

COMPARING PSA OUTCOME AFTER RADICAL PROSTATECTOMY OR MAGNETIC RESONANCE IMAGING-GUIDED PARTIAL PROSTATIC IRRADIATION IN SELECT PATIENTS WITH CLINICALLY LOCALIZED ADENOCARCINOMA OF THE PROSTATE

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ABSTRACT

Objectives. To determine whether high-dose radiation delivered to a subvolume of the prostate gland (peripheral zone) using intraoperative magnetic resonance imaging-guided brachytherapy provided comparable 5-year prostate-specific antigen (PSA) control rates to radical prostatectomy (RP) in select patients compared prospectively but in a nonrandomized setting.

Methods. Between 1997 and 2002, 322 and 196 patients with clinical Stage T1c, PSA less than 10 ng/mL, biopsy Gleason score 3 + 4 or less, and without perineural invasion underwent RP or intraoperative magnetic resonance imaging-guided brachytherapy, respectively, and had a 2-year minimal follow-up. Cox regression multivariable analysis was used to evaluate whether the initial therapy, pretreatment PSA level, biopsy Gleason score, percentage of positive biopsies, or prostate gland volume were predictors of the time to post-therapy PSA failure. PSA failure was estimated using the Kaplan-Meier method and defined using the American Society for Therapeutic Radiology Oncology consensus definition.

Results. Only the percentage of positive prostate biopsies ($P_{\text{Cox}} = 0.02$) was a significant predictor of the time to post-treatment PSA failure. However, the distribution of this parameter between RP and brachytherapy-treated patients was not significantly different ($P_{\text{chi-square}} = 0.25$). The initial therapy did not predict for the time to post-therapy PSA failure ($P_{\text{Cox}} = 0.18$). The 5-year estimate of PSA control was 93% versus 95% ($P_{\text{log-rank}} = 0.16$) for the RP and brachytherapy patients, respectively.

Conclusions. Despite only partial prostatic irradiation using intraoperative magnetic resonance imaging-guided brachytherapy, similar 5-year estimates of PSA control were found for both brachytherapy and RP-managed patients. UROLOGY 62: 1063–1067, 2003. © 2003 Elsevier Inc.

The introduction of serum prostate-specific antigen (PSA) determination has changed the presentation of prostate cancer worldwide. Pa-

tients now present at a younger age, with lower grade disease, and are more likely to have organ-confined cancer on pathologic evaluation of the radical prostatectomy (RP) specimen.¹ This migration toward smaller volume disease raises the possibility of more tailored therapy.

Brachytherapy is the therapeutic delivery of radiation to a diseased site by the insertion, either temporarily or permanently, of sources containing radioactive material. The current method of prostate brachytherapy in the United States commonly uses transrectal ultrasonography to guide radioactive seed placement.² Using this approach, the goal is to deliver 100% of the prescription dose to the entire prostate gland.

This work was supported in part by research grant R01: AG 19513-01.

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Submitted: May 19, 2003, accepted (with revisions): July 7, 2003

In the past 6 years, a real-time intraoperative magnetic resonance imaging (IMRI)-guided prostate brachytherapy technique³ that uses both MRI^{4,5} and dose-volume histogram analysis performed in real time intraoperatively has been designed and implemented. Using this technique, regions of the prostate gland (ie, the peripheral zone, transition zone, periurethral zone, and anterior base) can be delineated using MRI, providing the opportunity to focus the radiation dose delivery to specific zones of the prostate gland based on the likelihood of cancer presence using the individual patient's pretreatment clinical characteristics. In particular, several investigators have identified a subset of patients using the pretreatment PSA level, biopsy Gleason score, and clinical T stage in whom the presence of cancer in the anterior base is rare.^{6,7}

A direct correlation with the development of acute urinary morbidity and brachytherapy dose to the entire prostate gland has been documented.⁸ Given that the IMRI technique limits the dose to the anterior base and the transition zone anterior to the urethra to less than 100% while delivering 100% or more of the prescription dose to the peripheral zone of the prostate gland, this approach has permitted the treatment of patients with large prostate glands (greater than 60 cm³) with a resultant low risk of self-limited acute urinary retention⁹ and no need for neoadjuvant hormonal therapy to achieve prostate gland shrinkage. However, such an approach for patients with moderate prostate gland enlargement intentionally does not treat a portion of the prostate gland to a high dose. Therefore, whether treating part of the prostate gland in these patients to a high dose led to a decrement in PSA outcome compared at 5 years to the outcome of patients treated with maximal therapy (ie, RP) was the subject of this study.

