treated for

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salvage ($n = 17$) for local recurrence after prior EBRT were excluded. A total of 304 patients were available for review.

All patients were evaluated initially by a thorough history and physical examination (including digital rectal examination) followed by routine laboratory studies, including pelvic computed tomographic scans, bone scans, serum prostate-specific antigen (PSA) levels, and Gleason score (GS) determined by needle biopsy. All patients were restaged according to seventh edition of the American Joint Committee on Cancer Staging System. Patients were stratified further into low-risk (LR), intermediate-risk (IR), and high-risk (HR) groups as per National Comprehensive Cancer Network (NCCN) guidelines (8).

### *Treatment*

All patients were implanted using an interactive ultrasound (US)-guided transperineal technique. Under general anesthesia, patients were placed in the dorsal lithotomy position. Foley catheter was placed and temporarily clamped. Under transrectal US guidance, the prostate position was determined on both transverse and sagittal views. The prostate was then contoured on successive 5-mm cuts, and the prostate volume was determined planimetrically. Two 18-gauge needles were placed in the center of the prostate to help immobilize the gland. Needles were then placed evenly spaced around the periphery of the gland at the largest transverse image. Needles were spaced approximately every 0.7–1 cm under real-time transverse and longitudinal US guidance. Special attention was given to avoid the rectum, bladder, and urethra. Images of the prostate gland were then entered into the Variseed (Varian Medical Systems, Inc., Palo Alto, CA) planning computer system at 5-mm intervals. All critical anatomies, including the prostate, rectum, urethra, and seminal vesicle, were contoured on each slice. All *actual* needle positions were then entered into the planning system as well. Position and shape of all structures were then reviewed compared with real-time US feed on both the axial and sagittal planes. Using real-time US guidance in the sagittal plane, radioactive seeds accounting for 75% of the activity were then placed through the needles with a Mick applicator. Central needles were then placed using both transverse and sagittal information, carefully evaluating the position of the urethra. Different seed arrangements were then evaluated to optimize the dosimetry. Once an ideal solution is found, the inner seeds are placed under US guidance. Intraoperative dosimetry report is complete as soon as the last seed is positioned. Prostate $D_{90}$ 100% was 160 Gy for iodine implants alone and 100 Gy for palladium implants followed by EBRT. One month after implant, postoperative dosimetry is done. Three dimensional (3D)–based EBRT was done 8 weeks after the implant. EBRT was 3D based because they were treated before 2001 and subsequently the start of intensity-modulated radiation therapy at our institution.

Most LR patients were treated with brachytherapy alone, and all IR and HR patients received brachytherapy and external radiation. When used, EBRT was done based on 3D planning to the prostate and seminal vesicles alone. Total EBRT dose was 45 Gy in 1.8-Gy fractions.

### *Data analysis*

All dosimetric calculations were done on the date of implant and at 1 month after the implantation. Dates for all events were recorded based on the date of the finding by PSA, imaging, or physical examination. All possible attempts were made to determine the cause of death. This information was available for most cases. If the cause of death was not available, patients with known metastatic disease were considered to have died of prostate cancer. Biochemical failure was based on current nadir plus 2 ng/mL definition, start of AS regardless of PSA, or a clinical failure. Distant metastases were based on imaging findings with or without biopsy. Kaplan–Meier curves and Cox univariate and multivariate analyses (MVA) were used for all statistical calculations using Systat Software Inc., Chicago, IL, and a two-sided $p$-value lower than 0.05 was considered significant.

## Results

A total of 3760 patients have been treated with low-dose prostate brachytherapy in our program since 1997. Our initial 355 consecutive patients, all treated before January 10, 2001, were included. Of these 355 patients, 17 patients treated with brachytherapy for salvage and 34 patients lost to followup were excluded. A total of 304 patients were used for the current analysis. The median followup for our patient population was 10.3 years (range, 6 months–14 years). Patient characteristics are described in Table 1. AS was used because of the urologist preference or gland downsizing. Most patients had AS for 3 months or for shorter duration. As per our guidelines, HR patients were kept on AS for 9–12 months. Only 16 patients of the 247 treated with AS received it for more than 1 year.

### *Outcomes by risk group*

Outcomes were stratified by risk groups using the NCCN stratification. The results for overall survival (OS), cause-specific survival (CSS), freedom from distant metastasis (FDM), and biochemical control (BC) are summarized in Table 2.

Interestingly, for the LR and IR patients, no difference was seen in survival ($p = 0.8$), CSS ($p = 0.3$), FDM ($p = 0.6$), or BC ($p = 0.5$).

### *Analysis of risk factors*

In univariate analysis, GS, T-stage, and PSA were significant for OS, CSS, FDM, and BC ($p < 0.002$). Although perineural invasion (PNI) was significant for FDM and