Int. J. Radiation Oncology Biol. Phys., Vol. 67, No. 1, pp. 57–64, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.07.1382

CLINICAL INVESTIGATION **Prostate**

15-YEAR BIOCHEMICAL RELAPSE FREE SURVIVAL IN CLINICAL STAGE T1-T3 PROSTATE CANCER FOLLOWING COMBINED EXTERNAL BEAM RADIOTHERAPY AND BRACHYTHERAPY; SEATTLE EXPERIENCE

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Purpose: Long-term biochemical relapse-free survival (BRFS) rates in patients with clinical Stages T1-T3 prostate cancer continue to be scrutinized after treatment with external beam radiation therapy and brachytherapy.

Methods and Materials: We report 15-year BRFS rates on 223 patients with clinically localized prostate cancer that were consecutively treated with I^{125} or Pd ^{103} brachytherapy after 45-Gy neoadjuvant EBRT. Multivariate regression analysis was used to create a pretreatment clinical prognostic risk model using a modified American Society for Therapeutic Radiology and Oncology consensus definition (two consecutive serum prostate-specific antigen rises) as the outcome. Gleason scoring was performed by the pathologists at a community hospital. Time to biochemical failure was calculated and compared by using Kaplan-Meier plots.

Results: Fifteen-year BRFS for the entire treatment group was 74%. BRFS using the Memorial Sloan-Kettering risk cohort analysis (95% confidence interval): low risk, 88%, intermediate risk 80%, and high risk 53%. Grouping by the risk classification described by D'Amico, the BRFS was: low risk 85.8%, intermediate risk 80.3%, and high risk 67.8% ($p = 0.002$).

Conclusions: I^{125} or Pd^{103} brachytherapy combined with supplemental EBRT results in excellent 15-year biochemical control. Different risk group classification schemes lead to different BRFS results in the high-risk group cohorts. © 2007 Elsevier Inc.

Brachytherapy, Prostate cancer, Long-term results.

INTRODUCTION

Prostate brachytherapy continues to be a first-line treatment option for men with clinical stage T1-T2 prostate cancer. Technical advances are regularly reported, including the use of transrectal ultrasound guidance for preplanned or intraoperatively planned implants (1–3). Postimplant dosimetry has led to improved prostate coverage and a better understanding of the tolerances of adjacent critical structures (4). Data from the retropubic era showed that those patients with B1 (T2a) disease who received "adequate" implant dosimetry (based on orthogonal X-rays) achieved disease control rates similar to radical prostatectomy and external beam radiation therapy (EBRT) patients from that era (5). Improved implant quality has been demonstrated to result in better biochemical relapse-free survival (BRFS) outcomes in several modern studies (6–8).

Today's improved patient selection and improved implant quality has resulted in multiple brachytherapy reports demonstrating 5–10 year BRFS rates are equivalent to the best published radical prostatectomy and three-dimensional conformal radiation therapy results (8–21). We report the Seattle 15-year results of transperineal interstitial permanent prostate brachytherapy combined with moderate-dose neoadjuvant EBRT in a group of consecutively treated and prospectively followed patients with clinical T1-T3 prostate cancer.

METHODS AND MATERIALS

This is a prospective cohort study. Between January 1987 and December 1993, 232 patients presenting with clinically localized

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Acknowledgments—The authors would like to thank Jonathan Khanjian for assisting in the preparation of this manuscript.

Conflict of interest: none.

Received April 26, 2006, and in revised form July 19, 2006. Accepted for publication July 28, 2006.

prostate cancer were consecutively treated with I^{125}/Pd^{103} brachytherapy with neoadjuvant EBRT.

