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CLINICAL INVESTIGATION **Prostate**

10-YEAR EXPERIENCE WITH I-125 PROSTATE BRACHYTHERAPY AT THE PRINCESS MARGARET HOSPITAL: RESULTS FOR 1,100 PATIENTS

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Purpose: To report outcomes for 1,111 men treated with iodine-125 brachytherapy (BT) at a single institution.
Methods and Materials: A total of 1,111 men (median age, 63) were treated with iodine-125 prostate BT for low- or intermediate-risk prostate cancer between March 1999 and November 2008. Median prostate-specific antigen (PSA) level was 5.4 ng/ml (range, 0.9–26.1). T stage was T1c in 66% and T2 in 34% of patients. Gleason score was 6 in 90.1% and 7 or 8 in 9.9% of patients. Neoadjuvant hormonal therapy (2–6 months course) was used in 10.1% of patients and combined external radiotherapy (45 Gy) with BT (110 Gy) in 4.1% ($n = 46$) of patients. Univariate and multivariate Cox proportional hazards were used to determine predictors of failure.
Results: Median follow-up was 42 months (range, 6–114), but for biochemical freedom from relapse, a minimum PSA test follow-up of 30 months was required (median 54; $n = 776$). There were 27 failures, yielding an actuarial 7-year disease-free survival rate of 95.2% (96 at risk beyond 84 months). All failures underwent repeat 12-core transrectal ultrasound -guided biopsies, confirming 8 local failures. On multivariate analysis, Gleason score was the only independent predictor of failure ($p = 0.001$; hazard ratio, 4.8 (1.9–12.4). Median International Prostate Symptom score from 12 to 108 months ranged between 3 and 9. Of the men reporting baseline potency, 82.8% retained satisfactory erectile function beyond 5 years.
Conclusion: Iodine-125 prostate BT is a highly effective treatment option for favorable- and intermediate-risk prostate cancer and is associated with maintenance of good urinary and erectile functions.

Prostate neoplasms, Brachytherapy, Prostate-specific antigen, Radiotherapy.

INTRODUCTION

Although multiple treatment options exist for early-stage prostate cancer, randomized trials comparing efficacy and quality of life are difficult to conduct (1). Treatment choices are evaluated based on a growing body of reports, often describing single-center experience (2–4), which may not be representative of global outcomes. In Canada, provision of radiotherapy is centralized and confined to a relatively small number of university-affiliated centers. Prostate brachytherapy (BT) is a radiation oncology procedure and is performed only at these centers. Although prostate brachytherapy in the form of permanent seed implantation began in the late 1980s and by the mid 1990s was an accepted and popular modality for delivering a high and very effective dose of irradiation to the prostate (2–4), public funding in the province of Ontario was not obtained until 1999.

The iodine-125 prostate brachytherapy program at Princess Margaret Hospital commenced on March 1, 1999, and from its inception, demographic, dosimetric, and outcome data were prospectively recorded in a database. University and host hospital institutional review board approval was obtained for outcome analysis. We report our 10-year experience in terms of biochemical (PSA) outcome, and urinary and sexual side effects.

METHODS AND MATERIALS

Patient selection

A total of 1,111 consecutively treated patients with clinically localized prostate cancer received a permanent implant of iodine-125 seeds. All patients had biopsy-proven prostate adenocarcinoma; all external pathology was centrally reviewed by an experienced

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uropathologist. The majority of patients met the Ontario guidelines (5) for permanent seed implants for favorable risk (FR) prostate cancer. Intermediate-risk (IR) or high-risk patients were offered participation in an institutional review board-approved clinical trial. Baseline evaluation included a complete history and physical examination, transrectal ultrasound (TRUS) for prostate volume determination, and serum PSA level. Staging with abdominal/pelvic CT and bone scans was required for unfavorable disease characteristics (PSA >10 ng/ml; Gleason score >6). Urinary function was evaluated using the International Prostate Symptom Score (IPSS) (6), supplemented since 2001 with a voiding study measuring peak flow, voided volume, and postvoid residual volume. Erectile function was initially recorded as satisfactory, suboptimal, or absent, with or without pharmacologic assistance; but since 2005, the International Index of Erectile Function (7) has been used at baseline and annually.

Treatment

Initially, neoadjuvant hormonal therapy (HT) was used for downsizing prostates of >50 cc (~30% of patients). This practice diminished over time, and overall, neoadjuvant HT was used in only 10.1% of patients (mean duration, 3.7 ± 2.7 months standard deviation [SD]).

External beam (45 Gray in 25 fractions over 5 weeks) was prescribed prior to brachytherapy (110 Gy) for 46 men (4.1%). All patients but 1 were enrolled in Radiation Therapy Oncology Group (RTOG) trials (protocols 0019 and 0232) investigating the role of external beam radiotherapy (EBRT) combined with brachytherapy for IR prostate cancer.

