

Long-term tumor control after brachytherapy for base-of-prostate cancer

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Abstract

Purpose: To evaluate the outcomes of patients presenting with cancer at the base of the prostate after brachytherapy as monotherapy.

Material and methods: We retrospectively reviewed the medical records of all patients who had undergone transperineal ultrasound-guided implantation with ¹²⁵I or ¹⁰³Pd seeds as monotherapy between March 1998 and December 2006, at our institution. A minimum follow-up interval of 2 years was required for inclusion in our analysis. Dosimetry was assessed using computed tomography 30 days after the implant. Treatment failure was defined as the appearance of biopsy-proved tumor after seed implantation, radiographic evidence of metastases, receipt of salvage therapy, or elevation of the prostate-specific antigen level beyond the nadir value plus 2 ng/mL.

Results: With a median follow-up interval of 89 months (range 25-128 months), all 52 of the identified patients had no evidence of disease progression or biochemical failure. The mean number of cores sampled at the prostate base was 2.84 (median 2); Gleason scores assigned at central review were 6-8 in all patients. Of the 30 patients (58%) for whom dosimetric data were available at day 30, the median V100 values of the right and left base were 92.0% and 93.5%, respectively, and the median D90 values of the right and left base were 148 Gy and 151 Gy, respectively.

Conclusion: Permanent prostate brachytherapy as monotherapy results in a high probability of disease-free survival for men with cancer at the base of the prostate.

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Purpose

Low-dose-rate prostate brachytherapy has gained favor as an effective treatment for clinically localized prostate cancer over the past two decades [1]. The substantial increase in the use of low-dose-rate brachytherapy as definitive treatment necessitates ongoing investigation to ensure its adequacy and to establish criteria for identifying appropriate candidates for such treatment. The American Urological Association found that monotherapy with permanent interstitial low-dose-rate brachytherapy is an effective treatment for low-risk prostate cancer and that no advantage is gained from supplementing brachytherapy with external beam radiation therapy [2].

The appropriateness of brachytherapy as monotherapy for tumors in the base of the prostate has been questioned, however, because of concerns regarding adequate dose coverage [3]. The base of the prostate is adjacent to the bladder neck, which should be spared when placing brachytherapy seeds. Moreover, the incidence of seed displacement after

permanent brachytherapy seed implantation is highest when those seeds are placed near the prostate base [4]. The margin of error is lower for seed placement near the base of the prostate, because dosimetric contribution is limited to the caudal seeds within the prostate gland. Problems with attaining adequate dose coverage have resulted in local tumor recurrence, particularly with the use of older brachytherapy methods, and generally less-favorable outcomes [5-8]. Previous suggestions that brachytherapy should be supplemented with external beam radiation to fully treat tumors at the base of the prostate have not been supported by a survey of practice patterns [3, 9]. We hypothesize that disease control after use of a monotherapy approach with brachytherapy is sufficient without the use of supplemental external radiation therapy for patients presenting with base-of-prostate cancer. The purpose of this study was to evaluate the overall survival and patterns of treatment failure of men who presented with this disease and underwent brachytherapy as the sole form of radiation therapy.

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Material and methods

We retrospectively reviewed the medical records of all patients undergoing brachytherapy as monotherapy with curative intent for newly diagnosed prostate cancer at The University of Texas M D Anderson Cancer Center between March 1, 1998, and December 31, 2006, under a protocol approved by the institutional review board. Of the 301 such patients we identified, 122 were excluded for having biopsy samples that had not been labeled with their location of origin (the region of the prostate from which they were obtained, i.e., being labeled as coming from the right or left lobe of the prostate instead of from the base, middle or apex). Of the remaining 179 patients who did have biopsy samples labeled with their location of origin, 117 had disease limited to the apex, middle or lateral prostate, and 62 patients had disease involving the base of the prostate. Of those 62 patients with cancer at the base of the prostate, 52 had a minimum follow-up interval of 2 years, which was required for inclusion in our study cohort. Of the 10 patients not included in this analysis, 3 patients died of causes unrelated to the prostate cancer within 2 years after their treatment and had no evidence of prostate-specific antigen (PSA) biochemical progression at the time of death.