Seven patients did not meet the initial cohort criteria for inclusion because of androgen ablation therapy for downsizing purposes and 1 patient had inadequate follow-up, reducing the analytic cohort to 223. Median follow-up time was 9.43 years ranging from 0.62 to 17.07 years. Patients were evaluated with physical examinations, digital rectal examination (DRE), and prostate-specific antigen (PSA) every 3–6 months the first 2 years after implant, every 6 months the next 3 years, then yearly thereafter. Radiographic examinations were performed if clinically indicated. Extended follow-up was conducted by continued patient contact, other physician contact and Surveillance, Epidemiology and End Results (*i.e.,* SEER) registry follow-up. Patient permission for follow-up for outcomes was consented at the time of initial diagnosis and treatment. Pathology reports of those patients with intermediate risk disease were analyzed to determine the percentage of positive biopsy cores. Forty-one intermediate-risk patients had at least four ultrasound-guided needle biopsies and a description of the number of biopsy cores out of the total number of cores taken, allowing us to determine the percent of positive biopsy cores in those patients. Twenty-six of these 41 patients had ≥50% of their biopsy cores positive (63.4%).

All patients were initially evaluated with a medical history and physical, serum PSA, and where clinically indicated radiographic studies such as bone scan and computed tomography scan. The 1992 American Joint Committee on Cancer staging system was used to assign clinical stage. T stage was assigned by DRE results. Pathologic biopsies were reviewed and assigned Gleason scores, primarily by the pathology staff at a local community hospital.

Risk classification

The D'Amico method defines risk cohorts as low risk: PSA ≤10.0 ng/mL and Gleason score 2–6 and stage T1c-T2a, intermediate risk: PSA 10.1–20 ng/mL or Gleason 7 or stage T2b, and high risk: PSA >20.0 ng/mL or Gleason 8-10 or Stage T2c modified to also include patients with two or more of the intermediate-risk features (19).

The Memorial Sloan-Kettering Cancer Center risk groupings were initially described by Zelefsky and were subsequently adopted by Seattle and others (20). The risk groups are defined as low risk: initial serum PSA ≤10.0 ng/mL, Gleason summary score 2–6, and clinical stage by DRE <T2c (no unfavorable risk factors), intermediate risk: initial serum PSA >10.0 ng/mL or Gleason score >6, or >T2b stage disease (one unfavorable risk factor), and high-risk: two or three of the preceding unfavorable risk factors. BRFS was quantified using a modified American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition of biochemical failure after radiotherapy for localized prostate cancer. Instead of requiring three consecutive PSA rises for assignment of biochemical failure, two serum PSA rises were used; this is more sensitive at picking out biochemical failures than the traditional three-rise ASTRO definition (22).

Analytical methods

For Kaplan-Meier plots and survival analyses, patients were assigned a censor date as date of biochemical failure as measured by PSA, local or distant failure by observation of disease recurrence, last known date of "alive" vital status, or date of death if deceased. Biochemical PSA progression or failure was defined as two consecutive rises in serum PSA at time of last follow-up. Failure is also defined at time of intervention with androgen ablation. Patients that exhibit a temporary rise in PSA, followed by a decline without clinical therapeutic intervention ("PSA bounce") are noted as biochemical successes.

Serum PSA levels after documented failures are not reported to avoid the influence of androgen ablation or other therapeutic interventions that would alter the patient's PSA profile. Thus the PSA level at the time of documented biochemical failure is the last reported PSA for that patient. Clinical failure was defined as local if the follow-up DRE or prostate biopsy remained positive. Distant failure was noted if radiographically apparent disease developed.

The log–rank test was used to test for statistically significant differences between risk groups for BRFS. The Kaplan-Meier method was used to plot cumulative survival functions by risk groups.

Differences in clinical variables between isotopes were made using independent sample *t* tests (continuous variables) and chi-square tests (categorical variables). Univariate and multivariate (forward-progression) Cox regression analysis was used to determine if any of the clinical variables predicted for failure. Values of $p \leq 0.05$ were considered to indicate statistical significance. Statistical analysis was performed with SPSS version 13.0 software (SPSS, Inc., Chicago, IL).