MATERIAL AND METHODS

PATIENT POPULATION, STAGING, AND TREATMENT

Between 1997 and 2002, 634 patients with prostate cancer underwent RP (n = 406) or IMRI-guided prostate brachytherapy (n = 227) at the Brigham and Women's Hospital. All patients had clinical Stage T1c (American Joint Commission on Cancer staging system, 2002),¹⁰ PSA level less than 10 ng/mL, and biopsy Gleason score of 3 + 4 or less and did not have perineural invasion on biopsy. Of these patients, 322 from the RP group and 196 from the IMRI group had 2 years of minimal follow-up.¹¹ No patient received neoadjuvant or adjuvant androgen suppression or radiotherapy. Patients who had previously undergone transurethral resection of the prostate, had urinary daytime frequency of less than every 2 hours and/or nocturia exceeding 4 hours that was not medically correctable with an alpha_{1A} blocker were not eligible for brachytherapy. However, patients who had undergone previous abdominal perineal resection were not excluded. The IMRI-guided technique does not require a rectum to guide the source placement, because the imaging apparatus is extrinsic to the patient.¹² All patients provided institutional review

board-approved informed consent. All biopsy slides were reviewed by a single genitourinary pathology group at the Brigham and Women's Hospital, and all patients underwent at least a sextant biopsy. The prostate gland volume was determined in each case using a 1.5-Tesla staging endorectal MRI study and an ellipsoid approximation, where prostate gland volume = $\pi/6 \times \text{length} \times \text{width} \times \text{height}$. The median age of the RP and IMRI-brachytherapy patients at initial therapy was 60 years (range 44 to 75) and 62 years (range 49 to 79), respectively. Table 1 lists the pretreatment clinical characteristics of the RP and IMRI brachytherapy cohorts. The pretreatment medical management,³ intraoperative magnetic resonance unit,¹³ and IMRI technique¹⁴ have been previously described and mandated that the end of operating room dosimetry provided a V₁₀₀ (target volume receiving 100% of the prescription dose) of at least 100%.

FOLLOW-UP

For the 322 RP and 196 brachytherapy patients with a minimal follow-up of 2 years, the median follow-up was 4.2 and 3.95 years, respectively. Generally, serum PSA measurement and digital rectal examination were performed every 3 months for 2 years, every 6 months for 3 additional years, and annually thereafter. The median number of PSA values per patient was 14 (range 8 to 26). PSA failure was defined using the American Society for Therapeutic Radiology and Oncology consensus criteria.¹⁵ PSA determinations were made no more frequently than every 3 months and three consecutive increments were necessary to constitute a rise to avoid overcalling PSA failure in the brachytherapy patients owing to the PSA bounce phenomenon.¹⁶ The PSA level was not considered detectable postoperatively until it exceeded 0.2 ng/mL. No patient died of prostate cancer during the study period, and no patient was lost to follow-up.

STATISTICAL ANALYSIS

Cox regression multivariable analysis¹⁷ was performed to evaluate the ability of the treatment received (RP versus brachytherapy), pretreatment PSA level (continuous), percentage of positive biopsies (continuous), prostate gland volume (continuous), and biopsy Gleason score (continuous but could only take on integer values from 2 to 7 inclusive) to predict the time to post-treatment PSA failure. In addition, Cox regression analysis was performed to evaluate the ability of the categorical variables of initial treatment received (RP versus brachytherapy), PSA level (4 ng/mL or less versus greater than 4 to 10 ng/mL), biopsy Gleason score (3 + 4 versus 6 or less), percentage of positive biopsies (34% or more versus less than 34%), and prostate gland volume (45 cm³ or more versus less than 45 cm³) to predict the time to post-treatment PSA failure. The cut points for the categorical variables were selected on the basis of data suggesting their predictive value from previously reported studies for PSA, biopsy Gleason score, and percentage of positive biopsies.¹⁸ The cut point for prostate gland volume was selected according to the currently accepted maximal prostate gland volume recommended by the American Brachytherapy Society for transrectal ultrasound-guided brachytherapy.¹⁹

A chi-square metric was used to evaluate whether the distribution in age, PSA level, biopsy Gleason score, and percentage of positive prostate biopsies at the time of treatment were significantly different between the RP and brachytherapy patients. Estimates of PSA failure after RP or IMRI-guided brachytherapy were calculated using the Kaplan-Meier method²⁰ and graphically displayed for patients with a minimal follow-up of 2 years. Comparisons of PSA failure-free survival were made using the log-rank test, and time zero was defined as the date of diagnosis for all patients.

TABLE I. Pretreatment clinical characteristics

Clinical Characteristic	Surgery (n = 406)	Brachytherapy (n = 227)	<i>P</i> _{chi-square}
PSA (ng/mL)			0.0005
<4	9	19	
4–9.99	91	81	
Biopsy Gleason score			<0.0001
≤5	20	8	
6	65	81	
3 + 4	15	11	
Age at initial therapy (yr)			<0.0001
<60	48	32	
60–64	24	33	
65–69	21	17	
≥70	7	18	
Percentage of positive biopsies			0.25
<34	73	78	
34–50	17	12	
>50	11	10	
Prostate volume (cm ³)			<0.0001
<20	1	6	
20–44.9	26	58	
45–59.9	38	20	
60–99.9	30	15	
≥100	5	1	

KEY: PSA = prostate-specific antigen

Data presented as percentages; percentages may not sum to 100 because of rounding.

