Original paper

Prostate cancer-specific death in brachytherapy treated high-risk patients stratified by pre-treatment PSA

Gregory S. Merrick, MD[1,2], Robert W. Galbreath, PhD[1,3], Wayne M. Butler, PHD[1], Ryan Fiano, MPH[1], Edward Adamovich, MD[4]

[1]Schiffler Cancer Center and Wheeling Jesuit University, Wheeling, WV, [2]Wheeling Hospital, Department of Urology, Wheeling, WV, [3]Ohio University Eastern, St. Clairsville, OH, [4]Wheeling Hospital, Department of Pathology, Wheeling, WV, USA

Abstract

Purpose: To evaluate prostate-cancer specific mortality (PCSM) in a cohort of high-risk patients treated with a permanent prostate brachytherapy approach, stratified by pre-treatment PSA.

Material and methods: 448 high-risk patients (NCCN criteria) underwent permanent prostate brachytherapy. High risk patients were stratified by pre-treatment PSA (≤ 10.0, 10.1-20, and > 20 ng/ml). Biochemical failure (BF), prostate cancer-specific mortality (PCSM), distant failure (DM), and overall mortality (OM) were assessed as a function of prognostic group. Multiple clinical, treatment, and dosimetric parameters were evaluated for impact on outcome.

Results: The 10-year OM, BF, and PCSM for the entire cohort were 28.5%, 13.3%, and 4.9%, respectively. At 10 years, PCSM was 2.5%, 10.7%, and 4.5% in the PSA ≤ 10, 10.1-20, and > 20 ng/ml groups, respectively. No statistically significant differences in BF or overall survival (OS) were noted when stratified by pre-treatment PSA. DF was the most common in the 10.1-20 ng/ml cohort (8.6% at 10 years). In multivariate analysis, PCSM was most closely related to percent positive biopsies ($p = 0.001$) and tobacco ($p = 0.042$).

Conclusions: High-risk prostate cancer treated with permanent prostate brachytherapy and supplemental external beam radiotherapy resulted in excellent long-term biochemical control and PCSM. Overall, PCSM was low in all cohorts but highest in the intermediate PSA group (10.1-20 ng/ml).

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Key words: high-risk disease, prostate cancer, prostate cancer-specific death, PSA.

Purpose

The National Comprehensive Cancer Network (NCCN) defines high-risk prostate cancer according to the following criteria: clinical stage T3, Gleason score 8-10, and/or prostatic specific antigen (PSA) > 20 ng/ml [1]. Low-dose-rate (LDR) brachytherapy with supplemental external beam radiation therapy (EBRT) has been demonstrated to be a highly efficacious treatment for high-risk prostate cancer [2]. Recently, the ASCENDE-RT trial demonstrated marked improvement in biochemical disease-free survival when a brachytherapy boost was added to supplemental external beam radiation therapy compared to definitive intensity modulated external beam radiation therapy (IMRT) [3]. In addition, in multi-institutional studies, the results of dose-escalation using a brachytherapy boost in high-risk patients resulted in decreased prostate cancer-specific survival (PCSM) [4,5].

Mahal and colleagues using the Surveillance Epidemiology and End Results (SEER) database concluded that high-risk patients treated with either surgical or radiotherapeutic approaches presenting with either a very low (< 2.5 ng/ml) or very high (> 40 ng/ml) PSA had a markedly increased risk of PCSM [6]. The authors concluded that increased PCSM in patients with a low pre-treatment PSA and Gleason scores of 8-10 was suggestive of the presence of very aggressive low producing PSA cancers. Previously, we reported high rates of biochemical control in high-risk patients treated with a brachytherapy approach [2]. In this study, we evaluate the impact of pre-treatment PSA on PCSM in patients with high-risk disease treated with high quality brachytherapy (a post-implant dose to the prostate gland > 100% of prescription dose, D_{90}) with or without supplemental external beam radiation therapy (EBRT) and/or androgen deprivation therapy (ADT).