Treatment

The Seattle technique has been reported in previous articles (1–3). Briefly, when a preplanning transrectal ultrasound volume study is performed, target volumes outlined by the radiation oncologist are larger than the prostate volume, especially laterally. This usually includes the proximal 1 cm of the seminal vesicles. The minimum peripheral dose includes this outlined volume and is derived from standard radiation planning software. The dose for Pd^{103} boost was 90 Gy (~100 Gy NIST 99). The I^{125} boost dose was 120 Gy (108 Gy TG-43). Early in the study period, a uniform loading scheme was used; in 1992, the planning switched to a modified uniform peripheral loading format to limit the dose to the urethra to less than 150% of the prescription dose. Postimplant quality assurance was by the use of orthogonal films between 1987 and 1991. In 1992, postimplant computed tomography scan dosimetry was performed. These scans printed out isodose curves for a qualitative evaluation (good, fair, or poor), but dose–volume histogram analysis was not available at the time.

The EBRT portion of therapy was completed a median of 4 weeks before the implant date. Patients received 45 Gy by way of a four-field box technique with customized Cerrobend blocks via 6–15 MV X-rays. Field sizes varied from patient to patient; most received a "limited pelvic" field. Patients did not undergo lymph node dissections or androgen ablation therapy. Any patient receiving androgen ablation therapy at any time after treatment, for any reason (*e.g.,* benign PSA bounce), for any duration, is counted as a biochemical failure.

RESULTS

The clinical status at presentation is outlined in Table 1. The mean pretreatment PSA was 15.25 ng/mL, 63.3% of patients presented with T2b-T3 disease by DRE, and 35% had Gleason score 7-10. There were seven local failures (3.1%) based on a positive biopsy, or positive DRE, or androgen ablation therapy for suspected local recurrence.

Table 1. External beam radiation therapy + seed implant cohort (n = 223) characteristics

Variable	Mean (Range)
Age (years)	69.2 (49–88)
Preimplant PSA	15.3 (0.4–138.0)
	Count (%)
Gleason score	
2–6	145 (65.0)
7	55 (24.7)
8–10	23 (10.3)
Stage	
T1b	9 (4.0)
T1c	18 (8.1)
T2a	55 (24.7)
T2b	84 (37.7)
T2c	49 (22.0)
T3	8 (3.5)
iPSA*	
0–4 ng/mL	36 (16.1)
4.1–10 ng/mL	71 (31.8)
10.1–20.0 ng/mL	68 (30.5)
>20.0 ng/mL	46 (20.6)
MSKCC risk group	
Low	61 (27.4)
Intermediate	91 (40.8)
High	71 (31.8)
D'Amico risk groups	
Low	59 (26.5)
Intermediate	50 (22.4)
High	114 (51.1)

Abbreviations: PSA = prostate-specific antigen; iPSA = initial PSA; MSKCC = Memorial Sloan-Kettering Cancer Center.

* The iPSA data for 2 (0.9%) patients was not available.

The Kaplan-Meier BRFS for the entire study group is 74%, as depicted in Fig. 1. The BRFS by biopsy Gleason score, initial PSA, and clinical stage are shown in Figs. 2–4.

Univariate and multivariate analysis was performed based on pretreatment Gleason score, PSA, stage, and D'Amico risk group cohorts and are shown in Table 2.

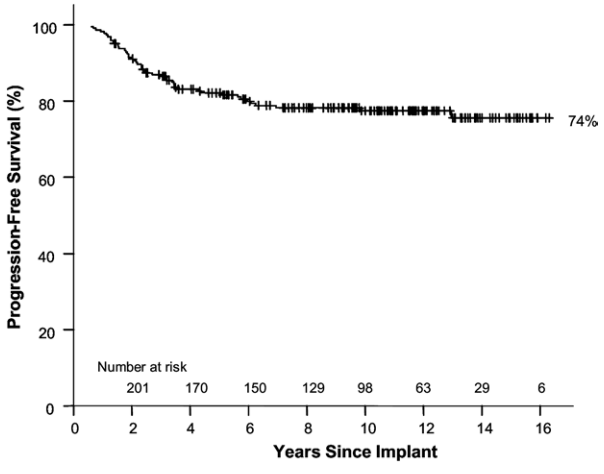

Fig. 1. External beam radiation therapy + seed implant (n = 223), biochemical relapse-free survival.