Patient evaluation

For all 52 patients meeting the eligibility criteria, the prostate cancer had been clinically staged using medical history, physical examination (including digital rectal examination), and serum PSA measurements. T status was assigned by digital rectal examination and was clinical T1c-T2b in all cases. Clinical disease stage was assigned according to the 2002 American Joint Committee on Cancer staging system [10]. Chest X-rays, bone scans or computed tomography (CT) scans of the pelvis were obtained when clinically indicated.

Pathologic confirmation of the diagnosis of prostate adenocarcinoma was obtained for all patients after ultrasound-guided biopsy. The number of biopsy samples acquired ranged from 6 to 18 cores per patient (median 7 cores; mean

8.82 cores). The median number of positive cores throughout the entire prostate volume was 2 per patient (mean 2.47). Each patient had at least 1 core that was positive for cancer at the base of the prostate, with some having as many as 3 positive cores. Most patients (41/52; 79%) had unilateral single-biopsy-core-positive disease; 8 (15%) had bilateral disease, and 3 (6%) had unilateral multiple-core-positive disease. In addition to disease at the base, 31 patients (60%) also had disease in the middle, apex, or lateral regions of the prostate.

Because of well-documented inconsistencies in assigning Gleason grades, specimens for all cases originating from outside institutions had been centrally reviewed by the Department of Pathology of MD Anderson Cancer Center, which assigned a Gleason score by the sum method before treatment plans were formulated [11]. Gleason scores were determined to be 6-8 for the entire cohort. The median patient age at the date of diagnosis and seed implantation was 66 years.

Treatment

Twenty patients (38%) received androgen deprivation therapy for cytoreduction before brachytherapy. Each of those 20 patients was treated with a luteinizing hormone-releasing hormone agonist and had completed cytoreductive therapy before the implant. Of those 20 patients, none was given androgen deprivation as adjuvant treatment, and none received further androgen deprivation after the date of the implantation.

All 52 patients received brachytherapy with curative intent. In 37 men (71%), treatment planning was done a few weeks before the procedure, whereas treatment planning for the remaining 15 men (29%) was done at the time of the procedure. The treatment volume included the sonographically defined prostate plus a discretionary margin of 3-5 mm, except posteriorly. Only the proximal portions of the seminal vesicles were included in the treatment volume. Standard brachytherapy treatment planning software (VariSeed 7.1, Varian Medical Systems, Milpitas, CA) was used to calculate a three-dimensional source matrix with a prescribed

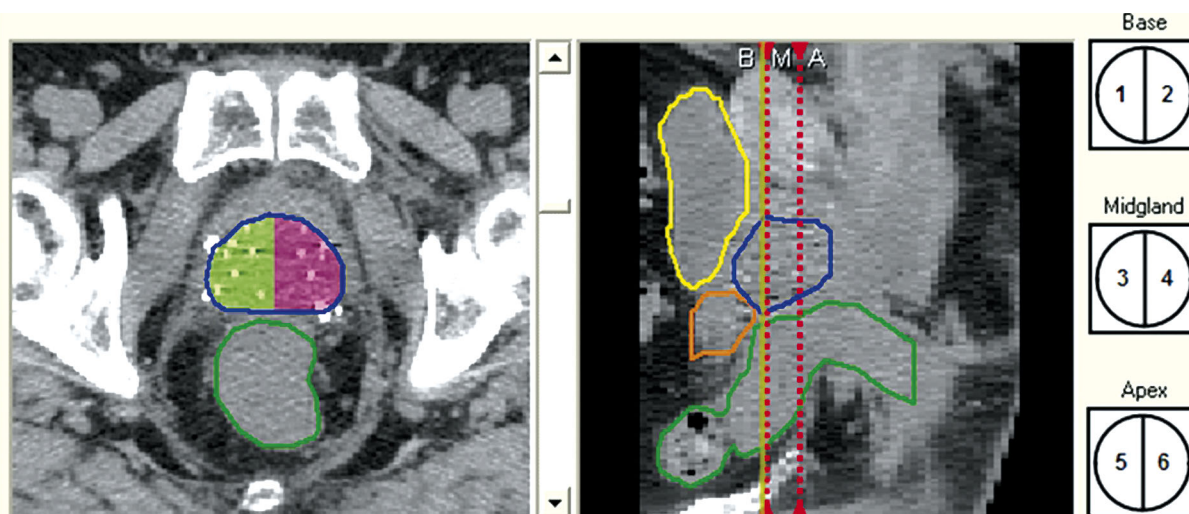


Fig. 1. The sector analysis tool was used to divide the prostate into six segments (left and right apex, middle, and base) in order to be consistent with prostate biopsy locations

dose of 145 Gy to the planning target volume. Sources were distributed in a modified peripheral loading pattern across the target volume.