RESULTS

As shown in Table I, statistically significant differences were evident in the distribution of the PSA level ($P = 0.0005$), biopsy Gleason score ($P < 0.0001$), and prostate gland volume ($P < 0.0001$) between the RP and brachytherapy patients. However, only the percentage of positive prostate biopsies ($P_{\text{Cox}} = 0.02$) was a significant predictor of the time to post-treatment PSA failure in the Cox regression multivariable analyses in which the pretreatment predictors were analyzed first as continuous and then as categorical variables (Table II). Importantly, the distribution of the percentage of positive biopsies between the RP and brachytherapy patients was not significantly different ($P_{\text{chi-square}} = 0.25$; Table I).

The median PSA nadir for the brachytherapy patients was 0.5 ng/mL (range less than 0.2 to 1.2). The initial therapy received did not predict for the time to post-therapy PSA failure ($P_{\text{Cox}} = 0.18$). Specifically, for patients with a minimal 2-year follow up and a median follow-up range of 3.95 to 4.2 years, the 5-year estimate of PSA control was 93% versus 95% ($P_{\text{log-rank}} = 0.16$) after RP or brachytherapy, respectively (Fig. 1).

COMMENT

Individualizing the precise delivery of high-dose radiation to the primary cancer volume has been a

TABLE II. P values from Cox regression multivariable analyses evaluating ability of initial therapy and pretreatment clinical characteristics to predict for time to PSA failure after treatment

Pretreatment Predictor	Continuous	Categorical*
Surgery vs. brachytherapy	0.18 [†]	0.18
Percentage of positive biopsies	0.02	0.02
PSA level	0.26	0.18
Biopsy Gleason score	0.42	0.57
Prostate volume	0.49	0.62

KEY: PSA = prostate-specific antigen.

* Percentage of positive biopsies, ≥34% vs. <34%; PSA, 4–9.99 ng/mL vs. <4 ng/mL; Gleason score, 3 + 4 vs. ≤6; prostate volume, ≥45 cm³ vs. <45 cm³.

[†] Evaluated as a categorical variable with surgery as the baseline.

long-held principle in the treatment of cancer to maximize local control and minimize toxicity.²¹ Although prostate cancer in a given individual is known to be multicentric, within the prostate gland, it has been previously shown that the peripheral zone is the most common site of cancer and the fibromuscular stroma of the anterior base is the least common.²² Moreover, studies that used whole mounting of the radical prostatectomy specimen have suggested that, for low-risk patients, the presence of prostate cancer in the anterior base is rare.^{6,7}

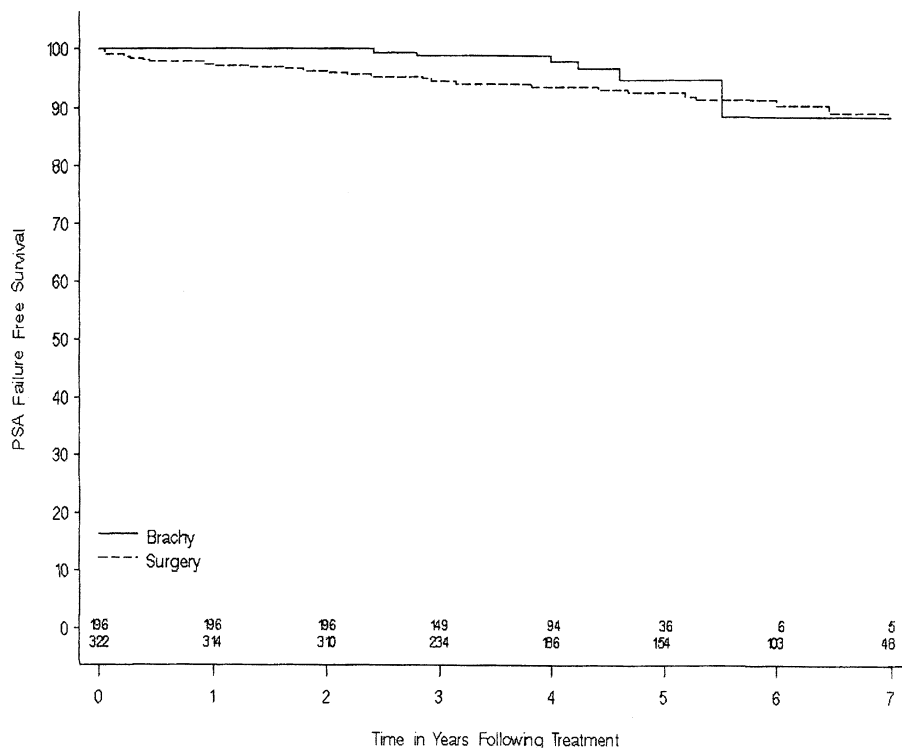


FIGURE 1. PSA failure-free survival for patients with a minimal follow-up of 2 years stratified by initial therapy received (RP versus brachytherapy; $P_{\log\text{-rank}} = 0.16$).