Material and methods

From April 1995 to January 2014, 448 patients with NCCN high-risk prostate cancer (clinical stage T3 or Gleason score 8-10, and/or PSA > 20 ng/ml) underwent permanent prostate brachytherapy by a single brachytherapist. The high-risk patients were divided into 3 cohorts based on pre-treatment PSA (≤ 10.0 ng/ml, $n = 248$; 10.1-

Address for correspondence: Gregory S. Merrick, MD, Schiffler Cancer Center, Wheeling Hospital, 1 Medical Park, Wheeling, WV 26003, USA, phone: +1 304 243 3490, fax: +1 304-243-5047, e-mail: gmerrick@urologicresearchinstitute.org

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20.0 ng/ml, n = 97; and > 20 ng/ml, n = 103). A secondary analysis was performed stratifying patients by PSA as per the SEER reported data [6]. The SEER data stratified patients into 5 categories: < 4 ng/ml, n = 16; 4-10.0 ng/ml, n = 232; 10.1-20 ng/ml, n = 97; 20.1-40 ng/ml, n = 85; and > 40 ng/ml, n = 18. Because of small numbers in some of the cohorts, the primary evaluation consisted of the above mentioned 3 patient group stratification. All patients underwent brachytherapy more than 3 years prior to analysis. Prior to implantation, all slides underwent review by a pathologist with significant expertise in prostate pathology. Our pre-planning technique, intraoperative approach, and dosimetric evaluation have been described previously [7,8]. Patients were clinically staged using medical history and physical examination including digital rectal examination and serum PSA. Bone scans and computed tomography of the abdomen and pelvis were obtained in all patients. In all patients, prophylactic alpha-blockers were initiated two weeks prior to implantation and continued until the urinary symptoms were resolved.

The brachytherapy planning target volume consisted of prostate gland with a 5 mm periprostatic margin in the proximal 1.0 cm of the seminal vesicles [7,8]. All post-implant dosimetric calculations were based on day 0 dosimetric evaluation. Within 2 hours of implantation, a thin-slice 3 mm CT scan was obtained for evaluation of post-implant dosimetric coverage. Evaluated dosimetric parameters included the percentage of the target volume receiving 100%, 150%, and 200% of the prescribed dose ($V_{100/150/200}$), and the minimum percentage of the dose covering 90% of the target volume (D_{90}).

Four-hundred and forty-five of the 448 patients (99.1%) received supplemental EBRT. In general, 45-50.4 Gy were delivered in 1.8 Gy fractions utilizing 15-18 MV photons delivered via either a 3-dimensional conformal or intensity modulated external beam radiation therapy technique. The target volume consisted of the prostate gland, seminal vesicles, and pelvic lymph nodes. The pelvic lymph nodes were treated superiorly to the L5-S1 interspace. The dose to 50% of the rectum (R50) was limited to ≤ 30 Gy. In all cases, supplemental EBRT was delivered prior to brachytherapy.

Three-hundred and twenty-five of the 448 patients (72.4%) received ADT. Two-hundred and seventy-three patients (60.8%) received long-term (> 6 months) ADT, while 52 patients (11.6%) received short-course (≤ 6 months) of ADT. When prescribed, ADT was initiated 3 months prior to implantation and consisted of a luteinizing hormone-releasing hormone agonist, or antagonist with or without an anti-androgen. The median ADT duration was 4 and 24 months in the short course and extended course groups, respectively (range, 3-36 months).

Patients were monitored by physical examination including digital rectal examination and PSA measurement at 3-6 month intervals. The primary endpoint of the analysis was prostate cancer-specific mortality (PCSM). The cause of death was determined for each deceased patient. Patients with metastatic prostate cancer and/or non-metastatic castrate-resistant disease who died of any cause were classified as prostate cancer death. All other deaths were attributable to the immediate cause of death. In addition, biochemical failure (BF) was analyzed. Biochemical failure was defined as a PSA ≤ 0.40 ng/ml after nadir. Patients who failed to achieve a PSA nadir ≤ 0.40 ng/ml were categorized as a BF. Multiple clinical, treatment, and dosimetric parameters were evaluated with further effect on outcome.

Patients were grouped based on pre-implant PSA. Clinical and treatment variables that were continuous were compared across groups using a one-way analysis of variance (ANOVA). Categorical variables were compared using a X^2 analysis. All-cause mortality was compared across the grouping of PSA and across the 3 levels of risk using a cox-regression analysis. Biochemical failure and PCSM across the 3 or 5 PSA groups were determined using competing risk analysis. STATA version 12.0 software (StataCorp, College Station, TX, USA) and SPSS version 17.0 (Chicago, Il, USA) were used for all analysis with significance set at $p \leq 0.05$.