The implantation procedure was performed on an out-patient basis using preloaded 18-gauge needles. Needle insertion and seed placement were performed under transrectal sonographic guidance using a transperineal template [12]. Needles were loaded with permanent ¹²⁵I sources (0.391 mCi/seed; 51 patients) or ¹⁰³Pd sources (1.547 mCi/seed, 1 patient). Mean total activity, calculated as the number of implanted seeds multiplied by the seed strength, was 39.421 mCi per patient. Upon completion of the procedure, each patient underwent an immediate CT scan to evaluate prostate coverage, and 42 patients returned 30 days after the implantation for a day 30 dosimetric evaluation.

A sector analysis tool was used to divide the prostate into six segments (left and right apex, middle, and the base) (Fig. 1). Post-implant dosimetric day 30 parameters using sector analysis at the right and left base of the prostate were analyzed in the treatment planning system. The dose parameters evaluated included the V100 (the percentage of the target volume receiving 100% of the prescribed dose) and the D90 (the minimum dose received by 90% of the evaluated target volume) by Gleason score. The medical records of 12 patients (19%) were destroyed by water damage during flooding in the institution in 2001, and an additional 10 patients (16%) had immediate post-implant dosimetry, but not day 30 dosimetry. Therefore, sector analysis dosimetric data were available for evaluation for only 30 (58%) of the 52 patients.

Follow-up

Patients were monitored by physical examination (including digital rectal examination) and serum PSA measurements at 4-month intervals during the first year after the implantation, at 6-month intervals during years 2-5, and yearly thereafter. Patients who were unable to return to MD Anderson were asked to have their laboratory results sent to the institution and were also asked to complete tumor registry questionnaires annually by mail that included questions on any known recurrence of or further treatments for prostate cancer. Treatment was considered to have failed if the patient had positive biopsy findings, radiographic evidence of local disease progression or distant metastases, salvage therapy or elevated PSA levels (defined as the nadir PSA level plus 2 ng/mL). Patients who showed no evidence of treatment failure at the time of our analysis were classified as having no evidence of disease. Five and ten-year survival estimates were calculated by the Kaplan-Meier method.

Results

The median age at treatment was 66 years (range 50-78 years). Pretreatment tumor grade, clinical stage and PSA levels are summarized in Table 1. At a median follow-up time of 89 months (range 25-128 months), all 52 patients were alive without biochemical or clinical progression of disease after brachytherapy, and the median PSA measurement was 0.1 ng/mL (range 0.01-2.30 ng/mL). The median biochemi-

cal follow-up time (i.e., from the date of seed implantation to the last known PSA measurement) was 69 months (range 25-124 months). The mean and median PSA levels for all patients at that time were 0.3 and 0.1, respectively (range 0-2.3 ng/mL). Biochemical disease-free survival curves for 62 patients (including the 10 with less than 2 years of follow-up) at their last known PSA measurement are shown in Fig. 2.

The day 30 dosimetric data for all 30 evaluable patients indicated that the median V100 values of the right and left base were 92.0% and 93.5%, respectively. The median D90 values of the right and left base were 148 Gy and 151 Gy, respectively, demonstrating adequate dose to the prostate volume. For sector analysis, 36 sectors at the base of the prostate had Gleason score 6 (28 sectors), 7 (7 sectors), or 8 (1 sector) disease. For the 28 sectors presenting with Gleason score 6 disease, the median right and left base V100 values were 89% and 94%, respectively, and the median D90 val-

Table 1. Pre-treatment clinical characteristics

Data	Number of patients	% of patients
Gleason grade		
6	52	83.9
7	9	14.5
8	1	1.6
Clinical stage		
T1c	43	69.4
T2a	16	25.8
T2b	3	4.8
Serum prostate-specific antigen (ng/mL)		
0.0-4.0	12	19.4
4.1-10.0	49	79.0
10.1-15.0	1	1.6
Range	0.6-12.7	
Median	5.30	
Mean	5.37	