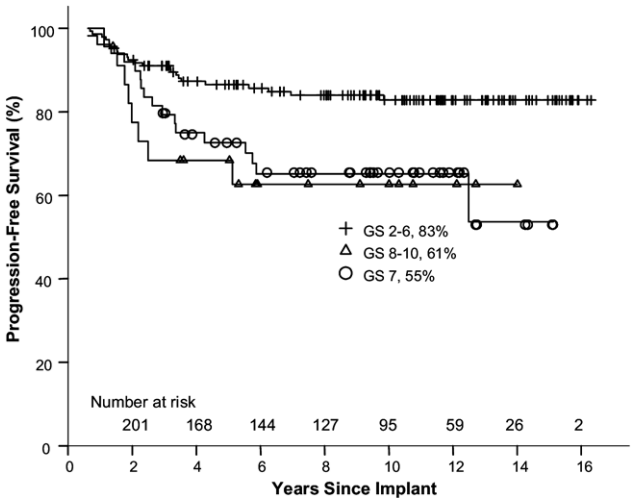

Fig. 2. External beam radiation therapy + seed implant (n = 223), biochemical relapse-free survival by Gleason score group.

Univariate and multivariate analysis based on isotope (Pd^{103}/I^{125}) is shown in Table 3.

Current 15-year BRFS results by the D'Amico risk grouping system are: low risk 85.8%, intermediate risk 80.3%, and high risk 67.8% (Fig. 5). The BRFS by the Zelefsky/Memorial Sloan-Kettering Cancer Center risk grouping system are low risk 88%, intermediate risk 80%, and high risk 53% (Fig. 6). Pairwise log–rank analysis comparisons were significant between risk groups, initial PSA (iPSA), isotope, Gleason score, and stage in univariate analysis. Pd^{103} was used more often than I^{125} for higher Gleason scores, thus isotope selection did not result in a significant difference in multivariate analysis outcomes. In multivariate analysis only, pretreatment Gleason score and stage were significant predictors of BRFS. The median posttreatment PSA nadirs for biochemical no evidence of disease individuals is 0.1 ng/mL.

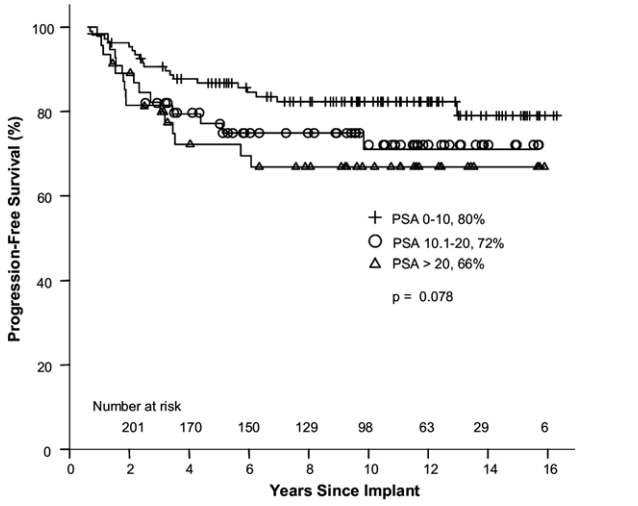

Fig. 3. External beam radiation therapy + seed implant (n = 223), biochemical relapse-free survival by initial prostate-specific antigen value group.