Results

Table 1 summarizes the clinical, treatment, and dosimetric parameters for the 448 patients stratified by pre-implant PSA (≤ 10 ng/ml, 10.1 ng/ml, and ≥ 20.0 ng/ml). The mean and median follow-up for entire group was 9.2 and 8.8 years, respectively. Compared to the other two cohorts, patients with a pre-treatment PSA > 20 ng/ml were statistically younger with longer follow-up, were less likely to present with Gleason 8-10 histology, were more likely to present with clinical ≥ T2b stage, to receive long term (> 6 month) ADT, were more likely to present with poor high risk disease and lower pre-treatment testosterone levels. The median post-treatment PSA for all biochemically controlled patients was < 0.02 ng/ml.

Figure 1 illustrates overall mortality (OM), biochemical failure (BF), and prostate cancer-specific mortality (PCSM) for the entire group at 10 and 15 years. At 10 years, OM, BF, and PCSM were 28.5%, 13.3%, and 4.9%, respectively. Figure 2 illustrates a competing risk analysis for biochemical failure stratified by pre-implant PSA with no statistically significant differences at 10 years (11.9%, 16.7%, and 13.9%, p = 0.339). The mean and median time to BF in PSA cohorts < 10, 10-20, and > 20 were 3.35 years and 3.22 years, 2.65 years and 2.56 years, and 1.84 years and 1.69 years, respectively. Figure 3 illustrates OS at 10 and 15 years stratified by the 3 PSA cohorts without statistically significant differences in survival (p = 0.310). When PCSM was stratified by the 3 pre-implant PSA cohorts (Table 2), statistically significant differences were discerned at 10 years (Figure 4). The 10-year PCSM for pre-treatment PSA ≤ 10, 10.1-20, and > 20 were 2.5%, 10.7%, and 4.5%, respectively (p = 0.0156). When patients were stratified into the 5 SEER cohorts, the number of patients in some of the individual groups were very small. No statistical difference in OM (p = 0.333) or BF (0.603) was discernible. PCSM and distant failure (DF) were substantially greater in patients with a pre-treatment PSA of 10.1-20.0 ng/ml compared to the other 4 cohorts (p < 0.001) for both PCSM and DF.

Table 1. High-risk patients stratified by pre-implant prostate-specific antigen (PSA)

	≤ 10.0 (*n* = 232)		10.1-20 (*n* = 97)		> 20 (*n* = 85)		*p*	Total (*n* = 448)	
Continuous variables	**Mean**	**Median**	**Mean**	**Median**	**Mean**	**Median**		**Mean**	**Median**
Age at implant	66.9	67.5	67.1	68	64.3	64	0.005	66.3	67
Follow-up (years)	8.7	8.0	9.2	8.9	10.3	10.1	0.010	9.2	8.8
Gleason score	8.4	8.0	8.5	8.0	7.4	7	< 0.001	8.2	8.0
Percent positive biopsies	48.7	43.7	58.5	53.6	57.2	58.3	0.003	52.8	50
BMI	29.2	28.3	29.3	28.4	28.8	27.8	0.770	29.1	28.3
$D_{90\%}$	122.3	123.3	120.4	120.5	120.8	120.8	0.317	121.5	122.1
V_{100}	97.5	98.5	96.7	98.1	96.9	97.9	0.071	97.2	98.3
V_{150}	71.6	73.9	70.7	72.8	69.2	73.2	0.097	71.0	73.5
V_{200}	42.9	43.5	42.6	43.9	40.7	44.4	0.188	42.3	43.8
Last PSA	0.01	< 0.02	0.01	< 0.02	0.01	< 0.02	< 0.001	0.01	< 0.02
Categorical variables	**Mean**	**Median**	**Mean**	**Median**	**Mean**	**Median**	***p***	**Mean**	**Median**
Gleason score									
6	0	(0.0)	1	(1.0)	18	(17.5)	< 0.001	19	(4.2)
7 (3 + 4)	1	(0.4)	0	(0.0)	13	(12.6)		14	(3.1)
7 (4 + 3)	1	(0.4)	1	(1.0)	30	(29.1)		32	(7.1)
8	151	(60.9)	49	(50.5)	20	(19.4)		220	(49.1)
9	95	(38.3)	46	(47.4)	22	(21.4)		163	(36.4)
Stage									
≤ T2a	187	(75.4)	69	(71.1)	61	(59.2)	0.010	317	(70.8)
≥ T2b	61	(24.6)	28	(28.9)	42	(40.8)		131	(29.2)
Isotope									
^{103}Pd	247	(99.6)	97	(100)	92	(89.3)	< 0.001	436	(2.7) (97.3)
^{125}I	1	(0.4)	0	(0.0)	11	(10.7)		12	
XRT									
No	2	(0.8)	2	(2.1)	0	(0.0)	0.640	4	(0.9)
Yes	246	(99.2)	95	(97.9)	103	(100)		445	(99.1)
ADT									
None	96	(38.7)	14	(14.4)	13	(12.6)	< 0.001	123	(27.6)
≤ 6 months	40	(16.1)	6	(6.2)	6	(5.8)		52	(11.6)
> 6 months	112	(45.2)	77	(79.4)	84	(81.6)		273	(60.8)
Testosterone#									
≤ 1/3 normal	130	(73.0)	50	(71.4)	33	(53.2)	0.001	214	(68.8)
Mid 1/3 normal	35	(19.7)	17	(24.3)	22	(35.5)		74	(23.8)
≥ 1/3 normal	13	(7.3)	3	(4.3)	7	(11.3)		23	(7.4)
Hypertension:									
No	101	(70.7)	46	(47.4)	49	(47.6)	0.433	196	(43.7)
Yes	147	(59.3)	51	(52.6)	54	(52.4)		252	(56.3)

