A comparative study of radical prostatectomy and permanent seed brachytherapy for low- and intermediate-risk prostate cancer

Daniel Taussky, MD;[1] Véronique Ouellet, MD;[2] Guila Delouya, MD;[1] Fred Saad, MD[3]

[1]Department of Radiation Oncology, Centre hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, Montreal, QC, Canada; [2]Research Centre, Centre hospitalier de l'Université de Montréal (CRCHUM), Montreal, QC, Canada; [3]Department of Surgery, Division of Urology, Centre hospitalier de l'Université de Montréal, Hôpital Saint-Luc, Montreal, QC, Canada

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Abstract

Introduction: We sought to compare the outcomes between radical prostatectomy (RP) and permanent seed prostate brachytherapy (PB) in patients with low- and low-intermediate-risk prostate cancer from a single tertiary care centre.

Methods: Patients were selected from our institute's internal database based on preoperative selection criteria from the National Comprehensive Cancer Network (NCCN) guidelines (2015) for low- and intermediate-risk patients. No patient had received any neo-adjuvant androgen-deprivation therapy. The endpoint was biochemical recurrence (BCR) or any salvage treatment for both RP and PB at 48 ± 4 months after treatment. The biochemical relapse threshold was set at prostate-specific antigen (PSA) ≥0.5 ng/mL for PB and two PSA values of ≥0.2 ng/mL for RP. Patients from both treatment groups were compared using non-parametric tests. A binary logistic regression analysis was performed to determine an association of treatment and pretreatment factors with a BCR at 48 months.

Results: A total of 575 patients were included in this study; 254 were treated with RP and 321 with PB. BCR was not different between both groups (p=0.84, Chi-square test), and occurred in 21.2% of patients treated with RP and in 20.6% with PB. Based on univariate and multivariate logistic regression analyses, younger age, higher percentage of positive biopsies, and initial PSA were predictive of BCR. Treatment modality was not predictive in either univariate (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.64–1.44; p=0.84) or multivariate (OR 1.43, 95% CI 0.89–2.30; p=0.14) analyses.

Conclusions: Using closely related cutoff values for BCR, both RP and PB did not have significantly different outcomes at four years post-treatment. A longer followup may be necessary to detect a difference between treatments.

Introduction

Radical prostatectomy (RP) and permanent seed prostate brachytherapy (PB) are two widely used treatment options for patients with low- and intermediate-risk prostate cancer. Both treatments are similar for excellent cancer control rates and patients often have difficulty deciding between the two. Published studies for both treatments are difficult to compare because of different definitions for recurrence and differences in baseline characteristics, such as age and comorbidity. Attempts at randomized, prospective trials comparing both treatments have failed because patients ultimately prefer to make their own treatment decisions.[1] Furthermore, different definitions of biochemical recurrence (BCR) have been proposed for each treatment. The American Urological Association Prostate Cancer guideline panel recently recommended standardizing the definition of BCR after RP to an initial prostate-specific antigen (PSA) level of 0.2 ng/mL or greater, with a second confirmatory PSA level of 0.2 ng/mL or greater.[2] The American Society for Therapeutic Radiology and Oncology considers BCR as a rise by 2 ng/mL or more above the nadir PSA (Phoenix definition).[3]

In this study, we compared patients treated with either RP or PB at a single university hospital, using closely related definitions of BCR. We defined BCR after RP as a PSA level of ≥0.2 ng/mL and BCR after PB as ≥0.5 ng/mL, at four years post-treatment.

Methods

With ethical review board approval, patients were selected as they underwent treatment for their prostate cancer at the Centre hospitalier de l'Université de Montréal between 2005 and 2011. Selection criteria were based on the National Comprehensive Cancer Network (NCCN) guidelines (2015) for patients with low- and low-intermediate-risk prostate cancer. All patients had Gleason score ≤3 + 4 disease and

a maximum of one intermediate risk factor. All selected patients had complete data on Gleason score, clinical staging, and pre-treatment PSA value, and none had received any neo-adjuvant androgen-deprivation therapy (ADT). A PSA value at 44–52 months post-treatment was available for all patients. The endpoint was BCR or any salvage treatment for both RP and PB. Biochemical relapse threshold was set as two PSA values ≥0.2 ng/mL for RP-treated patients, and PSA ≥0.5 ng/mL for PB-treated patients at 48 ± 4 months after either treatment.