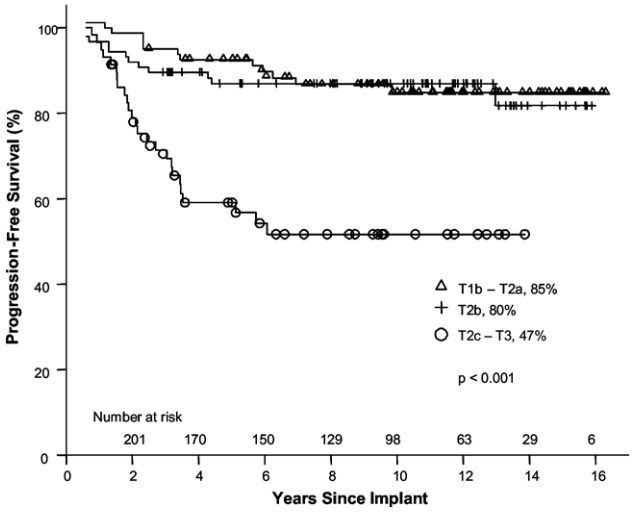

Fig. 4. External beam radiation therapy + seed implant ($n = 223$), biochemical relapse-free survival by stage at diagnosis group.

There were no treatment related deaths, deep venous thromboses, cardiopulmonary events, serious bleeding, sepsis, cerebral vascular events, or other serious perioperative complications.

DISCUSSION

We report the 15-year BRFS results of 223 consecutively treated clinical T1-T3 prostate cancer patients. Patients were treated with 45 Gy EBRT followed a few weeks later by a transperineal template-guided transrectal ultrasound-guided permanent interstitial implant with I^{125} or Pd^{103} radioactive seeds. None of these patients received hormonal therapy. The neoadjuvant EBRT was given because the authors felt these patients were at significant risk for extracapsular or seminal vesicle disease based on pretreatment clinical factors (GS, iPSA, stage, perineural invasion, and the number of positive biopsy cores).

Gleason score remains one of the most important predictors of biologic aggressiveness of prostate cancer, with high Gleason score correlating with a greater risk of biochemical failure after radical prostatectomy (RP), EBRT, and brachytherapy. The Gleason scores in this report were assigned by local community hospital pathologists. It has been well established that community hospital pathologists in the late 1980s and early 1990s tended to undergrade biopsy Gleason scores. Stenberg and colleagues reported significant undergrading of biopsy specimens by nonacademic-based pathologists. They reported that 22.3% of all outside biopsy specimens submitted for review at Johns Hopkins University were assigned Gleason Score 2-4 histology, with only 1.2% of the biopsies maintaining this classification after internal review (23). Epstein reported that no patient should be assigned Gleason score 2-4 on an ultrasound-guided needle biopsy (24). In addition, to assess whether the Johns Hopkins University grading of outside pathology specimens was biased, Steinberg correlated biopsy Gleason score to pathologic stage. Fifty-five percent of needle biopsies grade by outside pathologists as Gleason score 2-4 were not organ confined at RP, whereas all Johns Hopkins University–graded Gleason score 2-4 cases were organ confined. Thus the Gleason scores reported in this group of patients are most likely under-graded.

The 10-year EBRT plus brachytherapy outcomes we previously reported revealed BRFS of 90%, 84%, and 48% for the low-, intermediate-, and high-risk groups respectively (D'Amico risk grouping) (21). Our update of this data set shows that the low- and intermediate-risk patients continue to experience high disease-free survival rates. There was actually an improvement in the BRFS in the high-risk treatment cohort. This improvement was due to more extended and complete follow-up. Many of the high-risk patients that are currently without evidence of biochemical failure had relatively short follow-up in the previous article, thus carried less statistical weight in the Kaplan-Meier curves than those with longer follow-up at the time of that data analysis. Multiple studies have shown a year of treatment effect where more recently treated patients have significantly better BRFS than patients treated at the same institution just a few years earlier (25–27). These high-risk biochemical no evidence of disease patients now have significantly longer follow-up and thus have favorably influenced the Kaplan-Meier curves. A similar finding was also noted by Han *et al.,*when reporting an update of the Johns