Implant technique

TRUS preplanning took place 2 to 4 weeks before implantation, using a Leopard 2001 scanner (B&K Medical, Wilmington, MA) at 6.5 MHz or, more recently, a Profocus unit (B&K). Images were recorded every 5 mm and downloaded to a VariSeed version 7.1 treatment planning system (Varian, Palo Alto, CA). The dose prescribed to the planning target volume (prostate plus 3 mm anterior and lateral margins, 5 mm cranial-caudal) was 145 Gy. No posterior margin was added at the rectal interface, although the prescription isodose was always entirely outside the posterior prostate contour. Preplan dosimetry aimed for 99% of the prostate to receive >/= 100% of the prescribed dose (V100> 99%) and 90% of the prostate to receive 120-125% of the prescribed dose (D90) and a V150 of 55% to 60%. The urethral dose was limited initially to <150% of the prescribed dose, but was reduced in later years to <125%. Calculation algorithms were those recommended by the American Association of Physicists in Medicine Task Group no. 43 (TG-43) (8). Loose seeds were used in the majority of cases (82%), with a median activity of 0.32 mCi/seed (range, 0.27-0.39 mCi), and a mean of 104 ± 16 seeds. On average, 25% to 30% of the seeds were planned outside the prostate, but peripheral needles were steered medially to avoid periprostatic veins and to position externally located seeds closer to the prostate. Implants were performed under general anesthesia with ultrasound and fluoroscopic guidance using a standard template. During both mapping and implant, the urethra was identified with aerated gel.

Dosimetry

Postimplant dosimetry was performed on day 30, initially using CT images only, but, since September 2000, magnetic resonance (MR)-computed tomography (CT) fusion has been used for all patients without a contraindication to MR scanning. Axial CT images were taken in the supine position on a GE CT scanner (General Electric Medical Systems, Waukesha, WI). Slices were obtained at 2.5- to 3.0-mm intervals (no gap). A 14-French Foley urinary catheter was inserted for urethral visualization. Axial MR scans (1.5T; General Electric Medical Systems) were obtained immediately after the CT, using T_2-weighted sequences (Echo Time/Repetition Time = 90/4500 msec; Echo Train Length 10; field of view 18 to 20 cm; matrix, 320 × 224). Slice thickness was 3 mm (no gap). MR-CT fusion was performed manually, with brachytherapy seeds as fiducial markers. Seed location was determined in VariSeed, using CT images, and seed count was verified using orthogonal pelvic X-rays. All relevant soft tissue structures were contoured on the MR images. Critical organ contouring and dosimetry were performed as per American Brachytherapy Society guidelines (9). Dosimetric parameters assessed at 1 month included the prostate V100, V150, and V200, as well as the D90, the volume of rectal wall receiving >/= 100% of the prescribed dose (RV100), and urethral UD5 and UD30 (dose in Gray to 5% and 30% of the urethra).

Follow-up

Patients were monitored at 1, 3 and 6 months and then every 6 months by symptom assessment, digital rectal examination, and PSA test. Any patient with a single PSA level increase was contacted to switch to a 3-month schedule of PSA monitoring. Biochemical failure (BF) was defined by the ''nadir+2'' definition (10). To avoid confusing BF with a benign PSA bounce (11), BF was determined only for men with >30 months of PSA follow-up (n = 776); however, no patient with failure was excluded. TRUS-guided 12-core postimplant biopsies were performed for any patient with a rising PSA beyond 30 months.

Analysis

Categorical variables were presented as proportions, and continuous variables were described with means, medians, and ranges. Overall survival was estimated using the Kaplan-Meier method. Cox proportional hazards regression was used to explore predictors of time-to-event outcomes. The Mann-Whitney test was used to compare continuous parameters between temporal cohorts. All analyses were performed using SAS v9.1 software for Windows, and all p-values reported were 2-sided. A p-value of <0.05 was considered significant.

RESULTS

Tables 1 and 2 show baseline characteristics of the population as continuous (Table 1) or categorical (Table 2) variables, and Table 3 shows the dosimetric summary data. The mean D90 was 161 ± 20.8 Gy, the mean RV100 was 0.79 ± 0.55 cc, and the mean UD5 was 210.8 ± 29.8 Gy.

PSA nadir

PSA nadir was defined either as a PSA value <0.1 ng/ml or a PSA value >0.1 ng/ml that remained stable for three consecutive readings. The time to PSA nadir was defined as the earliest time that either of these definitions was met. As only 16 patients met the second definition, the times to PSA nadir were similar for both definitions. Patients with any type of failure or those who received neoadjuvant HT were excluded from the calculation of PSA nadir. The median and mean nadir values were 0.06 ± 0.02 ng/ml, achieved at a mean time of 37.3 ± 18.4 months. A higher D90 value was associated with a shorter time to nadir (correlation

Table 1. Summary statistics for baseline characteristics for continuous variables

Characteristic	Baseline value		
	Mean	SD	Range
Age (years)	63	7	40–83
PSA level (ng/ml)	5.7	2.6	0.29–26.1
IPSS baseline (×/35)	6.3	4.9	0–25
TRUS volume (cc)	35.4	9.5	13.2–76.0

Abbreviations: IPSS = international prostate symptom score; TRUS = transrectal ultrasound.

coefficient, −0.152, $p = 0.002$). Every 10-Gy decrease in dose resulted in a 1.4-year increase in time to nadir. By 60 months, 74% of patients had met one of the nadir definitions. Only 10% (48/481) of patients had a PSA of >0.2 ng/ml at 5 years, 2/3 of whom (32/48) are still showing a declining trend. PSA values at annual intervals are shown in Table 4.