All RPs were performed by either a radical, open retropubic approach or laparoscopic surgery. Among the 254 patients treated with RP, 24% had pT3 disease. The positive surgical margin rate was 50% and 21% for patients with pT3 and pT2, respectively.

PB was performed with an intraoperative planning system with real-time planned conformal technique and automated seed delivery, as previously described.[4] Postoperative dosimetry was performed on Day 30. The median D90 (dose in grays [Gy] that covers 90% of the prostate volume outlined in post-implant computed tomography [CT] images) in this study was 159.1 Gy (interquartile range [IQR] 140.9–176.7 Gy). The D90 was <130 Gy in 14% of implants, a value associated with a higher rate of biochemical failure.[5]

Both treatment options were compared using Chi-square test and Mann-Whitney U-test. A binary logistic

Table 1. Pre-treatment characteristics for treatment groups

Characteristics	RP (n=254)	PB (n=321)	All (n=575)	p value
Year treatment				<0.001#
2005–2008, n (%)	172 (68)	171 (53)	343 (60)	
2009–2011, n (%)	82 (32)	150 (47)	232 (40)	
Age (years)				<0.001*
Mean (SD)	61 (6)	64 (7)	62.9 (6)	
Range	46–72	48–78	46–78	
PSA at diagnosis (ng/mL)				0.37*
Mean (SD)	5.78 (2.63)	5.77 (2.39)	5.78 (2.49)	
Range	1.03-16.83	0.88-18.48	0.88-18.48	
Gleason score				0.005#
5, n (%)	0 (0)	6 (2)	6 (1)	
6, n (%)	179 (70)	250 (78)	429 (75)	
7, n (%)	75 (30)	65 (20)	140 (24)	
No. positive biopsies (%)				
Mean (SD)	44 (23)	34 (19)	39 (21)	<0.001*
≤33%, n (%)	116 (49)	205 (64)	321 (58)	<0.001#
≥50%, n (%)	121 (51)	116 (36)	237 (42)	
T-stage				0.005#
T1, n (%)	211 (83)	235 (73)	446 (78%)	
T2, n (%)	43 (17)	86 (27)	129 (22%)	
Biochemical recurrence				
Yes, n (%)	54 (21)	66 (21)	120 (21%)	0.84#
No, n (%)	200 (79)	255 (79%)	455 (79%)	
NCCN risk category				
Very low (%)	76 (30)	93 (29)	169 (29%)	0.021#
Low (%)	84 (33)	139 (43)	223 (39%)	
Intermediate (%)	94 (37)	89 (28)	183 (32%)	
Adjuvant treatment				
Radiation	0 (0)			
ADT	0 (0)			
Combined	0 (0)			
Salvage treatment				
Radiation, n (%)	13 (5)	1		
ADT, n (%)	13 (5)	4 (1)		
Combined/RP, n (%)	6 (2)	3 RP (1)		

*Mann-Whitney; #Chi-square; ADT: androgen-deprivation therapy; RP: radical prostatectomy; PB: prostate brachytherapy; PSA: prostate-specific antigen; SD: standard deviation.

Table 2. Univariate and multivariate analyses for biochemical recurrence at 48 months (± four months) with binary logistic regression analysis

Factor	Univariate				Multivariate			
	p value	Odds ratio	95% CI		p value	Odds ratio	95% CI	
			Lower	Upper			Lower	Upper
Treatment type*	0.84	0.96	0.64	1.44	0.14	1.43	0.89	2.30
Age	**0.01**	0.96	0.93	0.99	**0.001**	0.94	0.91	0.98
T-stage (T1 vs. T2)*	0.79	1.07	0.66	1.72	0.63	1.14	0.68	1.90
Positive biopsies (%)	**<0.001**	1.02	1.01	1.03	**0.001**	1.02	1.01	1.03
Gleason sum Gleason 5–6	reference							
Gleason 7	0.11	1.45	0.93	2.26	0.07	1.57	0.96	2.54
PSA	**<0.001**	1.15	1.06	1.24	**<0.001**	1.19	1.09	1.29
Year treatment*	0.56	0.96	0.85	1.09	0.39	0.94	0.82	1.08

*Odds ratio >1 favoured radical prostatectomy (treatment type), T1 (T-stage), and later year of treatment; CI: confidence interval; PSA: prostate-specific antigen.

regression analysis was used to determine an association with BCR. Statistical analyses were performed using the SPSS Statistics software, version 21 (IBM SPSS, Chicago, IL, U.S.).