Table 2. Univariate and multivariate analysis*

	Univariate		Multivariate	
Variable	*p*	Relative risk	*p*	Relative risk
Age	0.688	—	—	—
Pretreatment prostate-specific antigen	**0.016**	1.014	0.259	—
Gleason score	**0.002**	1.460	**0.011**	1.400
Stage: (≤T2b vs. >T2b)	**<0.001**	4.398	**<0.001**	4.162
Risk group (D'Amico):				
Low vs. intermediate	0.850	—	—	—
Low vs. high	**0.009**	2.789	0.963	—
Isotope (I-125 vs. P-103)	**0.007**	2.271	0.400	—

* Bold faced numbers indicate statistical significance.

Table 3. Clinical parameters, stratified by isotope*

Variable	I-125 Med.	I-125 Mean ± SD	Pd-103 Med.	Pd-103 Mean ± SD	*p*	Overall Med.	Overall Mean ± SD
Age (years)	70.0	69.1 ± 7.9	69.0	69.3 ± 7.0	0.875	69.0	69.2 ± 7.5
Gleason score	5.0	5.4 ± 1.0	7.0	6.5 ± 1.1	**<0.001**	6.0	6.0 ± 1.2
Preimplant prostate-specific antigen	9.2	15.2 ± 19.8	12.0	15.4 ± 12.4	0.934	10.5	15.3 ± 15.3
				Count (%)			
Clinical stage					**0.005**		
T1b-T2b		95 (81.9)		70 (65.4)			165 (74.0)
T2c-T3		21 (18.1)		37 (34.6)			58 (26.0)
D'Amico risk group:					**<0.001**		
Low		47 (40.9)		12 (11.2)			59 (26.6)
Intermediate		26 (21.7)		24 (22.4)			50 (22.1)
High		43 (37.4)		71 (66.4)			114 (51.4)

* Bold faced numbers indicate statistical significance.

Hopkins University radical prostatectomy outcomes, longer follow-up improved the 10 year BFRS from 68% to 74% (28, 29).

The 80% 15-year BRFS in the intermediate-risk patients is encouraging considering that the majority of these intermediate-risk patients were "unfavorable" intermediate-risk patients because 63.4% of them had ≥50% of their biopsy needle cores positive. Surgical studies reveal the number of positive biopsies to be an independent risk factor predicting poor outcomes (19). In the radical prostatectomy series reported by D'Amico, intermediate-risk patients at the Hospital of the University of Pennsylvania and Brigham and Women's Hospital with 34–50% of their needle biopsy specimens positive experienced ~50% 5-year BRFS. They noted a <20% 5-year BRFS in the intermediate-risk patients who had >50% of the needle biopsy cores positive. Gancarczyk and colleagues noted in a study of 1,510 men who underwent RP and were stratified by the percent positive biopsy cores that an increase in percent positive biopsy cores correlated with a substantial increase in extracapsular extension, but only minimal increase in seminal vesicle or pelvic lymph node involvement (30). In a brachytherapy report by Merrick *et al.*, a significant but slight difference in BRFS was noted at 8 years for the entire treatment cohort, but not when broken down by risk group (31). Brachytherapy may be less sensitive to extracapsular extension in comparison to RP because of its ability to obtain wider margins via either the use of supplemental external beam or carefully placed extracapsular seeds (32).