Table 1. Cont.

	≤ 10.0 (*n* = 232)		10.1-20 (*n* = 97)		> 20 (*n* = 85)		*p*	Total (*n* = 448)	
Categorical variables	Mean	Median	Mean	Median	Mean	Median		Mean	Median
Diabetes									
No	205	(82.7)	85	(87.6)	95	(92.2)	0.117	385	(85.9)
Yes	43	(17.3)	12	(12.4)	8	(7.77)		63	(14.1)
Hypercholesterolemia									
No	155	(62.5)	59	(60.8)	75	(72.8)	0.128	289	(64.5)
Yes	93	(37.5)	38	(39.2)	28	(27.2)		159	(35.5)
Cardiovascular disease									
No	195	(78.6)	73	(75.3)	83	(80.6)	0.650	351	(78.4)
Yes	53	(21.4)	24	(24.7)	20	(19.4)		97	(21.6)
Tobacco[#]									
Never	85	(34.7)	38	(39.6)	32	(31.4)	0.360	155	(35.0)
Former	125	(51.0)	41	(42.7)	48	(47.0)		214	(48.3)
Current	35	(14.3)	17	(17.7)	22	(21.6)		74	(16.7)
Perineural invasion									
No	128	(51.6)	35	(36.1)	49	(47.6)	0.034	212	(47.3)
Yes	120	(48.4)	62	(63.9)	54	(52.4)		236	(52.7)
High-risk									
Good	243	(98.0)	92	(94.9)	60	(58.3)	< 0.001	395	(88.2)
Intermediate	0	(0.0)	0	(0.0)	1	(1.0)		1	(0.2)
Poor	5	(2.0)	5	(5.2)	42	(40.7)		52	(11.6)

BMI – Body mass index, $D_{90\%}$ – percent of the prescription dose covering 90% of the clinical target volume, V_{100}, V_{150}, V_{200} – volumes of the anatomic volume receiving 100%, 150%, 200% of the prescribed dose, PSA – prostate specific antigen, XTR – external beam radiotherapy, ADT – androgen deprivation therapy
[#] – only 311 patients had testosterone values and 5 patients did not have tobacco data