Results

A total of 575 patients were included in this study; 254 were treated with RP and 321 with PB. All pre-treatment characteristics between both groups were significantly different except for PSA at diagnosis. Patients treated with RP were younger (mean 61 years, standard deviation [SD] 6 vs. 64 years, SD 7 for PB patients) and more likely to have cT1-stage cancers (83% vs. 73% for PB). RP patients also had a higher mean percentage of positive biopsies (44%, SD 23 vs. 34%, SD 19 for PB) and were more likely to be diagnosed with a Gleason 7 score (30%) than patients treated with PB (20%). Table 1 shows a full comparison of the pre-treatment characteristics between both treatments.

The predefined definitions of BCR were set at PSA ≥0.2 ng/mL for RP and ≥0.5 ng/mL for PB. Thus, BCR occurred in 54 patients (21.2%) in the RP group and in 66 patients (20.6%) in the PB group (p=0.84, Chi-square test). If the definition of PSA ≥0.2 ng/mL was applied to both groups, the BCR rate would have been 46% for PB patients in our cohort. However, if we had applied the Phoenix definition (nadir + 2 ng/ml) to the PB group, BCR would have occurred in only eight patients (2.5%) within the 48 months post-treatment. Within the RP group, 29 patients developed BCR, of whom 59% received ADT, 10% had salvage radiotherapy, and 28% are being observed. Within the PB group, three patients had RP, one patient salvage PB, and four patients received ADT. The rest is being observed to see whether the PSA will further decrease or whether the PSA will increase sharply.

Univariate and multivariate logistic regression analyses showed that younger age, higher percentage of positive biopsies, and PSA at diagnosis were predictive of BCR (Table 2). Treatment modality was not predictable by univariate analysis (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.64–1.44; p=0.84). However, RP was favoured over PB by multivariate analysis, but was not statistically significant (OR 1.43, 95% CI 0.89–2.30; p=0.14)

The BCR rate at four years with this definition of ≥0.2 ng/mL would have been 46% for PB patients in our cohort. However, if we had applied the Phoenix definition (nadir + 2 ng/ml), BCR would have occurred in only eight patients (2.5%) within the 48 months post-treatment in the PB group.

Discussion

We report very similar PSA outcomes for patients with low- and intermediate-risk prostate cancer four years after RP or PB treatment (p=0.84, Chi-square test). Using a definition of BCR of PSA ≥0.2 ng/mL, the rate was 21.2% after RP, and 20.6% for the PB group using a definition of BCR of PSA ≥0.5 ng/mL.

The PSA definition for BCR after PB was chosen for its sensitivity (96%) and specificity (52%) after PB[6] and for its previous use in randomized trials[7] to predict BCR. We believe that using the RP definition of BCR of ≥0.2 ng/mL would have misrepresented the PB group, since a followup longer than 48 months is often required to reach such a low nadir. Furthermore, a PSA value of >0.5 ng/mL had been previously used in a multi-institutional study on 2693 patients and showed that in patients with a PSA nadir of <0.5 ng/mL (59% of cases), three years was predictive of long-term outcome.[5] When the Phoenix definition was used, the eight-year PSA relapse-free survival was 88% at three years post-implant.[5] A study from Mount Sinai Medical Center, New York,[8] reported that within their cohort of 921 patients, among which 90% were treated exclusively with PB, 86.5% of them had a PSA <0.5 ng/mL at five years post-PB. A nadir of <0.5 ng/mL within five years was associated with a freedom from biochemical failure rate of 96.7%.[8]

Our decision to measure the time of PSA nadir after PB at four years and not five years is based on a Vancouver

study by Lo et al,[9] which analyzed the PSA levels of 1434 patients at 48 months following PB. Patients with a PSA ≤0.4 ng/mL at 48 months had a 10-year Kaplan-Meier, biochemical disease-free survival (using the Phoenix definition) of 97.5%. A PSA of ≤0.2 ng/mL at 48 months was observed in 78% of patients and a value of ≤0.4 ng/mL was observed in 90.2% of patients. This reflects a much better PSA outcome compared to our results and could be explained by the use of ADT, which was received by 65% of the patients in the Vancouver study. In contrast, none of the patients in our study received ADT. When comparing the median D90, a factor associated with biochemical outcome, the D90 was with 149 Gy in the Vancouver study, lower than the 159 Gy in our cohort.