Most brachytherapists use monotherapy for low-risk patients. The low-risk patients in this report received combination EBRT plus brachytherapy because of the authors' perception that they may be higher risk for relapse from a high number of positive biopsies and the virtual total lack of outcomes data with ultrasound-guided brachytherapy at the time we treated these patients. Currently, we rarely use

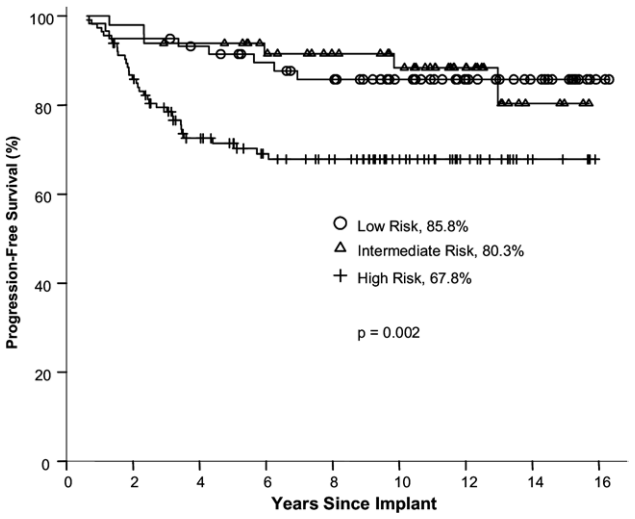

Fig. 5. Seattle long-term biochemical relapse-free survival outcomes, stratified by D'Amico risk groups.

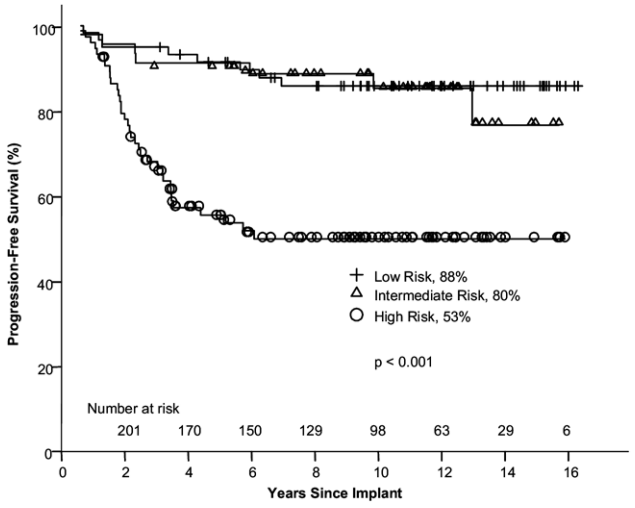

Fig. 6. External beam radiation therapy + seed implant ($n = 223$), biochemical relapse-free survival by Memorial Sloan-Kettering Cancer Center Risk Group.

Table 4. Long-term outcomes

	SPI-brachytherapy (n = 223)	JHH-RP (n = 2,404)	WU-RP (n = 3,478)
iPSA			
0–4	16.1%	29%	19%
4.1–10	31.8%	50%	63%
10.1–20	30.5%	17%	20%
>20	20.6%	5%	Above
	Clinical	Clinical	Path. GS
Gleason score			
2–6	65%	62%	63%
7	24.7%	31%	30%
8–10	10.3%	7%	7%
	Clinical	Clinical	Clinical
Stage			
T1-T2a	36.8%	78%	71%
T2b-T2c	59.7%	20%	28%
T3	3.5%	2%	1%
Relapse-free survival	15 years (74%)	15 years (66%)	10 years (68%)
Medium follow-up (range)	9.4 (1–17) years	6.3 (1–17) years	5.4 (0–19.4) years

Abbreviations: SPI = Seattle Prostate Institute; JHH-RP = Johns Hopkins Hospital-radical prostatectomy; WU-RP = Washington University-radical prostatectomy; iPSA = initial prostate-specific antigen.

combination brachytherapy plus EBRT in low-risk patients. The BRFS outcomes of the intermediate-risk patients in this series are almost as favorable as the low-risk patients. There is no statistically significant difference in the BRFS outcomes between low- and intermediate-risk patients in this series. The lack of difference in BRFS between low-risk and intermediate-risk patients treated with brachytherapy was also seen in the recent publication by Merrick (33). This may indicate that most intermediate-risk patients have a low risk of micrometastatic disease. The higher incidence of extracapsular extension and seminal vesicle invasion in intermediate-risk patients is well treated by EBRT plus brachytherapy. One could question whether brachytherapy alone with ~5-mm margins would do as well as EBRT plus brachytherapy. Hopefully, Radiation Therapy Oncology Group 0203 will accrue well and answer that question.