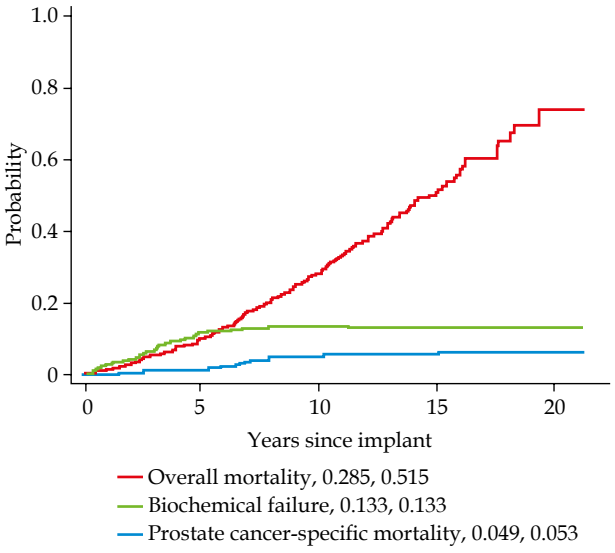

Fig. 1. Overall mortality (one-minus survival), biochemical failure (cumulative incidence), and prostate-specific failure (cumulative incidence) at 10 and 15 years

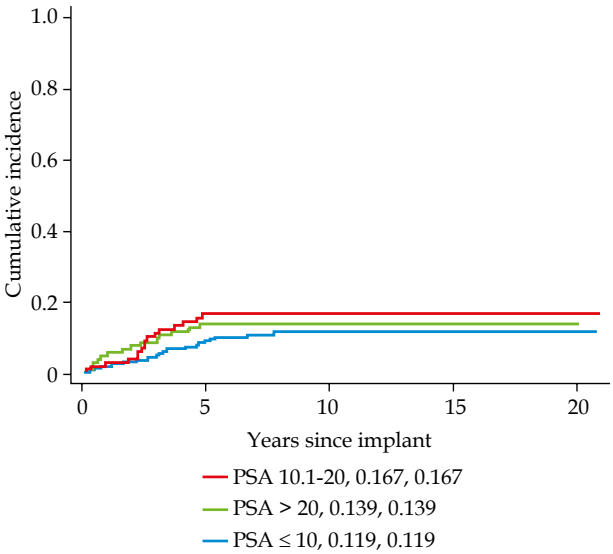

Fig. 2. Competing risks analysis for biochemical failure, stratified by pre-implant prostate-specific antigen (PSA) with probability provided at 10 and 15 years

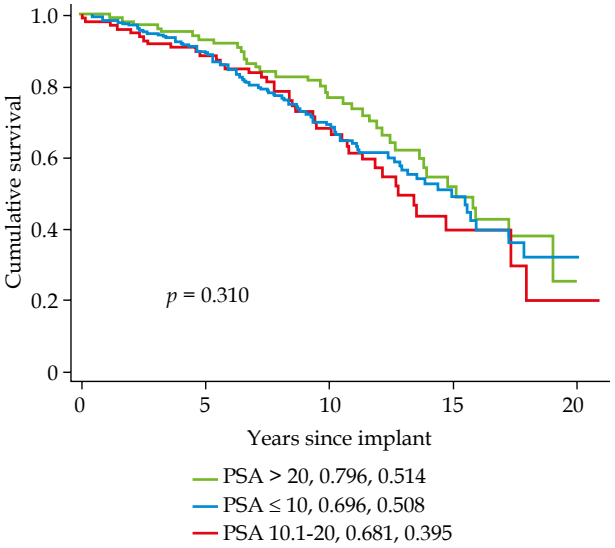

Fig. 3. Overall survival (Kaplan-Meier) stratified by pre-implant prostate-specific antigen (PSA) with probability provided at 10 and 15 years

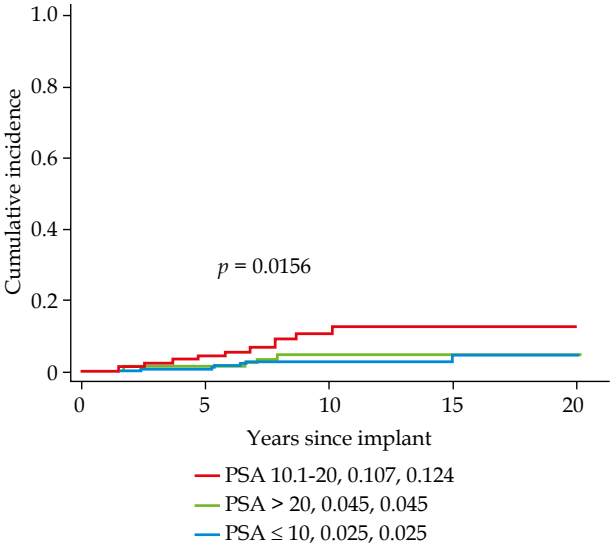

Fig. 4. Competing risks analysis for prostate cancer-specific mortality stratified by pre-implant prostate-specific antigen (PSA) with probability provided at 10 and 15 years