PSA bounce

A PSA bounce was defined as an increase of > 0.2 ng/ml at >3 months after brachytherapy, followed by a spontaneous decline without intervention. Of the cohort with >30 months of PSA follow-up and no neoadjuvant HT ($n = 697$), 42.9% experienced a PSA bounce starting at a median time of 9.0 ± 6.7 months. The mean magnitude was 1.09 ng/ml (range, 0.21–8.99). Of 299 patients with a resolved bounce, only eight bounces occurred after 36 months (6 at 36–48 months; 2 at 60–72 months). Univariate Cox proportional hazards regression (HR) was performed to look for predictors of a bounce excluding failures and those patients receiving neoadjuvant HT. The factors examined included age, T stage, prostate volume, quantifiers of tumour volume (percent positive cores and greatest involvement of any core), and dose. Only younger age was predictive for occurrence of a bounce ($p < 0.0001$, HR 0.94 [0.92–0.95]).

Table 2. Summary statistics for baseline characteristics for categorical variables

Characteristic	No. of patients	% of patients	Missing
Hormone therapy			
yes	112	10.1	0
no	999	90.1	
EBRT			
yes	46	4.1	0
no	1,065	95.9	
Potent at baseline			
yes	881	83.8	60
no	170	16.2	
Gleason score			
≤ 6	999	90.1	2
7-8*	110	9.9	
Risk group			
low	964	86.9	2
non-low	145	13.1	
MaxPerCore			
<25%	641	63.3	99
≥25%-<50%	192	19.0	
≥50%	179	17.7	
PercPosBiop			
<33.3%	495	63.3	329
≥33.3%	287	36.7	

Abbreviations: MaxPerCore = maximum percentage involvement of any core; PercPosBiop = percentage of the biopsies that show malignancy.

* Only 1 patient had a Gleason score of 8.

Table 3. Summary statistics for dosimetric data

Characteristic	Median	Mean	SD
No. of seeds	103	104	16
Activity/seed (mCi)	0.32	0.31	0.02
V100 (%)	95.5	93.8	5.6
V150 (%)	58.0	57.9	11.5
V200 (%)	26.9	27.5	8.6
D90 (Gy) (BT alone)	162	161	20.8
D90 (%) (all patients)	112.2	111.4	14.6
RV100 (cc)	0.71	0.79	0.55
UD5 (Gy)	210.3	210.8	29.8
UD30 (Gy)	188.5	187.9	22.4

Abbreviations: RV100 = volume of rectum (in cc) enclosed by prescription isodose; UD5/UD30 = minimum dose to 5% and 30% of urethral volume, respectively; BT = brachytherapy; SD = standard deviation; mCi = millicurie; D90% = isodose (as a percentage of the prescription) enclosing 90% of the prostate volume.

Survival analysis

There have been only 2 deaths from prostate cancer and 30 from other causes, yielding an actuarial overall survival rate of 95% at 7 years (confidence interval, 93%–97%) (Fig. 1).

Failure analysis

Disease-free survival (DFS) was measured from the date of implant to the first failure of any type. Since the majority of failures are heralded by a rising PSA level, the date of meeting the ''nadir + 2'' criteria was used for time to failure, but the type of failure was subsequently refined according to results of investigations. Patients without evidence of disease were censored at last follow-up or death. DFS for the entire cohort is shown in Fig. 2. There have been 27 failures of any type, including 8 local and 8 distant failures. Figures 3

Table 4. Summary statistics for PSA values

Month of PSA test	Mean ng/ml	Median ng/ml	SD	No. of patients
12	0.88	0.58	1.01	722
24	0.88	0.40	1.23	537
36	0.39	0.17	0.61	456
48	0.20	0.09	0.33	374
60	0.15	0.05	0.31	244
72	0.12	0.05	0.19	147
84	0.13	0.05	0.24	74
96	0.12	0.05	0.20	32
108	0.04	0.05	0.04	7

Summary statistics for PSA values at annual intervals are for patients without biochemical, local, or distant failure ($n = 1,111 - 27 = 1,084$). Patients receiving neoadjuvant hormone therapy are included (10.1%).