Two recent publications used a strict definition of BCR of ≥0.2 ng/mL five years after PB. Tanaka et al reported a failure rate of 25.9%[10] while Critz et al reported a failure rate of 15% in the largest single-centre study described.[11]

Others have used the same definitions of BCR for both PB and RP. In a systematic review published in 2009 on different techniques of RP, Ficarra et al reported a five-year disease free survival (DFS) of 70–92% after retropubic RP in patients who were not selected by criteria for pretreatment characteristics.[12] Critz et al used a definition of <0.2 ng/mL for BCR to compare their results post-PB with patients treated by RP and analyzed for low-, intermediate- and high-risk cancers over the same time range.[11] Using the same definition (<0.2 ng/ml) for both treatment modalities (PB vs. RP) gave similar results for 10- and 15-year DFS. Selecting patients who are treated during the same time span allows for comparison of Gleason scores and PSA levels that prescribe a therapy for active surveillance or initiate active treatment. In this context, comparing results of patients who were treated during the same time frame at a single university hospital, as performed in this study, ensures comparability; however, it cannot replace results from a randomized trial.

It is difficult to use the same definition for BCR in patients treated with RP and PB because RP is cytoablative, whereas PB will often leave some functional, benign tissue in place that is still capable of PSA production. It has been shown that using the Phoenix definition to compare between patients treated with RP and radiotherapy is not advisable because it initiates a systematic delay of approximately five years for the diagnosis of BCR in patients treated with RP; this is sufficient time for PSA values to progress from detectable to a value of nadir +2.[13]

Generally, most patients who show an interest in radiation treatment are referred for discussion of different treatment options. At our institution, patients are referred to a radiation oncologist when deemed appropriate by the urologist. When advising patients between various treatment modalities, they must be informed of the risks of BCR, as well as treatment-related side effects, which can impact the decision-making process. Since this study was retrospective, we were not able to control the recording of clinical data. Therefore, we did not have a complete number of RP patients who consulted with a radiation oncologist before surgery and could not determine if a consult would have influenced the patients' decision or study outcome.

While the treatments were not directly compared, principal side effects after PB included significant complications resulting in irritative urinary symptoms or obstruction, which did not develop to such extents after RP. Alternatively, problems with sexual performance presented as a moderate or large complication for quality of life at two years post-treatment in 43% of patients after RP and in 30% of patients after PB.[14] In the SPIRIT trial, at a median of 5.2 years after treatment, there was a borderline difference favouring PB for lower psychological stress and significantly better results favouring PB for less complications in the urinary and sexual domains.[15]

Although our study showed that intervention by RP or PB gave comparable oncological results at four years post-treatment, we believe our results provide useful information that can help patients decide which treatment is best suited to their medical needs while addressing their quality of life. It is possible that this study had inadequate power to detect a significant difference between both treatments. A longer followup would show whether both treatments remain similar in terms of BCR. With a longer followup, it is likely that more patients after PB treatment would attain PSA-levels of <0.2 ng/ml and permit an equal definition of BCR for both RP and PB. Taking these factors into consideration, future studies will involve comparing outcomes of other treatments, such as robotic prostatectomy, with PB.

Conclusion

For patients with low- and intermediate-risk prostate cancer, BCR rates at four years post-treatment were not significantly different between RP and PB. Whereas clinical T-stage, age, percentage of positive biopsies, and Gleason score were predictive of the outcome, both RP and PB treatment groups had approximately 20% of patients experiencing BCR, as measured with similar, but not identical PSA thresholds. A longer followup may be necessary to detect a difference in biochemical outcome between these treatments.

Competing interests: Dr. Delouya has been an Advisory Board member for Astellas, Bayer, Janssen, and Sanofi; has received grants/honoraria from Bayer and Janssen; and has participated in clinical trials for AbbVie, Janssen, and Sanofi. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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Correspondence: Dr. Daniel Taussky, **Department of Radiation Oncology, Centre hospit**alier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, Montreal, QC, Canada; daniel.taussky.chum@ssss.gouv.qc.ca