Table 3 summarizes the multivariate analysis for OM, BF, and PCSM. In multivariate analysis, OM was best predicted by patient age (p = 0.001), percent positive biopsies (p = 0.005), Gleason score (p = 0.039), and low/low normal testosterone (p = 0.005). For BF, percent positive biopsies (p = < 0.001) best predicted for outcome. For PCSM, percent positive biopsies (p = 0.001) and tobacco (p = 0.042) were the strongest predictors.

Discussion

Mahal and colleagues using the SEER data, which included radical prostatectomy and radiotherapy, treated patients with a median follow-up of 38 months, and demonstrated that PCSM was highest in patients with a pre-treatment PSA < 4.0 ng/ml or > 40.0 ng/ml [6]. The authors concluded that patients with very low PSA values have a prognosis similar to those with very high PSA levels. In our much smaller series but with substantially longer follow-up (mean and median follow-up 9.2 and 8.8 years), our brachytherapy results do not confirm the SEER data. In our series, PCSM was substantially lower for all PSA cohorts compared to the SEER data with the greatest risk of PCSM in patients with a pre-treatment PSA of 10.1-20 ng/ml. Consistent with our results, a radical prostatectomy (RP) series did not demonstrate any difference in failure between patients with a very low pre-treatment PSA compared to those with higher pre-treatment PSA [9]. In contrast, a RP series of patients with Gleason scores 8-10 revealed non-statistical trends toward biochemical failure and increased distant metastasis in patients with pre-treatment PSA ≤ 2.5 vs. 4.1-10 ng/ml [10].

D'Amico *et al*. reported that patients with high-grade disease and a pre-treatment PSA ≤ 4 ng/ml had a shorter time to biochemical recurrence than patients with a PSA of 4.1-10.0 ng/ml [11]. In our series, we did not demonstrate any substantial differences in failure when stratified by PSA < 4 vs. 4-10, but did note somewhat shorter times to failure in patients with a PSA > 20 ng/ml (median time to failure 1.69 years vs. patients with a pre-treatment PSA ≤ 10 ng/ml, 3.22 years).

Local control has been demonstrated to improve PCSM in high-risk patients. The addition of EBRT to ADT has improved biochemical control, PCSM, and overall

Table 2. Ten- and 15-year mortality or failure (overall mortality, biochemical failure, prostate cancer-specific mortality, and distant failure) stratified by pre-treatment prostate-specific antigen (PSA)

Failure type	< 4.0 (n = 16)		4.0-10.0 (n = 232)		10.1-20.0 (n = 97)		20.1-40.0 (n = 85)		> 40.0 (n = 18)		p
	10 yr	15 yr	10 yr	15 yr	10 yr	15 yr	10 yr	15 yr	10 yr	15 yr	
Overall mortality[1]	0.219	0.219	0.309	0.507	0.319	0.604	0.229	0.479	0.128	0.477	0.333
Biochemical failure[2]	0.103	0.103	0.120	0.120	0.168	0.168	0.132	0.132	0.167	0.167	0.603
Prostate cancer-specific mortality[2]	0.000	0.000	0.026	0.026	0.107	0.124	0.040	0.040	0.056	0.056	< 0.001
Distant failure[2]	0.000	0.000	0.022	0.022	0.086	0.086	0.012	0.012	0.056	0.056	< 0.001

[1]*One-minus survival*
[2]*Cumulative incidence*

Table 3. Univariate and multivariate analysis for predicting biochemical failure, overall mortality, and prostate cancer-specific mortality