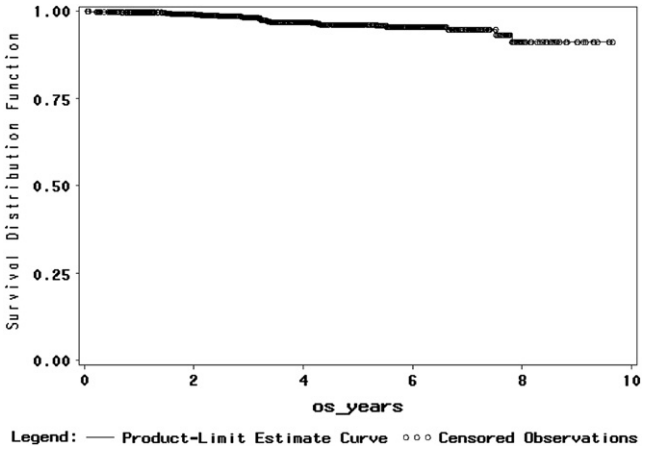

Fig. 1. Overall survival for entire cohort is 95% at 7 years (C.I. 93%-97%). There have been only 2 deaths from prostate cancer.

and 4 show the local failure (LF)-free survival of the entire cohort and by risk group. Cox proportional HR values showed predictors of DFS to be risk group (p = 0.0001), Gleason score ($p < 0.0001$), PSA level ($p = 0.005$), and combined EBRT/brachytherapy (p = 0.002) (Table 5). Specifically, brachytherapy dose (p = 0.83), and use of HT (p = 0.40) were not predictive. The influence of HT on DFS was also examined for men with a greater volume of disease (>33% positive cores or >50% maximum involvement per core) and again was not predictive of outcome ($p = 0.18$).

In multivariate analysis, to exclude having interdependent variables in the same model, Gleason score and baseline PSA are in one model and risk group in the other. Although the use of combined EBRT/brachytherapy was limited to IR patients, this was by random assignment according to the RTOG protocol so combined therapy was left in both models. In the absence of PSA level and Gleason score, risk group is a statistically significant predictor of DFS ($p = 0.006$). In the model excluding risk group, Gleason score is significant (p = 0.001), and baseline PSA level is nearly significant (p = 0.09), after adjusting for the other covariates. Age and the use of combined EBRT/brachytherapy were not predictive of outcome.

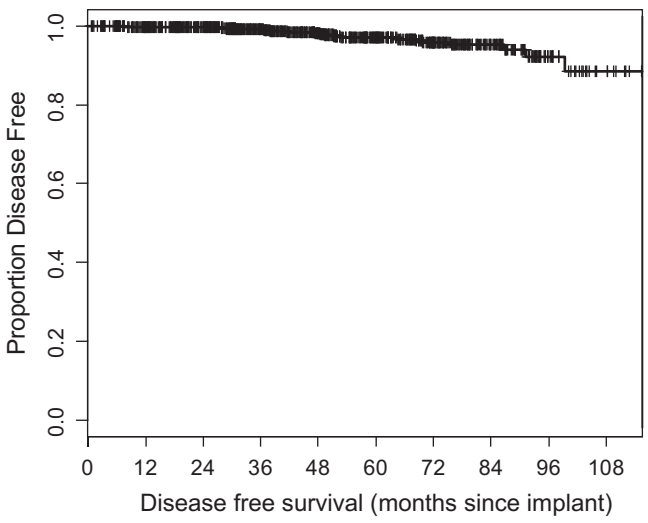

Fig. 2. Disease free survival of entire cohort.

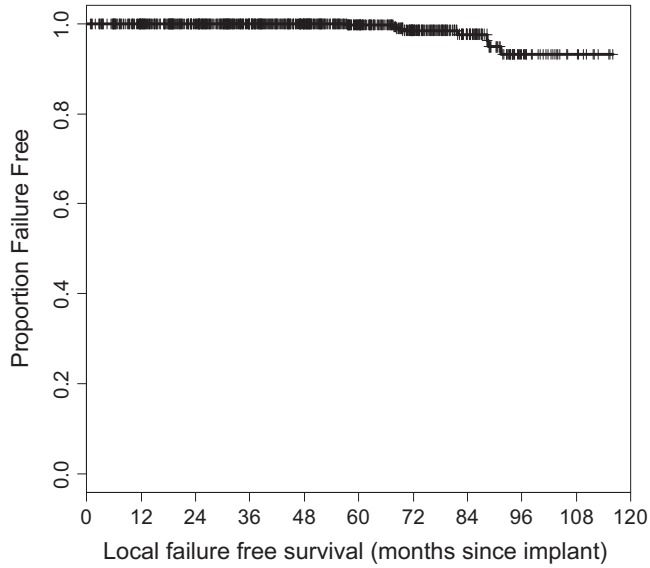

Fig. 3. Actuarial local failure free survival of entire cohort.