The high-risk patients in this series did well considering the era they were treated in. Whether or not the addition of androgen ablation therapy would have further improved the results is unknown. We are participating (with Merrick and Wallner) in a multi-institutional randomized trial in which high-risk patients are treated with whole pelvic EBRT plus a Pd^{103} boost and are randomized to no androgen ablation or to receive a 9-month course of neoadjuvant concurrent-adjuvant androgen ablation therapy in an attempt to answer that question.

Other long-term brachytherapy outcomes typically go out to 10-year data points. Grimm reported the 10-year BRFS of I^{125} monotherapy patients treated between 1988 and 1990 (8). The 10-year BRFS in this group was 87%, the mean follow-up was 94.5 months, and there was a 3% local failure rate. In all Seattle Prostate Institute reports, we use a two-rise definition for failure rather than a three-rise ASTRO definition because a two-rise definition is significantly more sensitive at picking up biochemical failures (22). Stock and Stone have recently reported the 10-year Mt. Sinai experience on a group of patients treated in the early late 1990s with brachytherapy ± EBRT (34). Patients had cT1-T2 disease a minimum follow-up of 4 years and received I^{125} with or without 6 months of androgen ablation. The overall 10-year BRFS was 78%, but the BRFS was 90% and local control was 95.2% in those patients that received high-quality implants, defined as a D90 of more than 140 Gy.

Sharkey recently published his group's long-term outcomes of Pd^{103} ± EBRT (35). The long-term BRFS for the brachytherapy patients were 89%, 89%, and 88%, for the low-, intermediate-, and high-risk groups, respectively. For the radical prostatectomy patients in his series, the BRFS was 94%, 58%, and 43% for low-, intermediate-, and high-risk patients, respectively. Critz reported 10-year BRFS in low-, intermediate-risk, and high-risk patients of 93%, 80%, and 61% respectively in a cohort of 1,469 men treated with 125I + EBRT and median follow-up of 6 years (36). Thus multiple brachytherapy centers have reported excellent 10-year BRFS with prostate brachytherapy ± EBRT proving that long-term brachytherapy outcomes are reproducible. Now the data at 15 years demonstrate that these outcomes continue to hold up long term.

Long-term surgical outcomes from centers of excellence do not hold up better than these brachytherapy results (Table 4) (4). Roehl reported on the 10-year BRFS results achieved by Catalona at Washington University (25). The results were not segregated by risk group analysis, but the mean iPSA, biopsy Gleason scores, and clinical T stages are

more favorable than this brachytherapy series. They noted a 10-year BRFS of 68% with a mean follow-up of 5.4 years.

The 15-year BRFS results of RP from Johns Hopkins Hospital were reported by Han and colleagues (37). The mean follow-up was 5.9 years. The pretreatment patient characteristics were more favorable than this Seattle brachytherapy series, and they excluded the more unfavorable patients from their analysis, specifically those found to have positive lymph nodes and patients that received immediate postoperative radiation or hormonal therapy for poor prognostic features found on final postoperative pathology. They reported a 66% 15-year freedom from relapse overall.

We expect improved BRFS outcomes in modern patients treated with modern brachytherapy equipment and techniques. Indeed, a recently reported modern brachytherapy series from Merrick and colleagues, using the Seattle preplan technique, reported an 8-year BRFS of 98%, 98%, and 88% for low-, intermediate-, and high-risk patients treated with I^{125}/Pd^{103} brachytherapy ± EBRT (33).

CONCLUSION

The 15-year BRFS outcomes with neoadjuvant EBRT and I^{125}/Pd^{103} boost continue to show excellent long-term disease control rates despite a relatively unfavorable patient population, older era of treatment, and less sophisticated EBRT and brachytherapy techniques than are available.

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