	Overall mortality				Biochemical failure				Prostate cancer-specific mortality			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
Continuous variables	*p*	HR	*p*	HR	*p*	SHR	*p*	HR	*p*	SHR	*p*	HR
PSA	0.113				0.145				0.512			
Age	< 0.001	1.055	0.001	1.055	0.060		0.301		0.046		0.209	
Percent positive biopsies	0.002	1.009	0.002	1.013	< 0.001	1.019	< 0.001	1.018	< 0.001	1.030	0.001	1.028
BMI	0.435				0.150				0.780			
$D_{90\%}$	0.792				0.668				0.836			
Categorical variables												
Perineural invasion	0.148				0.097		0.789		0.220			
Hypercholesterolemia	0.362				0.150				0.241			
Cardiovascular disease	0.142				0.085		0.223		< 0.001	*		
Diabetes	0.604				0.137				0.617			
Hypertension	0.972				0.056		0.116		0.026	0.333	0.052	
Tobacco	0.150				0.615				0.053			
Never vs. former	–				–				–		0.042	0.303
Never vs. current	–				–				–		0.533	
Gleason score	0.139				< 0.001				x			
6 vs. 7 (3 + 4)					< 0.001	> 100	***					
6 vs. 7 (4 + 3)					< 0.001	> 100	***					
6 vs. 8					< 0.001	> 100	***					
6 vs. 9					< 0.001	> 100	***					
ADT	0.924				0.264				0.204			
ADT duration:	0.587				0.341				0.4435			
0 vs. ≤ 6 months	–				–				–			
0 vs. > 6 months	–				–				–			
Pre-treatment PSA	0.221				0.597				< 0.001	**		
< 4.0	–				–				–			
4.1-10	–				–				–			
10.1-20	–				–				–			
20.1-40	–				–				–			
> 40.0	–				–				–			
Testosterone	0.021		0.016		0.350				< 0.001			
Low & low norm vs. mid norm	0.006	0.406	0.004	0.389	–				0.480	–		
Low & low norm vs. high & high norm	0.539		0.786		–				< 0.001	*		

PSA – prostate specific antigen, BMI – Body mass index, $D_{90\%}$ – percent of the prescription dose covering 90% of the clinical target volume, ADT – androgen deprivation therapy

**Approaching negative infinity, so these variables were not included in further analyses*

***Approaching positive infinity, so this variable was not included in further analyses. Also there was only one failure in the PSA ≤ 4.0 and > 40 groups*

****All sub-hazard ratios (SHR) were greater than 1 x 10^7 when each Gleason score was compared to a Gleason score of 6. So, Gleason score was not entered into multivariate analysis*

[X]There were no prostate specific deaths in the comparison group (Gleason score 6)

survival in patients with locally advanced prostate cancer [12,13]. Furthermore, 3 prospective randomized trials evaluating RP with or without adjuvant EBRT for prostate cancer with high-risk features demonstrated a 50% relative reduction in biochemical failure rates [14,15,16]. One study demonstrated a 9% statistically significant improvement in 10-year overall survival [14]. It is conceivable that the improved biochemical control rates and decreased PCSM in our cohort is due to high-quality prostate brachytherapy (day 0 D_{90} of 121.5% of prescription) with generous periprostatic treatment margins with the inclusion of supplemental nodal EBRT and ADT. In the SEER data, brachytherapy dosimetric quality, EBRT radiation doses, and RP pathologic assessment are not accessible, and may have artificially influenced their conclusions [6].

In the current study, patients with a pre-treatment PSA 10.1-20 ng/ml had a greater incidence of PCSM (Figure 4, $p = 0.0156$) and DF (Table 2, $p < 0.001$). The poorer outcome in patients with an intermediate pre-treatment PSA is most likely result in a greater incidence of Gleason score 9 patients in that cohort (Table 1). Consistent with other studies (Table 3), tobacco consumption was related to an increased risk of prostate cancer death [17]. In addition, low pre-treatment testosterone levels were associated with decreased OS, which is consistent with one of our previous publications [18].

Shortcomings of our study include a relatively small number of patients treated at a single institution by a single brachytherapist. In addition, all retrospective evaluations were with inherent treatment bias. ADT was administered based on assessment of the treating physician without protocol guidelines, and as such its role in the management of these patients cannot be determined. Strengths of the study include that all patients were treated with a consistent brachytherapy and EBRT techniques with documented high-quality post-implant dosimetry.

Conclusions

High-risk prostate cancer treated with permanent prostate brachytherapy and supplemental EBRT results in excellent long-term biochemical control and PCSM. Overall, PCSM was low in all cohorts but highest in the intermediate PSA group (10.1-20 ng/ml).

Disclosure

Authors report no conflict of interest.

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