Given this finding and also realizing that the risk of acute urinary symptoms is associated with the total prostate gland dose,⁸ a prospective study using an IMRI-guided brachytherapy technique that can visualize the zonal anatomy of the prostate gland in real time intraoperatively was undertaken. We compared the data from 227 consecutive patients treated using IMRI-guided brachytherapy with the data from 406 comparable RP patients treated at the same institution during the same period. The dose to the anterior base and transition zone anterior to the urethra was kept at less than 100% (range 40% to 95%) of the prescription dose and the peripheral zone was kept at 100% or more of the prescription dose in the brachytherapy patients.

The only pretreatment factor that influenced the time to post-treatment PSA failure was the percentage of positive prostate biopsies ($P_{\text{Cox}} = 0.02$; Table II), and the distribution of this parameter between the RP and brachytherapy patients was similar ($P_{\text{chi-square}} = 0.25$; Table I). In addition, the median follow-up was closely approximated at 4.2 and 3.95 years for the RP and brachytherapy groups, respectively. A Cox proportional hazards model was used to adjust for statistically significant predictors of the time to PSA failure after initial therapy between the two treatment groups, and no statistically significant difference in PSA outcome was found on the basis of the 5-year estimates in this study (Fig. 1; $P_{\log\text{-rank}} = 0.16$).

A few points are worth noting. First, although a Cox proportional hazards model was used to adjust for significant predictors of the time to PSA failure after initial therapy between the two treatment groups, factors not yet discovered that predict for the time to PSA failure after RP or IMRI-guided brachytherapy may be imbalanced between the two treatment arms and may have confounded the results of this study. Therefore, our findings should be viewed as hypothesis generating and not conclusive.

Second, regardless of the definition of PSA failure used, a bias in favor of radiation remains because of the time it takes to reach a nadir before a rise can be scored compared with after surgery for which any value greater than 0.2 ng/mL would be considered detectable. This bias has been previously described and noted,¹⁸ and is also noted in this study. Careful examination of Figure 1 will reveal that the brachytherapy patients' PSA control curve is slightly above the RP control curve during the early years of follow-up, reflecting this potential bias.

Third, after brachytherapy, the PSA bounce has been described, and in this study population, nearly two thirds of patients have been reported to experience this effect.¹⁶ As a result, PSA failure could potentially have been overestimated in the brachytherapy group. To minimize this problem, PSA determinations were made no more frequently than every 3 months and three consecutive incre-

ments in the PSA level of at least 0.2 ng/mL needed to be observed to define PSA failure.

However, the prostate gland volume was not a significant predictor of the time to post-therapy PSA failure when considered as a continuous ($P_{\text{Cox}} = 0.49$) or categorical ($P_{\text{Cox}} = 0.62$) variable for a gland volume greater than or less than 45 cm³ using a Cox regression multivariable analysis (Table II). Therefore, in the patients selected for implant monotherapy in this study who also had moderate benign prostatic hyperplasia (BPH; n = 81 of 227 or 36% of all study patients who had prostate gland volumes of at least 45 cm³), delivering radiation doses to regions of the transition zone anterior to the urethra that were less than the prescription dose did not appear to impact negatively on the PSA outcome.

This lack of impact of prostate gland volume on PSA outcome may be explained by suggesting that patients with moderate BPH would also be expected to have smaller volume cancers compared with patients without BPH and the same PSA level, because some of the serum PSA in patients with BPH was contributed from the benign component of the prostate gland. Another potential explanation may be that for the select group of patients with low-risk disease treated in this study, prostate cancer residing in the transition zone may be an infrequent finding. However, given the slow rate of progression expected for the low-risk patients selected for treatment in this study, additional follow-up is needed to evaluate whether these results are maintained.

CONCLUSIONS

The 5-year estimates of PSA control after either RP or partial prostatic irradiation using an IMRI guidance technique³ in select patients were not significantly different statistically. Longer follow-up is needed to determine whether these results are maintained.

ACKNOWLEDGMENT. To Drs. Sanjaya Kumar, Michael O'Leary, Kemal Tuncali, and George Topulos and Daniel Katcher, M.S., Angela Kanan, R.N., James Rosato, B.S., Lynn Lopes, R.N., and Kristin Valentine, B.S., for their professional support in clinical operations and management.

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