Urinary and sexual function

Median baseline IPSS was 5 (range, 0–25). Alpha blockers, typically tamsulosin, 0.4 mg, were started 1 week prior to brachytherapy. Catheterization was required acutely in 13.1% of patients and was managed with intermittent self-catheterization (duration <1 week for 35.9%; 1–4 weeks for 39.7%; >1 month for 24.4% of patients). Baseline IPSS was missing in 27 patients and not recorded subsequently in 233 patients. For the remainder, the median time to return to baseline ±3 points was 12 months, with 71% of patients recovered by 2 years and 83% of patients by 3 years. The median IPSS at 5 years was 6 and at 10 years was 3.

Satisfactory erectile function was reported in 83.1% of patients at baseline (missing data in 60 patients). Of those patients with >5 years follow-up and prior potency (n = 238), erectile function was satisfactory in 74.8% of patients,

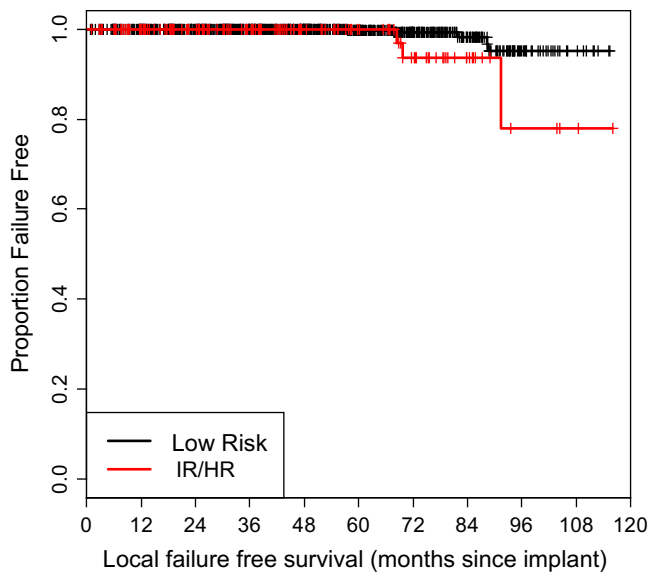

Fig. 4. Actuarial Local failure free survival by risk group.

Table 5. Cox proportional hazards model for predictors of disease-free survival

Variable	Parameter	*p* value	Category	Referent	HR	HR 95% LCL	HR 95% UCL	No. of observations used
Categorical	Age	0.18	>55	≤55	3.96	0.54	29.22	1,111
	Risk	0.0001*	Non-low	Low	4.79	2.17	10.57	1,109
	Gleason	<0.0001*	7-8	≤6	6.02	2.68	13.54	1,109
	T-stage	0.86	2	1	1.08	0.48	2.42	1,105
	Comb RT+BT	0.002*	Combined	BT only	5.42	1.84	15.94	1,111
	HT	0.40	1	0	0.59	0.18	2.00	1,111
	MaxPerCore	0.25						
		0.67	≥25%-<50%	<25%	0.77	0.22	2.63	1,012
		0.14	≥ 50%	<25%	1.96	0.80	4.79	
	PercPosBiop	0.99	≥ 33.3%	<33.3%	1.01	0.35	2.93	782
Continuous	Age	0.06	—	—	1.06	1.00	1.12	1,111
	PSA-0	0.005*	—	—	1.19	1.05	1.34	1,111
	D90 (%)	0.83	—	—	1.00	0.98	1.03	1,110
	V100	0.50	—	—	1.02	0.96	1.10	1,110

Abbreviations: Comb RT + BT = combined external radiotherapy and brachytherapy; HT = hormone therapy; MaxPerCore = maximum percentage involvement of any core; PercPosBiop = percentage of the biopsies that show malignancy; HR LCL and UCL = hazard ratio, lower confidence limit, upper confidence limit; PSA-0 = PSA level at baseline.

suboptimal in 7.6% of patients, and absent in 17.6% of patients. Use of phosphodiesterase (PDE-5′) inhibitors was encouraged and not considered in the evaluation of potency.

DISCUSSION

Brachytherapy has become widely accepted for treating localized prostate cancer with excellent and durable intermediate- to long-term results from many centers (2–4, 12, 13). These results have been obtained with a variety of approaches including the use of intraoperative vs. preplanning, loose vs. stranded seeds, and preloaded needles vs. a Mick applicator, and debate continues over the superiority of one approach over another. The unifying underlying theme is the desire for consistently high-quality implants. The importance of quality is reflected in the presence of a well-established dose-response relationship (14, 15), and much emphasis has thus been placed on quality assurance. Given the uncertainty in CT-based postplan dosimetry (16), we adopted MR-CT fusion as our standard of postplan assessment very early in the program. With careful analysis of postplan results and meticulous attention to detail, a mean D90 of >160 Gy (equivalent to a biologically effective dose of 169 Gy with an α/β ratio of 2) (17) was achieved by 2003 and subsequently maintained. For 90% of implants, the D90 was in the desired range of 140 to 180 Gy.