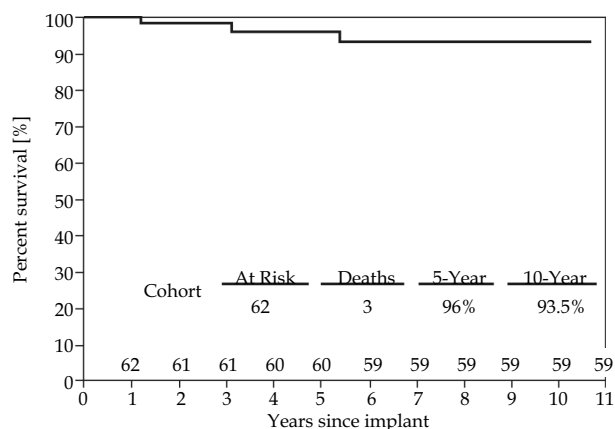


Fig. 2. Biochemical disease-free survival curves for 62 patients at their last PSA measurement (including the 10 with less than 2 years' follow-up)

ues were 143 Gy and 152 Gy, respectively. For the 26 sectors that did not have any biopsy-positive disease in the right or left base sectors, the median right and left base V100 values were 97% and 92%, respectively, and the median D90 values were 165 Gy and 150 Gy, respectively.

Discussion

This retrospective review of monotherapy for base-of-prostate cancer at MD Anderson Cancer Center suggests that brachytherapy as the sole form of radiation therapy can result in excellent outcomes. Our findings indicate that permanent ^{125}I or ^{103}Pd brachytherapy can result in a high probability of disease-free survival for patients with clinical T1c-T2b (2002 AJCC) adenocarcinoma at the base of the prostate gland. The lack of treatment failure among the 52 patients in this study provides further evidence, albeit indirect, that adding external radiation therapy is unnecessary when adequate doses of radiation are delivered to the prostate by brachytherapy.

Brachytherapy has been shown to be appropriate as the sole radiation-based treatment for patients with organ-confined, low-risk prostate adenocarcinoma [2, 13-17]. Studies with 5- and 12-year follow-up intervals have confirmed the efficacy of this approach and have further demonstrated that combination therapy is superfluous in low-risk disease [18, 19]. Indeed, when patients are stratified in terms of their pretreatment PSA levels, biochemical progression-free survival curves are practically identical between those treated with high-quality brachytherapy alone and those treated with brachytherapy plus supplemental external beam radiation therapy [20-22]. Our results are consistent with and strengthen these findings, as our cohort comprised mainly men with organ-confined, low-risk disease that was present specifically at the base of the prostate. Our analysis supports these and other studies demonstrating the adequacy of low-dose-rate brachytherapy as the primary treatment modality for prostate cancer; our findings further imply that the positive outcomes in these studies extend to men with tumors at the base of the prostate.

Currently, some clinicians opt to treat low-risk disease at the prostate base with combination therapy, which often consists of a permanent seed implant and external beam radiation to the prostate and periprostatic tissue [23]. Findings from early experience with brachytherapy suggested that it may not provide the necessary dose coverage required for successful outcomes [8]. This experience, however, involved the use of an open laparotomy for men with more advanced disease and occurred before the PSA era. More recent findings generated with improved imaging methods and better treatment techniques have shown that adequate dosing can be attained with permanent interstitial brachytherapy [2, 18, 24]. Our study further supports the notion that adequate coverage of the base can be achieved with a permanent implant using modern imaging and implantation techniques, resulting in excellent outcomes.

Although increasing numbers of patients with low-risk carcinoma are being treated with brachytherapy [1], some clinicians avoid using brachytherapy as monotherapy when treating patients with known disease at the base of the prostate [3]. Outcomes after brachytherapy vary among

physicians, as does experience with the implant procedure [25-27]. Permanent interstitial brachytherapy requires a skilled clinician and careful attention to the base of the prostate throughout seed implantation, with continuous visualization of the prostate/bladder interface via sagittal imaging to ensure proper needle position and subsequent source placement. This process is essential for ample dosing of the entire prostate tumor volume and for maintaining the integrity of surrounding vital structures.

Conclusions

In conclusion, brachytherapy can produce excellent outcomes for men presenting with cancer at the base of the prostate gland. Clinicians can be reassured that adequate dose coverage of the prostate base can be achieved, and supplemental external beam radiation is not required.

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