In this dose range, brachytherapy is clearly an ablative procedure. Only 10% of patients at 5 years have PSA level of >0.2 ng/ml, and 2/3 of these patients are still showing a decreasing trend. This is very similar to observations in the report by Stock *et al.* (18) where only 10.9% of 742 patients had a PSA level of >0.2 ng/ml at 5 years. The 10-year freedom from BF was 98% for a 5-year PSA level of <0.2 and 81% for a PSA level of >0.2 ng/ml. Grimm *et al.* (4) reported in 2001 that the proportion of patients with a PSA of <0.2 ng/ml continues to increase for up to 7 to 8 years, but to our knowledge, we are the first to explain this phenomenon by reporting the association between dose and time to nadir. Every 10-Gy increase in D90 shortens the time to nadir by 1.4 years. Our reported mean time to nadir of 37 months will get longer as later nadirs are registered.

The majority of this population (87%) had FR disease. Although 37% of subjects had >33% positive cores and 18% had maximum involvement in any core >50%, some with relatively low- volume disease could almost certainly have been safely watched. The controversy over who should be treated continues. The median age in this cohort is 62, and in the absence of reliable biomarkers of potentially aggressive disease, many physicians will continue to recommend definitive treatment for younger men rather than surveillance. Even healthy older men will frequently prefer definitive treatment (19).

The recently published experience with active surveillance by Klotz *et al.* (20) illustrates the dilemma for both practitioners and patients alike. In that study, those men in a cohort of active surveillance (n = 453) who later underwent definitive treatment (n = 137) had remarkably unsuccessful outcomes, with a biochemical no-evidence-of-disease (bNED) rate of <50% at 3 years. This is a sobering statistic, and although the authors could not demonstrate an overall survival detriment with active surveillance, given their short median follow-up of <7 years, a young man who is likely to require treatment within a 10- to 15-year period can be more assured of a successful outcome if treated sooner rather than later.

For those patients requiring or desirous of definitive treatment, brachytherapy represents a highly effective option, with a 7-year DFS rate of 97.2% for FR disease and 81.3% for IR disease. The lower DFS for IR still compares favorably to results from dose-escalated EBRT, despite the fact that EBRT is often combined with HT (21, 22–24). The actuarial freedom from LF at 7 years for IR patients was 93.5%, comparing very favorably to our institutional experience with 75.6-Gy three-dimensional conformal EBRT (50% positive 3-year post-RT biopsies) (21) and 79.8-Gy IMRT (5-year bNED of 76.5%) (25). Further

escalation to doses exceeding 80 Gy may bring additional improvement, but follow-up times are still short for ultrahigh EBRT doses (23, 26).

The question of possible benefit of combining EBRT and brachytherapy for IR patients remains open, to be addressed by on-going multicenter randomized trials such as RTOG protocol 0232. Our practice with IR patients is to enter them whenever possible in randomized trials.

Unlike the experience of Morris *et al.* (2) where 65% of patients received neoadjuvant HT, only 10% in the present cohort had HT, and notably none of the IR patients HT was used solely for prostate size reduction, and several factors led to decreasing use over time: increasing confidence in handling the technical challenges of larger prostates, use of systematic baseline voiding studies to select men less likely to have urinary retention despite a larger prostate, and an analysis indicating that short-course HT did not prevent postimplant urinary retention (27). In addition, the detrimental effects on potency and quality of life are factors which are often crucial to younger men in treatment selection. In this analysis, the use of HT was not predictive of DFS in univariate analysis, in keeping with that of numerous reports in the literature showing lack of benefit of HT when combined with an optimal implant (17, 28–30). Unlike the study by Beyer *et al.* (30), we did not see a detriment to overall survival with the use of HT, but our population was more than a decade younger.

Efficacy is only one factor on which men base their choice of treatment. The potential for long-term toxicity and effects on quality of life are clearly also important deciding factors. Although we demonstrate a satisfactory return to baseline urinary function in the majority of patients, recovery can be prolonged, and 17% of the men reported sustained or late deterioration in urinary symptoms. Our analysis is based on the most recent IPSS; some higher scores may represent a transient urinary ''flare,'' documented to occur in 30% to 35% of patients (31). On the other hand, maintenance of erectile function was excellent; 75% of men who were potent at baseline reported satisfactory erections at 5 years, with an additional 7.9 % having suboptimal erections but still capable of intercourse. A previous analysis indicated that two-thirds of our population use, or have used, PDE-5's (32). This may be a factor in maintenance of potency, and although we did not routinely offer PDE-5's following BT, erectile function was discussed, and PDE-5 use was encouraged (33–36). A current randomized RTOG trial is investigating the routine use of PDE-5's following BT.

One of the strengths of this study is its ability to define patterns of failure after consistent high-quality prostate brachytherapy. All men with a rising PSA level beyond 30 months were investigated with 12-core TRUS-guided biopsies, initially, when the PSA reached 3 to 4 ng/ml. If negative, systemic staging would be initiated as the PSA approached 10 ng/ml, and in the absence of metastatic failure, a final TRUS-guided biopsy was encouraged before initiating HT. Based on a previous practice of systematic postradiotherapy prostate biopsies (37), TRUS-guided biopsies were initially routinely offered at 2.5 to 3 years following brachytherapy. For the first 125 patients, 120 had negative biopsy results, and only 5 patients had indeterminate results, all of whom demonstrated a continuous decline in PSA level. Based on this, further post-BT biopsies were reserved for those few men with a rising PSA level beyond 30 months.

Although we were not able to demonstrate a relationship between the standard dose parameters (V100 and D90) and LF, very few implants had a D90 of <140 Gy. Within the recommended dose range of 140 to 180 Gy, local failures are extremely rare events. We previously reported MRI-defined treatment margins with this planning approach and demonstrated satisfactory coverage of a 3-mm margin around the MRI-defined prostate (38). It may be that those patients failing locally had disease extent beyond this margin, but it is more likely that they had either disease in a region of deficient margin or inherent radioresistance. Nonetheless, 7-year LF-free survival rates of 98.3% for FR patients and 93.5% rates for IR patients are excellent and in keeping with the extremely low local failure rates reported in the literature (15).

CONCLUSIONS

These results add to the growing body of literature demonstrating excellent and durable results from high-quality permanent seed prostate brachytherapy. We make no claims as to the superiority of our technique, which is a standard preplanned, preloaded Seattle-based approach using predominantly loose seeds. However, the use of MR-CT fusion assures the accuracy of postplan quality assessment, and rigorous follow-up and investigation of failures have elucidated the pattern of failure in this dose range.

REFERENCES

1. Wallace K, Fleshner N, Jewett M, Basiuk J, Crook J. Impact of a multi-disciplinary patient education session on accrual to a difficult clinical trial: The Toronto experience with the surgical prostatectomy versus interstitial radiation intervention trial. *J Clin Oncol* 2006;24(25):4158–4162.
2. Morris WJ, Keyes M, Palma D, Spadinger I, McKenzie MR, Agranovich A, *et al.* Population-based study of biochemical and survival outcomes after permanent 125I brachytherapy for low- and intermediate-risk prostate cancer. *Urology* 2009; 73(4):860–867.
3. Potters L, Morgenstern C, Calugaru E, Fearn P, Jassal A, Presser J, *et al.* 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005;173(5):1562–1566.
4. Grimm PD, Blasko JC, Sylvester JE, Meier RM, Cavanagh W. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51(1):31–40.
5. Crook J, Lukka H, Klotz L, Bestic N, Johnston M, for the Genitourinary Cancer Disease Site Group of the Cancer Care

Ontario Practice Guidelines Initiative. Systematic overview of the evidence for brachytherapy in clinically localized prostate cancer. *CMAJ* 2001;164(7):975–981.
6. Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, *et al*. The American urological association symptom index for benign prostatic hyperplasia. The measurement committee of the american urological association. *J Urol* 1992;148(5):1549–1557.
7. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the international index of erectile function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;11(6):319–326.
8. Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS. Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM radiation therapy committee task group no. 43. American Association of Physicists in Medicine. *Med Phys* 1995;22(2):209–234.
9. Crook JM, Potters L, Stock RG, Zelefsky MJ. Critical organ dosimetry in permanent seed prostate brachytherapy: Defining the organs at risk. *Brachytherapy* 2005;4(3):186–194.
10. Roach M III, Hanks G, Thames H Jr., Schellhammer P, Shipley WU, Sokol GH, *et al*. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO phoenix consensus conference. *Int J Radiat Oncol Biol Phys* 2006 Jul 15;65(4):965–974.
11. Crook J, Gillan C, Yeung I, Austen L, McLean M, Lockwood G. PSA kinetics and PSA bounce following permanent seed prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2007 Oct 1;69(2):426–433.
12. Sylvester JE, Grimm PD, Blasko JC, Millar J, Orio PF III, Skoglund S, *et al*. 15-year biochemical relapse free survival in clinical stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007;67(1):57–64.
13. Stock RG, Stone NN, Cesaretti JA, Rosenstein BS. Biologically effective dose values for prostate brachytherapy: Effects on PSA failure and posttreatment biopsy results. *Int J Radiat Oncol Biol Phys* 2006;64(2):527–533.
14. Potters L, Roach M III, Davis BJ, Stock RG, Ciezki JP, Zelefsky MJ, *et al*. Postoperative nomogram predicting the 9-year probability of prostate cancer recurrence after permanent prostate brachytherapy using radiation dose as a prognostic variable. *Int J Radiat Oncol Biol Phys* 2010;76(4):1061–1065.
15. Stone NN, Stock RG, Cesaretti JA, Unger P. Local control following permanent prostate brachytherapy: Effect of high biologically effective dose on biopsy results and oncologic outcomes. *Int J Radiat Oncol Biol Phys* 2009 Jul 23.
16. Crook J, Milosevic M, Catton P, Yeung I, Haycocks T, Tran T, *et al*. Interobserver variation in postimplant computed tomography contouring affects quality assessment of prostate brachytherapy. *Brachytherapy* 2002;1(2):66–73.
17. Ho AY, Burri RJ, Cesaretti JA, Stone NN, Stock RG. Radiation dose predicts for biochemical control in intermediate-risk prostate cancer patients treated with low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75(1):16–22.
18. Stock RG, Klein TJ, Cesaretti JA, Stone NN. Prognostic significance of 5-year PSA value for predicting prostate cancer recurrence after brachytherapy alone and combined with hormonal therapy and/or external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2009;74(3):753–758.
19. Barocas DA, Cowan JE, Smith JA Jr., Carroll PR, for the CaPSURE Investigators. What percentage of patients with newly diagnosed carcinoma of the prostate are candidates for surveillance? An analysis of the CaPSURE database. *J Urol* 2008; 180(4):1330–1334.
20. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010; 28(1):126–131.
21. Nichol A, Chung P, Lockwood G, Rosewall T, Divanbiegi L, Sweet J, *et al*. A phase II study of localized prostate cancer treated to 75.6 Gy with 3D conformal radiotherapy. *Radiother Oncol* 2005;76(1):11–17.
22. Kupelian PA, Ciezki J, Reddy CA, Klein EA, Mahadevan A. Effect of increasing radiation doses on local and distant failures in patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;71(1):16–22.
23. Cahlon O, Zelefsky MJ, Shippy A, Chan H, Fuks Z, Yamada Y, *et al*. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: Toxicity and biochemical outcomes. *Int J Radiat Oncol Biol Phys* 2008;71(2):330–337.
24. Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O, *et al*. Long-term results of conformal radiotherapy for prostate cancer: Impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. *Int J Radiat Oncol Biol Phys* 2008;71(4):1028–1033.
25. Martin JM, Bayley A, Bristow R, Chung P, Gospodarowicz M, Menard C, *et al*. Image guided dose escalated prostate radiotherapy: Still room to improve. *Radiat Oncol* 2009;4:50.
26. Pickles T, Keyes M, Morris WJ. Brachytherapy or conformal external radiotherapy for prostate cancer: A single-institution matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2010;76(1):43–49.
27. Martens C, Pond G, Webster D, McLean M, Gillan C, Crook J. Relationship of the international prostate symptom score with urinary flow studies, and catheterization rates following 125I prostate brachytherapy. *Brachytherapy* 2006;5(1):9–13.
28. Stock RG, Yamalachi S, Hall SJ, Stone NN. Impact of hormonal therapy on intermediate risk prostate cancer treated with combination brachytherapy and external beam irradiation. *J Urol* 2010; 183(2):546–550.
29. Martinez A, Galalae R, Gonzalez J, Mitchell C, Gustafson G, Kovacs G. No apparent benefit at 5 years from a course of neoadjuvant/concurrent androgen deprivation for patients with prostate cancer treated with a high total radiation dose. *J Urol* 2003;170(6 Pt 1):2296–2301.
30. Beyer DC, McKeough T, Thomas T. Impact of short course hormonal therapy on overall and cancer specific survival after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2005;61(5):1299–1305.
31. Crook J, Fleshner N, Roberts C, Pond G. Long-term urinary sequelae following 125iodine prostate brachytherapy. *J Urol* 2008;179(1):141–145.
32. Crook J, Webster D, Virtue D. 140 sexual function following iodine 125 prostate brachytherapy. *Radiother Oncol* 2006; 80(Suppl 1):S41.
33. Mabjeesh N, Chen J, Beri A, Stenger A, Matzkin H. Sexual function after permanent 125I-brachytherapy for prostate cancer. *Int J Impot Res* 2005;17(1):96–101.
34. Merrick GS, Butler WM, Galbreath RW, Stipetich RL, Abel LJ, Lief JH. Erectile function after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2002;52(4):893–902.
35. Stone NN, Stock RG. Long-term urinary, sexual, and rectal morbidity in patients treated with iodine-125 prostate brachytherapy followed up for a minimum of 5 years. *Urology* 2007; 69(2):338–342.
36. Schiff JD, Bar-Chama N, Cesaretti J, Stock R. Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function. *BJU Int* 2006;98(6):1255–1258.
37. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdolell M. Postradiotherapy prostate biopsies: What do they really mean? Results for 498 patients. *Int J Radiat Oncol Biol Phys* 2000;48(2):355–367.
38. Crook J, Patil N, Ma C, McLean M, Borg J. Magnetic resonance imaging-defined treatment margins in iodine-125 prostate brachytherapy. *Int J Radiat Oncol Biol Phys 2009*. e-pub ahead of print.